



No. 14-143289- 00000-0000

Fecha: 2014-07-03 15:16:33

Dep. 2020 DIR.NUEVASCR

Tra. 11 PATENTEIYII

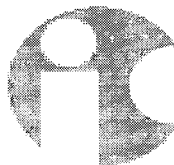
Eve: 378 FASENACIONALI

Act. 411 PRESENTACION

Folios: 9/10

IM IAMAYO
PATENTS · TRADEMARKS

T = F = 9

**Industria y Comercio**
SUPERINTENDENCIA**DELEGATURA PROPIEDAD INDUSTRIAL****División de Nuevas Creaciones****SOLICITUD DE:****PATENTE DE INVENCION****PCT FASE NACIONAL**

21. EXPEDIENTE No. _____

54. TITULO: COMPOSICIONES INTRANASALES DE
DEXMEDETOMIDINA Y MÉTODOS DE USO DE ELLAS71. SOLICITANTE : RECRO PHARMA, INCDOMICILIO: MALVERN, PENNSYLVANIA, USA74.- APODERADO: JOHAN SEBASTIAN GOMEZ VILLA22.- Bogotá, JUNIO 07 DE 2014

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-143289- -00000-0000

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Eve: 378 FASENACIONALI
Folios: 910

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD FASE NACIONAL -PCT

1	TIPO DE SOLICITUD	☒ Patente de invención ☒ Capítulo I	☐ Patente de Modelo de Utilidad ☐ Capítulo II
2	DATOS SOLICITUD INTERNACIONAL PCT (86)		
Solicitud Internacional No.		PCT/US2012/068988	Fecha 2012/12/11
Publicación Internacional No.		WO/2013/090278 A2	Fecha 2013/06/20
3	TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)		
COMPOSICIONES INTRANSALES DE DEXMEDETOMIDINA Y MÉTODOS DE USO DE ELLAS			
4	CLASIFICACIÓN INTERNACIONAL (CIP)		
5	SOLICITANTE (S) ☐ Esta persona también es inventor. Para datos adicionales utilizar hoja de información complementaria		
APELLIDOS O RAZÓN SOCIAL		NOMBRE	IDENTIFICACIÓN TIPO
1. RECRO PHARMA, INC.			EXTRANJERA
6	DATOS DEL SOLICITANTE		
DIRECCIÓN		55 Valley Stream Parkway Suite 100 Malvern, Pennsylvania 19355	
CIUDAD		Malvern	
DEPARTAMENTO/ESTADO		Pennsylvania	
PAÍS DE RESIDENCIA		USA	
No. TELÉFONO			
CORREO ELECTRÓNICO			
NACIONALIDAD O LUGAR DE CONSTITUCIÓN			
7	INVENTOR (ES) Para datos adicionales utilizar hoja de información complementaria		
APELLIDOS		NOMBRES	NACIONALIDAD
1.HENWOOD,		Geraldine A.	US
2.MACK,		Randall J.	US
3.KOLENG,		JR., John Joseph	US
4.SHARR,		Christopher T.	US
5.FREYER,		Charles Alexander.	US
DIRECCIÓN DE CORREO ELECTRÓNICO:			
8	DATOS INVENTOR (ES)		
PAÍS RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
1.US	Pennsylvania	Malvern	3 Jorrocks Lane, Malvern, Pennsylvania 19355
2.US	Pennsylvania	Paoli	1633 Valley Greene Road, Paoli,, Pennsylvania 19301
3.US	Texas	Austin	1111 Alison Parke Trail, Austin, Texas 78750
4.US	Pennsylvania	Malvern	907 Brookmont Circle, Malvern, Pennsylvania.
5.US	Pennsylvania	Malvern	55 Valley Stream Parkway, Suite 100, Malvern, Pennsylvania 19355
OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)			
☐ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación.			
9	☐ REPRESENTANTE LEGAL ☒ APODERADO		
APELLIDOS		NOMBRES	IDENTIFICACIÓN
GÓMEZ VILLA		Johan Sebastian	C.C. 9868640 T.P. 202.892
DIRECCIÓN		Cra. 13 A No. 28-38 Ofc. 230 MZ 2 PARQUE BAVARIA	
CIUDAD		BOGOTÁ D.C.	
PAÍS		COLOMBIA	
No. TELÉFONO		3 419841	
CORREO ELECTRÓNICO		consultas@tmtamayo.net	
No. RADICACIÓN DE PROTOCOLO DE PODER GENERAL			

10	DECLARACIONES DE PRIORIDAD ☒ SI ☐ NO			
(33) PAÍS DE ORIGEN		CÓDIGO PAÍS	(31) NÚMERO	(32) FECHA (AAAA/MM/DD)
1. USA		US	61/569,255	2011/12/11
2.				
3.				
11	DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS			
<i>Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen.</i>				
☐ SI ☒ NO				
Nota: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro, expedido por la Autoridad competente.				
12	DECLARACIÓN SOBRE USO DE CONOCIMIENTOS TRADICIONALES			
<i>Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.</i>				
☐ SI ☒ NO				
Nota: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado, o número de registro expedido por la Autoridad competente.				
13	REDUCCIÓN DE TASAS			
<i>Declaro que carezco de medios económicos para presentar la solicitud de patente.</i>				
☐ SI ☒ NO				
Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.				
Micro, pequeñas y medianas empresas ☐				
Universidades públicas o privadas ☐				
Entidades sin ánimo de lucro ☐				
Debe aportar los documentos que se indican en el numeral 17 de anexos				
14	AUTORIZACIÓN DE NOTIFICACIÓN EN LÍNEA ☐ SI ☒ NO			
Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en línea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.				
15	COMPROBANTE DE PAGO O PAGO ELECTRÓNICO		N° 14-0066829	Fecha 25-06-2014
	COMPROBANTE POR REIVINDICACIÓN ADICIONAL A 10		No 14-0066830	Fecha 25-06-2014
16	FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL			
Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)				
 JOHAN SEBASTIAN GOMEZ VILLA (Apoderado)				
17	ANEXOS			
Documentación Técnica Solicitud Internacional en castellano		Documentación Jurídica		
1. ☒ Descripción N° de folios: 23		9. ☒ Poderes, si fuera el caso.		
2. ☒ Reivindicaciones N° Reivindicaciones: 57		10. ☐ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.		
3. ☒ Dibujos y/o figuras N° folios: 117		11. ☐ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.		
4. ☒ Resumen.		12. ☐ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.		
5. ☐ Certificado de depósito de material biológico si fuera el caso.		13. Reducción de tasas		
6. ☐ Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso.		Micro, pequeñas o medianas empresas		
7. ☒ Arte final 12 x 12.		☐ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea.		
8. ☐ Anexo formato digital.		☐ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.		
		Universidades públicas o privadas		
		☐ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación		
		Entidades sin ánimo de lucro		
		☐ Copia de registro vigente en Cámara de comercio.		
		☐ Hoja de información complementaria.		
		☐ Otros, especificar		
		14. ☒ Comprobante de pago de la tasa de presentación de la solicitud.		
		15. ☐ Comprobante de pago por reivindicación de prioridad.		
		16. ☐ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.		
		17. ☒ Comprobante de pago por reivindicación adicional a 10.		

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

-/-



Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0066829

Bogotá D.C., Junio 25 de 2014 - 12:16:41

RECIBIDO DE : TM TAMAYO Y ASOCIADOS LTDA

NI 830.091.650

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	603161226	25/06/2014	2.651.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	515.000.00	515.000.00
				\$515.000.00

SON: **QUINIENTOSQUINCE MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios 9/10

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Junio 25 de 2014 - 12:16:41

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



Industria y Comercio

SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0066830

Bogotá D.C., Junio 25 de 2014 - 12:16:41

RECIBIDO DE : TM TAMAYO Y ASOCIADOS LTDA

NI 830.091.650

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	603161226	25/06/2014	2.651.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
47 50005-01-01	SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	31.000.00	1.457.000.00
				<u>\$1.457.000.00</u>
			=====	

SON: **UN MIL & OACUTE;N CUATROCIENTOS CINCUENTA Y SIETE MIL PESOS MONEDA CORRIENTE***

Responsable: _____

***_

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 14-143289- -00000-0000

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Act. 411 PRESENTACION Folios: 10

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

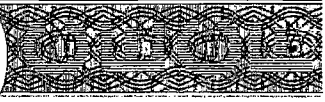
Web: www.sic.gov.co e-mail: Info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Junio 25 de 2014 - 12:16:41

Nº 17.755



ACTUACION NOTARIAL
LEY 404



N 017742818

CECBA - LEY 404 CABA
LEGALIZACION
140626 297944



10:43:39
26/06/2014

1 FOLIO 670.- PRIMERA COPIA.- ESCRITURA NUMERO TRESCIENTOS TREINTA
2 Y UNO.- En la Ciudad de Buenos Aires, Capital de la República Argentina, a veinti-
3 cuatro de junio de dos mil catorce/
4 GOYTIA, argentino, mayor de edad, casado, Libreta de Enrolamiento número
5 4.526.965, domiciliado en Bartolomé Mitre 226, 4º piso, de esta Ciudad.- El compa-
6 reciente es persona de mi conocimiento, doy fe, así como que DICE: I.- Que por
7 escritura de fecha 29 de diciembre de 2011, pasada ante mí al folio número 2.649
8 del Protocolo de este Registro, al que me remito, doy fe, se protocolizó un Poder
9 otorgado por Recro Pharma, Inc., con domicilio en 55 Valley Stream Parkway, Suite
10 100, Malvern, PA 19355, USA, a su favor, el que transcripto en sus partes pertinen-
11 tes DICE: " ... Apostilla - Los abajo firmantes - Recro Pharma, Inc. - domiciliados
12 en - 55 Valley Stream Parkway, Suite 100, Malvern, PA 19355, USA - por el presen-
13 te otorgan a DANIEL GOYTIA domiciliado en Buenos Aires, Argentina, poder amplio
14 y suficiente para recabar de las autoridades nacionales que corresponda, sean es-
15 tas administrativas y/o judiciales, la obtención de "Marcas, Patentes, Modelos y
16 Diseños en países Latinoamericanos y del sudeste asiático" y realizar todos los
17 trámites conducentes para proteger los derechos de la mandante, a cuyo efecto, los
18 faculta para efectuar ante dichas autoridades nacionales, administrativas y/o judicia-
19 les todos los trámites necesarios a los objetos indicados; presentar solicitudes, ale-
20 gatos, oposiciones, protestas, apelaciones y demandas; desistir, arreglar y transigir;
21 aceptar cesiones y transferencias; solicitar testimonios; recibir documentos y otros
22 valores; justificar explotaciones; cobrar y percibir; firmar instrumentos públicos, pri-
23 vados y escrituras públicas; para renunciar o no a las gestiones judiciales; y hacer
24 cuanto fuere necesario ante las autoridades nacionales, judiciales y/o administrati-
25 vas, sea como demandante o como demandado, para proteger los intereses del



N 017742818

demandante, con facultad de substituir este instrumento y revocar tal substitución.
Se deja constancia que las facultades enumeradas en este mandato, son meramen-
te ejemplificativas y no limitativas de otras facultades implícitas, por cuyo motivo,
los mandatarios quedan autorizados para ejercer sin restricción alguna todos los
derechos que acuerde la ley que se relacionen y/o emerjan y/o que sean conse-
cuencia del objeto del presente poder y ya sea ello en razón de la legislación vigen-
te y/o que en el futuro se promulgue.- Este poder ratifica todo acto anterior de nues-
tros apoderados referido a derechos de propiedad industrial.- El presente documen-
to tendrá vigencia a partir del 4 de noviembre de 2011 ... "- LO TRANSCRIPTO ES
COPIA FIEL, doy fe, de las partes pertinentes del mandato relacionado.- II.- El
compareciente continúa diciendo que viene por la presente a **SUSTITUIR** el citado
mandato, reservándose para si las facultades, a favor de "**CARLOS TAMAYO Y
ASOCIADOS SAS**" y/o **CARLOS ORLANDO MAYA RODRIGUEZ y/o JOHAN SE-
BASTIAN GÓMEZ VILLA y/o CAMILO ANDRES CRUZ BRAVO**, con domicilio en
Carrera 13A N° 28-38, Buffette 245, Manzana 02, Parque Central Bavaria, Bogotá,
COLOMBIA, para actuar exclusivamente **COLOMBIA** con todas y cada una de las
facultades enumeradas precedentemente.- LEIDA y ratificada, así lo expresó, otor-
gó, aceptó y firmó, por ante mi, doy fe.- "**SIGUE UNA FIRMA**".- Esta mi sello.- Ante
mi: **ALEJANDRO M. LIPORACE**.- CONCUERDA con su matriz que pasó ante mi, al
folio 670 del Protocolo del Registro 1331 a mi cargo.- **PARA LOS APODERADOS**
expido esta **PRIMERA COPIA** en UNA FOJA de Actuación Notarial números N
017742818 que sello y firmo en el mismo lugar y fecha de su otorgamiento, doy fe.

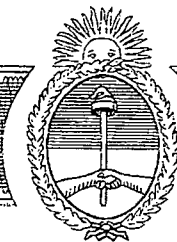
Sobrescrito de obs. - Incl. catore - Jde. - Entre las:
incl. catore - Jde. -

ALEJANDRO M. LIPORACE
MATRICULA 3837
ESCRIBANO PUBLICO



LEGALIZACION

LEY 484



L 012145181

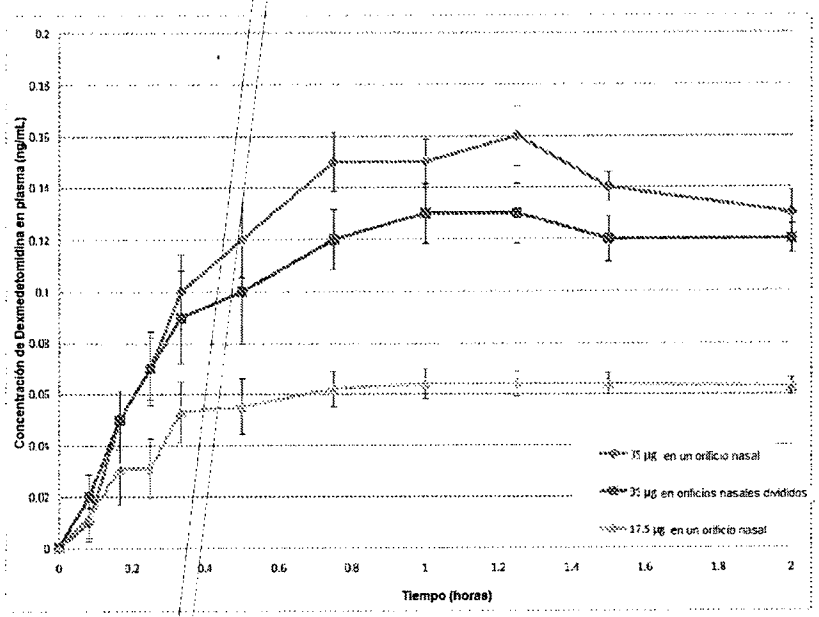
EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley orgánica vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE obrantes en el documento anexo, presentado en el día de la fecha bajo el N° 140626297944/5 La presente legalización no juzga sobre el contenido y forma del documento.

Buenos Aires, Jueves 26 de Junio de 2014



ESC. VIOLETA NILOS
COLEGIO DE ESCRIBANOS
LEGALIZADORA

Figura 1:



		PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA RELACIÓN DE ANEXOS	
Dependencia:	2020	Fecha: <u>14</u> <u>07</u> <u>3</u> AAAA MM DD	Recorrido: 4
Tipo de Radicación: Entrada: ☒ Salida: ☐ Traslado: ☐ Convenio: ☐			
Radicator:			Planilla:

ID	No. Radicación	Consecutivo	Item
1	14-143289	0	7
2			
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Item	Unidad de Conservación
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	Otro
Item	Soporte Documental
7	CDX
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones: El cd anexo contiene un total de Archivos: 6. archivos en formato PDF, los cuales fueron procesados en el folio (9), 4. Archivos que se encuentran en formato PDF, el cual se encuentran en una carpeta de Archivos, por lo tanto fue procesado correctamente, 1. Archivo en imagen, la cual por no cumplir la circular no se proceso. (pendiente verificar este archivo) Caudia6

PATENTE DE INVENCION ☒

MODELO DE UTILIDAD ☐

Art 33 Decisión 486/00

☒	Indicación que se solicita una patente.
☒	Datos de identificación del solicitante o de la persona que presenta la solicitud
☒	Descripción de la invención
☒	Dibujos de ser estos pertinentes
☒	Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
Completa ☐ Incompleta ☐	

PATENTE DE INVENCION PCT ☐

MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única

☐	Indicación que se solicita una PCT
☐	Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
Completa ☐ Incompleta ☐	

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

☐	Indicación que se solicita Diseño industrial
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
☐	Comprobante de pago de las tasas establecidas
Completa ☐ Incompleta ☐	

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

☐	Indicación que se solicita un esquema de trazado
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica de un esquema de trazado
☐	Comprobante de pago de las tasas establecidas
Completa ☐ Incompleta ☐	

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 14-143289- -00000-0000

PI02-F08 (2009-11-18)

Fecha: 2014-07-03 15:16:33 Dep. 2020 DIR.NUEVAS
Tra. 11 PATENTEIYII Eve: 378 FASENACIONAL
Act. 411 PRESENTACION Folios: 10

(12) SOLICITUD DE PATENTE INTERNACIONAL PUBLICADA CONFORME AL TRATADO DE COOPRACIÓN EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual

Oficina Internacional

(43) Fecha de Publicación Internacional:

20 de junio de 2013 (20-06-2013)

(51) Clasificación Internacional de Patentes

A61K 9/00 (2006.01) A61K 45/06 (2006.01)

A61K 32/4174 (2006.01)

(21) Solicitud de Patente Internacional Número:

PCT/US2012/068988

(22) Fecha de Presentación Internacional:

11 de diciembre de 2012 (11-12-2012)

(25) Idioma de presentación:

Inglés

(26) Idioma de publicación:

Inglés

(30) Datos de la Prioridad:

61/569.255 11 de diciembre de 2011 (11/12/2011) US

(71) Solicitante: **RECRO PHARMA, INC.** [US/US]; 55 Valley Stream Parkway, Suite 100, Malvern, PA 19355 (US).

(72) Inventores: **HENWOOD, Geraldine A.**; 3 Jorrock Lane, Malvern, Pennsylvania 19355 (US). **MACK, Randall J.**; 1633 Valley Greene Road, Paoli, PA 19301 (US). **KOLENG, JR., John Joseph**; 1111 Alison Parke Trail, Austin, Texas 78750 (US). **SHARR, Christopher T.**; 907 Brookmont Circle, Malvern, PA 19355 (US). **FREYER, Charles Alexander**; 55 Valley Stream Parkway, Suite 100, Malvern, Pennsylvania 19355 (US).



(10) Publicación Internacional Número:

WO 2013/090278 A2

(84)

Agente: **LEGAARD, Paul K.**; Pepper Hamilton LLP, 400 Berwyn Park, 899 Cassatt Road, Berwyn, Pennsylvania 19312 (US).

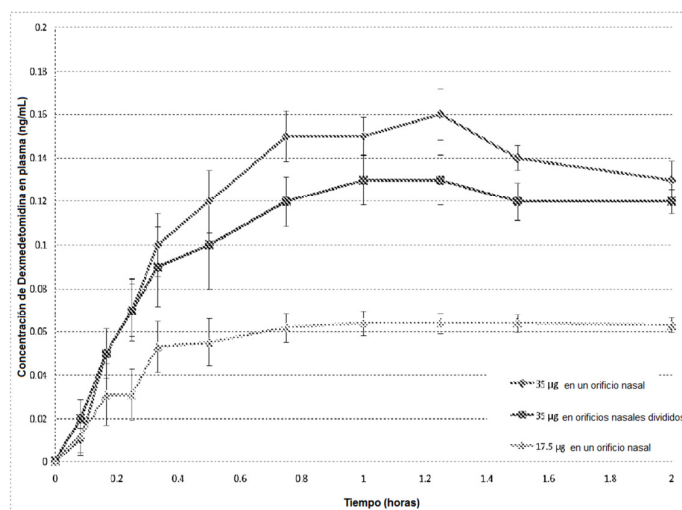
(81) Estados Designados (salvo que se indique de otro modo, para todos los tipos de protección nacional existentes): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Estados Designados (existe que se indique de otro modo, para todos los tipos de protección regional existentes): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasia (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europeo (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continúa en la página siguiente]

(56) Título: **COMPOSICIONES INTRANASALES DE DEXMEDETOMIDINA Y MÉTODOS DE USO DE ELLAS**

Figura 1:



(57) Resumen de la invención: La presente invención provee formulaciones intranasales que comprenden dexmedetomidina, o una sal farmacéuticamente aceptable de ella, y sus usos.

Publicada:

-- *sin informe de búsqueda internacional y se publicará nuevamente cuando se reciba dicho informe (Norma 48.2(g)).*

Figura 1:

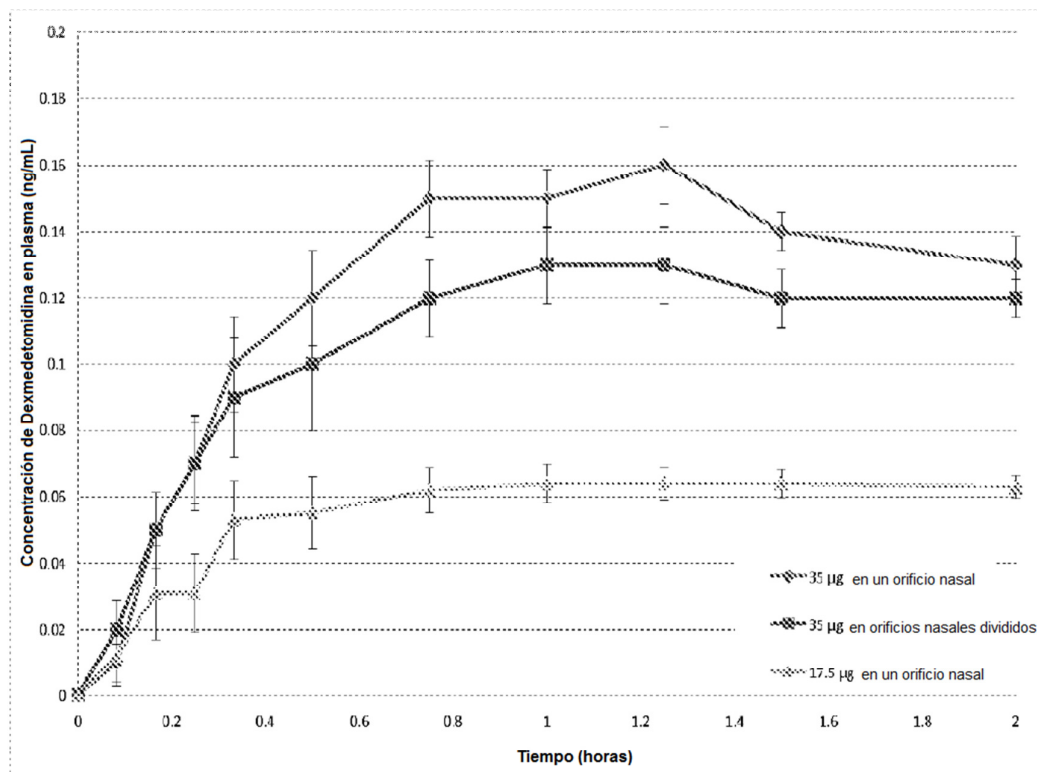
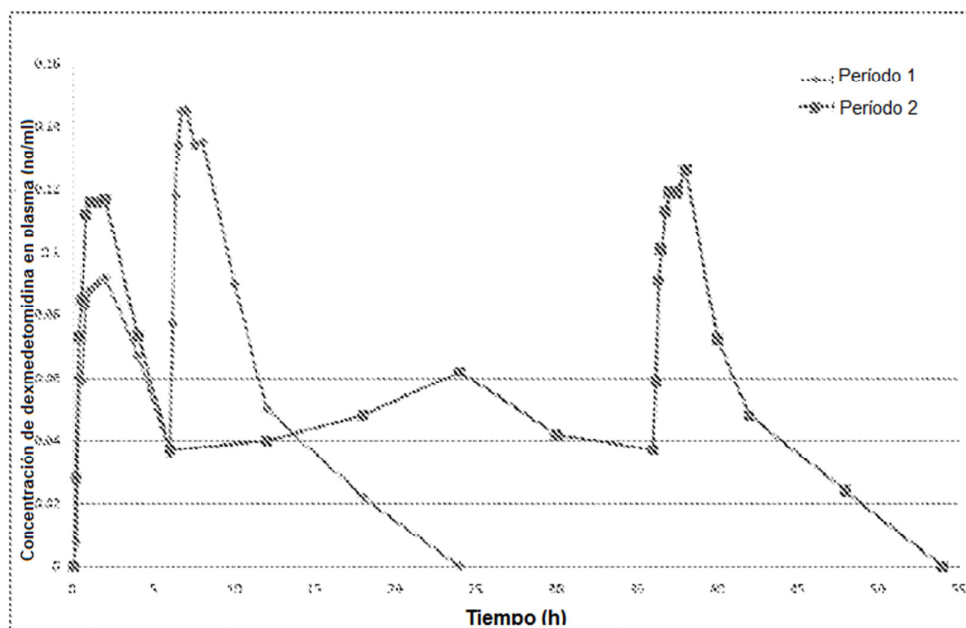


Figura 2



TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

De la AUTORIDAD DE BÚSQUEDA INTERNACIONAL

Para: PAUL K. LEGAARD PEPPER HAMILTON LLP 400 BERWYN PARK 899 CASSATT ROAD BERWYN, PA 19312	PCT NOTIFICACIÓN DE REMISIÓN DEL INFORME DE BÚSQUEDA INTERNACIONAL Y DE LA OPINIÓN ESCRITA DE LA AUTORIDAD DE BÚSQUEDA INTERNACIONAL, O LA DECLARACIÓN (Norma 44.1 del PCT) Fecha de remisión (día/mes/año) 22 de febrero de 2013 (22-02-2013)
Referencia de archivo del Solicitante o Agente 13761700402	PARA OTROS TRAMITES Véanse los párrafo 1 y 4 a continuación
Solicitud de Patente Internacional N° PCT/US 12/68988	Fecha de presentación internacional (día/mes/año): 11 de diciembre de 2012 (11- 12-2012)
Solicitante: RECRO PHARMA, INC. et al 1. [x] Por la presente se notifica al solicitante que el informe de búsqueda internacional y la opinión escrita de la Autoridad de Búsqueda Internacional se han establecido y se transmiten con la presente: Presentación de modificaciones y testimonio conforme a la Cláusula 19.	

El solicitante tiene derecho, si lo desea, de modificar las reivindicaciones de la solicitud de patente internacional (véase la Norma 46):

¿Cuándo? El plazo para presentar dichas modificaciones es normalmente de 2 meses desde la fecha de transmisión del Informe de Búsqueda Internacional.

¿Dónde? Directamente a la Oficina Internacional de la WIPO, 34, chemin de Colombettes, 1211 Ginebra 20, Suiza, Fax: (41-22)338-8270

Para obtener instrucciones más detalladas, véanse las notas en la página adjunta.

2. [] Por la presente se notifica al solicitante que no se establecerá informe de búsqueda internacional y que la declaración conforme al Artículo 17(2)(a) a tal efecto y la opinión escrita de la Autoridad de Búsqueda Internacional se transmiten con la presente.

3. [] Con respecto la protesta contra el pago de (un) arancel(es) adicionales conforme a la Norma 40.2, se notifica al solicitante que:

[] la protesta así como la resolución sobre ella ha sido transmitida a la Oficina Internacional junto con el pedido del solicitante de remitir los textos de la

protesta y de la resolución sobre ella a las Oficinas designadas.

[] aún no ha habido resolución sobre la protesta; el solicitante será notificado en cuanto haya una resolución.

4. Recordatorios:

Poco después de los **18 meses** desde la fecha de prioridad, la Oficina Internacional publicará la solicitud de patente internacional. Si el solicitante desea impedir o postergar la publicación, un escrito de retiro de la solicitud de patente internacional, o de la reivindicación de prioridad, deberán ser presentados ante la Oficina Internacional según lo previsto en las Normas 90bis.1 y 90bis.3, respectivamente, antes de la finalización de los preparativos técnicos para la publicación internacional.

El solicitante podrá presentar ante la Oficina Internacional observaciones en forma informal acerca de la opinión escrita de la Autoridad de Búsqueda Internacional. La Oficina Internacional remitirá una copia de esas observaciones a todas las oficinas designadas a menos que se haya establecido o se deba establecer un informe del examen preliminar internacional. Estas observaciones también estarían disponibles para el público pero no con anterioridad al vencimiento del plazo de 30 meses des de la fecha de

prioridad.

Dentro de los **19 meses** desde la fecha de prioridad, deberá presentarse un pedido de examen preliminar internacional si el solicitante desea postergar el ingreso en la fase nacional hasta los 30 meses desde la fecha de prioridad (en algunas Oficinas más); de lo contrario el solicitante deberá, dentro de los 20 meses, realizar los trámites previstos para el ingreso en la fase nacional ante aquellas Oficinas designadas. Con respecto a las demás Oficinas designadas, el plazo de 30 meses (o con posterioridad) será aplicable aún cuando no se presente ningún pedido dentro de los 19 meses.

Véase el Anexo al Formulario PCT/IB/301 y, para detalles acerca de los plazos aplicables, Oficina por Oficina, véase la Guía del Solicitante de PCT, Volumen II, Sedes Nacionales y el sitio de Internet de la WIPO.

Nombre y domicilio para correspondencia de la Autoridad de Búsqueda Internacional/ Casilla de Correo PCT, Atención: ISA/US Comisario de Patentes P.O. Box 1450, Alexandria, Virginia 22313-1450 Tel. 571-273-3201	Funcionario Autorizado: Lee W. Young Número Telefónico: Escritorio de Ayuda del PCT: 571-272-4300 OSP de PCT: 571-272-7774
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TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

INFORME DE BÚSQUEDA INTERNACIONAL

(Cláusula 18 y Normas 43 y 44 del PCT)

Referencia de Archivo del Solicitante o agente: 13761700402	PARA REALIZAR Véase Notificación de OTROS Transmisión de Informe de TRAMITES Búsqueda Internacional (Formulario PCT/ISA/220) y, si fuere aplicable, del punto 5 más abajo.	
Solicitud de Patente Internacional No: PCT/US 12/68988	Fecha de Presentación Internacional (día/mes/año): 11 de diciembre de 2012 (11-12-2012)	Fecha de Prioridad (Más antigua) (día/mes/año): 11 de diciembre de 2011 (11-12-2011)
Solicitante: RECRO PHARMA, INC. et al		
Este informe de búsqueda internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y es transmitido al solicitante conforme a la Cláusula 18. Se transmite una copia del mismo a la Oficina Internacional. Este informe de búsqueda internacional consta de <u>4</u> páginas. [] Está acompañado asimismo de una copia de cada documento de arte previo citado en el informe.		

1. Fundamento de Informe

a. Con respecto al **idioma**, la búsqueda internacional se llevó a cabo basada en:

☒ la solicitud de patente internacional en el idioma en que ésta se presentó.

☐ una traducción de la solicitud de patente internacional al _____, que es el idioma de la traducción provista para los fines de la búsqueda internacional (Normas 12.3(a) y 23.1(b)).

b. ☐ Este informe de búsqueda internacional se ha establecido tomando en cuenta la **rectificación de un error evidente** autorizada o notificada por a esta Autoridad conforme a la Norma 91 (Norma 43.6bis(a)).

c. ☐ Con respecto a cualquier **secuencia de nucleótidos y/o de aminoácidos** revelada en la solicitud de patente internacional, véase el Casillero N° I

2. ☒ **Ciertas reivindicaciones se consideraron no buscables** (Véase Casillero N° II)

3. ☐ **Falta Unidad de Invención** (Véase Casillero N° III).

4. Con respecto al **título**:

☒ el texto se aprueba tal como lo presentó el solicitante

☐ el texto ha sido establecido por esta Autoridad como sigue:

5. Con respecto al **resumen**:

☐ el texto es aprobado como lo presentó el solicitante

☒ el texto ha sido establecido, conforme a la Norma 38.2(b), por esta Autoridad como aparece en el Casillero N° IV. El Solicitante puede, dentro de un mes desde la fecha de remisión de este informe de búsqueda internacional, presentar comentarios ante esta Autoridad.

6. Con respecto a los **dibujos**,

a. La Lámina de **dibujos** que se publicará con el resumen es: Figura No. 1 .

☒ sugerida por el Solicitante

☐ seleccionada por esta Autoridad, debido a que el Solicitante no sugirió una Figura.

☐ seleccionada por esta Autoridad, debido a que ésta es la figura que mejor caracteriza a la invención

b. ☐ No se debe publicar ninguna de las figuras con el resumen.

INFORME DE BÚSQUEDA INTERNACIONAL	Solicitud de Patente Internacional N° PCT/US 12/68988
Casillero N° II. Observaciones cuando ciertas reivindicaciones se consideraron no buscables (Continuación del punto 2 de la página 1).	
El presente informe de búsqueda internacional no se ha establecido con respecto a ciertas reivindicaciones conforme a la Cláusula 17(2)(a) por los siguientes motivos: 1. ☐ Reivindicaciones N°: porque se relacionan con un objeto que no se requiere que busque esta Autoridad, a saber: 2. ☐ Reivindicaciones N°: porque se relacionan con partes de la solicitud de patente internacional que no cumplen con los requisitos establecidos en tal magnitud que no se puede realizar una búsqueda significativa, específicamente: 3. ☒ Reivindicaciones N°: 8-23 y 27-57 porque son reivindicaciones dependientes y no están redactadas de acuerdo con la segunda y tercera oraciones de la Norma 6.4(a).	

Casillero N° III. Observaciones cuando falta unidad de invención (Continuación del punto 3 de la página 1)

Esta Autoridad de Búsqueda Internacional encontró varias invenciones en esta solicitud de patente internacional, a saber:
--

1. [] Como todos los aranceles de búsqueda adicionales se pagaron oportunamente por el solicitante, este informe de búsqueda internacional abarca todas las reivindicaciones buscables.
--

2. [] Como las reivindicaciones buscables pudieron buscarse sin esfuerzo que justifique un arancel adicional, esta Autoridad no intima al pago de ningún arancel adicional.
--

3. [] Como ninguno de los aranceles de búsqueda adicionales requeridos se pagaron oportunamente por el solicitante, este informe de búsqueda internacional abarca solamente aquellas reivindicaciones para las cuales se pagaron aranceles, específicamente las reivindicaciones N°:

4. [] El solicitante no pagó ninguno de los aranceles de búsqueda adicionales. En consecuencia, este informe de búsqueda internacional se limita a la invención mencionada en primer lugar en las reivindicaciones; está abarcada por las reivindicaciones N°:

Observación Bajo Protesta:

[] Los aranceles de búsqueda adicionales estuvieron acompañados por la protesta del solicitante y cuando correspondía por el arancel de protesta

[] Los aranceles de búsqueda adicionales estuvieron acompañados por la protesta del solicitante pero el arancel de protesta aplicable no se pagó dentro del plazo especificado en la invención.

[] Ninguna protesta acompañó el pago de los aranceles de búsqueda adicionales.

INFORME DE BÚSQUEDA INTERNACIONAL	Solicitud de Patente Internacional N° PCT/US 12/68988
Casillero N° IV. Texto del resumen de la invención (Continuación del punto 5 de la página 1)	
La presente invención provee formulaciones intranasales que comprenden dexmedetomidina, o una sal farmacéuticamente aceptable de ella, que son analgésicas pero sin sedación importante, métodos para tratar o prevenir el dolor que comprenden administrar las formulaciones intranasales a un mamífero y dispositivos de dosis medida para administrar la formulación intranasal como una aspersion, en donde las gotitas de la aspersion tienen un Dv90 menor de 150 µm.	

INFORME DE BÚSQUEDA INTERNACIONAL	Solicitud de Patente Internacional N° PCT/US 12/68988
A. Clasificación de la Materia: IPC(8)– A61K 31/4174 (2013.01) USPC– 514/396 De acuerdo con la Clasificación Internacional de Patentes (IPC) o con la clasificación nacional e IPC.	
B. CAMPOS DE BÚSQUEDA	
Documentación mínima buscada (sistema de clasificación seguido por símbolos de clasificación) IPC{8): A61K 31/4174 (2013.01) USPC: 514/396 (búsqueda de texto)	
Documentación buscada además de la documentación mínima en la medida en que tales documentos están incluidos en los campos de búsqueda: USPC: 514/816; 424/400 (búsqueda de texto) Encontrará los términos de búsqueda a continuación.	
Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda usados): PubWEST (PGPB, USPT, USOC, EPAB, JPAB), Google Scholar, PatBase dexmedetomidina, intranasal, nasal, orificio nasal,	

composición, formulación, sedante, sedación, analgésico, dolor, tratar, aliviar, Dv90		
C. Documentos Considerados Relevantes		
Categoría*	Cita de documento, indicando, si corresponde, los pasajes relevantes	Relevante para la reivindicación N°
X	WO 2011/085162 A2 (HENWOOD et al.) 14 de	3, 24 y
--	Julio de 2011 (14-07-2011) párrafos	26/24
Y	[0005]-[0006], [0020], [0027]-[0039], [0060]	----- 1-2, 4-7, 25 y 26/25
Y	IIROLA et al. Biodisponibilidad de dexmedetomidina después de la administración intranasal, Eur J Clin Pharmacol, 2011, Vol. 67, páginas 825-831. Publicada en línea: 12 de febrero de 2011, [Recuperada de internet el 1 de febrero de 2013 de la URL: < http://link.springer.com/article/10.1007%2Fs00228-011-1002-y >]. Resumen; página 826, columna 2, párrafo 2-párrafo 3; página 827, columna 2, párrafo 4; Tabla 1; Figura 1; página	1-2 y (5-7)/(1-3)

	830, columna 2, párrafo 2	
Y	US 2008/0004305 A1 (WERMELING) 3 de enero de 2008 (3-01-2008) párrafos [0011]-[0012], [0066]-[0069]	4, (5-7)/4, 25 y 26/25
A	US2011/0021588A1 (HENWOOD et al.) 27 de enero de 2011 (27.01.2011) párrafo [0004]-[0008]	1-7 y 24-26
A	US 2011/0021426 A1 (TOLL et al.) 27 de enero de 2011 (27.01.2011) párrafos [0011]-[0013], [0041]-[0045], [0082]	1-7 y 24-26
[] Se mencionan otros documentos en la continuación del Casillero C. []		
* Categorías especiales de "T": documento posterior documentos citados: publicado con posterioridad a "A": documento que define el la fecha de presentación estado general del arte que no internacional o a la fecha de se considera de particular prioridad y que no está en relevancia conflicto con la solicitud de "E": documento anterior pero patente pero citado para publicado en la fecha de comprender un principio o presentación internacional o teoría que sustenta la con posterioridad a ella. invención. "L": documento que puede "X": documento de particular arrojar dudas sobre la relevancia: la invención		

reivindicación de prioridad o reivindicada no puede que se cita para establecer la considerarse nueva o no puede fecha de publicación de otra considerarse que implica un cita o por otra razón especial paso inventivo cuando el (especificada). documento se toma solo. "O": documento que refiere a "Y": documento de particular una revelación oral, uso, relevancia: la invención exhibición u otro medio. reivindicada no puede "P": documento publicado antes considerarse que implica un de la fecha de presentación paso inventivo cuando el internacional pero con documento se combina con otro posterioridad a la fecha de u otros documentos, siendo prioridad reivindicada. dicha combinación obvia para un experto en el arte. "&": documento miembro de la misma familia de patentes.	
Fecha de la finalización efectiva de la búsqueda internacional 1 de febrero de 2013 (1-02-2013)	Fecha de envío del informe de búsqueda internacional 22 de febrero de 2013
Nombre y domicilio para correspondencia de la ISA/ Casilla de Correo PCT,	Funcionario Autorizado Lee W. Young

Atención: ISA/US Comisario de Patentes P.O. Box 1450, Alexandria, Virginia 22313-1450 Tel. 571-273-3201	
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COMPOSICIONES INTRANASALES DE DEXMEDETOMIDINA Y MÉTODOS DE USO DE ELLAS

Campo de la invención

La presente invención se refiere, en parte, a formulaciones intranasales de desxmedetomidina, o una sal farmacéuticamente aceptable de ellas, que son analgésicas pero sin una sedación importante, así como los métodos de uso de ellas.

Antecedentes de la invención

La dexmedetomidina, 5-[(1S)-1-(2,3-dimetilfenil)etil]-1H-imidazol, es un agonista α_2 adrenoceptor no narcótico con propiedades sedantes y analgésicas. Actualmente, la dexmedetomidina está comercialmente disponible solamente como una formulación inyectable indicada para la sedación de pacientes inicialmente intubados y con ventilación mecánica durante el tratamiento en una sala de terapia intensiva y para la sedación de pacientes no intubados antes y/o durante cirugías y otros procedimientos y la debe administrar por vía intravenosa un profesional de la salud experimentado y matriculado. Si bien la dexmedetomidina tiene propiedades analgésicas, una formulación intranasal útil como un analgésico sin sedación, sin embargo, no está comercialmente

disponible. Además, por una variedad de motivos, la formulación inyectable disponible comercialmente no es adecuada para su uso como un analgésico que se puede autoadministrar. Existe una necesidad continua e insatisfecha de medicamentos analgésicos basados en dexmedetomidina que, por ejemplo, se puedan autoadministrar para producir analgesia (o tratar o prevenir el dolor de otro modo) sin una sedación importante.

Breve Descripción de los Dibujos

La Figura 1 muestra la farmacocinética de la dexmedetomidina intranasal para algunas realizaciones.

La Figura 2 muestra concentraciones en plasma promedio de dexmedetomidina (ng/mL) para algunas realizaciones.

Resumen de la invención

La presente invención provee métodos para tratar o prevenir el dolor sin una sedación importante en un mamífero comprende administrar por vía intranasal una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al mamífero por lo cual la cantidad efectiva intranasal de dexmedetomidina, o la sal

farmacéuticamente aceptable de ella, produce una C_{plasma} de 0,1 ng/ml dentro de 15 minutos a 20 minutos de la administración y tiene un efecto analgésico sin una sedación importante.

La presente invención también proporciona métodos para tratar o prevenir el dolor sin una sedación importante en un humano adulto, que comprende administrar por vía intranasal una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al humano adulto por lo cual la cantidad efectiva intranasal de dexmedetomidina, o la sal farmacéuticamente aceptable de ella, no produce una sedación importante en el adulto dentro de un período de tiempo de dos horas posteriores a la administración y tiene un efecto analgésico dentro del período de tiempo.

La presente invención también proporciona métodos para tratar o prevenir el dolor sin una sedación importante en un mamífero, que comprende administrar por vía intranasal dexmedetomidina, o una sal farmacéuticamente aceptable de ella, a un solo orificio nasal del mamífero, particularmente un humano.

La presente invención también proporciona métodos para tratar o prevenir el dolor sin una sedación importante en un mamífero, que comprende asperjar por vía intranasal en el

mamífero una composición farmacéutica que comprende dexmedetomidina, o una sal farmacéuticamente aceptable de ella, en donde la aspersion comprende gotitas que tienen un Dv_{90} menor de 150 μm .

La presente invención también proporciona dispositivos de dosis medida que comprenden una composición farmacéutica que comprende dexmedetomidina, o una sal farmacéuticamente aceptable de ella, en donde el dispositivo de dosis medida suministra una aspersion de dosis medida de la composición farmacéutica por vía intranasal que es analgésica en un mamífero sin producir una sedación importante.

Descripción de Realizaciones

A menos que se definan de otro modo, todos los términos técnicos y científicos tienen la misma definición que entiende comúnmente un experto en el arte al cual pertenecen las realizaciones reveladas.

Como se usa en la presente, los términos “un” o “una” significa “por lo menos uno” o “uno o más” a menos que el contexto lo indique claramente de otro modo.

Como se usa en la presente, el término “aproximadamente” significa que el valor numérico es aproximado y las pequeñas variantes no afectarían significativamente la práctica de las realizaciones reveladas. Cuando se usa una limitación numérica, a menos que el contexto lo indique de otro modo, “aproximadamente” significa que el valor numérico puede variar en $\pm 10\%$ y permanece dentro del alcance de las realizaciones reveladas.

Como se usa en la presente, el término “analgesia” se refiere al alivio (parcial o completo) o la eliminación de la sensación de dolor.

Como se usa en la presente, por el término “portador” se entiende un diluyente, un coadyuvante, o un excipiente con el cual se administra un compuesto. Los portadores farmacéuticos pueden ser líquidos, tales como agua y aceites, que incluyen aquellos de petróleo, de origen animal, vegetal o sintético, tales como aceite de maní, aceite de soja, aceite mineral, aceite de sésamo y similares. Los portadores farmacéuticos también pueden ser solución salina, goma de acacia, gelatina, pasta de almidón, talco, queratina, sílice coloidal, urea, y similares. Además, se pueden usar agentes auxiliares, estabilizadores, espesantes, lubricantes y colorantes.

Como se usa en la presente, por el término "compuesto" se entiende todos los estereoisómeros, tautómeros e isótopos de los compuestos, o sus sales farmacéuticamente aceptables, que incluyen todos y cada uno de los metabolitos descritos en la presente.

Como se usa en la presente, los términos "que comprende" (y todas las formas de que comprende, tales como "comprenden", "comprende" y "comprendido"), "que tiene" (y todas las formas de que tiene, tales como "tienen" y "tiene"), "que incluye" (y todas las formas de que incluye, tales como "incluye" e "incluyen"), o "que contiene" (y todas las formas de que contiene, tales como "contiene" y "contienen"), son inclusivos o ilimitados y no excluyen elementos o pasos de un método adicionales, no mencionados.

Como se usa en la presente, por el término "que pone en contacto" se entiende que se ponen en contacto juntos de dos elementos en un sistema in vitro o un sistema in vivo. Por ejemplo, "que pone en contacto" un compuesto o una composición descritos en la presente con un individuo o un paciente o una célula incluye la administración del compuesto a un individuo o a un paciente, tal como un humano.

Como se usa en la presente, por el término "Dv90" se entiende el valor que representa el tamaño de las partículas por debajo del cual existe el 90% del volumen de una pluralidad de gotitas (por ejemplo, tal en un rocío de aspersión, a diferencia de una gota nasal que comprende una o más gotas).

Como se usa en la presente, por el término "individuo" o "paciente", usados en forma indistinta, se entiende cualquier animal, que incluye mamíferos, tales como ratones, ratas, otros roedores, conejos, perros, gatos, cerdos, ganado vacuno, ovejas, caballos, o primates, tales como humanos.

Como se usa en la presente, por la frase "que lo necesita" se entiende que se ha identificado que el animal o el mamífero tiene una necesidad del método o tratamiento particular. En algunas realizaciones, la identificación puede ser cualquier medio de diagnóstico. En todos los métodos y tratamientos descritos en la presente, el animal o el mamífero puede necesitarlos. En algunas realizaciones, el animal o el mamífero están en un medioambiente o están viajando hacia un medioambiente en el cual predomina una enfermedad, trastorno, o condición particular. Por ejemplo, un mamífero o un animal pueden necesitar un tratamiento o una prevención del dolor sin sedación o sin sedación importante.

Como se usa en la presente, la frase "dispositivo de dosis medida" se refiere a un dispositivo que proporciona una dosis especificada.

Como se usa en la presente, por la frase "de X a Y" se entiende cualquier número entre X e Y e incluye los extremos. Por ejemplo, por la frase "de 1 a 5" se entiende 1, 2, 3, 4, o 5.

Como se usa en la presente, "dolor" se refiere a una amplia gama de manifestaciones clínicas y tiene una definición amplia. La percepción del dolor es muy subjetiva y diferentes individuos experimentan el dolor de diferentes maneras y con intensidades muy diferentes. La Asociación Internacional para el Estudio del Dolor define el dolor como "una experiencia sensorial y emocional desagradable asociada al daño real o potencial del tejido, o descrita en términos de dicho daño". Dicho más simplemente, el dolor incluye todas las experiencias sensoriales que producen sufrimiento y están asociadas a la conciencia desagradable del propio cuerpo. Los tipos y causas no taxativas del dolor incluyen neuralgia, mialgia, hiperalgesia, hiperpatía, neuritis y neuropatía. El dolor suele ser un síntoma de una anomalía fisiológica subyacente, tal como cáncer o artritis. Algunos tipos de dolor no tienen ninguna causa claramente identificada, tal como

dolor de cabeza de migraña. El dolor puede estar causado por trauma físico, tal como quemaduras o cirugía. Las infecciones virales, tales como Herpes zóster (varicela y herpes zóster), también pueden provocar dolor. El retiro de la dependencia química del alcohol o de las drogas de abuso también puede estar asociado a síntomas de dolor. Por consiguiente, se entiende que el "dolor" en la presente tiene un significado muy amplio.

Como se usa en la presente, el término "farmacéuticamente aceptable" incluye aquellos compuestos, materiales, composiciones y/o formas de dosificación que están dentro del alcance del juicio médico razonable y adecuados para su uso en contacto con los tejidos de seres humanos y animales. En algunas realizaciones, por "farmacéuticamente aceptable" se entiende aprobado por una agencia reguladora del Gobierno Federal o de un Estado como se enumera en la Farmacopea Estadounidense o en otras farmacopeas generalmente reconocidas para su uso en animales y más específicamente en humanos.

Como se usa en la presente, la frase "sal(es) farmacéuticamente aceptables" incluye, en forma no taxativa, las sales grupos ácidos o básicos. Los compuestos que son básicos son capaces de formar una amplia variedad de sales con diversos ácidos inorgánicos y orgánicos. Los ácidos que se

pueden usar para preparar sales de adición ácidas farmacéuticamente aceptables de tales compuestos básicos son aquellos que forman sales de adición ácidas no tóxicas, es decir, sales que contienen aniones farmacéuticamente aceptables que incluyen, en forma no taxativa, sulfúrico, tiosulfúrico, cítrico, maleico, acético, oxálico, clorhidrato, bromhidrato, yodhidrato, nitrato, sulfato, bisulfato, bisulfito, fosfato, fosfato de ácido, isonicotinato, borato, acetato, lactato, salicilato, citrato, citrato de ácido, tartrato, oleato, tannato, pantotenato, bitartrato, ascorbato, succinato, maleato, gentisinato, fumarato, gluconato, glucaronato, sacarato, formato, benzoato, glutamato, metanosulfonato, etanosulfonato, bencenosulfonato, p-toluenosulfonato, bicarbonato, malonato, mesilato, esilato, napsidisilato, tosilato, besilato, ortofosfato, trifluoroacetato, y pamoato (es decir, 1,1'-metileno-bis-(2-hidroxí-3-naftoato)). Los compuestos que incluyen un grupo amino pueden formar sales farmacéuticamente aceptables con diversos aminoácidos, además de los ácidos mencionados anteriormente. Los compuestos que son de naturaleza ácida son capaces de formar sales de bases con diversos cationes farmacéuticamente aceptables. Ejemplos de tales sales incluyen, en forma no taxativa, sales de metales alcalinos o de metales alcalinotérreos y particularmente, sales de calcio, magnesio, amonio, sodio, litio, zinc, potasio y hierro. La

presente invención también puede incluir sales de amonio cuaternario de los compuestos.

Como se usan en la presente, por los términos “prevención” o “que previene” se entiende una reducción del riesgo de adquirir una enfermedad, condición o trastorno particular.

Como se usa en la presente, por el término “profármaco” se entiende un derivado de un fármaco de acción directa conocido, cuyo derivado ha mejorado características de suministro y el valor terapéutico comparado con el fármaco y se transforma en el fármaco activo mediante un proceso enzimático o químico.

Como se usa en la presente, por el término “sedación” se entiende la conciencia deprimida en la cual un paciente o sujeto retiene la capacidad de mantener en forma independiente y continua una vía respiratoria abierta y un patrón de respiración regular y de responder en forma apropiada y racional a la estimulación física y a órdenes verbales.

Como se usa en la presente, la frase “sedación importante” es consistente con una autoevaluación del paciente en la Escala de Somnolencia de Stanford, donde los pacientes Sujetos califican su nivel de sedación como mayor o igual al Nivel 3, en donde: Nivel 1 = Me siento activo, vital, alerta, o

completamente despierto; Nivel 2 = Funcionamiento a niveles altos, pero no máximo; capacidad de concentración; Nivel 3 = Despierto, pero relajado; con respuesta pero no completamente alerta; Nivel 4 = Algo apagado, disminuido; Nivel 5 = Apagado; comienzo a perder interés en permanecer despierto; lento; Nivel 6 = Somnoliento, confuso, lucho contra el sueño; prefiero estar acostado; o Nivel 7 = Ya no lucho contra el sueño, comienzo a dormir pronto; tengo pensamientos similares a sueños. Por "Sedación importante" también se entiende que el paciente o el sujeto experimenta sedación del Nivel 4 o mayor en la Escala de Sedación de Ramsay, en donde: Nivel 1 = El paciente está ansioso, agitado o inquieto, o ambos; Nivel 2 = El paciente es cooperativo, orientado y tranquilo; Nivel 3 = El paciente responde a las órdenes solamente; Nivel 4 = dormido; respuesta enérgica a un toque glabellar ligero o a un estímulo auditivo fuerte; Nivel 5 = dormido; respuesta lenta a toque glabellar ligero o a un estímulo auditivo fuerte; Nivel 6 = dormido; ninguna respuesta a ningún estímulo doloroso. Por "sedación importante" también se entiende que el paciente o el sujeto experimenta una sedación del Nivel 5 o menor en la Escala Modificada de Evaluación de Alerta/Sedación del Observador, en donde: Nivel 6 = Parece alerta y despierto, responde rápidamente al nombre dicho en tono normal; Nivel 5 = Parece dormido pero responde rápidamente al nombre dicho en tono normal; Nivel 4 = respuesta aletargada al nombre dicho en

tono normal; Nivel 3 = responde solamente después de que el nombre se dice en voz alta o reiteradamente; Nivel 2 = responde solamente después de empujarlo o sacudirlo en forma moderada; Nivel 1 = no responde cuando se lo empuja o se lo sacude moderadamente; y Nivel 0 = no responde a un estímulo nocivo.

Como se usa en la presente, por la frase "agente solubilizador" se entiende agentes que derivan en la formación de una solución micelar o una solución verdadera del fármaco.

Como se usa en la presente, por el término "solución/suspensión" se entiende una composición líquida en donde la primera parte del agente activo está presente en solución y una segunda parte del agente activo está presente en forma particulada, en suspensión en una matriz líquida.

Como se usa en la presente, por la frase "aislada sustancialmente" se entiende un compuesto que está por lo menos parcial o sustancialmente separado del medioambiente en el cual se forma o se detecta.

Como se usa en la presente, por la frase "cantidad terapéuticamente activa" se entiende generalmente la cantidad del compuesto activo o del agente farmacéutico que produce la

respuesta biológica o medicinal que está buscando un investigador, un veterinario, un médico u otro clínico, en un tejido, sistema, animal, individuo o humano. El efecto terapéutico depende del trastorno que se está tratando o del efecto biológico que se desee. Como tal, el efecto terapéutico puede ser una disminución en la gravedad de los síntomas asociados al trastorno y/o una inhibición (parcial o completa) del progreso del trastorno, o un tratamiento, curación, prevención o eliminación mejorada de un trastorno, o de efectos colaterales. La cantidad necesaria para producir la respuesta terapéutica se puede determinar basado en la edad, la salud, el tamaño y el sexo del sujeto. Las cantidades óptimas también se pueden determinar basado en el monitoreo de la respuesta del sujeto al tratamiento. En algunas realizaciones, la cantidad terapéuticamente efectiva es una cantidad específica o una gama descrita en la presente.

Como se usa en la presente, por los términos "tratar", "tratado", o "que trata" se entiende tanto el tratamiento terapéutico como medidas profilácticas o preventivas en donde el objetivo es prevenir o hacer lenta (disminuir) una condición, trastorno o enfermedad fisiológica no deseada, u obtener resultados clínicos beneficiosos o deseados. Con los propósitos de la presente invención, los resultados clínicos beneficiosos o deseados incluyen, en forma no taxativa, el

alivio de síntomas; la disminución de la magnitud de la condición, el trastorno o la enfermedad; estado estabilizado (es decir, que no empeora) de la condición, trastorno o enfermedad; retardo en el inicio o lentitud del progreso de la condición, el trastorno o la enfermedad; mejoramiento de la condición, el trastorno o el estado o remisión de la enfermedad (sea parcial o total), sea detectable o no detectable; un mejoramiento de por lo menos un parámetro físico medible, no necesariamente discernible por el paciente; o mejoramiento de la condición, el trastorno o la enfermedad. El tratamiento incluye producir una respuesta analgésica clínicamente importante sin niveles excesivos de los efectos colaterales, tales como, en forma no taxativa, sedación importante. Por lo tanto, por el “tratamiento del dolor” o “que trata el dolor” se entiende una actividad que previene, alivia o mejora cualquiera de los fenómenos principales o síntomas secundarios asociados al dolor.

Como se usa en la presente, por “sin sedación importante” se entiende que el paciente experimenta un nivel de sedación no mayor que el Nivel 3 en la Escala de Sedación de Ramsay, no mayor que el Nivel 2 en la Escala de Somnolencia de Stanford y/o no menor que el Nivel 6 de la Escala Modificada de Evaluación de Alerta/Sedación del Observador.

También se aprecia que determinadas características descritas en la presente, que se describen, para la claridad, en el contexto de realizaciones por separado, también se pueden proporcionar en combinación en una sola realización. A la inversa, diversas características que se describen, para mayor brevedad, en el contexto de una sola realización, también se pueden proporcionar por separado o en cualquier subcombinación adecuada.

La dexmedetomidina es un agonista de receptor alfa-2-adrenérgico específico que provoca sedación, anestesia, y analgesia en los mamíferos. En los humanos, la dexmedetomidina está disponible comercialmente para la sedación de pacientes intubados inicialmente y con ventilación mecánica durante el tratamiento en una sala de terapia intensiva, así como la sedación de pacientes sin intubación antes o durante una cirugía y otros procedimientos. Véanse, por ejemplo, las Patentes Estadounidenses N° 6.716.867 y 6.313.311, cada una de las cuales se incorpora en la presente como referencia.

La dexmedetomidina contiene un átomo de nitrógeno básico capaz de formar sales farmacéuticamente aceptables con ácidos farmacéuticamente aceptables. El término "sales farmacéuticamente aceptables" a este respecto se refiere a las sales de adición de ácidos inorgánicos y orgánicos

relativamente no tóxicos de dexmedetomidina. Estas sales se pueden preparar in situ durante el aislamiento y la purificación final de dexmedetomidina o haciendo reaccionar por separado la dexmedetomidina purificada en su forma de base libre con un ácido orgánico o inorgánico adecuado y posteriormente aislando la sal así formada. Además, la sal se puede formar durante un proceso de fabricación para producir la formulación de aspersión. Las sales farmacéuticamente aceptables representativas incluyen sales de hidrohaluro (que incluyen bromhidrato y clorhidrato), sulfato, bisulfato, fosfato, nitrato, acetato, valerato, oleato, palmitato, estearato, laurato, benzoato, lactato, fosfato, tosilato, citrato, maleato, fumarato, succinato, tartrato, naftilato, mesilato, glucoheptonato, lactobionato, 2-hidroxietilsulfonato, y laurilsulfonato y similares. Véase, por ejemplo "Sales Farmacéuticas," Berge et al., J. Pharm. Sci. 66, 1-19 (1977). El clorhidrato de dexmedetomidina es un ejemplo de una sal farmacéuticamente aceptable. El uso de clorhidrato de dexmedetomidina se puede usar, en parte porque, en algunos casos, la sal de clorhidrato tiene mayor solubilidad en agua y estabilidad contra la oxidación por el oxígeno ambiente.

Los derivados de dexmedetomidina pueden incluir modificaciones covalentes que crean un profármaco. Luego de la

administración, el derivado de profármaco experimenta una modificación química por el mamífero que produce dexmedetomidina. Los profármacos se pueden usar para alterar favorablemente la biodistribución o la farmacocinética de dexmedetomidina o para producir otras características deseables. Por ejemplo, un nitrógeno reactivo de dexmedetomidina se puede obtener con un grupo funcional que se descompone, en forma enzimática o no enzimática, en forma reductiva, en forma oxidativa, o en forma hidrolítica, para revelar el ingrediente farmacéutico activo. Los usos de determinados tipos de profármacos son conocidos (véase, por ejemplo, R.B. Silverman, 1992, "La Química Orgánica del Diseño de Fármacos y la Acción del Fármaco", Academic Press, Capítulo 8). Por ejemplo, se pueden preparar profármacos in situ durante el aislamiento y la purificación final de los compuestos, o haciendo reaccionar por separado el compuesto purificado en su forma de base libre con un agente de derivación adecuado.

La presente invención describe el resultado(s) sorpresivo e inesperado que se puede desarrollar una formulación intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, para el tratamiento del dolor que tiene un tiempo reducido al inicio del alivio del dolor que corresponde a C_{plasma} , una C_{max} y un tiempo reducido a T_{max} , que puede derivar

en el alivio o la prevención del dolor sin sedación o sin sedación importante en un mamífero.

La presente invención proporciona métodos para tratar o prevenir el dolor sin sedación importante en un mamífero que comprende administrar en forma intranasal una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al mamífero. La dexmedetomidina, o una sal farmacéuticamente aceptable de ella, o composiciones que la comprenden, se pueden administrar de cualquier forma de manera tal que la composición se administre por vía intranasal. Es decir, la composición se pone en contacto con la cavidad nasal. Las composiciones también se pueden administrar, por ejemplo, implantando la composición de manera tal que se absorba por vía intranasal.

En algunas realizaciones, la dexmedetomidina, o una sal farmacéuticamente aceptable de ella, se absorbe a través de la mucosa nasal. En algunas realizaciones, por lo menos 10%, por lo menos 20%, por lo menos 30%, por lo menos 40%, por lo menos 50%, por lo menos 60%, por lo menos 70%, por lo menos 80%, por lo menos 90%, por lo menos 95%, por lo menos 96%, por lo menos 97%, por lo menos 98%, o por lo menos 99% de la composición se absorbe a través de la mucosa nasal. En algunas realizaciones,

la dexmedetomidina, o una sal farmacéuticamente aceptable de ella, no se absorbe a través de la mucosa nasal.

En algunas realizaciones, el método comprende tratar o prevenir el dolor sin sedación o sedación importante. En algunas realizaciones, el nivel de sedación es no mayor que el Nivel 1 en la Escala de Sedación de Ramsay. En algunas realizaciones, el nivel de sedación es no mayor que el Nivel 2 en la Escala de Sedación de Ramsay. En algunas realizaciones, el nivel de sedación es no mayor que el Nivel 3 en la Escala de Sedación de Ramsay. En algunas realizaciones, el nivel de sedación es no mayor que el Nivel 1 en la Escala de Sedación de Ramsay. En algunas realizaciones, el nivel de sedación es no mayor que el Nivel 2 en la Escala de Sedación de Ramsay. En algunas realizaciones, el nivel de sedación es no menor que el Nivel 6 en la Escala Modificada de Evaluación de Alerta/Sedación del Observador. En algunas realizaciones, durante la hora inmediatamente posterior a la administración de la dexmedetomidina, o la sal farmacéuticamente aceptable de ella, al mamífero o al humano, el nivel de sedación es no mayor que el Nivel 3 en la Escala de Sedación de Ramsay. En algunas realizaciones, durante la hora inmediatamente posterior a la administración de la dexmedetomidina, o la sal farmacéuticamente aceptable de ella, al mamífero o al humano, el nivel de sedación es no mayor que el Nivel 2 en la Escala

de Sedación de Ramsay. En algunas realizaciones, durante la hora inmediatamente posterior a la administración de la dexmedetomidina, o la sal farmacéuticamente aceptable de ella, al mamífero o al humano, el nivel de sedación no es mayor que el Nivel 1 en la Escala de Sedación de Ramsay. En algunas realizaciones, durante la hora inmediatamente posterior a la administración de la dexmedetomidina, o la sal farmacéuticamente aceptable de ella, al mamífero o al humano, el nivel de sedación no es mayor que el Nivel 2 en la Escala de Somnolencia de Stanford. En algunas realizaciones, durante la hora inmediatamente posterior a la administración de la dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al mamífero o al humano, el nivel de sedación no es mayor que el Nivel 1 en la Escala de Somnolencia de Stanford. En algunas realizaciones, durante la hora inmediatamente posterior a la administración de la dexmedetomidina, o la sal farmacéuticamente de ella, al mamífero o al humano, el nivel de sedación no es menor que el Nivel 6 en la Escala Modificada de Evaluación de Alerta/Sedación del Observador.

En algunas realizaciones, el dolor es dolor idiopático. En algunas realizaciones, el dolor idiopático es neuralgia, mialgia, hiperalgia, hiperpatía, neuritis, o neuropatía. En algunas realizaciones, el dolor está asociado o provocado por cáncer, infección viral, trauma físico, artritis, dolor de

cabeza, migraña, o dolor de espalda inferior. En algunas realizaciones, el trauma físico está asociado o causado por cirugía, una quemadura, trauma de fuerza contundente, u otro trauma que puede provocar dolor, tal como sufrir un accidente.

En algunas realizaciones, los medios y métodos para administrar las composiciones descritas en la presente son conocidos. Los medios y métodos para la administración son conocidos en el arte y un experto en el arte puede referirse a diversas referencias farmacológicas como guía (véanse, por ejemplo, Farmacéutica Moderna, Banker y Rhodes, Marcel Dekker, Inc. (1979); y La Base Farmacéutica de la Terapia de Goodman y Gilman, 6ª Edición, MacMillan Publishing Co., Nueva York (1980)).

En algunas realizaciones, la cantidad del compuesto que se debe administrar es aquella cantidad que es terapéuticamente efectiva o efectiva intranasal. La dosificación que se debe administrar puede depender de las características del sujeto a quien se está tratando, por ejemplo, el animal particular tratado, la edad, el peso, la salud, los tipos de tratamiento concurrente, si existieran y la frecuencia del tratamiento y un experto en el arte la puede determinar fácilmente (por ejemplo, por el clínico). La selección del régimen de dosificación específico se puede seleccionar o ajustar o

tratar por el clínico de acuerdo con los métodos conocidos para el clínico para obtener la respuesta clínica deseada o se describen en la presente. Además, la cantidad de un compuesto que se describe en la presente que es efectiva en el tratamiento y/o en la prevención de una enfermedad, condición, o trastorno particular depende de la naturaleza y la medida de la enfermedad, la condición o el trastorno y se puede determinar mediante técnicas clínicas normales. Además, los ensayos in vitro o in vivo se pueden emplear opcionalmente para contribuir a identificar gamas de dosificación óptimas. Las dosificaciones pueden ser, por ejemplo, las dosis descritas en la presente.

Los compuestos, o la composición los comprende, se pueden administrar en diversas formas de dosificación adecuadas para la administración intranasal. La cantidad de dosificación presente en la forma de dosificación puede ser una cantidad efectiva farmacéutica o intranasal. En algunas realizaciones, la cantidad efectiva es una cantidad suficiente para tratar o prevenir el dolor. En algunas realizaciones, la cantidad efectiva es una cantidad que no produce sedación. En algunas realizaciones, la cantidad efectiva no produce sedación importante. En algunas realizaciones, la cantidad efectiva es una cantidad suficiente para tratar o prevenir el dolor, aunque no produce sedación o sedación importante.

La C_{plasma} es la concentración de dexmedetomidina en el plasma de un mamífero o un humano en un momento particular después de la administración. En algunas realizaciones, la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, produce una C_{plasma} de 0,1 ng/ml dentro de 15 minutos a 20 minutos de la administración y tiene un efecto analgésico sin sedación importante. Por lo tanto, en algunas realizaciones, dentro de 15 minutos a 20 minutos de la administración de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, a un mamífero o a un humano, el mamífero o el humano tiene una C_{plasma} de 0,1 ng/ml. En algunas realizaciones, la C_{plasma} es de 0,09 ng/ml a 0,11 ng/ml, de 0,08 ng/ml a 0,12 ng/ml, de 0,06 ng/ml a 0,09 ng/ml, de 0,07 ng/ml a 0,09 ng/ml, o de 0,08 ng/ml a 0,09 ng/ml. En algunas realizaciones, la C_{plasma} deseada se alcanza dentro de 8 minutos a 30 minutos, dentro de 10 minutos a 30 minutos, dentro de 12 minutos a 30 minutos, dentro de 8 minutos a 20 minutos, dentro de 10 minutos a 20 minutos, dentro de 12 minutos a 20 minutos, dentro de 8 minutos a 15 minutos, dentro de 10 minutos a 15 minutos, dentro de 12 minutos a 15 minutos, dentro de 8 minutos a 10 minutos, dentro de 8 minutos a 12 minutos, dentro de 15 minutos a 20 minutos, dentro de 15 minutos a 20 minutos, dentro de 15 minutos, dentro de 12 minutos, dentro de 10 minutos, o dentro de 8 minutos de la administración y tiene un efecto analgésico sin sedación

importante. El punto de tiempo puede reflejar el inicio del alivio del dolor (es decir, un efecto analgésico).

En algunas realizaciones, el inicio del alivio del dolor es menor de 60 minutos, menor de 55 minutos, menor de 50 minutos, menor de 45 minutos, menor de 40 minutos, menor de 35 minutos, menor de 30 minutos, menor de 25 minutos, menor de 20 minutos, menor de 15 minutos, menor de 12 minutos, menor de 10 minutos, 15 minutos, 12 minutos, 10 minutos, u 8 minutos. El inicio del alivio del dolor es el tiempo en que el mamífero siente que el dolor es menor que el anterior a la administración de un compuesto o una composición descritos en la presente. En algunas realizaciones, el alivio del dolor es completo y el mamífero ya no siente el dolor que se estaba aliviando.

La presente invención también proporciona métodos para tratar o prevenir el dolor sin sedación importante en un humano adulto que comprende administrar por vía intranasal una cantidad efectiva de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al humano adulto mediante lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, no produce una sedación importante en el adulto dentro de un período de tiempo de dos horas después de la administración y tiene un efecto analgésico dentro del período de tiempo. En algunas

realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 1,5 hora después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 1,0 hora después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, una sedación importante en el adulto no se produce dentro de un período de tiempo de 45 minutos después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 30 minutos a 1,5 hora después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 40 minutos a 75 minutos después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 45 minutos a 70 minutos después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo desde 50 minutos a 65

minutos después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 55 minutos a 60 minutos después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo.

La presente invención también proporciona métodos para tratar o prevenir el dolor sin sedación importante en un mamífero que comprende administrar por vía intranasal dexmedetomidina, o una sal farmacéuticamente aceptable de ella, a un solo orificio nasal del mamífero, particularmente a un humano. La administración a un solo orificio nasal significa que la dosis unitaria completa se administra en un solo orificio nasal comparada con una parte de la dosis unitaria que se administra a ambos orificios nasales. Es decir, si se administra una dosificación cada 4 horas, la dosificación se administra a solamente un orificio nasal cada 4 horas. El orificio nasal al cual se administran las composiciones se puede alternar entre los dos orificios nasales, aunque, en algunas realizaciones, los métodos comprenden no administrar dexmedetomidina o una sal farmacéuticamente aceptable de ella o una composición descrita en la presente a más de un orificio nasal (por ejemplo, a dos orificios nasales).

La presente invención también proporciona métodos para tratar o prevenir el dolor sin sedación importante en un mamífero que comprende asperjar por vía intranasal en el mamífero una composición farmacéutica que comprende dexmedetomidina, o una sal farmacéuticamente aceptable de ella, en donde la aspersion comprende gotitas que tienen un Dv_{90} menor de 150 μm . En algunas realizaciones, la aspersion comprende gotitas que tienen un Dv_{90} menor de 125 μm . En algunas realizaciones, la aspersion comprende gotitas que tienen un Dv_{90} menor de 100 μm . En algunas realizaciones, la aspersion comprende gotitas que tienen un Dv_{90} de 60 μm a 150 μm , de 60 μm a 125 μm , o de 60 μm a 100 μm . En algunas realizaciones, la aspersion comprende gotitas que tienen un Dv_{90} mayor de 40 μm . En algunas realizaciones, la aspersion comprende gotitas que tienen un Dv_{90} mayor de 50 μm . En algunas realizaciones, la aspersion comprende gotitas que tienen un Dv_{90} mayor de 60 μm . En algunas realizaciones, la aspersion comprende gotitas que tienen un Dv_{90} mayor de 70 μm .

En algunas realizaciones, la presente invención proporciona métodos para tratar o prevenir el dolor sin sedación importante en un mamífero que comprende administrar por vía intranasal una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al mamífero por lo cual la cantidad efectiva intranasal

de dexmedetomidina, o sales farmacéuticamente aceptables de ella, produce una C_{plasma} de 0,1 ng/ml dentro de 15 minutos a 20 minutos de la administración y tiene un efecto analgésico sin sedación importante y por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, no produce sedación importante dentro de un período de tiempo de dos horas después de la administración y tiene un efecto analgésico dentro del período de tiempo.

En algunas realizaciones, la presente invención proporciona métodos para tratar o prevenir el dolor sin sedación importante en un mamífero que comprende administrar por la vía intranasal una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente de ella, a un solo orificio nasal del mamífero, específicamente a un humano, por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, produce una C_{plasma} de 0,1 ng/ml dentro de 15 minutos a 20 minutos de la administración y tiene un efecto analgésico sin sedación importante.

En algunas realizaciones, la presente invención proporciona métodos para tratar o prevenir el dolor sin sedación importante en un mamífero que comprende la aspersión por vía intranasal de una cantidad efectiva intranasal de

dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al mamífero por lo cual la cantidad efectiva intranasal de dexmedetomidina, o la sal farmacéuticamente aceptable de ella, produce una C_{plasma} de 0,1 ng/ml dentro de 15 minutos a 20 minutos de la administración y tiene un efecto analgésico sin sedación importante y por lo cual la aspersion comprende gotitas que tienen un Dv_{90} menor de 150 μm .

En algunas realizaciones, la presente invención también proporciona métodos para tratar o prevenir el dolor sin sedación importante en un humano adulto que comprende administrar por vía intranasal una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, a un solo orificio nasal del humano adulto, por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, no produce sedación importante en el adulto dentro de un período de tiempo de dos horas después de la administración y tiene un efecto analgésico dentro del período de tiempo.

En algunas realizaciones, la presente invención también proporciona métodos para tratar o prevenir el dolor sin sedación importante en un humano adulto que comprende la aspersion por vía intranasal de una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente

aceptable de ella, al humano adulto por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, no produce sedación importante en el adulto dentro de un período de tiempo de dos horas posteriores a la administración y tiene un efecto analgésico dentro del período de tiempo, y en donde la aspersión comprende gotitas que tienen un Dv_{90} menor de 150 μm .

En algunas realizaciones, la presente invención también proporciona métodos para tratar o prevenir el dolor sin sedación importante en un mamífero que comprende la aspersión por vía intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, a un solo orificio nasal del mamífero, particularmente un humano, en donde la aspersión comprende gotitas que tienen un Dv_{90} menor de 150 μm .

En algunas realizaciones, la presente invención proporciona métodos para tratar o prevenir el dolor sin sedación importante en un humano que comprende la administración por vía intranasal de una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, a un solo orificio nasal del humano por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, produce una C_{plasma} de 0,1

ng/ml dentro de 15 minutos a 20 minutos de la administración y tiene un efecto analgésico sin sedación importante, por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, no produce sedación importante en el humano dentro de un período de tiempo de dos horas después de la administración y tiene un efecto analgésico dentro del período de tiempo.

En algunas realizaciones, la presente invención proporciona métodos para tratar o prevenir el dolor sin sedación importante en un mamífero que comprende la aspersión por vía intranasal de una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al mamífero por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, produce una C_{plasma} de 0,1 ng/ml dentro de 15 minutos a 20 minutos de la administración y tiene un efecto analgésico sin sedación importante, por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, no produce una sedación importante en el mamífero dentro de un período de tiempo de dos horas después de la administración y tiene un efecto analgésico dentro del período de tiempo y por lo cual la aspersión comprende gotitas que tienen un Dv_{90} menor de 150 μm .

En algunas realizaciones, la presente invención proporciona métodos para tratar o prevenir el dolor sin sedación importante en un humano que comprende la aspersión por vía intranasal de una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, a un solo orificio nasal del humano por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, produce una C_{plasma} de 0,1 ng/ml dentro de 15 minutos a 20 minutos de la administración y tiene un efecto analgésico sin sedación importante, en donde la aspersión comprende gotitas que tienen un Dv_{90} menor de 150 μm .

En algunas realizaciones, la presente invención también proporciona métodos para tratar o prevenir sin sedación importante en un humano que comprende la aspersión por vía intranasal de una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, no produce una sedación importante en el humano dentro de un período de tiempo de dos horas después de la administración y tiene un efecto analgésico dentro del período de tiempo, en donde la aspersión comprende gotitas que tienen un Dv_{90} menor de 150 μm .

En algunas realizaciones, la presente invención proporciona métodos para tratar o prevenir el dolor sin sedación importante en un humano que comprende la aspersión por vía intranasal de una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, a un solo orificio nasal del humano por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, produce una C_{plasma} de 0,1 ng/ml dentro de 15 minutos a 20 minutos de la administración y tiene un efecto analgésico sin sedación importante por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, no produce sedación importante en el humano dentro de un período de tiempo de dos horas después de la administración y tiene un efecto analgésico dentro del período de tiempo y en donde la aspersión comprende gotitas que tienen un Dv_{90} menor de 150 μm .

En cualquiera de los métodos descritos en la presente, la C_{max} de dexmedetomidina en el plasma es de 0,08 ng/ml a 0,25 ng/ml, de 0,08 ng/ml a 0,2 ng/ml, de 0,1 ng/ml a 0,2 ng/ml, de 0,08 ng/ml a 0,15 ng/ml, de 0,1 ng/ml a 0,15 ng/ml, o de 0,15 ng/ml a 0,2 ng/ml. En algunas realizaciones, la C_{max} de dexmedetomidina en el plasma es de 0,08 ng/ml a 0,2 ng/ml. En algunas realizaciones, la C_{max} de dexmedetomidina en el plasma

es de 0,15 ng/ml. En algunas realizaciones, la $C_{\max}$ de dexmedetomidina en el plasma es de 0,2 ng/ml. En algunas realizaciones, la $C_{\max}$ de dexmedetomidina en el plasma es de 0,25 ng/ml.

En cualquiera de los métodos descritos en la presente, el $T_{\max}$ es menor de 60 minutos, menor de 50 minutos, menor de 40 minutos, menor de 35 minutos, o menor de 30 minutos. En algunas realizaciones, el $T_{\max}$ es de 20 minutos a 60 minutos, de 20 minutos a 50 minutos, de 20 minutos a 40 minutos, de 20 minutos a 30 minutos, de 30 minutos a 60 minutos, de 30 minutos a 50 minutos, de 30 minutos a 40 minutos, de 40 minutos a 60 minutos, de 40 minutos a 50 minutos, o de 50 minutos a 60 minutos. En algunas realizaciones, el $T_{\max}$ de dexmedetomidina es menor de 1 hora. En algunas realizaciones, el $T_{\max}$ es menor de 50 minutos.

En cualquiera de los métodos descritos en la presente, el compuesto o la composición se pueden administrar de acuerdo con un esquema específico. En algunas realizaciones, la composición se administra cada 2 horas, cada 4 horas, cada 6 horas, cada 8 horas, cada 10 horas, cada 12 horas, o cada 24 horas. La composición también se puede administrar según sea necesario. En algunas realizaciones, la dexmedetomidina, o la

sal farmacéuticamente aceptable de ella, o una composición que la comprende, se administra cada 6 horas.

En cualquiera de los métodos descritos en la presente, la dexmedetomidina, o la sal farmacéuticamente aceptable de ella, se administra como una dosis unitaria de 10 μg a 100 μg , de 10 μg a 90 μg , de 10 μg a 80 μg , de 10 μg a 70 μg , de 10 μg a 60 μg , de 10 μg a 50 μg , de 10 μg a 40 μg , de 10 μg a 30 μg , de 10 μg a 20 μg , de 25 μg a 100, de 25 μg a 90 μg , de 25 μg a 80 μg , de 25 μg a 70 μg , de 25 μg a 60 μg , de 25 μg a 50 μg , de 25 μg a 40 μg , de 25 μg a 35 μg , de 25 μg a 30 μg , de 30 μg a 45 μg , de 35 μg a 45 μg , de 30 μg a 40 μg , o de 25 μg a 45 μg . En algunas realizaciones, la dexmedetomidina, o la sal farmacéuticamente aceptable de ella, se administra como una dosis unitaria de 10 μg , 15 μg , 20 μg , 25 μg , 30 μg , 35 μg , 40 μg , 45 μg , 50 μg , 55 μg , 60 μg , 70 μg , 75 μg , 80 μg , 85 μg , 90 μg , 95 μg , o 100 μg . En algunas realizaciones, la dexmedetomidina, o la sal farmacéuticamente aceptable de ella, se administra como una dosis unitaria menor de 100 μg , menor de 90 μg , menor de 80 μg , menor de 70 μg , menor de 60 μg , menor de 50 μg , menor de 40 μg , menor de 30 μg , menor de 20 μg , o menor de 10 μg . En algunas realizaciones, la dexmedetomidina, o la sal farmacéuticamente aceptable de ella, se administra como

una dosis unitaria de 10 μg , 25 μg , 30 μg , 35 μg , 40 μg , 50 μg , 75 μg , o 100 μg . Como se discute en la presente, la dosis unitaria se puede administrar de muchas maneras. En algunas realizaciones, la dosis unitaria se administra a través de una sola aspersión nasal. En algunas realizaciones, la dosis unitaria se administra a través de una sola aspersión nasal usando un dispositivo de aspersión de una sola dosis que no necesita iniciación. Se puede administrar una sola dosis a través de un solo accionamiento de un dispositivo de aspersión nasal. Un ejemplo del dispositivo de aspersión no necesita inicio incluye, en forma no taxativa, Aptar Unitdose Intranasal Systems. El dispositivo de aspersión puede, en algunas realizaciones, suministrar un volumen de 100 μl . En algunas realizaciones, el volumen es de 10, 20, 30, 40, 50, 60, 70, 80, o 90 μl . En algunas realizaciones, el volumen es de 10-100, de 20-100, de 30-100, de 40-100, de 50-100, de 60-100, de 70-100, de 80-100, de 90-100 μl .

En cualquiera de los métodos descritos en la presente, el método comprende no tener ningún efecto o tener un efecto mínimo sobre la presión sanguínea después de la administración. En algunas realizaciones, no hay ningún efecto sobre la presión sanguínea dentro de la hora inmediatamente posterior a la administración de un compuesto descrito en la

presente, hay un efecto sólo mínimo sobre la presión sanguínea dentro de la hora inmediatamente posterior a la administración de un compuesto descrito en la presente. En algunas realizaciones, la presión sanguínea arterial promedio en reposo del mamífero no se ve afectada en más de 5 mmHg, más de 10 mmHg, más de 15 mmHg, más de 20 mmHg, más de 25 mmHg, o más de 30 mmHg. La presión sanguínea arterial promedio se puede medir mediante cualquier método conocido en el arte. En algunas realizaciones, no hay ningún efecto o hay un efecto mínimo sobre la presión sanguínea después de la administración de la dexmedetomidina, o la sal farmacéuticamente aceptable de ella.

En cualquiera de los métodos descritos en la presente, el método además comprende administrar en una combinación simultánea, alternada, o secuencial al humano o mamífero, uno o más agentes terapéuticos adicionales. Uno o más agentes terapéuticos adicionales se eligen de un analgésico, tal como un analgésico opioide (por ejemplo, morfina, oxicodona, hidromorfona, etc.), un analgésico de tipo opioide sintético (por ejemplo, meperidina, fentanilo, pentazocina, butorfanol, etc.), o un analgésico no opioide (por ejemplo, NSAID, ketamina, salicilatos, esteroides, etc.); una vitamina; un vasodilatador; una benzodiacepina (por ejemplo, clonazepam, alprazolam, lorazepam, etc.); un triptan (y otros compuestos

para el dolor de cabeza de migraña); un anticonvulsivo (por ejemplo, pregabalina, ácido valproico, gabapentina, etc.); un antidepresivo (por ejemplo, tricíclicos tales como amitriptilina, nortriptilina, etc.; inhibidores de la recaptación de serotonina y norepinefrina tales como duloxetina, fluoxetina, venlafaxina, etc.); un medicamento contra las náuseas (por ejemplo, metoclopramida, proclorperazina, ondansetrón, granisetron, etc.); y un antihipertensivo (por ejemplo, beta bloqueantes tales como propranolol y bloqueadores de los canales de calcio tales como verapamil, etc.).

La presente invención también proporciona una o más cualquiera de las composiciones descritas en la presente para tratar el dolor en un mamífero sin sedación importante.

La presente invención también proporciona una o más cualquiera de las composiciones descritas en la presente para su uso en la fabricación de un medicamento para tratar el dolor en un mamífero sin sedación importante.

En cualquiera de los métodos descritos en la presente, la dexmedetomidina, o la sal farmacéuticamente aceptable de ella, se puede administrar por vía intranasal con un dispositivo. En algunas realizaciones, el dispositivo es un dispositivo de

dosis medida. En algunas realizaciones, el dispositivo de dosis medida es un dispositivo de varias dosis, de dosis unitaria o de dos dosis.

En algunas realizaciones, el dispositivo es adecuado para la administración intranasal. Se puede usar cualquier dispositivo que sea adecuado para la administración intranasal. En algunas realizaciones, el dispositivo es un dispositivo de dosis medida. El dispositivo de dosis medida puede suministrar una cantidad de dosificación específica de la composición. El dispositivo de dosis medida puede ser un dispositivo de dosis unitaria de dos dosis o de varias dosis. La cantidad farmacéuticamente efectiva que se puede administrar usando un dispositivo de dosis medida puede ser un dispositivo de dosis unitaria. La dosis medida puede, en algunas realizaciones, ser un dispositivo que puede suministrar una composición farmacéutica por vía intranasal. Ejemplos de dispositivos de dosis medida incluyen, en forma no taxativa, dispositivos que son dispositivos de bomba, dispositivos mecánicos, dispositivos presurizados y/o dispositivos electromecánicos. Ejemplos de un dispositivo de dosis medida incluyen, en forma no taxativa, una bomba de aspersión, una bomba de aspersión nasal de precompresión, un dispositivo de válvula medida, un dispositivo de aspersión medida, un dispositivo de aspersión de accionamiento lateral, un dispositivo de aspersión nasal de

jeringa (por ejemplo, una jeringa que tiene un atomizador para suministrar una aspersion a la cavidad nasal), un dispositivo de atomización mucosal, un dispositivo de bomba electromecánica (con y sin contador), y similares. Ejemplos de dispositivos de dosis medida también incluyen, en forma no taxativa, dispositivos fabricados por Aptar Pharma (Congers, NY) y están comercialmente disponibles. Ejemplos de dispositivos de dosis medida también incluyen, en forma no taxativa, UDS (Aptar Pharma), BDS (Aptar Pharma), eDevices (Aptar Pharma), Equadel (Aptar Pharma), Latitude (Aptar Pharma), DF30 (Aptar Pharma), VP7 (Aptar Pharma), Dispositivo Nasal Clásico (Aptar Pharma), Dispositivo de Fármaco Nasal MAD (Wolf Tory Medical, Inc.), BD Accuspray SCF™ (Becton Dickinson), y similares. Otro ejemplo incluye, en forma no taxativa, un Sistema Intranasal de Dosis Unitaria de Aptar.

Las formulaciones intranasales analgésicas de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, se pueden administrar en dosificaciones medidas de manera tal que una cantidad predeterminada del ingrediente farmacéutico activo se administre correctamente al sujeto en una cantidad farmacéuticamente efectiva. Por ejemplo, la formulación intranasal se puede empaquetar como un líquido global que contiene varias dosis en un sistema de aspersion de bomba que comprende un contenedor sellado equipado con una bomba

medidora. En algunas realizaciones, se trata a un paciente humano mediante autoadministración intranasal, tal como mediante uno o más accionamientos desde una bomba de aspersión. Una ventaja de los ejemplos de suministros de aspersiones intranasales de la presente es la capacidad de titular sujetos mediante una sola dosis según si se provee a través de uno solo o de varios accionamientos discretos. Esta ventaja normalmente está ausente en otras formas de suministro de fármaco (por ejemplo, parches, pastillas, tabletas, y supositorios) en donde una dosificación de un tamaño se ajusta a todos se administra en un régimen estándar. Otras ventajas de las formulaciones de aspersiones intranasales incluyen su facilidad de uso, especialmente cuando se autoadministran sin la presencia de un profesional de la salud que atiende al paciente.

En algunas realizaciones, el dispositivo de dosis medida es un dispositivo de suministro de aspersión que incluye una unidad de base, un accionador de descarga, un orificio para que la formulación se libere desde el dispositivo y un depósito. El depósito se puede llenar con dexmedetomidina, o una sal farmacéuticamente aceptable de ella, y opcionalmente otros excipientes, tales como aquellos descritos en toda la presente aplicación, antes de la distribución al paciente, por ejemplo, en el lugar de fabricación. El depósito puede contener una

cantidad medida de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, o un derivado de ella, que se debe descargar luego de la activación. El cuerpo del depósito puede ser cualquier material aceptable, por ejemplo, formado simplemente mediante una sección de un hueco cilíndrico de un material de plástico, de acero, tal como acero inoxidable, un material transparente, o similar de manera tal que su producción sea muy simple. Un accionador, que es móvil en relación con el orificio para activar la descarga, se puede proveer sobre o con el dispositivo. En el transcurso del movimiento de accionamiento, el depósito se abre, por ejemplo, mediante punción, para administrar una sola dosificación a través de un orificio. Durante una parte del recorrido del accionamiento después de la posición inicial se acumula una presión elevada. En una parte posterior del movimiento de accionamiento que continúa en la misma dirección, el medio se puede aliviar de la presión en uno de los costados y se comunica a un orificio. De tal manera, el medio se empuja desde el depósito y a través del orificio por la acción de la presión.

En algunas realizaciones, cuando la formulación líquida sale del orificio, las gotitas líquidas siguen una trayectoria que está influida por la forma del orificio, así como por la presión ejercida. En algunas realizaciones, el tamaño de las

gotitas, la geometría de la aspersión y el patrón de la aspersión dependen del diseño de la bomba y/o de las propiedades de la formulación. En algunas realizaciones, la orientación del accionador, el diseño de la bomba y las propiedades de la formulación influyen en la simetría y la forma de la aspersión. El patrón de la aspersión también se puede optimizar para dispersar las gotitas sobre una vía más ancha aumentando de ese modo la superficie a través de la cual se puede absorber el compuesto. El dispositivo también se puede diseñar para facilitar el uso y la colocación por el paciente de la aspersión administrada a regiones específicas de la mucosa nasal.

Las aspersiones de acción de bomba se pueden caracterizar por la aplicación de presión externa para el accionamiento, por ejemplo, presión manual externa, mecánica o iniciada en forma eléctrica. Esto es diferente de los sistemas presurizados, por ejemplo, aerosol impulsado por propulsores o aspersiones de gas comprimido, donde el accionamiento normalmente se realiza mediante la liberación controlada de presión, por ejemplo, mediante la apertura controlada de una válvula. En algunas realizaciones, se usan aspersiones de bomba. El uso de una aspersión de bomba con las formulaciones de la presente permite la administración de gotitas o partículas que tienen un diámetro promedio pequeño y una distribución de tamaños

controlable de gotitas. En algunas realizaciones, los sistemas presurizados que contienen un depósito de gas propulsor presurizado (por ejemplo, dióxido de carbono, nitrógeno, clorofluorocarbonos, hidrofluoroalcanos, etc.) pueden producir partículas o gotitas adecuadas. Las gotitas o partículas líquidas que tienen un diámetro que es demasiado pequeño tienen el potencial de entrar en los pulmones de un humano después de la administración. En algunas realizaciones, el tamaño de las gotitas de las formulaciones suministradas también provee un aumento en la superficie asperjando en forma intranasal por oposición a la colocación en un orificio nasal, por ejemplo, con un gotero. El tamaño de las partículas de aspersión y la forma del patrón de aspersión también puede contribuir a si el ingrediente activo se absorbe en sistemas corporales diferentes de la mucosa nasal (por ejemplo, los pulmones).

Como se describe en la presente, el dispositivo de bomba de aspersión se puede medir previamente o, alternativamente, el aparato se puede medir con el dispositivo. Los dispositivos medidos previamente pueden contener dosis medidas previamente o una fracción de dosis en algún tipo de unidades (por ejemplo, una cantidad de una sola dosis unitaria de solución, uno o varios blísteres u otras cavidades) que se pueden incluir en el dispositivo durante la fabricación o por el

paciente antes de usarlo. Las unidades medidas por el dispositivo típicas tienen un depósito que contiene la formulación suficiente para varias dosis que se suministran como aspersiones medidas por el propio dispositivo cuando lo activa el paciente. El dispositivo se puede medir tanto en la cantidad de la sustancia farmacológica suministrada (es decir, la dosificación por cada accionamiento), así como la duración de tiempo entre cada dosificación. La limitación del tiempo entre cada dosificación puede prevenir el uso excesivo limitando con qué frecuencia se puede suministrar una dosificación al paciente.

Las realizaciones de los dispositivos descritos en la presente, no han de ser taxativas. En algunas realizaciones, las formulaciones que contienen dexmedetomidina se pueden proveer alternativamente o además como otras formas de dosificación intranasal. Por ejemplo, las composiciones intranasales se pueden proporcionar como un líquido compatible con la administración por un gotero o un dispositivo similar. La formulación intranasal se puede proporcionar como un polvo que se debe administrar en la cavidad nasal. Las formulaciones por ejemplo se pueden empaquetar en ampollas de dosis unitarias farmacéuticamente aceptables con tapas que se rompen para permitir que la ampolla abierta se inserte en la cavidad

nasal del paciente para distribuir una sola dosis de la formulación.

En aún otra realización, los compuestos se pueden suministrar en un sistema de liberación controlada. En una realización, se puede usar una bomba (véanse Langer, arriba; Sefton, CRC Crit. Ref. Biomed. Eng., 1987, 14, 201; Buchwald et al., Cirugía, 1980, 88, 507 Saudek et al., N. Engl. J. Med., 1989, 321, 574). En otra realización, se pueden usar materials polimerizados (véanse Aplicaciones Médicas de Liberación Controlada, Langer y Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Biodisponibilidad de Fármaco Controlado, Diseño y Desempeño de Productos Farmacológicos, Smolen y Ball (eds.), Wiley, New York (1984); Ranger et al., J. Macromol. Sci. Rev. Macromol. Chem., 1983, 23, 61; véanse también Levy et al., Ciencia, 1985, 228, 190; During et al., Ann. Neurol., 1989, 25, 351; Howard et al., J. Neurosurg., 1989, 71, 105). Otros sistemas de liberación controlada discutidos en la revista de Langer, Ciencia, 1990, 249, 1527-1533, se pueden usar y se pueden adaptar para la administración intranasal.

En algunas realizaciones, las composiciones intranasales de dexmedetomidina acuosa se pueden administrar como gotas o como un rocío fino. La administración como un rocío fino puede mejorar la reproducibilidad de la dosificación facilitando la

deposición pareja de la composición sobre la mucosa nasal. En algunas realizaciones, un dispositivo de bomba se usa para generar un rocío fino desde la composición en solución nasal global. Los dispositivos de dosis unitaria y de dos dosis se pueden usar para las composiciones de aspersion nasal de dexmedetomidina ya que estos dispositivos pueden limitar la dosis total y/o el número de dosis que se pueden suministrar desde un solo dispositivo que por lo tanto reduce el potencial para la sobredosis/el abuso. Además, los dispositivos de dosis unitaria y/o de dos dosis pueden necesitar un volumen empaquetado menor para suministrar el volumen de aspersion reduciendo la cantidad necesaria de la solución perdida al cebar la bomba. En algunas realizaciones, los dispositivos de varias dosis se usan debido a su menor costo de fabricación y menor desperdicio de empaquetado.

La presente invención también proporciona dispositivos de dosis medida que comprenden una composición farmacéutica que comprende dexmedetomidina, o una sal farmacéuticamente aceptable de ella, en donde el dispositivo de dosis medida suministra una aspersion de dosis medida de la composición farmacéutica por vía intranasal que es analgésica en un mamífero sin sedación importante.

En algunas realizaciones, la aspersion de dosis medida producida por el dispositivo comprende gotitas que comprenden dexmedetomidina, o una sal farmacéuticamente aceptable de ella, que tienen un Dv_{90} menor de 150 μm . En algunas realizaciones, la aspersion comprende gotitas que tienen un Dv_{90} menor de 125 μm . En algunas realizaciones, la aspersion comprende gotitas que tienen un Dv_{90} menor de 100 μm . En algunas realizaciones, la aspersion comprende gotitas que tienen un Dv_{90} de 60 μm a 150 μm , de 60 μm a 125 μm , o de 60 μm a 100 μm .

En algunas realizaciones, la aspersion de dosis medida producida por el dispositivo comprende una dosis medida de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, de 10 μg a 100 μg , de 10 μg a 90 μg , de 10 μg a 80 μg , de 10 μg a 70 μg , de 10 μg a 60 μg , de 10 μg a 50 μg , de 10 μg a 40 μg , de 10 μg a 30 μg , de 10 μg a 20 μg , de 25 μg a 100, de 25 μg a 90 μg , de 25 μg a 80 μg , de 25 μg a 70 μg , de 25 μg a 60 μg , de 25 μg a 50 μg , de 25 μg a 40 μg , de 25 μg a 35 μg , de 25 μg a 30 μg , o de 25 μg a 45 μg . En algunas realizaciones, la aspersion de dosis medida producida por el dispositivo comprende una dosis medida de 10 μg , 15 μg , 20 μg , 25 μg , 30 μg , 35 μg , 40 μg , 50 μg , 55 μg , 60 μg , 70 μg , 75 μg , 80 μg , 85 μg , 90 μg , 95 μg , o 100 μg . En algunas realizaciones, la aspersion de dosis medida producida por el

dispositivo comprende una dosis medida menor de 100 μg , menor de 90 μg , menor de 80 μg , menor de 70 μg , menor de 60 μg , menor de 50 μg , menor de 40 μg , menor de 30 μg , menor de 20 μg , o menor de 10 μg . En algunas realizaciones, la aspersion de dosis medida producida por el dispositivo comprende una dosis medida de 10 μg , 25 μg , 35 μg , 50 μg , 75 μg , o 100 μg .

En algunas realizaciones, la aspersion de dosis medida producida por el dispositivo comprende un volumen menor de 150 μl , menor de 140 μl , menor de 130 μl , menor de 120 μl , menor de 110 μl , menor de 100 μl , menor de 75 μl , o menor de 50 μl . En algunas realizaciones, la aspersion de dosis medida producida por el dispositivo comprende un volumen de 150 μl , 140 μl , 130 μl , 120 μl , 110 μl , 100 μl , 75 μl , o 50 μl .

En algunas realizaciones, la aspersion de dosis medida producida por el dispositivo produce una C_{plasma} en el mamífero de 0,09 ng/ml a 0,11 ng/ml, de 0,08 ng/ml a 0,12 ng/ml, o de 0,1 ng/ml dentro de 12 minutos a 30 minutos, de 12 minutos a 20 minutos, de 15 minutos a 20 minutos, o dentro de 15 minutos de la administración y tiene un efecto analgésico sin sedación importante. En algunas realizaciones, la aspersion de dosis medida producida por el dispositivo produce una C_{plasma} en el mamífero de 0,1 ng/ml dentro de 15 minutos a 20 minutos de la administración.

En algunas realizaciones, la aspersión de dosis medida produce un inicio del alivio del dolor menor de 60 minutos, menor de 55 minutos, menor de 50 minutos, menor de 45 minutos, menor de 40 minutos, menor de 35 minutos, menor de 30 minutos, menor de 25 minutos, menor de 20 minutos, o de 15 minutos.

En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo no produce sedación importante en un adulto dentro de un período de tiempo de dos horas después de la administración y tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de 1,5 hora después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 1,0 hora después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 45 minutos después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 30 minutos a 1,5 hora después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas

realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 40 minutos a 75 minutos después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 45 minutos a 70 minutos después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 65 minutos posteriores a la administración, pero aún tiene un efecto analgésico dentro del período de tiempo. En algunas realizaciones, la sedación importante en el adulto no se produce dentro de un período de tiempo de 55 minutos a 60 minutos después de la administración, pero aún tiene un efecto analgésico dentro del período de tiempo.

En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo produce una $C_{\max}$ en el plasma en el mamífero de 0,08 ng/ml a 0,25 ng/ml, de 0,08 ng/ml a 0,2 ng/ml, de 0,1 ng/ml a 0,25 ng/ml, de 0,1 ng/ml a 0,2 ng/ml, de 0,08 ng/ml a 0,15 ng/ml, de 0,1 ng/ml a 0,15 ng/ml, de 0,15 ng/ml a 0,2 ng/ml, o de 0,15 ng/ml a 0,25 ng/ml. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo produce una $C_{\max}$ en plasma en el mamífero de 0,08

ng/ml a 0,25 ng/ml. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo produce una $C_{\max}$ en el plasma en el mamífero de 0,08 ng/ml a 0,2 ng/ml. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo produce una $C_{\max}$ en plasma en el mamífero de 0,15 ng/ml. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo produce una $C_{\max}$ en el plasma en el mamífero de 0,08 ng/ml, 0,1 ng/ml, de 0,2 ng/ml, o de 0,25 ng/ml.

En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo produce un $T_{\max}$ en el mamífero menor de 60 minutos, menor de 50 minutos, menor de 40 minutos, menor de 35 minutos, o menor de 30 minutos. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo produce un $T_{\max}$ en el mamífero de 20 minutos a 60 minutos, de 20 minutos a 50 minutos, de 20 minutos a 40 minutos, de 20 minutos a 30 minutos, de 30 minutos a 60 minutos, de 30 minutos a 50 minutos, de 30 minutos a 40 minutos, de 40 minutos a 60 minutos, de 40 minutos a 50 minutos, o de 50 minutos a 60 minutos. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo produce un $T_{\max}$ en el mamífero menor de 1 hora. En algunas realizaciones, la aspersión de dosis medida producida

por el dispositivo produce un $T_{\max}$ en el mamífero menor de 50 minutos.

En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo durante la hora inmediatamente posterior a la administración al mamífero produce un nivel de sedación no mayor que el Nivel 1, el Nivel 2, o el Nivel 3 en la Escala de Sedación de Ramsay. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo durante la hora inmediatamente posterior a la administración al mamífero produce un nivel de sedación no mayor que el Nivel 3 en la Escala de Sedación de Ramsay. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo durante la hora inmediatamente posterior a la administración al mamífero produce un nivel de sedación no mayor que el Nivel 2 en la Escala de Sedación de Ramsay.

En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo durante la hora inmediatamente posterior a la administración al mamífero produce un nivel de sedación no mayor que el Nivel 1 o el Nivel 2 en la Escala de Somnolencia de Stanford. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo durante la hora inmediatamente posterior a la administración al

mamífero produce un nivel no mayor que el Nivel 2 en la Escala de Somnolencia de Stanford.

En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo durante la hora inmediatamente posterior a la administración al mamífero produce un nivel de sedación no menor que el Nivel 6 en la Escala Modificada de Evaluación de Alerta/Sedación del Observador.

En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo no tiene ningún efecto o tiene un efecto mínimo sobre la presión sanguínea del mamífero después de la administración. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo no tiene ningún efecto o tiene un efecto mínimo sobre la presión sanguínea dentro de la hora inmediatamente posterior a la administración de un compuesto descrito en la presente. En algunas realizaciones, la aspersión de dosis medida producida por el dispositivo tiene un efecto solamente mínimo sobre la presión sanguínea dentro de la hora inmediatamente posterior a la administración de un compuesto en la presente. En algunas realizaciones, la presión sanguínea arterial promedio en reposo del mamífero no se ve afectada en más de 5 mmHg, más de 10 mmHg, más de 15 mmHg, más de 20 mmHg, más de 25 mmHg, o más de 30 mmHg.

En algunas realizaciones, cualquiera de las composiciones descritas en la presente también puede comprender uno o más agentes terapéuticos adicionales. Uno o más agentes terapéuticos adicionales se eligen de un analgésico, tal como un analgésico opioide (por ejemplo, morfina, oxicodona, hidromorfona, etc.), un analgésico tipo opioide sintético (por ejemplo, meperidina, fentanilo, pentazocina, butorfanol, etc.), o un analgésico no opioide (por ejemplo, NSAID, ketamina, salicilatos, esteroides, etc.); una vitamina; un vasodilatador; una benzodiacepina (por ejemplo, clonazepam, alprazolam, lorazepam, etc.); un triptan (y otros compuestos para el dolor de cabeza de migraña); un anticonvulsivo (por ejemplo, pregabalina, ácido valproico, gabapentina, etc.); un antidepresivo (por ejemplo, tricíclicos tales como amitriptilina, nortriptilina, etc.; inhibidores de la recaptación de serotonina y norepinefrina tales como duloxetina, fluoxetina, venlafaxina, etc.); un medicamento contra las náuseas (por ejemplo, metoclopramida, proclorperazina, ondansetrón, granisetron, etc.); y un antihipertensivo (por ejemplo, beta bloqueantes tales como propranolol y bloqueadores de los canales de calcio tales como verapamil, etc.).

Ejemplos de otros agentes analgésicos incluyen, en forma no taxativa, narcóticos, NSAID, inhibidores de Cox-2, esteroides,

y similares. Otros ejemplos incluyen, en forma no taxativa, aspirina, codeína, oxycodona, ibuprofeno, butalbital, acetaminofeno (APAP), cafeína, aspirina, hidrocodona, acetaminofeno, propoxifeno n-apap, propoxifeno HCl, tartrato de butorfanol, pentazocina-apap, pentazocina-naloxona, tramadol, tramadol de liberación extendida, fentanilo, morfina, meperidina HCl, hidromorfona HCl, metadona, tartrato de levorfanol, oximorfona, buprenorfina, celecoxib, rofecoxib, naltrexono, naproxeno, flurbiprofeno, diclofenac, sulindac, oxaprozina, piroxicam, indometacina, etodolac, meclofenamato, meloxicam, fenoprofeno, ketoprofeno, nabumetona, tolmetina, ketorolac trometamina, salsalato, diflunisal, salicilatos de colina y magnesio, o cualquier combinación de ellos. Los compuestos o sus sales y las composiciones que comprenden los mismos, que se describen en la presente se pueden administrar solos o en combinación (simultánea o en serie) con los demás agentes farmacéuticos. En algunas realizaciones, las composiciones descritas en la presente se pueden administrar con uno o más agentes analgésicos.

En algunas realizaciones, la composición también comprende un excipiente portador. En algunas realizaciones, la composición farmacéutica además comprende fosfato de sodio y/o citrato de sodio. En algunas realizaciones, la composición farmacéutica también comprende citrato de sodio, ácido cítrico, y cloruro

de sodio. En algunas realizaciones, la composición farmacéutica además comprende del 0,2% al 0,3% (p/p) de citrato de sodio y del 0,005% al 0,015% (p/p) de ácido cítrico.

En algunas realizaciones, la composición comprende una sal, tal como una sal farmacéuticamente aceptable. En algunas realizaciones, la composición comprende cloruro de sodio cloruro de potasio, o cualquier combinación de ellos. En algunas realizaciones, la composición comprende ácido cítrico. En algunas realizaciones, la composición comprende citrato de sodio, ácido cítrico y una sal, que incluye, en forma no taxativa, cloruro de sodio. En algunas realizaciones, la composición comprende del 0,1% al 0,5%, del 0,1% al 0,4%, del 0,2% al 0,5%, del 0,2% al 0,4%, del 0,2% al 0,3% (p/p) de citrato de sodio. En algunas realizaciones, la composición comprende del 0,005% al 0,015%, del 0,005% al 0,05%, del 0,005% al 0,004%, del 0,005% al 0,03%, del 0,005% al 0,02%, o del 0,005% al 0,0175% (p/p) de ácido cítrico.

En algunas realizaciones, la composición farmacéutica también comprende un quelante o un estabilizador que se puede usar para mejorar la estabilidad química cuando sea necesario. Los estabilizadores adecuados incluyen, en forma no taxativa, agentes quelantes o agentes que forman complejos, tales como,

por ejemplo, un agente que forma un complejo de calcio y ácido etileno diamina tetraacético (EDTA), una sal de EDTA, ácido cítrico, quitosano, sorbitol, y ácido tartático. Por ejemplo, una cantidad apropiada de EDTA o una sal de él, por ejemplo, la sal disódica, se puede incluir en la composición para formar un complejo de iones de calcio y prevenir la formación de gel durante el almacenamiento. EDTA o una sal de él se puede incluir adecuadamente en una cantidad del 0,01% al 0,5%. En aquellas realizaciones que contienen un conservante diferente de EDTA, el EDTA o una sal de él, más específicamente EDTA disódico, puede estar presente en una cantidad del 0,025% al 0,1% en peso. Sin atarnos a la teoría, los agentes quelantes pueden prevenir la degradación catiónica multivalente de dexmedetomidina u otros componentes de la composición.

En algunas realizaciones, las composiciones intranasales descritas en la presente opcionalmente pueden incluir un sistema de tampón compuesto de un par de ácido y base resistente a los cambios en el pH. El pH de las composiciones se puede controlar para limitar la irritación de la aspersión nasal. En algunas realizaciones, se puede usar un pH de la solución de 6,0 a 6,5 para ser compatible con el pH de las secreciones nasales mientras mantiene el fármaco en solución. Los tampones farmacéuticamente aceptables que proporcionan un

pH compatible con la mucosa nasal incluyen citrato, fosfato y similares. En algunas realizaciones, el pH de la composición es menor de 7, menor de 6,9, menor de 6,8, menor de 6,7, menor de 6,6, menor de 6,5, menor de 6,4, menor de 6,2, o menor de 6,1. En algunas realizaciones, el pH de la composición es de 6 a 6,1, de 6 a 6,2, de 6 a 6,3, de 6 a 6,4, de 6 a 6,5, de 6 a 6,6, de 6 a 6,7, de 6 a 6,8, de 6 a 6,9, o de 6 a 7,0. En algunas realizaciones, el pH de la composición es tal que la composición no irrite la cavidad nasal.

En algunas realizaciones, la composición farmacéutica también comprende uno o más conservantes antimicrobianos. Ejemplos de conservantes incluyen, en forma no taxativa, sustancias que contienen mercurio tales como sales fenilmercúricas (por ejemplo, acetato, borato y nitrato fenilmercúrico) y timerosal; dióxido de cloro estabilizado; compuestos de amonio cuaternario tales como cloruro de benzalconio, bromuro de cetoltrimetolamonio y cloruro de cetilpiridinio; imidazolidinil urea; parabenos tales como metilparabeno, etilparabeno, propilparabeno y butilparabeno y sales de ellos; fenoxietanol; clorofenoxietanol; fenoxipropanol; clorobutanol; clorocresol; alcohol de feniletilo; EDTA disódico; y ácido sórbico y sales de él. Los conservantes pueden precipitar en la presencia de otros excipientes en la composición. Por ejemplo, el cloruro de benzalconio puede precipitar. Por lo

tanto, en algunas realizaciones en donde está presente un conservante, el conservante es aquel que no precipita pero permanece en solución en la composición. Un conservante adecuado es el alcohol de feniletilo. Se pueden incluir uno o más conservantes antimicrobianos, por ejemplo, para suprimir el crecimiento microbiano y fúngico en los sistemas de suministro finales.

En algunas realizaciones, la composición farmacéutica además comprende uno o más antioxidantes. Los antioxidantes adecuados pueden opcionalmente incluirse en la composición nasal, por ejemplo, para estabilizar la formulación contra los efectos prolongados de la oxidación. Ejemplos de antioxidantes incluyen, en forma no taxativa, Vitamina E (y sus derivados), Vitamina C (y sus derivados), BHT, BHA, galato de propilo, ácido cítrico, ácido eritórbico, monotioglicerol, un metabisulfito (de sodio o de potasio), ácido propiónico, sulfito de sodio y timol.

En algunas realizaciones, la composición farmacéutica además comprende uno o más excipientes de confirmación de dosis, que contribuyen a facilitar el uso correcto y/o a evitar la sobredosificación. Para medicamentos que se administran por vía intranasal, puede ser difícil para el sujeto determinar si el medicamento a ha administrado correctamente. La inclusión

de un excipiente de confirmación de dosis puede brindar una retroalimentación positiva al sujeto después de la administración, que confirma que la dosis se ha administrado por vía intranasal. En algunas realizaciones, el excipiente que confirma la dosis no tiene un olor que permita que el sujeto confirme que la dosis se administró y se tomó o se depositó en la nariz. Se pueden usar otros mecanismos de retroalimentación para confirmar que la dosis se ha administrado apropiadamente. El olor es un ejemplo no taxativo. En algunas realizaciones, el excipiente de confirmación de la dosis es alcohol de feniletilo. Sin atarnos a ninguna teoría, los excipientes de confirmación de la dosis brindan una retroalimentación sensorial al paciente para confirmar que se ha suministrado una dosis, aumentando de ese modo el cumplimiento del régimen de dosificación prescrito y reduciendo el potencial de sobredosificación. El alcohol de feniletilo tiene un olor distinguible y puede servir como antimicrobiano y también como excipiente de confirmación de la dosis en las composiciones descritas previamente.

En algunas realizaciones, la composición farmacéutica además comprende uno o más humectantes. Ejemplos de humectantes incluyen, en forma no taxativa, glicerina, propilenglicol, polietilenglicol, y azúcar/alcohol de azúcar, o cualquier

combinación de ellos. Los humectantes pueden proporcionar efectos hidratantes y reducir la irritación nasal.

En algunas realizaciones, la composición farmacéutica además comprende uno o más agentes de osmolaridad. La osmolaridad de la composición intranasal también puede ser relevante para la captación del medicamento por vía intranasal. Los agentes de ajuste de la osmolaridad adecuados incluyen, en forma no taxativa, cloruro de sodio, dextrosa, azúcares, o cualquier combinación de ellos. Los agentes de ajuste de la osmolaridad también pueden estar incluidos en la composición para producir soluciones que son menos irritantes para la mucosa nasal alineando la osmolaridad de la solución administrada con la mucosa nasal.

En algunas realizaciones, la composición farmacéutica está libre de un agente mejorador de la viscosidad. Los agentes mejoradores de la viscosidad que incluyen, en forma no taxativa, Methocel E4M opcionalmente se pueden agregar para aumentar el tiempo de residencia de la solución instilada o asperjada en la mucosa nasal. Sin embargo, en el caso de la dexmedetomidina, el uso de un agente mejorador de la viscosidad puede derivar en niveles en plasma disminuidos de dexmedetomidina y puede en consecuencia omitirse en determinadas condiciones, tales como cuando la composición de

dexmedetomidina está destinada a la captación rápida. En consecuencia, se halló sorpresivamente que la viscosidad de la composición intranasal puede afectar la captación del ingrediente activo. Por lo tanto, en algunas realizaciones, un aumento en la viscosidad puede reducir la captación de dexmedetomidina. Por consiguiente, en algunas realizaciones, la composición está libre de un polímero que aumenta la viscosidad de un excipiente o composición líquida. En algunas realizaciones, el polímero es un polímero soluble en agua. Ejemplos de un polímero soluble en agua incluyen, en forma no taxativa, un éter de celulosa (por ejemplo, hidroxipropil metilcelulosa), otros polímeros basados en celulosa (metilcelulosa, hidroxietil celulosa, hidroxipropil celulosa, etc.), povidona, alcohol polivinílico, gomas (por ejemplo goma xantana), polietilenglicol (PEG), óxido de polietileno (PEO), ácido hialurónico (y derivados y sales de él), carragenina, dextrano, y poloxámero. En algunas realizaciones, el éter de celulosa es hidroxipropil metilcelulosa (HPMC). Por lo tanto, en algunas realizaciones, la composición está libre de HPMC. En algunas realizaciones, la viscosidad de la composición intranasal no es mayor que la viscosidad del agua.

En algunas realizaciones, la viscosidad de la composición intranasal es no mayor de 110%, no mayor de 120%, no mayor de 130%, no mayor de 140%, no mayor de 150%, no mayor de 160%, no

mayor de 170%, no mayor de 180%, no mayor de 190%, o no mayor de 200% de la viscosidad del agua. En algunas realizaciones, la viscosidad de la formulación intranasal es 1 mPa*s, 2 mPa*s, 3 mPa*s, 4 mPa*s, o 5 mPa*s. En algunas realizaciones, la viscosidad de la formulación intranasal es menor de 1 mPa*s, 2 mPa*s, 3 mPa*s, 4 mPa*s, o 5 mPa*s. En algunas realizaciones, la viscosidad de la formulación intranasal es de 1 mPa*s a 2 mPa*s, de 1 mPa*s a 3 mPa*s, de 1 mPa*s a 4 mPa*s, de 1 mPa*s a 5 mPa*s, de 1,5 mPa*s a 2,5 mPa*s, de 2 mPa*s a 3 mPa*s, de 2 mPa*s a 4 mPa*s, o de 2 mPa*s a 5 mPa*s.

La viscosidad de una composición se puede calcular mediante diversos métodos. La viscosidad también se puede medir directamente usando diversas técnicas. Por ejemplo, la viscosidad de una composición se puede calcular de acuerdo con la siguiente ecuación. La ecuación expresa la relación aproximada ilustrada entre la viscosidad y la concentración del polímero es $\eta^{1/8} = (C * \alpha) + 1$, donde η es la viscosidad de la solución en milipascuales-segundos, C es la concentración del polímero en la solución (expresada en porcentaje), y α es una constante específica del peso molecular. Por ejemplo, el valor de α se puede calcular mediante sustitución y luego se puede usar para calcular la viscosidad aproximada a la concentración deseada.

También se sabe en el arte que los compuestos y las composiciones que los comprenden pueden estar contenidos en formulaciones con diluyentes, rellenos, desintegradores, ligantes, lubricantes, surfactantes, excipientes hidrófobos, excipientes solubles en agua, emulsionantes, tampones, humectantes, hidratantes, solubilizantes, conservantes farmacéuticamente aceptables y similares. En algunas realizaciones, los compuestos y las composiciones que los comprenden pueden estar contenidos en formulaciones que no comprenden diluyentes, rellenos, desintegradores, ligantes, lubricantes, surfactantes, excipientes hidrófobos, excipientes solubles en agua, emulsionantes, tampones, humectantes, hidratantes, solubilizantes, conservantes farmacéuticamente aceptables y similares. En algunas realizaciones, los compuestos y las composiciones que los comprenden pueden estar contenidos en formulaciones que no comprenden un surfactante. Las composiciones farmacéuticas también pueden comprender portadores o excipientes de fase sólida o de gel adecuados. Además de otros excipientes descritos en la presente, ejemplos de tales portadores o excipientes incluyen, en forma no taxativa, carbonato de calcio, fosfato de calcio, diversos azúcares, almidones, derivados de celulosa, gelatina, y polímeros tales como polietilenglicoles. En algunas realizaciones, los compuestos descritos en la presente se pueden usar con agentes que incluyen, en forma no taxativa,

analgésicos tópicos (por ejemplo, lidocaína), dispositivos de barrera (por ejemplo, GelClair), o enjuagues (por ejemplo, Caphosol).

En algunas realizaciones, cuando se administran a un humano, los compuestos pueden ser estériles. El agua puede ser un portador adecuado cuando el compuesto se administra por vía intranasal. Las soluciones salinas y las soluciones en dextrano y glicerol también se pueden emplear como portadores líquidos. Los portadores farmacéuticos adecuados también incluyen excipientes tales como, en forma no taxativa, almidón, glucosa, lactosa, sacarosa, gelatina, malta, arroz, harina, tiza, gel de sílice, estearato de sodio, monoestearato de glicerol, talco, cloruro de sodio, leche descremada deshidratada, glicerol, propileno, glicol, agua, etanol y similares. Las presentes composiciones, si se desea, también pueden contener cantidades menores de agentes humectantes o emulsionantes, o agentes tampones del pH.

Las composiciones descritas en la presente pueden tomar la forma de una solución, suspensión, emulsión, polvo, formulación de liberación sostenida, aerosol, aspersión, o cualquier otra forma adecuada para los usos descritos en la presente. Ejemplos de portadores farmacéuticos adecuados se

describen en Ciencias Farmacéuticas de Remington, A.R. Gennaro (Editor) Mack Publishing Co.

En algunas realizaciones, los compuestos se formulan de acuerdo con procedimientos de rutina como una composición farmacéutica adaptada para la administración a humanos. En algunas realizaciones, los compuestos son soluciones en un tampón acuoso isotónico estéril y, por ejemplo, con las demás composiciones descritas en la presente. Cuando sea necesario, las composiciones también pueden incluir un agente solubilizante. Las composiciones opcionalmente pueden incluir un anestésico local tal como lidocaína para aliviar el dolor en el lugar de la administración que se puede deber, por ejemplo, a la irritación provocada por la composición.

En algunas realizaciones, la presente invención también proporciona paquetes o estuches farmacéuticos que comprenden uno o más contenedores que contienen uno o más compuestos descritos en la presente. Opcionalmente asociado a dicho contenedor puede haber un aviso en la forma prescrita por la repartición gubernamental que regula la fabricación, el uso o la venta de productos farmacéuticos o biológicos, cuyo aviso refleje la aprobación por la repartición, de la fabricación, el uso o la venta para administración humana para tratar una condición, enfermedad o trastorno descritos en la presente. En

algunas realizaciones, el estuche contiene más de un compuesto descrito en la presente. En algunas realizaciones, el estuche comprende un compuesto descrito en la presente en una sola forma de dosificación, tal como una sola dosis dentro de un dispositivo que se puede administrar intranasal tal como un dispositivo de dosis medida que administra una aspersion o un polvo a una cavidad nasal.

En algunas realizaciones, los componentes descritos en la presente se proveen por separado o mezclados juntos en una forma de dosificación unitaria, por ejemplo, los componentes se pueden combinar para crear una formulación intranasal. Ejemplos de fabricación de la formulación se describen en la presente y se pueden modificar para producir cualquier formulación intranasal adecuada.

Las composiciones farmacéuticas pueden estar en la forma de dosificación unitaria. En tal forma, la composición se puede dividir en dosis unitarias que contienen cantidades apropiadas del componente activo. La forma de dosificación unitaria puede ser una preparación empaquetada, el paquete contiene cantidades discretas de la preparación. La forma de dosificación puede ser cualquier forma que incluya, en forma no taxativa, la forma descrita en la presente.

En algunas realizaciones, una composición de la presente invención está en la forma de un líquido en donde el agente activo está presente en solución, en suspensión, como una emulsión, o como una solución/suspensión. En algunas realizaciones, la composición líquida está en la forma de un gel. En otras realizaciones, la composición líquida es acuosa. En otras realizaciones, la composición está en la forma de un ungüento. La composición líquida también puede ser una aspersión.

El excipiente líquido se refiere al líquido en el cual la dexmedetomidina se suspende o se disuelve. Ejemplos de los excipientes líquidos incluyen, en forma no taxativa, agua, solución salina, una solución acuosa, DMSO y similares.

En algunas realizaciones, la composición farmacéutica comprende, además de dexmedetomidina, lo siguiente (todo basado en el % p/p): 0,245% de citrato de sodio anhidro, 0,01% de ácido cítrico anhidro, 0,7% de cloruro de sodio, 99,045% de agua purificada, a un pH inicial de 6,31 ajustado a un pH final de 6,78 con 2N hidróxido de sodio. En algunas realizaciones, la composición farmacéutica comprende, además de dexmedetomidina, lo siguiente (todo basado en % p/p): 0,245% de citrato de sodio anhidro, 0,01% de ácido cítrico anhidro, 0,1% de Methocel E4M, 0,7% de cloruro de sodio,

98,945% de agua purificada, a un pH inicial de 6,36 ajustado a un pH final de 6,83 con 2N hidróxido de sodio. En algunas realizaciones, la composición farmacéutica comprende, además de dexmedetomidina, lo siguiente (todo basado en el % p/p): 0,193% de fosfato de sodio monobásico (monohidrato), 0,162% de fosfato de sodio dibásico (heptahidrato), 0,7% de cloruro de sodio, 98,946% de agua purificada, a un pH inicial de 6,37 ajustado a un pH final de 6,53 con 2N hidróxido de sodio. En algunas realizaciones, la composición farmacéutica comprende, además de dexmedetomidina, lo siguiente (todo basado en el % p/p): 0,193% fosfato de sodio monobásico (monohidrato), 0,162% de fosfato de sodio dibásico (heptahidrato), 0,75% de cloruro de sodio, 98,896% de agua purificada, a un pH inicial de 6,37 ajustado a un pH final de 6,53 con 2N hidróxido de sodio. En algunas realizaciones, la composición farmacéutica comprende, además de dexmedetomidina, lo siguiente (todo basado en el % p/p): 0,193% de fosfato de sodio monobásico (monohidrato), 0,162% de fosfato de sodio dibásico (heptahidrato), 0,25% de alcohol de feniletilo, 0,68% de cloruro de sodio, 98,616% de agua purificada, a un pH inicial de 6,15 ajustado a un pH final de 6,51 con 2N hidróxido de sodio. En algunas realizaciones, la composición farmacéutica comprende, además de dexmedetomidina, lo siguiente (todo basado en % p/p): 0,226% de citrato de sodio anhidro, 0,024% de ácido cítrico anhidro, 0,25% de alcohol de feniletilo, 0,76% de cloruro de

sodio, 98,64% de agua purificada, a un pH inicial de 5,68 ajustado a un pH final de 6,04 con 2N hidróxido de sodio.

Las composiciones que comprenden dexmedetomidina que se describen en la presente son estables. Para un 0,035% de formulación de aspersion intranasal de clorhidrato de dexmedetomidina, por ejemplo, la estabilidad es de por lo menos 3 meses, por lo menos 6 meses, por lo menos 9 meses, o por lo menos un año en donde las condiciones de almacenamiento son 25°C al 60% de humedad relativa, y por lo menos 1 mes, por lo menos 3 meses, por lo menos 6 meses en donde las condiciones de almacenamiento son 40°C al 75% de humedad relativa.

Cuando dexmedetomidina, o una sal farmacéuticamente aceptable de ella, se usan en cualquier método o dispositivo descritos en la presente, se entiende que todos y cada uno de los metabolitos de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, también se pueden usar en forma similar.

Para que la invención revelada en la presente se pueda comprender eficientemente, a continuación se dan ejemplos. Se debe entender que estos ejemplos tienen propósitos de ejemplificación solamente y que no se debe interpretar que limitan la invención de ninguna manera.

Ejemplos

Ejemplo 1: Preparación de Formulaciones intranasales

A un contenedor, se agregó agua purificada, USP. Con el agua, se mezclaron ácido cítrico anhidro, dihidrato de citrato de sodio, cloruro de sodio, alcohol de feniletilo y EDTA disódico. El pH de la solución se modificó, si fuera necesario, de manera que estuviera en la gama de 6,0 a 6,5. Con la mezcla continua, se agregó HCl de dexmedetomidina hasta que se disolvió. Se agregó agua para ajustar el HCl de dexmedetomidina a una concentración seleccionada final.

Ejemplo 2: Formulaciones Intranasales de Dexmedetomidina

El suministro nasal de HCl de dexmedetomidina (DEX) se evaluó desde aspersiones acuosas para proporcionar perfiles farmacocinéticos que proporcionan analgesia sin sedación importante. La vía de administración nasal suele ser deseada por los pacientes que padecen dolor que no pueden o no desean tolerar el tratamiento por una vía oral (por ejemplo, bucal, sublingual, deglución), por una vía rectal (por ejemplo, espumas, supositorios, etc), o una vía de inyección. Además de las aspersiones nasales acuosas desarrolladas inicialmente para la evaluación de DEX administrada por vía intranasal, las

formulaciones se pueden modificar para incluir polvos secos, suspensiones, y/o vapores como sería evidente a partir de la descripción contenida en la presente.

Un tamizado inicial de composiciones nasales acuosas de DEX administradas como gotas nasales se evaluó en un modelo canino. La influencia de la especie y la viscosidad del tampón se evaluaron en las siguientes composiciones básicas.

Componente	Primera Composición de Base de Placebo (% p/p)		
	Formulación 1	Formulación 2	Formulación 3
Citrato de sodio, anhidro	0,245	0,245	--
Ácido cítrico, Anhidro	0,010	0,010	--
Methocel E4M	--	0,100	--
Fosfato de sodio Monobásico, Monohidrato	--	--	0,193
Fosfato de sodio Dibásico, Heptahidrato	--	--	0,162
Cloruro de sodio	0,700	0,700	0,700
Agua purificada	99,045	98,945	98,946
Total	100,000	100,000	100,000

pH inicial	6,31	6,36	6,37
pH final ¹	6,78	6,83	6,53
¹ Ajustado con 2N Hidróxido de sodio.			

DEX se disolvió en las Composiciones de Base de Placebo para preparar soluciones de Formulaciones que suministrarían 50 µg DEX en 100 µL de volumen. Las composiciones de DEX se expresan de la siguiente manera:

Componente	Composición de Gotas Nasales de DEX (% p/v)		
	Formulación 1-DEX	Formulación 2-DEX	Formulación 3-DEX
HCl de Dexmedetomidina	0,059	0,059	0,059
Formulación 1	99,941	--	--
Formulación 2	--	99,941	--
Formulación 3	--	--	99,941
Total	100,000	100,000	100,000

La densidad de la composición de gotas nasales de DEX tenía aproximadamente 1 g/mL a temperatura ambiente y se dejó que el peso y el volumen se usaran indistintamente. Las tres Composiciones de Gotas Nasales de DEX se administraron a perros. Sorpresivamente, las composiciones sin éter de celulosa, que es un agente mejorador de la viscosidad, tal

como la Formulaci3n 1-Dex y la Formulaci3n 3-Dex, proporcionaron niveles en el plasma importantes en menos de 15 minutos posteriores a la administraci3n. Tambi3n sorpresivamente, la Formulaci3n 2-Dex, que contenía 0,1% de Methocel E4M y tenía la viscosidad máxima de la soluci3n, derivó en niveles en el plasma despreciables de DEX, que indican que la viscosidad aumentada de la soluci3n disminuy3 la efectividad de DEX administrada por vía intranasal. Este resultado fue inesperado.

La influencia de otros aditivos de formulaciones adicionales se investig3 tambi3n a partir de la soluci3n de DEX acuosa que se administr3 como rocíos finos desde bombas de aspersi3n acuosa de varias dosis. Se prepararon las siguientes composiciones de base de placebo.

Componente	Segunda Composici3n de Base de Placebo (% p/p)		
	Formulaci3n 4	Formulaci3n 5	Formulaci3n 6
Citrato de sodio, Anhidro	--	--	0,226
Ácido cítrico, Anhidro	--	--	0,024
Fosfato de Sodio	0,193	0,193	--

Monobásico, Monohidrato			
Fosfato de Sodio Dibásico, Heptahidrato	0,162	0,162	--
Alcohol de Feniletilo	--	0,250	0,250
Dihidrato de Edetato Disódico	--	0,100	0,100
Cloruro de Sodio	0,750	0,680	0,760
Agua Purificada	98,896	98,616	98,640
Total	100,000	100,000	100,000
pH inicial	6,37	6,15	5,68
pH final ¹	6,53	6,51	6,04
¹ Ajustado con 2N Hidróxido de sodio.			

DEX se disolvió en el segundo grupo de Composiciones de Base de Placebo para preparar soluciones que administrarían 50 µg DEX en 100 µL volumen. Las composiciones de DEX se expresan de la siguiente manera.

Componente	Composición de Aspersión Nasal de DEX (% p/v)		
	Formulación 4-Dex	Formulación 5-Dex	Formulación 6-Dex
HCl de Dexmedetomidina	0,059	0,059	0,059
Formulación 4	99,941	--	--

Formulación 5	--	99,941	--
Formulación 6	--	--	99,941
Total	100,000	100,000	100,000
Osmolaridad Calculada (mOsm/kg)	288	368	306

La densidad de las composiciones de aspersión nasal de DEX fue aproximadamente 1 g/mL a temperatura ambiente y se dejó que el peso y el volumen se usaran indistintamente. Las tres composiciones de aspersión nasal de DEX se administraron a perros usando una bomba nasal activada manualmente. Los resultados del estudio canino indicaron niveles en plasma medibles tan pronto como 5 minutos y reducción de niveles en plasma de acuerdo con Formulación 4-DEX > Formulación 5-DEX > Formulación 6-DEX.

Se preparó otra composición de base de placebo como se define a continuación.

Componentw	Tercera Composición de Base de Placebo (% w/w)
	Formulación 7
Citrato de Sodio, Anhidro	0,230
Ácido Cítrico, Anhidro	0,020
Alcohol de Feniletilo	0,250

Dihidrato de Edetato de Disodio	0,100
Cloruro de sodio	0,760
Agua purificada	98,640
Total	100,000
pH inicial	5,79
pH final ¹	6,27
¹ Ajustado con 2N Hidróxido de sodio.	

DEX se disolvió en la tercera Composición de Base de Placebo para preparar una solución que suministraría 25 µg DEX en 100 µL de volumen. La composición de DEX se expresa de la siguiente manera.

Componente	Composición de Aspersión Nasal de DEX (% p/v)
	Formulación 7-Dex
HCl de Dexmedetomidina	0,0295
Formulación 7	99,9705
Total	100,0000
pH final	6,20

La densidad de la composición de aspersión nasal de DEX fue aproximadamente 1 g/mL a temperatura ambiente y se dejó que el

peso y el volumen se usaran indistintamente. Las composiciones nasales de DEX se desarrollaron como una solución acuosa que podría administrarse como gotas nasales o como un rocío fino desde el dispositivo de aspersión nasal. La composición nasal de DEX contenía mínimamente DEX disuelta en agua purificada a una concentración adecuada para suministrar la dosis de DEX deseada en 25 μL a 200 μL . Los volúmenes menores de 25 μL pueden derivar en la administración variable mientras que los volúmenes de las dosis mayores de 200 μL pueden derivar en un exceso que escapa desde la cavidad nasal. Las composiciones nasales acuosas opcionalmente pueden contener materiales adicionales para facilitar el suministro intranasal de DEX.

Ejemplo 3: Determinación del Tamaño de las Partículas de las Gotitas

El desempeño de la bomba de aspersión in vitro del Producto Farmacológico (DEX-IN.02 50 μg API/100 μL de Aspersión Intranasal y DEX-IN.03 25 μg API/50 μL de Aspersión Intranasal) y Placebo (DEX-IN.02P 100 μL de Aspersión Intranasal) se basó en la distribución de tamaños de las gotitas como se midió mediante difracción láser usando un Malvern Spraytec. El Malvern Spraytec funciona basado en el principio de difracción laser y es una técnica usada comúnmente para caracterizar distribuciones de tamaños de

gotitas desde aspersiones nasales. La distribución de tamaños de las gotitas se caracterizó mediante la siguiente métrica: distribución de volumen (Dv10, Dv50, Dv90), Span y porcentaje (%) menor de 10 μm según la Guía de CMC de la FDA para Aspersiones Nasales (2002) y el Proyecto de Guía de la FDA para la Industria: Estudios de Biodisponibilidad y Bioequivalencia para Aerosoles Nasales y Aspersiones Nasales para la Acción Local, abril de 2003.

Ejemplo 4: Estudio de Farmacocinética de Formulaciones de Dexmedetomidina Después de la Administración Intranasal o Sublingual en Perros

Uno de los objetivos del presente estudio fue comparar la farmacocinética de varias formulaciones experimentales de dexmedetomidina con la farmacocinética de una formulación comercial de dexmedetomidina cuando se administra por vía intranasal o sublingual en los fármacos. Para cada evento de dosificación, se dosificó a cinco perros macho por vía intranasal o sublingual con 50 μg de base libre de dexmedetomidina (equivalente a 59 μg de HCl de dexmedetomidina) en 100 μL de la formulación, excepto por la Formulación 7-Dex, donde se dosificó a los perros con 25 μg de base libre de dexmedetomidina (equivalente a 29,5 μg de HCl de

dexmedetomidina) en 100 μL , y la formulación de PRECEDEX[®], que contenía 50 μg de base de dexmedetomidina equivalente en 500 μL de solución. La dosificación se realiza en 10 eventos de dosificación en tres segmentos con las formulaciones, con un intervalo mínimo de 2 días entre los eventos de dosificación, como se muestra en la siguiente tabla:

Segmento	Evento de Dosificación	Formulación	Vía de dosis
1	1	Formulación 1-Dex*	Intranasal
	2	Formulación 3-Dex*	Intranasal
	3	Formulación 2-Dex*	Intranasal
	4	PRECEDEX [®] *	Intranasal
2	5	Formulación 4-Dex*	Intranasal
	6	Formulación 5-Dex*	Intranasal
	7	Formulación 6-Dex*	Intranasal
3	8**	Formulación 6-Dex*	Intranasal
	9	Formulación 7-Dex***	Intranasal
	10	DEX-SL.01*	Sublingual

*Dosis = 50 μg de base libre de dexmedetomidina (equivalente a 59 μg de HCl de dexmedetomidina).

**Nueva dosis de Formulación 6-Dex usando un aspersor nuevo.

***Dosis = 25 μg de base libre de dexmedetomidina (equivalente a 29,5 μg de HCl de dexmedetomidina).

Los Parámetros farmacocinéticos promedio para dexmedetomidina se resumen a continuación

Formulación (Evento de Dosificación)	T _{max} (h)	t _{1/2} (h)	C _{max} (ng/ml)	AUC _{última} (hr*ng/ml)	AUC _{0-∞} (hr*ng/ml)
Formulación 1-DEX (1)	0,7	0,93	8,88	7,72	7,18
Formulación 2-DEX (2)	0,7	NC1	16,9	12,3	NC1
Formulación 3-DEX (3)	0,42	0,43	1,30	1,10	1,16
PRECEDEX [®] (4)	0,38	0,52	12,2	6,68	6,69
Formulación 4-DEX (5)	0,4	0,47	1,35	1,12	0,984
Formulación 5-DEX (6)	0,80	0,50	2,46	2,44	2,62
Formulación 6-DEX (7)	0,42	0,56	9,05	6,57	2,18
Formulación 6-DEX (8) *	0,27	0,79	5,92	3,61	6,06
Formulación 7-DEX (9)	0,32	0,63	1,33	1,18	1,09
DEX-SL.01 (10)	0,60	1,72	2,15	2,27	4,75

NC1 = El valor no se pudo calcular por WinNonlin debido a puntos de datos insuficientes para la fase de eliminación.

*Nueva dosis de la Formulación 6-DEX usando un aspersor nuevo.

Para la administración intranasal (eventos de dosis 1 a 9), $T_{\max}$ y la semivida de eliminación para dexmedetomidina fueron similares entre la formulación de PRECEDEX[®] y las dosis experimentales 1-3 y 5-9. El $T_{\max}$ medio para dexmedetomidina para la formulación de PRECEDEX[®] fue 0,38 hora, y el $T_{\max}$ promedio para dexmedetomidina para las formulaciones experimentales que se administraron por vía intranasal (dosis 1-3, 5-9) estuvo en la gama de 0,32 hora a 0,80 hora. La semivida de eliminación promedio para dexmedetomidina para la formulación de PRECEDEX[®] fue 0,52 hora, y la semivida de eliminación promedio para dexmedetomidina para las formulaciones experimentales que se administraron por vía intranasal (dosis 1-3, 5-9) estuvo en la gama de 0,43 hora a 0,93 hora. Para la administración sublingual (evento de dosificación 10, formulación de DEX-SL.01), el $T_{\max}$ promedio fue 0,60 hora similar al $T_{\max}$ obtenido después de la administración intranasal de PRECEDEX[®] y las dosis experimentales 1-9, mientras que la semivida de eliminación promedio para la formulación de DEX-SL.01 fue 1,72 hora, más prolongada que la semivida de eliminación obtenida después de

la administración intranasal de PRECEDEX[®] y las dosis experimentales 1-3 y 5-9.

Basado en $C_{\max}$ y $AUC_{\text{última}}$, la exposición de dexmedetomidina después de la administración intranasal fue la más alta para la formulación de la Formulación 3-DEX. La $C_{\max}$ promedio para la formulación de la Formulación 3-DEX fue aproximadamente el 140% de la $C_{\max}$ promedio para PRECEDEX[®], mientras que la $AUC_{\text{última}}$ para la formulación de la Formulación 3-DEX fue aproximadamente 180% de la $AUC_{\text{última}}$ promedio para PRECEDEX[®]. La $AUC_{\text{última}}$ promedio para las formulaciones Formulación 6-Dex y Formulación 1-DEX fue similar a aquella de PRECEDEX[®], mientras que la $C_{\max}$ promedio para estas formulaciones fue 70% de la $C_{\max}$ promedio para PRECEDEX[®]. La $C_{\max}$ promedio y $AUC_{\text{última}}$ para todas las demás formulaciones experimentales dosificadas por vía intranasal fueron más bajas que aquella para PRECEDEX[®]. La exposición de dexmedetomidina después de la administración intranasal fue la más baja para las formulaciones de Formulación 2-DEX y Formulación 7-DEX. Sorpresivamente, la exposición de dexmedetomidina después de la administración sublingual de la formulación DEX-SL.01 fue sustancialmente más baja que para la administración intranasal de PRECEDEX[®]; la $C_{\max}$ promedio para la formulación de DEX-SL.01 fue 18% de la $C_{\max}$ promedio para PRECEDEX[®], y la $AUC_{\text{última}}$ promedio para la

formulación de DEX-SL.01 fue 34% de la AUC_{última} promedio para PRECEDEX®.

Formulación (Evento de Dosificación)	T _{max} (h)	t _{1/2} (h)	C _{max} (ng/mL)	AUC _{última} (hr*ng/m L)	AUC _{0-∞} (hr*ng/mL)
Formulación 1-DEX (1)	1,75	NC ¹	0,272	0,355	NC ¹
Formulación 2-DEX (2)	1,80	NC ¹	0,291	0,386	NC ¹
Formulación 3-DEX (3)	0,65	NC ¹	0,285	0,203	NC ¹
PRECEDEX® (4)	1,55	NC ¹	0,248	0,358	NC ¹
Formulación 4-DEX (5)	1,00	NC ¹	0,0847	0,111	NC ¹
Formulación 5-DEX (6)	1,35	1,28	0,116	0,169	0,233
Formulación 6-DEX (7)	0,90	NC ¹	0,221	0,319	NC ¹
Formulación 6-DEX (8) *	1,15	7,29	0,168	0,265	2,38
Formulación 7-DEX (9)	1,25	8,70	0,0999	0,109	1,15
DEX-SL.01 (10)	1,80	NC ¹	0152	0,204	NC ¹

NC1 = El valor no se pudo calcular por WinNonlin debido a puntos de datos insuficientes para la fase de eliminación.

*Nueva dosis de la Formulación 6-Dex usando un aspersor.

Para la administración intranasal (eventos de dosis 1 a 9), el $T_{\max}$ para esta tabla fue generalmente similar entre la formulación de PRECEDEX® y las dosis experimentales 1-3 y 5-9. El $T_{\max}$ promedio para la formulación de PRECEDEX® fue 1,55 hora, y el $T_{\max}$ promedio para las formulaciones experimentales administradas por vía intranasal (dosis 1-3, 5-9) estuvo en la gama de 0,65 hora a 1,80 hora. Para la mayor parte de las formulaciones, la semivida de eliminación no se calculó o no se informó debido a los puntos de datos insuficientes para la fase de eliminación o a la mala bondad de ajuste ($R^2 < 0,8$) para la fase de eliminación. Cuando fue calculable, la semivida estuvo en la gama de 1,3 hora a 8,7 horas. Para la administración sublingual (evento de dosificación 10, formulación DEX-SL.01), el $T_{\max}$ promedio fue 1,80 hora, similar al $T_{\max}$ obtenido después de la administración intranasal de PRECEDEX® y las dosis experimentales 1-3 y 5-9.

Basado en $C_{\max}$ y $AUC_{\text{última}}$, la exposición después de la administración intranasal fue la más alta para la formulación de Formulación 3-Dex. La $C_{\max}$ promedio para la formulación de Formulación 3-Dex fue aproximadamente 117% de la $C_{\max}$ promedio

para PRECEDEX[®], mientras que la AUC_{última} promedio para la formulación de Formulación 3-Dex fue aproximadamente 108% de la AUC_{última} promedio para PRECEDEX[®]. La C_{max} promedio AUC_{última} para todas las demás formulaciones experimentales administradas por vía intranasal fueron similares a aquella para PRECEDEX[®], excepto por la Formulación 4-DEX y la Formulación 7-DEX (la cantidad de dexmedetomidina dosificada con la Formulación 7-DEX fue la mitad de aquella de las demás formulaciones). La exposición después de la administración sublingual de la formulación DEX-SL.01 fue más baja que para la administración intranasal de PRECEDEX[®]; la C_{max} promedio para la formulación de DEX-SL.01 fue aproximadamente 61% de la C_{max} promedio para PRECEDEX[®], y la AUC_{última} promedio para la formulación de DEX-SL.01 fue aproximadamente 57% de la AUC_{última} promedio para PRECEDEX[®].

Los resultados presentados en la presente muestran sorpresivamente que cuando se compara con la formulación DEX-SL.01 administrada por vía sublingual, la absorción ocurre más rápidamente por la vía nasal. En consecuencia, la administración intranasal de DEX sorpresivamente puede proporcionar un alivio del dolor y/o una prevención del dolor más rápidamente comparada con la sublingual o los métodos para administrar DEX a través de la mucosa oral, sin sedación

importante y con escaso o ningún efecto sobre la presión sanguínea.

Dosificación

Las dosis 1-3 se administraron por vía intranasal con una micropipeta la cabeza invertida para la dosificación. La dosificación fue 50 μg de base libre de dexmedetomidina (equivalente a 59 μg de HCl de dexmedetomidina) en 100 μL de formulación. La dosis 4 se administró usando un frasco de aspersión nasal comercial. Se invirtió la cabeza durante 30 segundos a 1 minuto después de la administración de la aspersión. El frasco de aspersión administra 100 μL por cada aspersión y se necesitaron cinco aspersiones para suministrar la dosificación de 50 μg de base libre de dexmedetomidina (equivalente a 59 μg de HCl de dexmedetomidina). El frasco de aspersión se cebó en un área remota de la dosificación antes de la administración de la dosis para impedir la posible contaminación cruzada. Además, la dosificación se realizó en un área remota desde la extracción de sangre para prevenir la posible contaminación de las muestras de sangre con el artículo de ensayo de aerosol.

Las dosis 5-7 se administraron usando un frasco nasal comercial. Las dosis de aspersión se administraron con la cabeza hacia arriba. La cabeza se invirtió durante 30 segundos a 1 minuto después de la administración de aspersión. El frasco de aspersión administra 100 μL por cada aspersión y se necesitó una aspersión para suministrar la dosificación de 50 μg de base libre de dexmedetomidina (equivalente a 59 μg de HCl de dexmedetomidina). El frasco de aspersión se cebó usando cinco accionamientos de aspersión en un área remota desde la dosificación antes de la administración de la dosis para prevenir la posible contaminación cruzada. Además, la dosificación se prefirió en un área remota desde la recolección de sangre para prevenir la posible contaminación de las muestras de sangre con el artículo de ensayo de aerosol.

La dosis 8 se administró usando un frasco de aspersión comercial. Las dosis de aspersión se administraron con la cabeza hacia arriba. Se invirtió la cabeza durante 30 segundos a 1 minuto después de la administración de la aspersión. El frasco de aspersión administró 100 μL por cada aspersión y se necesitó una aspersión para suministrar la dosificación de 50 μg de base libre de dexmedetomidina (equivalente a 59 μg de HCl de dexmedetomidina). El frasco de aspersión se cebó usando

cinco accionamientos de aspersión en un área remota desde la dosificación antes de la administración de la dosis para prevenir la posible contaminación cruzada. Además, la dosificación se realizó en un área remota desde la extracción de sangre para prevenir la posible contaminación de las muestras de sangre con el artículo de ensayo de aerosol.

La dosis 9 se administró usando un frasco de aspersión nasal comercial. Las dosis de aspersión se administraron con la cabeza hacia arriba. Se invirtió la cabeza durante 30 segundos a 1 minuto después de la administración de aspersión. El frasco de aspersión administró 100 μL por cada aspersión y se necesitó una aspersión para suministrar la dosificación de 25 μg de base libre de dexmedetomidina (equivalente a 29,5 μg de HCl de dexmedetomidina). El frasco de aspersión se cebó usando cinco accionamientos de aspersión en un área remota desde la dosificación antes de la administración de la dosis para prevenir la posible contaminación cruzada. Además, la dosificación se realizó en un área remota desde la extracción de sangre para prevenir la posible contaminación de las muestras de sangre con el artículo de ensayo de aerosol.

La dosis 10 se administró por vía sublingual con una micropipeta. La dosificación fue 50 μg de base libre de

dexmedetomidina (equivalente a 59 μg de HCl de dexmedetomidina) en 100 μL la formulación.

Para la administración intranasal, las formulaciones se administraron por vía intranasal. Después de la dosificación, los orificios de nasales del perro se mantuvieron cerrados y se invirtió la cabeza durante aproximadamente 1 minuto. Cada evento de dosificación estuvo separado por un mínimo de dos días para permitir un lavado apropiado.

Después de la dosificación, se extrajeron muestras de sangre y se ensayaron por los niveles de DEX en plasma.

Ejemplo 5: Farmacocinética de Dexmedetomidina administrada por vía intranasal en humanos

Se usaron cuatro formulaciones diferentes de DEX. PRECEDEX® (Tratamiento A) a una dosis de 25 μg que se administró por vía intranasal durante 10 minutos y 3 dosificaciones o formulaciones intranasales diferentes. La Formulación B (35 μg administrados en 100 μl en un orificio nasal a través de 1 aspersión); la Formulación C (35 μg administrada totalmente a través de 2 orificios nasales); y la Formulación D (17,5 μg

administrados en 50 μl en un orificio nasal a través de 1 aspersion).).

	Tratamiento A Precedex IV 25 μg	Tratamiento B DEX-IN.01 35 μg 100 μl en un orificio nasal	Tratamiento C DEX-IN.01 35 μg 50 μl en cada orificio nasal	Tratamiento D DEX-IN.01 17.5 μg 50 μl en un orificio nasal
C_{max} (ng/ml)	0,61 (58,7%)	0,17 (21,7%)	0,14 (34,0%)	0,08 (31,9%)
AUC_{0-24} (h ng/ml)	0,71 (27,7%)	0,83 (23,6%)	0,75 (22,5%)	0,38 (16,6%)
T_{max} (horas)	0,17 (0,17, 0,25)	1,00 (0,33, 4,00) [†]	1,25 (0,33, 4,00)	1,13 (0,33, 2,00)
$t_{1/2}$ (horas)	2,04 $\pm$ 0,200 [‡]	2,43 $\pm$ 0,825 [§]	2,64 $\pm$ 0,777 [§]	1,60 (NA) [¥]

[1] Promedio geométrico (CV%) para C_{max} y AUC_{0-24} mediana (min, max) para T_{max} ; promedio aritmético $\pm$ SD para $t_{1/2}$; [†] n=11; [‡] n=10; [§] n=4; [¥] n=1

La farmacocinética observada mostró el resultado sorpresivo de que la administración de la dosis en una sola aspersion a un solo orificio nasal (Tratamiento B) proporcionó una mejor C_{max} y un T_{max} más corto comparado con la misma dosis total administrada en dos orificios nasales a través de 2 aspersiones (la mitad de la dosis se administra en cada

orificio nasal). El resultado no pudo haber sido predicho y es el opuesto de aquel que habría esperado un experto en el arte, en parte, debido a una comparación de superficies. Las concentraciones en plasma promedio producidas por el Tratamiento B alcanzaron una concentración deseada mínima (0,1 ng/ml) dentro de los 20 minutos después de la dosificación. Este resultado sorpresivo de la administración a un solo orificio nasal puede facilitar el inicio más rápido de la actividad (por ejemplo, el alivio del dolor) en poblaciones de pacientes blanco. La velocidad de absorción observada en el Tratamiento B fue más rápida que las formulaciones o vías de administración estudiadas previamente. Esta absorción más rápida inesperada puede permitir el inicio de la fase de los efectos analgésicos. De hecho, los efectos analgésicos pueden comenzar en menos de 20 minutos. Las concentraciones en plasma logradas con la administración intranasal de 17,5 y 35 µg se proporcionan en la Figura 1.

Dosificación

Se administró a voluntarios sanos la dosis seleccionada por vía intranasal o, si estaba indicado, por otra vía de administración. Se administró a un solo orificio nasal por vez tapando con un dedo el orificio nasal sin tratar. Se

extrajeran muestras de sangre y se midieron las concentraciones de DEX como se indicó.

Ejemplo 6: Evaluación de Varias Dosis, de Dos Períodos, de Marcador Abierto de la Seguridad, Tolerabilidad y Farmacocinética de Dexmedetomidina Intranasal en Voluntarios Sanos

El principal objetivo de este estudio fue evaluar el perfil farmacocinético de varias dosis de dexmedetomidina intranasal en sujetos masculinos y femeninos sanos. Los objetivos secundarios de este estudio fueron evaluar la seguridad y la tolerabilidad de la dexmedetomidina intranasal en voluntarios sanos.

Metodología

Éste fue un estudio de dosis repetida, de dos períodos, de marcador abierto, de Fase 1, en sujetos sanos para investigar la seguridad, la tolerabilidad y la farmacocinética de dexmedetomidina intranasal. Se planificó y se inscribió a un total de 12 sujetos (6 hombres y 6 mujeres). Se tamizó a sujetos sanos de edades de entre 18 y 50 años, inclusive, para la participación en un sitio de estudio en los Estados Unidos de América dentro de 28 días antes de la administración del

fármaco del estudio. Se realizaron historia clínica, exámenes físicos, análisis de laboratorio de línea base, electrocardiograma (ECG) de 12 derivaciones, análisis de embarazo, medición de signos vitales, y consentimiento informado durante la visita de tamizado.

Todas las dosis del estudio fueron una dosis de 35 µg de DEX-IN.01 administrada como una sola aspersión de 100 µL en el orificio nasal izquierdo. DEX-IN.01 contenía 35 µg de dexmedetomidina en cada 100 µL de solución, así como excipientes que incluyen: ácido cítrico, citrato de sodio, cloruro de sodio, alcohol de feniletilo, EDTA disódico y agua purificada. Las dosis de DEX-IN.01 utilizaron una tobera de aspersión de 100 µL para la administración en el orificio nasal de acuerdo con la asignación del tratamiento.

Durante el Período 1, los sujetos recibieron dos dosis del medicamento del estudio, separadas por seis horas. Durante el Período 2, los participantes del estudio recibieron siete dosis del medicamento del estudio administrado en intervalos de seis horas. Los Períodos de Estudio estuvieron separados por no menos de 24 horas entre la última dosis del Período 1 y la primera dosis del Período 2.

Durante el Período 1, se confinó a los sujetos desde la noche anterior a la dosificación (Día -1) hasta aproximadamente 18 horas después de la Dosis 2 (Día 2). Durante el Período 2, se aisló a los sujetos desde la noche anterior a la dosificación (Día -1) hasta aproximadamente 24 horas después de la última dosis del estudio (Día 3). Mientras estuvieron aislados, los sujetos recibieron una dieta diaria estandarizada.

Se extrajeron muestras de sangre en serie a intervalos definidos durante cada período del estudio para evaluar las propiedades farmacocinéticas de la dexmedetomidina administrada por vía intranasal y su metabolito. Se extrajo sangre entera en tubos de ensayo evacuados de 6 mL tratados con K₂EDTA.

Las muestras de plasma se debían extraer dentro de los ± 2 minutos del tiempo después de la dosis programado, hasta 60 minutos después de la dosificación, las muestras extraídas de 75 minutos a 6 horas después de la dosificación se pudieron extraer dentro de ± 5 minutos y las muestras extraídas a las 12 horas y más de 12 horas después de la dosificación pudieron ser extraídas dentro de ± 15 minutos del tiempo después de la dosis programado. Los tiempos reales debieron ser registrados para todos los eventos y cualquier desviación fuera de las

gamas específicas debió ser claramente documentada en los registros del estudio del sujeto.

Inmediatamente después de la extracción de cada muestra, el tubo de ensayo debió ser invertido suavemente y luego colocado en hielo húmedo. Dentro de los 20 minutos de la extracción, los tubos se centrifugaron a 2.000 x gravedad durante 10-15 minutos para separar las células del plasma. No se debió usar ninguna ayuda para la separación. Dos alícuotas ($\geq 0,5$ mL cada una) de plasma se transfirieron desde cada muestra con pipetas limpias y se colocaron en 2 tubos de almacenamiento de polipropileno en volúmenes iguales. Los tubos de almacenamiento se rotularon con la siguiente información: número de protocolo, número de sujeto, día del estudio y tiempo relativo de la muestra (por ejemplo, Período 1, Dosis 1, 10 minutos después de la dosificación) y la matriz biológica que se debía analizar (por ejemplo, el plasma). Dentro de los 60 minutos del horario de la extracción, se debían colocar los tubos de almacenamiento en congeladores a -20°C o menos; permanecieron dentro de los congeladores hasta el transporte para el análisis.

Para los análisis de la farmacocinética en el Período 1, se extrajeron hasta 12 muestras de sangre de cada sujeto antes y después de la administración de cada dosis de estudio. Éstas

se extrajeron antes de la dosis (Tiempo 0) y en los tiempos aproximados siguientes después de cada dosis del medicamento del estudio: 10, 20, 30, 45, 60, y 90 minutos y 2 y 4 horas; se extrajeron muestras de sangre adicionales a las 6, 12 y 18 horas después de la Dosis 2. En el Período 2, se extrajeron hasta 13 muestras de sangre de cada sujeto antes y después de la administración de la Dosis 1 y la Dosis 7. Éstas se extrajeron antes de la dosis (Tiempo 0) y en los siguientes tiempos aproximados después de la dosificación con el medicamento del estudio: 10, 20, 30, 45, 60, y 90 minutos y 2 y 4 horas; se extrajeron muestras de sangre adicionales a las 6, 12, 18 y 24 horas después de la Dosis 7. Las muestras de sangre para la Dosis 2 hasta la Dosis 6 se extrajeron antes de la dosis (Tiempo 0) solamente.

Una tabla de resumen de las visitas del estudio, y los puntos de tiempo asignados, se proporciona para el estudio completo, Período 1, Período 2 Dosis 1 y 7, y Período 2 Dosis 2 a 6 en la tabla siguiente.

Tabla: Resumen de Visitas del Estudio

Evento de Estudio	Período 1				Lavado	Período 2								
	Día -1	Día 1 (h)				Día -1	Día 1 (h)				Día 2 (h)			Día 3 (h)
		0	6	24			0	6	12	18	24	30	36	60
Aislamiento	<-----X- ----->					<----- X----- >								
Dosificación del Estudio		X	X				X	X	X	X	X	X	X	

Criterios de Inclusión:

Los sujetos cumplieron los siguientes criterios para participar en el estudio: 1) ser hombre o mujer de entre 18 y 50 años, inclusive; 2) para las mujeres potencialmente fértiles, ser quirúrgicamente estériles, usar anticonceptivos de doble barrera, practicar la abstinencia (deben aceptar usar anticonceptivos de doble barrera en el caso de actividad sexual) o usar un anticonceptivo insertable, inyectable, transdérmico u oral de combinación aprobado por la FDA hasta el final del estudio y tener resultados negativos en un análisis de embarazo en suero realizado antes de la administración del medicamento del estudio y tener resultados negativos en análisis de embarazo en orina posteriores (las

mujeres que son postmenopáusicas [que no tuvieron ninguna menstruación durante por lo menos dos años] también son elegibles para participar); 3) tener un índice de masa corporal (IMC) ≤ 32 kg/m² y un peso corporal de entre 50 y 95 kg, inclusive; y 4) poder comprender los procedimientos del estudio, aceptar participar en el programa del estudio y prestar voluntariamente el consentimiento informado por escrito.

Tratamientos administrados

El personal del estudio administró todas las dosis del medicamento del estudio de acuerdo con el programa del tratamiento. Las dosis de dexmedetomidina se administraron usando el dispositivo de administración intranasal en el orificio nasal izquierdo. Se administraron dosis en el orificio nasal asignado tapando el orificio nasal sin tratar con un dedo. Se mantuvo la cabeza del sujeto en una posición vertical con el aplicador de la aspersion insertado aproximadamente ½" dentro del orificio nasal. El sujeto inhaló a través del orificio nasal tratado cuando se oprimió la bomba y se suministró la dosis.

Después de la administración del medicamento del estudio, se permitió a los participantes moverse por las instalaciones del

estudio y realizar actividades no agotadoras. El investigador del estudio puede haber pedido a sujetos que permanezcan sentados durante un período de tiempo si se consideró inseguro que el sujeto se moviera por el sitio del estudio sin ser acompañado por personal del estudio.

Posteriormente se evaluaron las dosis en un estudio de una sola dosis en voluntarios sanos donde DEX-IN se evaluó usando una sola y dos administraciones de aspersion a dosis de 17,5 y 35 µg. Basado en la farmacocinética observada, se determinó que el nivel de dosis de 35 µg administrado en un solo orificio nasal sería el más apropiado para explorar adicionalmente para lograr las concentraciones en plasma deseadas. Las concentraciones en plasma logradas con las dosis intranasales de 17,5 y 35 µg se proveen en la Figura 1.

Escala de Sedación de Ramsay

El investigador, o el diseñador, usaron la Escala de Sedación de Ramsay para evaluar el nivel de sedación de cada sujeto. Para cada sujeto en cada punto de tiempo, el nivel de sedación se evaluó de acuerdo con las categorías de calificación de Ramsay. La Escala de Sedación de Ramsay se realizó antes de la dosis (Tiempo 0) y a 30, 60 y 90 minutos después de cada dosis del estudio. Todas las calificaciones

volvieron a su nivel de línea base (Calificación 2) dentro de las seis horas después de la dosificación. Aunque se asignó una calificación de la RSS de 5 a dos sujetos durante el transcurso del estudio, la mayor parte de los sujetos no experimentó sedación importante. Se administró a los sujetos dosis del estudio cada seis horas y realizaron actividades de monitoreo de la seguridad después de cada dosis, durante todo el día para siete dosis durante el Período 2; el efecto de confusión de este programa no se enfrenta en la herramienta de evaluación/resultados.

Criterios para exclusión

Los parámetros farmacocinéticos para las concentraciones de dexmedetomidina y su metabolito principal (ORM-14305) en el plasma se calcularon para las Dosis 1 y 2 durante el Período 1 y para las Dosis 1 y 7 durante el Período 2. Los parámetros calculados incluyeron la concentración del fármaco en el plasma observada pico (máximo) ($C_{\max}$), el tiempo a $C_{\max}$ ($T_{\max}$), el área debajo de la curva de concentración en el tiempo (AUC) desde Tiempo 0 hasta el último tiempo de extracción de muestra (t) con una concentración del fármaco en el plasma cuantificable (AUC_{0-t}), AUC desde el Tiempo 0 hasta 6 horas después de la dosificación (AUC_{0-6}), AUC desde Tiempo 0 hasta el infinito ($AUC_{0-\infty}$, para el Período 1 Dosis 2, y el Período 2

Dosis 7), y la semivida de eliminación de la fase final ($t_{1/2}$, para el Período 1 Dosis 2, y el Período 2 Dosis 7).

Resultados:

Los parámetros farmacocinéticos observados, $C_{\max}$, $T_{\max}$, y AUC_{0-6} de dexmedetomidina se presentan en la tabla siguiente.

Parámetros Farmacocinéticos de Dexmedetomidina

Parámetros [1]	Período 1 Dosis 1	Período 1 Dosis 2	Período 2 Dosis 1	Período 2 Dosis 7
$C_{\max}$ (ng/mL)	0,09 (30,6) [†]	0,16 (22,8) [†]	0,12 (35,8) [‡]	0,13 (31,3) [‡]
$T_{\max}$ (h)	1,26 (0,33, 4,00) [†]	0,88 (0,33, 2,02) [†]	1,01 (0,50, 2,00) [‡]	1,50 (0,33, 2,00) [‡]
AUC_{0-6}	0,39 (31,7) [†]	0,61 (19,2) [†]	0,47 (32,6) [‡]	0,50 (31,1) [‡]
$AUC_{\text{última}}$ (hr·ng/mL)	0,38 (35,2) [†]	0,63 (22,2) [†]	0,47 (32,6) [‡]	0,51 (55,0) [‡]
[1] Promedios geométricos (% CV) para $C_{\max}$, AUC_{0-6} , y $AUC_{\text{última}}$; mediana (min, max) para $T_{\max}$ † n=12; ‡ n=10				

Comparación de Parámetros Farmacocinéticos entre Dosis

Dosis	C_{max} (ng/mL)	AUC_{última} (h · ng/mL)	AUC₀₋₆ (h · ng/mL)
Período 1 Dosis 2: Período 1 Dosis 1	164,1 (138,0, 195,0)	164,2 (134,1, 201,0)	156,9 (134,7, 182,8)
Período 2 Dosis 7: Período 2 Dosis 1	106,3 (82,5, 136,9)	108,4 (77,8, 151,0)	105,5 (81,1, 137,3)
Período 2 Dosis 1: Período 1 Dosis 1	127,7 (112,4, 145,2)	125,1 (105,4, 148,6)	122,8 (106,5, 141,7)
Período 2 Dosis 7: Período 1 Dosis 2	86,8 (71,0, 106,1)	84,4 (66,5, 107,2)	85,2 (72,0, 100,9)

Los datos presentados son el % de Relación (90% CI)

Concentraciones en Plasma de Dexmedetomidina Promedio
Observadas (ng/mL)

Tiempo después de la dosis	Período 1 (N=12)		Período 2 (N=10)	
	Dosis 1	Dosis 2	Dosis 1	Dosis 7
0 min	0	0,033 ± 0,014	0	0,037 ± 0,016
10 min	0,008 ± 0,014	0,077 ± 0,033	0,028 ± 0,035	0,059 ± 0,028
20 min	0,060 ± 0,028	0,118 ± 0,054	0,073 ± 0,050	0,091 ± 0,033
30 min	0,059 ± 0,020	0,134 ± 0,044	0,085 ± 0,041	0,101 ± 0,034
45 min	0,083 ± 0,028	0,145 ± 0,040	0,112 ± 0,046	0,113 ± 0,032
60 min	0,088 ± 0,024	0,145 ± 0,023	0,116 ± 0,041	0,119 ± 0,031
90 min	0,090 ± 0,025	0,134 ± 0,014	0,116 ± 0,036	0,119 ± 0,031
2 hrs	0,092 ± 0,026	0,135 ± 0,019	0,117 ± 0,039	0,126 ± 0,033
4 hrs	0,067 ± 0,024	0,090 ± 0,023	0,073 ± 0,026	0,072 ± 0,072
6 hrs	0,036 ± 0,010	0,050 ± 0,018	0,037 ± 0,012	0,048 ±

				0,013
12 horas		0,022 ± 0		0,024 ± 0
18 horas		0		0
24 horas				0

Concentraciones en Plasma de ORM-14305 Promedio Observadas
(ng/mL)

Tiempo después de la dosis	Período 1 (N=12)		Período 2 (N=10)	
	Dosis 1	Dosis 2	Dosis 1	Dosis 7
0 min	0	0,032 ± 0,019	0	0,085 ± 0,037
10 min	0	0,032 ± 0,019	0	0,085 ± 0,036
20 min	0	0,035 ± 0,015	0	0,083 ± 0,036
30 min	0	0,042 ± 0,013	0	0,081 ± 0,032
45 min	0	0,039 ± 0,014	0	0,078 ± 0,029
60 min	0	0,042 ± 0,013	0	0,084 ± 0,034
90 min	0	0,045 ± 0,014	0,002 ±	0,080 ±

			0,006	0,034
2 horas	0,010 ± 0,013	0,053 ± 0,014	0,017 ± 0,015	0,088 ± 0,038
4 horas	0,032 ± 0,019	0,064 ± 0,019	0,039 ± 0,014	0,087 ± 0,035
6 horas	0,038 ± 0,013	0,062 ± 0,021	0,043 ± 0,016	0,079 ± 0,035
12 horas		0,048 ± 0,011		0,061 ± 0,027
18 horas		0,032 ± 0,011		0,045 ± 0,021
24 horas				0,031 ± 0,011

Estos resultados se ilustran en la Figura 2.

Este estudio respaldó la seguridad y la tolerabilidad de la dosificación repetida con la administración intranasal. Cuando se administró en el intervalo de dosificación de seis horas, hubo escasas pruebas de la acumulación de dexmedetomidina comparando la AUC para la Dosis 1 a la Dosis 7. Se demostró que DEX-IN.01 se toleró bien luego de la dosificación repetida con hasta siete dosis administradas en un intervalo de seis horas. No hubo ningún un aumento evidente en los eventos

adversos, cambios en los signos vitales o irritación nasal grave con la dosificación repetida. Cuando se administró como una dosis de 35 µg inicial, DEX-IN.01 alcanzó concentraciones en plasma pico después de 1,01-1,26 horas (mediana) con una $C_{\max}$ promedio de 0,09-0,12 ng/mL. No se observó ninguna sedación importante en los sujetos a diversos puntos de tiempo durante el estudio.

Ejemplo 7: Una Evaluación de Cruce de Tres Períodos, con Control Placebo, a ciegas tanto para el paciente como para el observador, de distribución al azar, de la Eficacia, Seguridad y Farmacocinética de Dexmedetomidina Intranasal en Sujetos con Dolor de Espalda Inferior Crónico

Se realizó un estudio para evaluar al eficacia, seguridad y farmacocinética de dos niveles de dosis de dexmedetomidina intranasal (DEX-IN.02 y DEX-IN.03) comparada con placebo en sujetos con dolor de espalda inferior crónico.

Métodos: Sujetos adultos con síntomas de dolor de espalda inferior crónico presentes durante más de tres meses y una intensidad del dolor de 24 horas de línea base ≥ 4 (escala de 0-10) fueron elegibles para participar. Se asignó a los sujetos en forma aleatoria a una secuencia de tratamiento con DEX-IN.02 (50 µg; 50 µg/100 µL), DEX-IN.03 (25 µg; 25 µg/50

µL) y placebo igualador. Las dosis del estudio se administraron como una aspersion intranasal usando un dispositivo de aspersion de una sola dosis que no necesita cebado. Las dosis se administraron a un solo orificio nasal. Los dispositivos de dosificación se llenaron con el volumen apropiado de sedación farmacológica para administrar la dosis de 25 o 50 µg designada de dexmedetomidina. Las dosis del estudio se administraron en días consecutivos, con un lavado mínimo de 24 horas entre las dosis. Se dejó que los sujetos con terapia de analgésicos crónica continuaran su régimen durante todo el estudio, pero no se administró ninguna dosis dentro de 2 horas del tratamiento del estudio (a menos que se necesitara un rescate de analgésico). Los analgésicos de rescate estuvieron disponibles a pedido del sujeto de acuerdo con el régimen de dolor de línea base del individuo.

Las evaluaciones de eficacia incluyeron medidas de intensidad del dolor (PI), alivio del dolor (PR) y desempeño de medicamento global (GMP). Las medidas de la eficacia se usaron para calcular la diferencia de intensidad del dolor (PID), la diferencia de intensidad del dolor sumada (SPID) y el alivio del dolor total (TOTPAR) en varios puntos de tiempo después de la dosis y para determinar el número de sujetos con respuestas parciales y completas a la terapia. Las evaluaciones de seguridad incluyeron la toma de signos vitales, la evaluación

de síntomas nasales, sedación y eventos adversos. Se extrajeron muestras de plasma a intervalos durante las primeras 12 horas después de la dosis para el análisis farmacocinético.

Resultados: El estudio inscribió y trató a 24 sujetos con DEX-IN.02, DEX-IN.03, y placebo; todos los sujetos inscriptos terminaron todas las dosis del estudio programadas. Los sujetos eran principalmente de raza blanca (91,7%) y hombres (58,3%), con una edad promedio de $33,7 \pm 10,19$ años. Los sujetos tenían principalmente dolor visceral (91,7%) con antecedentes promedio de síntomas con una duración de $6,75 \pm 6,85$ años. Un tercio de los sujetos utilizaban analgésicos opioides para sus síntomas de dolor.

La mejora promedio en los valores de PID de los sujetos fueron mucho mayores para la dosis de 50 µg (DEX-IN.02) comparado con placebo de 45 minutos a 2 horas después de la dosis (45 minutos: 2,2 contra 1,2, $p=0,0291$; 1 hora: 2,2 contra 0,8, $p=0,0082$; 1,5 hora: 2,2 contra 0,7, $p=0,0028$; 2 horas: 2 contra 0,9, $p=0,0126$). El valor de SPID promedio fue mucho mayor para la dosis de 50 µg que placebo a los 60 minutos después de la dosis (7,1 contra 3,6; $p=0,0352$). TOTPAR promedio fue mucho más alto para la dosis de 50 µg que para placebo tanto a 45 como a 60 minutos después de la dosis (4,3

contra 2,5; $p=0,0298$ y 6,2 contra 3,3; $p=0,0097$, respectivamente). Los resultados para el estudio se muestran en las siguientes tablas.

Tabla: Resumen de Valores de PID Promedio $\pm$ SD para todos los puntos de tiempo después de la dosis

Punto de tiempo	Placebo (N=24)	DEX-IN.03 (N=24)	DEX-IN.02 (N=24)
10 min	0,2 $\pm$ 0,48	0,3 $\pm$ 0,53	0,5 $\pm$ 0,93
15 min	0,6 $\pm$ 0,93	0,7 $\pm$ 1,09	0,8 $\pm$ 1,18
20 min	1,0 $\pm$ 1,33	0,9 $\pm$ 1,25	1,5 $\pm$ 1,32
30 min	1,0 $\pm$ 1,44	1,3 $\pm$ 1,36	1,9 $\pm$ 1,85
45 min	1,2 $\pm$ 1,63	1,4 $\pm$ 1,44	2,2 [§] $\pm$ 1,72
60 min	0,8 $\pm$ 1,49	1,5 $\pm$ 1,47	2,2 [¥] $\pm$ 1,82
90 min	0,7 $\pm$ 1,16	1,4 $\pm$ 1,41	2,2 [¥] $\pm$ 1,81
2 horas	0,9 $\pm$ 1,28	1,3 $\pm$ 1,23	2,0 [§] $\pm$ 1,76
4 horas	1,1 $\pm$ 1,75	1,5 $\pm$ 1,38	1,8 $\pm$ 1,81
6 horas	1,5 $\pm$ 1,56	1,5 $\pm$ 1,10	1,6 $\pm$ 1,71

§ $p < 0,05$; ¥ $p < 0,01$

Tabla: Resumen de Valores de SPID Promedio $\pm$ SE

Punto de tiempo	Placebo (N=24)	DEX-IN.03 (N=24)	DEX-IN.02 (N=24)
15 min	0,6 $\pm$ 0,19	0,7 $\pm$ 0,22	0,8 $\pm$ 0,24
30 min	1,6 $\pm$ 0,47	1,9 $\pm$ 0,48	2,7 $\pm$ 0,59
45 min	2,8 $\pm$ 0,78	3,3 $\pm$ 0,75	4,9 $\pm$ 0,90
60 min	3,6 $\pm$ 1,05	4,8 $\pm$ 1,03	7,1* $\pm$ 1,24

*p = 0,0352

Tabla: Resumen de Valores de TOTPAR Promedio $\pm$ SE

Punto de tiempo	Placebo (N=24)	DEX-IN.03 (N=24)	DEX-IN.02 (N=24)
15 min	0,6 $\pm$ 0,15	0,5 $\pm$ 0,15	0,8 $\pm$ 0,20
30 min	1,5 $\pm$ 0,35	1,3 $\pm$ 0,32	2,4 $\pm$ 0,39
45 min	2,5 $\pm$ 0,56	2,4 $\pm$ 0,48	4,3 [§] $\pm$ 0,59
60 min	3,3 $\pm$ 0,74	3,5 $\pm$ 0,68	6,2 [¥] $\pm$ 0,81

§ p < 0,05; ¥ p < 0,01

Las calificaciones de GMP promedio fueron similares entre los tres grupos de tratamiento durante los puntos de tiempo después de la dosis de 30 así como de 60 minutos. El grupo tratado con 50 µg de dexmedetomidina tuvo más sujetos con una mejora $\geq 33\%$ y $\geq 50\%$ a todos los puntos de tiempo después de 15 minutos después de la dosis; 11 sujetos tratados con DEX-

IN.02 informaron $\geq 50\%$ de mejora a los 90 minutos (95% CI, 1,02-7,44) y 10 sujetos a las 2 horas (95% CI, 1,05-10,63), comparados con 4 sujetos a los 90 minutos y 3 sujetos a las 2 horas en el grupo placebo. Ningún sujeto de ninguno de los grupos de tratamiento necesitó medicamentos de rescate.

Los eventos adversos fueron generalmente moderados en los sujetos tratados con DEX-IN, con 5 eventos que se determinó que fueron moderados a graves (2 BP reducido, 1 mareo, 1 somnolencia y 1 hipersensibilidad). No ocurrió ningún SAE, muerte, o retiro debido a AE durante la realización del estudio. Los cambios en la presión sanguínea sistólica y diastólica (SBP y DBP respectivamente) fueron mayores en los sujetos tratados con DEX-IN.02 que en los sujetos tratados con DEX-IN.03 y placebo. Los cambios en el ritmo cardíaco (HR) fueron similares después de DEX-IN.03 y placebo, mientras que los sujetos tratados con DEX-IN.02 tuvieron una mayor disminución en el ritmo cardíaco; el porcentaje promedio máximo de cambio por debajo de la línea base fue -1% para placebo y -9% para DEX-IN.02, mientras que los HR promedio para DEX-IN.03 nunca se redujeron por debajo de la línea base. Los resultados de la evaluación nasal de la irritación nasal fueron similares entre todos los grupos de tratamiento en todos los puntos de tiempo con una calificación promedio que no excedió 1 en los sujetos tratados con DEX-IN.02 a una hora

después de la dosis (escala de 0-10). Los sujetos del grupo de tratamiento con DEX-IN.02 experimentaron los valores máximos en la Escala de Somnolencia de Stanford a los 60 minutos después de la dosis con 17 sujetos que informaron una calificación ≥ 5 .

Una sola dosis de DEX-IN.03 (25 μg) dio una C_{max} promedio de 0,11 ng/mL con un T_{max} mediano de 0,75 hora, mientras que una sola dosis de DEX-IN.02 (50 μg) dio una C_{max} promedio de 0,25 ng/mL con un T_{max} promedio de 0,51 hora. Las tablas siguientes resumen estos resultados.

Tabla: Concentraciones en Plasma de Dexmedetomidina Promedio Observadas (ng/mL)

Tiempo después de la dosis	DEX-IN.03 (25 μg)	DEX-IN.02 (50 μg)
0 min	0	0
10 min	0,047	0,098
15 min	0,081	0,182
20 min	0,096	0,215
30 min	0,111	0,212
45 min	0,110	0,228
60 min	0,102	0,196

75 min	0,094	0,183
90 min	0,085	0,169
2 horas	0,077	0,149
4 horas	0,048	0,101
6 horas	0,030	0,050
12 horas	0	0,027

Tabla: Propiedades Farmacocinéticas Observados de Dexmedetomidina

Parámetro	DEX-IN.03 (25 µg)	DEX-IN.02 (50 µg)
$C_{\max}$ (ng/mL)	0,11 (71,4)	0,25 (38,3)
$T_{\max}$ (horas)	0,75 (0,25, 4,00)	0,51 (0,25, 4,00)
$AUC_{\inf}$ (h·ng/mL)	0,48 (13,7)	0,92 (26,0)
AUC_{0-1} (h·ng/mL)	0,08 (110,4)	0,16 (64,1)
$AUC_{\text{última}}$ (h·ng/mL)	0,24 (182,4)	0,75 (21,6)
$t_{1/2}$ (horas)	2,24 (1,60, 2,45)	2,05 (1,52, 3,07)

[1] Promedios geométricos (CV%) para $C_{\max}$, AUC_{0-1} , $AUC_{\text{última}}$, y $AUC_{\inf}$, mediana (min, max) para $T_{\max}$; y promedio aritmético $\pm$ SD para $t_{1/2}$

El estudio muestra que la vía intranasal es un medio no invasivo viable para administrar dexmedetomidina. La dosificación con DEX-IN.02 y DEX-IN.03 produjo una absorción más rápida con concentraciones en plasma pico de dexmedetomidina más altas que las formulaciones exploradas previamente. El análisis de los valores de SPID y TOTPAR demuestra los efectos analgésicos importantes de una dosis de 50 µg de dexmedetomidina intranasal comparado con una dosis de 25 µg o placebo en sujetos con CLBP que se inició 45 minutos después de la dosis. En general, DEX-IN fue bien tolerada; los AE informados tuvieron generalmente una gravedad leve, mientras que no se informó ningún SAE.

REIVINDICACIONES

1. Un método para tratar o prevenir el dolor sin sedación importante en un mamífero que comprende administrar por vía intranasal una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al mamífero por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, produce una C_{plasma} de 0,1 ng/ml dentro de los 15 minutos a 20 minutos de la administración y tiene un efecto analgésico sin sedación importante.
2. Un método para tratar o prevenir el dolor sin sedación importante en un humano adulto que comprende administrar por vía intranasal una cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al humano adulto por lo cual la cantidad efectiva intranasal de dexmedetomidina, o una sal farmacéuticamente aceptable de ella, no produce sedación importante en el adulto dentro de un período de tiempo de dos horas después de la administración y tiene un efecto analgésico dentro del período de tiempo.
3. Un método para tratar o prevenir el dolor sin sedación importante en un humano que comprende administrar por vía

intranasal dexmedetomidina, o una sal farmacéuticamente aceptable de ella, a un solo orificio nasal del humano.

4. Un método para tratar o prevenir el dolor sin sedación importante en un mamífero que comprende asperjar por vía intranasal en el mamífero una composición farmacéutica que comprende dexmedetomidina, o una sal farmacéuticamente aceptable de ella, en donde la aspersion comprende gotitas que tienen un Dv_{90} menor de 150 μm .
5. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 4, en donde la C_{max} en plasma de dexmedetomidina es de 0,08 ng/ml a 0,2 ng/ml.
6. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 4, en donde la C_{max} en plasma de dexmedetomidina es de 0,15 ng/ml.
7. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 4, en donde la C_{max} en plasma de dexmedetomidina es de 0,2 ng/ml.
8. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 7, en donde el T_{max} de dexmedetomidina es menor de 1 hora.

9. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 7, en donde el $T_{\max}$ de dexmedetomidina es menor de 50 minutos.
10. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 9, en donde la dexmedetomidina, o una sal farmacéuticamente aceptable de ella, se administra como una dosis unitaria de 10 μg , 25 μg , 35 μg , 40 μg , 50 μg , 75 μg , o 100 μg .
11. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 10, en donde durante la hora inmediatamente posterior a la administración de la dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al mamífero o humano, el nivel de sedación es no mayor que el Nivel 2 en la Escala de Sedación de Ramsay.
12. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 11, en donde durante la hora inmediatamente posterior a la administración de la dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al mamífero o humano, el nivel de sedación es no mayor que el Nivel 1 en la Escala de Sedación de Ramsay.
13. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 12, en donde durante la hora

inmediatamente posterior a la administración de la dexmedetomidina, o una sal farmacéuticamente aceptable de ella, al mamífero o humano, el nivel de sedación es no mayor que el Nivel 6 en la Escala Modificada de Evaluación de Alerta/Sedación del Observador.

14. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 13, en donde no hay ninguno o escaso efecto sobre la presión sanguínea después de la administración de dexmedetomidina, o una sal farmacéuticamente aceptable de ella.

15. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 14, que además comprende administrar al humano o mamífero uno o más agentes terapéuticos adicionales.

16. El método de acuerdo con la reivindicación 15, en donde uno o más agentes terapéuticos adicionales se elige de un analgésico tópico, un analgésico tipo opioide sintético, un analgésico no opioide, una vitamina, un vasodilatador, una benzodiacepina, un triptan, un anticonvulsivo, un antidepresivo, un medicamento contra las náuseas y un antihipertensivo.

17. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 16, en donde la dexmedetomidina, o una

sal farmacéuticamente aceptable de ella, se administra cada 6 horas.

18. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 17, en donde el dolor es dolor idiopático.

19. El método de acuerdo con la reivindicación 18, en donde el dolor idiopático es neuralgia, mialgia, hiperalgia, hiperpatía, neuritis, neuropatía.

20. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 17, en donde el dolor está asociado al dolor provocado por cáncer, infección viral, trauma físico, artritis, dolor de cabeza, migraña, o dolor de espalda inferior.

21. El método de acuerdo con la reivindicación 20, en donde el trauma físico está asociado o provocado por una cirugía, una quemadura, o trauma de fuerza contundente.

22. El método de acuerdo con una cualquiera de las reivindicaciones 1 a 20, en donde la dexmedetomidina, o una sal farmacéuticamente aceptable de ella, se administra por vía intranasal con un dispositivo de dosis medida.

23. El método de acuerdo con la reivindicación 22, en donde el dispositivo de dosis medida es un dispositivo de varias dosis, de dosis unitaria o de dos dosis.
24. Un dispositivo de dosis medida que comprende una composición farmacéutica que comprende dexmedetomidina, o una sal farmacéuticamente aceptable de ella, en donde el dispositivo de dosis medida suministra una aspersión de dosis medida de la composición farmacéutica por vía intranasal que es analgésica en un mamífero sin sedación importante.
25. El dispositivo de dosis medida de acuerdo con la reivindicación 24, en donde la aspersión de dosis medida producida por el dispositivo comprende gotitas que comprende dexmedetomidina, o una sal farmacéuticamente aceptable de ella, que tienen un Dv_{90} menor de 150 μm .
26. El dispositivo de dosis medida de acuerdo con la reivindicación 24 o la reivindicación 25, en donde la aspersión de dosis medida producida por el dispositivo comprende una dosis medida de 10 μg , 25 μg , 35 μg , 50 μg , 75 μg , o 100 μg de dexmedetomidina, o una sal farmacéuticamente aceptable de ella.

27. Un dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 26, en donde la aspersión de dosis medida producida por el dispositivo comprende un volumen menor de 150 μl , menor de 140 μl , menor de 130 μl , menor de 120 μl , menor de 110 μl , menor de 75 μl , o menor de 50 μl .
28. El dispositivo de dosis unitaria de acuerdo con una cualquiera de las reivindicaciones 24 a 27, en donde la aspersión de dosis medida producida por el dispositivo produce una C_{plasma} en el mamífero de 0,1 ng/ml dentro de 15 minutos a 20 minutos de la administración.
29. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 28, en donde la aspersión de dosis medida producida por el dispositivo no produce una sedación importante en un adulto dentro de un período de tiempo de dos horas posteriores a la administración y tiene un efecto analgésico dentro del período de tiempo.
30. El dispositivo de dosis medida de acuerdo con cualquiera de las reivindicaciones 24 a 29, en donde la aspersión de dosis medida producida por el dispositivo produce una C_{max} en el plasma en el mamífero de 0,08 ng/ml a 0,2 ng/ml.

31. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 29, en donde la aspersión de dosis medida producida por el dispositivo produce una $C_{\max}$ en el plasma en el mamífero de 0,15 ng/ml.
32. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 29, en donde la aspersión de dosis medida producida por el dispositivo produce una $C_{\max}$ en el plasma en el mamífero de 0,2 ng/ml.
33. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 29, en donde la aspersión de dosis medida producida por el dispositivo produce un $T_{\max}$ en el mamífero menor de 1 hora.
34. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 29, en donde la aspersión de dosis medida producida por el dispositivo produce un $T_{\max}$ en el mamífero menor de 50 minutos.
35. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 34, en donde la aspersión de dosis medida producida por el dispositivo durante la hora inmediatamente posterior a la administración al mamífero produce un nivel de sedación que no es mayor que el Nivel 3 en la Escala de Sedación de Ramsay.

36. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 35, en donde la aspersión de dosis medida producida por el dispositivo durante la hora inmediatamente posterior a la administración al mamífero produce un nivel de sedación que no es mayor que el Nivel 2 en la Escala de Somnolencia de Stanford.
37. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 36, en donde la aspersión de dosis medida producida por el dispositivo durante la hora inmediatamente posterior a la administración al mamífero produce un nivel de sedación que no es menor que el Nivel 6 en la Escala Modificada de Evaluación de Alerta/Sedación del Observador.
38. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 37, en donde la aspersión de dosis medida producida por el dispositivo no tiene ningún efecto o tiene un efecto mínimo sobre la presión sanguínea del mamífero después de la administración.
39. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 38, en donde la composición farmacéutica además comprende uno o más agentes terapéuticos adicionales.

40. El dispositivo de dosis medida de acuerdo con la reivindicación 39, en donde uno o más agentes terapéuticos adicionales se elige de un analgésico opioide, un analgésico tipo opioide sintético, un analgésico no opioide, una vitamina, un vasodilatador, una benzodiacepina, un triptan, un anticonvulsivo, un antidepresivo, un medicamento contra las náuseas, y un antihipertensivo.
41. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 40 que es un dispositivo de varias dosis, de dosis unitaria o de dos dosis.
42. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 41, en donde la composición farmacéutica que además comprende un excipiente portador.
43. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 42, en donde la composición farmacéutica además comprende fosfato de sodio y/o citrato de sodio.
44. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 43, en donde la composición farmacéutica además comprende un quelante.

45. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 44, en donde la composición farmacéutica está libre de un agente mejorador de la viscosidad.
46. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 45, en donde la composición farmacéutica además comprende citrato de sodio, ácido cítrico y cloruro de sodio.
47. El dispositivo de dosis medida de acuerdo con la reivindicación 46, en donde la composición farmacéutica además comprende del 0,2% al 0,3% (p/p) de citrato de sodio y del 0,005% al 0,015% (p/p) de ácido cítrico.
48. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 47, en donde el pH de la composición farmacéutica es de 6 a 6,5.
49. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 48, en donde la composición farmacéutica además comprende uno o más conservantes antimicrobianas.
50. El dispositivo de dosis medida de acuerdo con la reivindicación 49, en donde el conservante es alcohol de feniletilo.

51. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 50, en donde la composición farmacéutica que además comprende uno o más antioxidantes.
52. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 51, en donde la composición farmacéutica además comprende uno o más excipientes de confirmación de la dosis.
53. El dispositivo de dosis medida de acuerdo con la reivindicación 52, en donde uno o más excipientes de confirmación de la dosis es alcohol de feniletilo.
54. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 53, en donde la composición farmacéutica además comprende uno o más humectantes.
55. El dispositivo de dosis medida de acuerdo con la reivindicación 54, en donde uno o más humectantes son glicerina, propilenglicol, polietilenglicol, o un azúcar/alcohol de azúcar, o cualquier combinación de ellos.
56. El dispositivo de dosis medida de acuerdo con una cualquiera de las reivindicaciones 24 a 55, en donde la

composición farmacéutica además comprende uno o más agentes de ajuste de la osmolaridad.

57. El dispositivo de dosis medida de acuerdo con la reivindicación 56, en donde uno o más agentes de ajuste de la osmolaridad es cloruro de sodio, dextrosa, u otro azúcar, o cualquier combinación de ellos.

RESUMEN DE LA INVENCION

La presente invención provee formulaciones intranasales que comprenden dexmedetomidina, o una sal farmacéuticamente aceptable de ella, y sus usos.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: PAUL K. LEGAARD
PEPPER HAMILTON LLP
400 BERWYN PARK
899 CASSATT ROAD
BERWYN, PA 19312

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

22 FEB 2013

Applicant's or agent's file reference
13761700402

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 12/68988

International filing date (day/month/year)

11 December 2012 (11.12.2012)

Priority date (day/month/year)

11 December 2011 (11.12.2011)

International Patent Classification (IPC) or both national classification and IPC

IPC(8) - A61K 31/4174 (2013.01)

USPC - 514/396

Applicant RECRO PHARMA, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Date of completion of this opinion

01 February 2013 (01.02.2013)

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/68988

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43 *bis*.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/68988

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 8-23 and 27-57

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. see below are so unclear that no meaningful opinion could be formed (*specify*):

Claims 8-23 and 27-57 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 8-23 and 27-57

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13~~ter~~.1(a) or (b).

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 12/68988

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-7 and 25-26	YES
	Claims	24	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-7 and 24-26	NO
Industrial applicability (IA)	Claims	1-7 and 24-26	YES
	Claims	None	NO

2. Citations and explanations:

Claim 24 lacks novelty under PCT Article 33(2) as being anticipated by WO 2011/085162 A2 to Henwood et al. (hereinafter 'Henwood')

Regarding claim 24, Henwood teaches a metered dose device (para [0034]-[0035]) comprising a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof (para [0033]), wherein the metered dose device delivers a metered dose spray of the pharmaceutical composition intranasally (para [0027]-[0029], administration directly to the nasal mucosa; para [0033]) that is analgesic in a mammal without significant sedation (para [0006], [0060]).

Claims 3 and 26/24 lack an inventive step under PCT Article 33(3) as being obvious over Henwood.

Regarding claim 3, Henwood teaches a method of treating or preventing pain without significant sedation in a human comprising intranasally administering dexmedetomidine, or a pharmaceutically acceptable salt thereof to the nostril of a human (para [0005]-[0006], [0020], transmucosal; para [0027]-[0029], administration directly to the nasal mucosa; para [0060]). Henwood does not expressly teach administering dexmedetomidine to a single nostril of the human. It would, however, have been obvious to one of ordinary skill in the art to have optimized the method of administering dexmedetomidine intranasally to a subject, in order to build up a therapeutically effective plasma concentration of dexmedetomidine upon said administration and to thereby provide rapid analgesic effect to said subject, through routine experimentation, given such practice in the art.

Regarding claim 26/24, Henwood teaches the metered dose device of claim 24, as above, wherein the metered dose spray produced by the device comprises a metered dose of dexmedetomidine or a pharmaceutically acceptable salt thereof (para [0033]-[0035], [0039]), but does not specifically teach the dose being about 10 ug, about 25 ug, about 35 ug, about 50 ug, about 75 ug or about 100 ug of dexmedetomidine, or a pharmaceutically acceptable salt thereof. It would, however, have been obvious to one of ordinary skill in the art to have optimized the effective dosage to be intranasally administered via the metered-dose device disclosed in Henwood to a subject, in order to effectively treat pain in said subject, based on the age, weight and medical condition of the subject, through routine experimentation, given such practice in the art.

Claims 1-2 and (5-7)/(1-3) lack an inventive step under PCT Article 33(3) as being obvious over Henwood in view of the article entitled, 'Bioavailability of dexmedetomidine after intranasal administration', by Irola et al. (hereinafter 'Irola').

Regarding claim 1, Henwood teaches a method of treating or preventing pain without significant sedation in a mammal comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof (para [0005]-[0006], [0020], transmucosal; para [0027], nasal), to the mammal (para [0029]), whereby the intranasally effective amount of dexmedetomidine or pharmaceutically acceptable salt thereof has an analgesic effect without significant sedation (para [0006], [0028], [0060]), but does not expressly teach whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration.

Irola teaches pharmacokinetic and pharmacodynamic studies of intranasally administered dexmedetomidine in comparison with its intravenous administration and discloses significant bioabsorption of dexmedetomidine upon intranasal administration, wherein said administration produces a median C_{max} of 0.34 ng/ml and a median T_{max} of 38 min at the studied dosage (abstract; pg 826, col 2, para 2 - para 3; pg 827, col 2, para 4; Table 1; Fig 1; pg 830, col 2, para 2).

In view of the efficacy of intranasal administration toward building up plasma concentration of dexmedetomidine disclosed in Irola, it would have been obvious to one of ordinary skill in the art that intranasal administration of dexmedetomidine according to the method disclosed in Henwood, would be likely to bring about therapeutically effective plasma levels within minutes of administration thereby providing rapid onset of analgesic effect in a subject. Further, it would have been obvious to one of ordinary skill in the art to have determined the effective amount for intranasal administration of dexmedetomidine, in order to produce plasma concentrations of dexmedetomidine in the claimed range in the treated subject, based on the age, weight and medical condition of said subject, through routine experimentation, given such practice in the art.

=====Continued in Supplemental Box=====

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 12/68988

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V.2.Citations and Explanations:

Regarding claim 2, see the discussion set forth above for claim 1. As discussed above, the combination of Henwood and Iriola teaches a method of treating or preventing pain without significant sedation in an adult human comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the adult human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult and has an analgesic effect within a period of two hours (Henwood - para [0005]-[0006], [0020], [0027]-[0029], [0060]; Iriola - abstract; pg 826, col 1, para 2; col 2, para 2 - para 3; pg 827, col 2, para 4; Table 1; Fig 1; pg 830, col 2, para 2). The combination of Henwood and Iriola does not expressly teach the composition not producing sedation within a period of time of about two hours after administration. However, the relative sedative and analgesic efficacies of the intranasal administration of an effective amount of dexmedetomidine disclosed by the combination of Henwood and Iriola within two hours of administration, would have been obvious to one of ordinary skill in the art as determined through routine experimentation, in order to evaluate and/or establish utility of said administration toward treating pain in a subject.

Regarding claims (5-7)/(1-3), see the discussion set forth above for claim 1. As discussed above, the combination of Henwood and Iriola teaches the method of anyone of claims 1 to 3, wherein the mean plasma C_{max} of dexmedetomidine is about 0.34 ng/ml at an intranasally administered dosage of 84 ug (Iriola - pg 826, col 2, para 2; pg 827, col 2, para 4; pg 828, Table 1). The combination of Henwood and Iriola does not specifically teach the plasma C_{max} of dexmedetomidine being 0.08 ng/ml to about 0.2 ng/ml or about 0.15 ng/ml or about 0.2 ng/ml. It would however have been obvious to one of ordinary skill in the art to have optimized the effective amount of intranasally administered dexmedetomidine such that C_{max} levels in the claimed range are produced upon administration, thereby providing effective analgesic relief to a subject, through routine experimentation, given such practice in the art.

Claims 4, (5-7)/4, 25 and 26/25 lack an inventive step under PCT Article 33(3) as being obvious over Henwood in view of US 2008/0004305 A1 (Wermeling).

Regarding claim 4, Henwood teaches a method of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying in the mammal a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof (para [0005]-[0006], [0020], transmucosal; para [0027]-[0029], administration directly to the nasal mucosa; para [0033]-[0034], [0060]), wherein the spray comprises droplets (para [0039]), but does not specifically teach wherein the droplets have a Dv90 of less than about 150 μ m.

Wermeling teaches an intranasal opioid analgesic formulation having enhanced bioavailability (para [0011]-[0012]), wherein the intranasal spray comprises droplets that have a Dv90 of less than about 150 μ m (para [0066]-[0069]).

It would have been obvious to one of ordinary skill in the art to add the teachings of Wermeling concerning the preferred droplet sizes of an intranasal analgesic spray formulation having enhanced bioavailability, to the teachings of Henwood comprising a spray formulation of dexmedetomidine for intranasal administration to treat pain in a subject, as both Henwood and Wermeling teach intranasally administered analgesic formulations, in order to practice the claim as described, without undue experimentation. This would have provided for use of a spray device for the dexmedetomidine formulation that produces droplet sizes in the range disclosed in Wermeling, in order to have optimized intranasal absorption of dexmedetomidine and the resultant bioavailability and analgesic efficacy of said formulation.

Regarding claims (5-7)/4, the combination of Henwood and Wermeling teaches the method of claim 4, as above (Henwood - para [0005]-[0006], [0020], [0027]-[0029], [0033]-[0034], [0060]; Wermeling - para [0011]-[0012], [0066]-[0069]), but does not specifically teach the plasma C_{max} of dexmedetomidine being 0.08 ng/ml to about 0.2 ng/ml or about 0.15 ng/ml or about 0.2 ng/ml. It would, however, have been obvious to one of ordinary skill in the art to have optimized the effective amount of dexmedetomidine and the droplet size of the intranasal spray formulation in the method of treatment disclosed by the combination of Henwood and Wermeling such that C_{max} levels in the claimed range are produced upon administration, thereby providing effective analgesic relief to a subject, through routine experimentation, given such practice in the art.

Regarding claim 25, see the discussion set forth above for claims 4 and 24. As discussed above, the combination of Henwood and Wermeling teaches the metered dose device of claim 24, wherein the metered dose spray produced by the device comprises droplets comprising dexmedetomidine or a pharmaceutically acceptable salt thereof (Henwood - para [0033]-[0035], [0039]), that have a Dv90 of less than about 150 μ m (Wermeling - para [0066]-[0069]).

Regarding claim 26/25, the combination of Henwood and Wermeling teaches the metered dose device of claim 25, as above, wherein the metered dose spray produced by the device comprises a metered dose of dexmedetomidine or a pharmaceutically acceptable salt thereof (Henwood - para [0033]-[0035], [0039]), but does not specifically teach the dose being about 10 ug, about 25 ug, about 35 ug, about 50 ug, about 75 ug or about 100 ug of dexmedetomidine, or a pharmaceutically acceptable salt thereof. It would, however, have been obvious to one of ordinary skill in the art to have optimized the effective dosage of dexmedetomidine to be intranasally administered via the metered-dose device disclosed by the combination of Henwood and Wermeling to a subject, in order to effectively treat pain, based on the age, weight and medical condition of said subject, through routine experimentation, given such practice in the art.

Claims 1-7 and 24-26 have industrial applicability as defined by PCT Article 33(4), because the subject matter can be made or used in industry.



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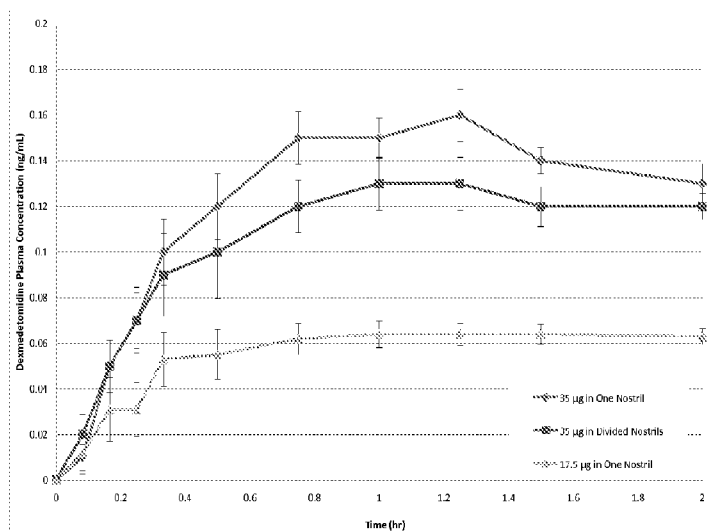
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[Continued on next page]

(54) Title: INTRANASAL DEXMEDETOMIDINE COMPOSITIONS AND METHODS OF USE THEREOF

Figure 1:



(57) Abstract: The present invention provides intranasal formulations comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, and uses thereof.

Published:

- *without international search report and to be republished
upon receipt of that report (Rule 48.2(g))*

Intranasal Dexmedetomidine Compositions And Methods Of Use Thereof

Field Of The Invention

The present invention is directed, in part, to intranasal formulations of
5 dexmedetomidine, or a pharmaceutically acceptable salt thereof, that are analgesic but without
significant sedation, as well as methods of use thereof.

Background

Dexmedetomidine, 5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole, is a non-
10 narcotic α_2 -adrenoceptor agonist with sedative and analgesic properties. Currently,
dexmedetomidine is only commercially available as an injectable formulation indicated for
sedation of initially intubated and mechanically ventilated patients during treatment in an
intensive care setting and sedation of non-intubated patients prior to and/or during surgical and
other procedures, and it must be administered intravenously by an experienced and licensed
15 health care professional. Although dexmedetomidine has analgesic properties, an intranasal
formulation useful as an analgesic without sedation, however, is not commercially available.
Moreover, for a variety of reasons, the commercially available injectable formulation is not
suitable for use as an analgesic that can be self-administered. A continuing and unmet need exists
for a dexmedetomidine-based analgesic medicine that, for example, may be self-administered by
20 the patient intranasally to produce analgesia (or otherwise treat or prevent pain) without
significant sedation.

Brief Description of Drawings:

Figure 1 shows intranasal dexmedetomidine pharmacokinetics for some embodiments.
25 Figure 2 shows mean dexmedetomidine plasma concentrations (ng/mL) for some
embodiments.

Summary of the Invention

The present invention provides methods of treating or preventing pain without
30 significant sedation in a mammal comprising intranasally administering an intranasally effective
amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal
whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable
salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of
administration and has an analgesic effect without significant sedation.

The present invention also provides methods of treating or preventing pain without significant sedation in an adult human comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the adult human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult within a period of time of about two hours after administration and has an analgesic effect within the period of time.

The present invention also provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally administering dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the mammal, particularly a human.

The present invention also provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying in the mammal a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

The present invention also provides metered dose devices comprising a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the metered dose device delivers a metered dose spray of the pharmaceutical composition intranasally that is analgesic in a mammal without significant sedation.

Description Of Embodiments

Unless defined otherwise, all technical and scientific terms have the same meaning as is commonly understood by one of ordinary skill in the art to which the embodiments disclosed belongs.

As used herein, the terms “a” or “an” means that “at least one” or “one or more” unless the context clearly indicates otherwise.

As used herein, the term “about” means that the numerical value is approximate and small variations would not significantly affect the practice of the disclosed embodiments. Where a numerical limitation is used, unless indicated otherwise by the context, “about” means the numerical value can vary by $\pm 10\%$ and remain within the scope of the disclosed embodiments.

As used herein, the term “analgesia” refers to the alleviation (partial or complete) or elimination of the sensation of pain.

As used herein, the term “carrier” means a diluent, adjuvant, or excipient with which a compound is administered. Pharmaceutical carriers can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical carriers can also be saline, gum

acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents can be used.

As used herein, the term, “compound” means all stereoisomers, tautomers, and isotopes of the compounds, or pharmaceutically acceptable salts thereof, including any and all metabolites described herein.

As used herein, the terms “comprising” (and any form of comprising, such as “comprise”, “comprises”, and “comprised”), “having” (and any form of having, such as “have” and “has”), “including” (and any form of including, such as “includes” and “include”), or “containing” (and any form of containing, such as “contains” and “contain”), are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

As used herein, the term “contacting” means bringing together of two elements in an *in vitro* system or an *in vivo* system. For example, “contacting” a compound or composition described herein with an individual or patient or cell includes the administration of the compound to an individual or patient, such as a human.

As used herein, the term “Dv90” means the value which represents the particle size below which 90% of the volume of a plurality of droplets exist (e.g., such as in a spray mist; in contrast to a nasal drop comprising one or two drops).

As used herein, the term “individual” or “patient,” used interchangeably, means any animal, including mammals, such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, such as humans.

As used herein, the phrase “in need thereof” means that the animal or mammal has been identified as having a need for the particular method or treatment. In some embodiments, the identification can be by any means of diagnosis. In any of the methods and treatments described herein, the animal or mammal can be in need thereof. In some embodiments, the animal or mammal is in an environment or will be traveling to an environment in which a particular disease, disorder, or condition is prevalent. For example, a mammal or animal may be in need of treatment or prevention of pain without sedation or without significant sedation.

As used herein, the phrase “metered dose device” refers to a device that provides a specified dose.

As used herein, the phrase “X to Y” means any number between X and Y and includes the endpoints. For example, the phrase “1 to 5” means 1, 2, 3, 4, or 5.

As used herein, “pain” refers to a wide range of clinical manifestations, and it has a broad meaning. Pain perception is highly subjective, and different individuals experience pain in different ways and with greatly different intensities. The International Association for the Study

of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” More simply stated, pain includes any sensory experience that causes suffering and is associated with an unpleasant awareness of one’s own body. Non-limiting types and causes of pain include neuralgia, myalgia, hyperalgesia, hyperpathia, neuritis, and neuropathy. Pain is often a symptom of an underlying physiological abnormality, such as cancer or arthritis. Some types of pain have no clearly identified causes, such as migraine headache pain. Pain may also be caused by physical trauma, such as burns or surgery. Viral infections, such as Herpes zoster (chicken pox and shingles), can also cause pain. Withdrawal from chemical dependence on alcohol or drugs of abuse is also often associated with pain symptoms. Accordingly, “pain” is understood herein to have a very broad meaning.

As used herein, the phrase “pharmaceutically acceptable” means those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with tissues of humans and animals. In some embodiments, “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

As used herein, the phrase “pharmaceutically acceptable salt(s),” includes, but is not limited to, salts of acidic or basic groups. Compounds that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. Acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions including, but not limited to, sulfuric, thiosulfuric, citric, maleic, acetic, oxalic, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, bisulfite, phosphate, acid phosphate, isonicotinate, borate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, bicarbonate, malonate, mesylate, esylate, napsydisylate, tosylate, besylate, orthophosphate, trifluoroacetate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include, but are not limited to, alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, ammonium,

sodium, lithium, zinc, potassium, and iron salts. The present invention can also include quaternary ammonium salts of the compounds.

As used herein, the terms “prevention” or “preventing” mean a reduction of the risk of acquiring a particular disease, condition, or disorder.

5 As used herein, the term “prodrug” means a derivative of a known direct acting drug, which derivative has enhanced delivery characteristics and therapeutic value as compared to the drug, and is transformed into the active drug by an enzymatic or chemical process.

10 As used herein, the term “sedation” means depressed consciousness in which a patient or subject retains the ability to independently and continuously maintain an open airway and a regular breathing pattern, and to respond appropriately and rationally to physical stimulation and verbal commands.

As used herein, the phrase “significant sedation” is consistent with a patient’s self-evaluation on the Stanford Sleepiness Scale, with Subject patients rating their degree of sedation as greater than or equal to Level 3, wherein: Level 1 = Feeling active, vital, alert, or wide awake; Level 2 = Functioning at high levels, but not at peak; able to concentrate; Level 3 = Awake, but relaxed; responsive but not fully alert; Level 4 = Somewhat foggy, let down; Level 5 = Foggy; losing interest in remaining awake; slowed down; Level 6 = Sleepy, woozy, fighting sleep; prefer to lie down; or Level 7 = No longer fighting sleep, sleep onset soon; having dream-like thoughts. “Significant sedation” also means that the patient or subject experiences sedation of Level 4 or greater on the Ramsay Sedation Scale, wherein: Level 1 = Patient is anxious and agitated or restless, or both; Level 2 = Patient is co-operative, oriented, and tranquil; Level 3 = Patient responds to commands only; Level 4 = Asleep; brisk response to light glabellar tap or loud auditory stimulus; Level 5 = asleep; sluggish response to light glabellar tap or loud auditory stimulus; Level 6 = asleep; no response to painful stimulus. “Significant sedation” also means that the patient or subject experiences sedation of Level 5 or less on the Modified Observer’s Assessment of Alertness/Sedation Scale, wherein: Level 6 = Appears alert and awake, responds readily to name spoken in normal tone; Level 5 = Appears asleep but responds readily to name spoken in normal tone; Level 4 = lethargic response to name spoken in normal tone; Level 3 = responds only after name is called loudly or repeatedly; Level 2 = responds only after mild prodding or shaking; Level 1 = does not respond to mild prodding or shaking; and Level 0 = does not respond to noxious stimulus.

As used herein, the phrase “solubilizing agent” means agents that result in formation of a micellar solution or a true solution of the drug.

As used herein, the term “solution/suspension” means a liquid composition wherein a first portion of the active agent is present in solution and a second portion of the active agent is present in particulate form, in suspension in a liquid matrix.

As used herein, the phrase “substantially isolated” means a compound that is at least partially or substantially separated from the environment in which it is formed or detected.

As used herein, the phrase “therapeutically effective amount” generally means the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician. The therapeutic effect is dependent upon the disorder being treated or the biological effect desired. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disorder and/or inhibition (partial or complete) of progression of the disorder, or improved treatment, healing, prevention or elimination of a disorder, or side-effects. The amount needed to elicit the therapeutic response can be determined based on the age, health, size and sex of the subject. Optimal amounts can also be determined based on monitoring of the subject’s response to treatment. In some embodiments, the therapeutically effective amount is a specific amount or range described herein.

As used herein, the terms “treat,” “treated,” or “treating” mean both therapeutic treatment or prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder or disease, or obtain beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of extent of condition, disorder or disease; stabilized (i.e., not worsening) state of condition, disorder or disease; delay in onset or slowing of condition, disorder or disease progression; amelioration of the condition, disorder or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder or disease. Treatment includes eliciting a clinically significant analgesic response without excessive levels of side effects, such as, but not limited to, significant sedation. Thus, “treatment of pain” or “treating pain” means an activity that prevents, alleviates or ameliorates any of the primary phenomena or secondary symptoms associated with pain.

As used herein “without significant sedation” means that the patient experiences a level of sedation not greater than Level 3 on the Ramsay Sedation Scale, not greater than Level 2 on the Stanford Sleepiness Scale, and/or not less than Level 6 on the Modified Observer’s

Assessment Of Alertness/Sedation Scale.

It is further appreciated that certain features described herein, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

Dexmedetomidine is a specific alpha-2-adrenergic receptor agonist that causes sedation, anesthesia, and analgesia in mammals. In humans, dexmedetomidine is commercially available for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting, as well as sedation of non-intubated patients prior to or during surgical and other procedures. See, e.g., U.S. Patent Nos. 6,716,867 and 6,313,311, each of which are hereby incorporated by reference in their entirety.

Dexmedetomidine contains a basic nitrogen atom capable of forming a pharmaceutically acceptable salt with a pharmaceutically acceptable acid. Pharmaceutically acceptable salts, in this respect, refers to the relatively non-toxic, inorganic, and organic acid addition salts of dexmedetomidine. These salts may be prepared *in situ* during final isolation and purification of dexmedetomidine or by separately reacting purified dexmedetomidine in its free base form with a suitable organic or inorganic acid, and thereafter isolating the salt thus formed. Furthermore, the salt may be formed during a manufacturing process to produce the spray formulation. Representative pharmaceutically acceptable salts include, but are not limited to, the hydrohalide (including hydrobromide and hydrochloride), sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, 2-hydroxyethylsulfonate, and laurylsulphonate salts, and the like. See, e.g., "Pharmaceutical Salts," Berge et al., J. Pharm. Sci., 1977, 66, 1-19. Dexmedetomidine hydrochloride is an example of a pharmaceutically acceptable salt. Use of dexmedetomidine hydrochloride may be used, in part because, in some cases, the hydrochloride salt has greater water solubility and stability against oxidation by ambient oxygen.

Dexmedetomidine derivatives include covalent modifications that create a prodrug. Upon administration, the prodrug derivative undergoes chemical modification by the mammal that yields dexmedetomidine. Prodrugs may be used to favorably alter the biodistribution or the pharmacokinetics of dexmedetomidine or to produce other desirable characteristics. For example, a reactive nitrogen of dexmedetomidine may be derivatized with a functional group that is cleaved, enzymatically or non-enzymatically, reductively, oxidatively, or hydrolytically, to reveal the active pharmaceutical ingredient. Uses of certain types of prodrugs are known (see,

e.g., R. B. Silverman, 1992, "The Organic Chemistry of Drug Design and Drug Action," Academic Press, Chp. 8). For example, prodrugs may be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free base form with a suitable derivatizing agent.

5 The present disclosure describes the surprising and unexpected result(s) that an intranasal formulation of dexmedetomidine, or a pharmaceutically acceptable salt thereof, can be developed for the treatment of pain that has a reduced time to the onset of pain relief corresponding to C_{plasma} , a C_{max} , and a reduced time to T_{max} , that can lead to pain relief or prevention without sedation or significant sedation in a mammal.

10 The present invention provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal. The dexmedetomidine, or a pharmaceutically acceptable salt thereof, or compositions comprising the same, can be administered in any conventional manner such that the composition is administered
15 intranasally. That is, the composition is contacted with the nasal cavity. The compositions can also be administered, for example, by implanting the composition so that it is absorbed intranasally.

 In some embodiments, the dexmedetomidine, or pharmaceutically acceptable salt thereof, is absorbed through the nasal mucosa. In some embodiments, at least 10%, at least 20%,
20 at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% of the composition is absorbed through the nasal mucosa. In some embodiments, dexmedetomidine, or a pharmaceutically acceptable salt thereof, is not absorbed through the oral mucosa.

 In some embodiments, the method comprises treating or preventing pain relief without
25 sedation or significant sedation. In some embodiments, the level of sedation is no greater than Level 1 on the Ramsay Sedation Scale. In some embodiments, the level of sedation is no greater than Level 2 on the Ramsay Sedation Scale. In some embodiments, the level of sedation is no greater than Level 3 on the Ramsay Sedation Scale. In some embodiments, the level of sedation is no greater than Level 1 on the Stanford Sleepiness Scale. In some embodiments, the level of
30 sedation is no greater than Level 2 on the Stanford Sleepiness Scale. In some embodiments, the level of sedation is no less than Level 6 on the Modified Observer's Assessment of Alertness/Sedation Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 3 on the Ramsay Sedation

Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 2 on the Ramsay Sedation Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 1 on the Ramsay Sedation Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 2 on the Stanford Sleepiness Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 1 on the Stanford Sleepiness Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not less than Level 6 on the Modified Observer's Assessment Of Alertness/Sedation Scale.

In some embodiments, the pain is idiopathic pain. In some embodiments, the idiopathic pain is neuralgia, myalgia, hyperalgia, hyperpathia, neuritis, or neuropathy. In some embodiments, the pain is associated with or caused by cancer, viral infection, physical trauma, arthritis, headache, migraine, or lower back pain. In some embodiments, the physical trauma is associated with or caused by surgery, a burn, blunt force trauma, or other trauma that can cause pain, such as being in an accident.

In some embodiments, the means and methods of administering the compositions described herein are known. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance (see, for example, *Modern Pharmaceutics*, Banker & Rhodes, Marcel Dekker, Inc. (1979); and Goodman & Gilman's *The Pharmaceutical Basis of Therapeutics*, 6th Edition, MacMillan Publishing Co., New York (1980)).

In some embodiments, the amount of compound to be administered is that amount which is therapeutically effective or intranasally effective. The dosage to be administered can depend on the characteristics of the subject being treated, e.g., the particular animal treated, age, weight, health, types of concurrent treatment, if any, and frequency of treatments, and can be easily determined by one of skill in the art (e.g., by the clinician). The selection of the specific dose regimen can be selected or adjusted or titrated by the clinician according to methods known to the clinician to obtain the desired clinical response or as they are described herein. Further, the

amount of a compound described herein that will be effective in the treatment and/or prevention of a particular disease, condition, or disorder will depend on the nature and extent of the disease, condition, or disorder, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The dosages can be, for example, the doses described herein.

The compounds, or composition comprising the same, can be administered in various dosage forms suitable for intranasal administration. The dosage amount present in the dosage form can be a pharmaceutically or intranasally effective amount. In some embodiments, the effective amount is an amount sufficient to treat or prevent pain. In some embodiments, the effective amount is an amount that does not produce sedation. In some embodiments, the effective amount does not produce significant sedation. In some embodiments, the effective amount is an amount sufficient to treat or prevent pain, yet does not produce sedation or significant sedation.

C_{plasma} is the concentration of dexmedetomidine in the plasma of a mammal or human at a particular time after administration. In some embodiments, the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation. Thus, in some embodiments, within about 15 minutes to about 20 minutes of administration of dexmedetomidine, or pharmaceutically acceptable salt thereof, to a mammal or human, the mammal or human will have a C_{plasma} of about 0.1 ng/ml. In some embodiments, the C_{plasma} is from about 0.09 ng/ml to about 0.11 ng/ml, from about 0.08 ng/ml to about 0.12 ng/ml, from about 0.06 ng/ml to about 0.09 ng/ml, from about 0.07 ng/ml to about 0.09 ng/ml, or from about 0.08 ng/ml to about 0.09 ng/ml. In some embodiments, the targeted C_{plasma} is reached within about 8 minutes to about 30 minutes, within about 10 minutes to about 30 minutes, within about 12 minutes to about 30 minutes, within about 8 minutes to about 20 minutes, within about 10 minutes to about 20 minutes, within about 12 minutes to about 20 minutes, within about 8 minutes to about 15 minutes, within about 10 minutes to about 15 minutes, within about 12 minutes to about 15 minutes, within about 8 minutes to about 10 minutes, within about 8 minutes to about 12 minutes, within about 15 minutes to about 20 minutes, within about 15 minutes to about 20 minutes, within about 15 minutes, within about 12 minutes, within about 10 minutes, or within about 8 minutes of administration and has an analgesic effect without significant sedation. This time point can reflect the onset of pain relief (i.e., an analgesic effect).

In some embodiments, the onset of pain relief is less than about 60 minutes, less than

about 55 minutes, less than about 50 minutes, less than about 45 minutes, less than about 40 minutes, less than about 35 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, less than about 12 minutes, less than about 10 minutes, about 15 minutes, about 12 minutes, about 10 minutes, or about 8 minutes. The onset of pain relief is the time when a mammal feels that the pain is less than prior to the administration of a compound or composition described herein. In some embodiments, the pain relief is complete and the mammal no longer feels the pain that was being relieved.

The present invention also provides methods of treating or preventing pain without significant sedation in an adult human comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the adult human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult within a period of time of about two hours after administration and has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 1.5 hours after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 1.0 hours after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 45 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 30 minutes to about 1.5 hours after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 40 minutes to about 75 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 45 minutes to about 70 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 50 minutes to about 65 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 55 minutes to about 60 minutes after administration, but yet has an analgesic effect within the period of time.

The present invention also provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally administering dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the mammal, particularly a human.

Administration to a single nostril means that the entire unit dose is administered to a single nostril as compared to a portion of the unit dose being administered to both nostrils. In some embodiments, the unit dose is only administered to a single nostril. That is, if a dosage is given every 4 hours, the dosage is administered to only a single nostril every 4 hours. The single nostril to which the compositions are administered may alternate between the two nostrils, however. In some embodiments, the methods comprise not administering dexmedetomidine or a pharmaceutically acceptable salt thereof or a composition described herein to more than one nostril (*e.g.*, two nostrils).

The present invention also provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying in the mammal a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the spray comprises droplets which have a Dv90 of less than about 150 μm . In some embodiments, the spray comprises droplets which have a Dv90 of less than about 125 μm . In some embodiments, the spray comprises droplets which have a Dv90 of less than about 100 μm . In some embodiments, the spray comprises droplets which have a Dv90 from about 60 μm to about 150 μm , from about 60 μm to about 125 μm , or from about 60 μm to about 100 μm . In some embodiments, the spray comprises droplets which have a Dv90 of more than about 40 μm . In some embodiments, the spray comprises droplets which have a Dv90 of more than about 50 μm . In some embodiments, the spray comprises droplets which have a Dv90 of more than about 60 μm . In some embodiments, the spray comprises droplets which have a Dv90 of more than about 70 μm .

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation, and whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation within a period of time of about two hours after administration and has an analgesic effect within the period of time.

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof,

to a single nostril of the mammal, particularly a human, whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation.

5 In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20
10 minutes of administration and has an analgesic effect without significant sedation, and wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In some embodiments, the present invention also provides methods of treating or preventing pain without significant sedation in an adult human comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically
15 acceptable salt thereof, to a single nostril of the adult human, whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult within a period of time of about two hours after administration and has an analgesic effect within the period of time.

In some embodiments, the present invention also provides methods of treating or preventing pain without significant sedation in an adult human comprising intranasally spraying
20 an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the adult human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult within a period of time of about two hours after administration and has an analgesic effect within
25 the period of time, and wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In some embodiments, the present invention also provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying
dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the
30 mammal, particularly a human, wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a human comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof,

to a single nostril of the human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation, whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the human within a period of time of about two hours after administration and has an analgesic effect within the period of time.

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation, whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the mammal within a period of time of about two hours after administration and has an analgesic effect within the period of time, and wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a human comprising intranasally spraying an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation, wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In some embodiments, the present invention also provides methods of treating or preventing pain without significant sedation in a human comprising intranasally spraying an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the human within a period of time of about two hours after administration and has an analgesic effect within the period of time, wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a human comprising intranasally spraying an intranasally

effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation, whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the human within a period of time of about two hours after administration and has an analgesic effect within the period of time, and wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In any of the methods described herein, the plasma C_{max} of dexmedetomidine is from about 0.08 ng/ml to about 0.25 ng/ml, about 0.08 ng/ml to about 0.2 ng/ml, from about 0.1 ng/ml to about 0.2 ng/ml, from about 0.08 ng/ml to about 0.15 ng/ml, from about 0.1 ng/ml to about 0.15 ng/ml, or from about 0.15 ng/ml to about 0.2 ng/ml. In some embodiments, the plasma C_{max} of dexmedetomidine is from about 0.08 ng/ml to about 0.2 ng/ml. In some embodiments, the plasma C_{max} of dexmedetomidine is about 0.15 ng/ml. In some embodiments, the plasma C_{max} of dexmedetomidine is about 0.2 ng/ml. In some embodiments, the plasma C_{max} of dexmedetomidine is about 0.25 ng/ml.

In any of the methods described herein, the T_{max} is less than about 60 minutes, less than about 50 minutes, less than about 40 minutes, less than about 35 minutes, or less than about 30 minutes. In some embodiments, the T_{max} is from about 20 minutes to about 60 minutes, from about 20 minutes to about 50 minutes, from about 20 minutes to about 40 minutes, from about 20 minutes to about 30 minutes, from about 30 minutes to about 60 minutes, from about 30 minutes to about 50 minutes, from about 30 minutes to about 40 minutes, from about 40 minutes to about 60 minutes, from about 40 minutes to about 50 minutes, or from about 50 minutes to about 60 minutes. In some embodiments, the T_{max} of dexmedetomidine is less than about 1 hour. In some embodiments, the T_{max} is less than about 50 minutes.

In any of the methods described herein, the compound or composition can be administered according to a specific schedule. In some embodiments, the composition is administered about every 2 hours, about every 4 hours, about every 6 hours, about every 8 hours, about every 10 hours, about every 12 hours, or about every 24 hours. The composition can also be administered as needed. In some embodiments, dexmedetomidine, or pharmaceutically acceptable salt thereof, or composition comprising the same, is administered about every 6 hours.

In any of the methods described herein, the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered as a unit dose of about 10 μg to about 100 μg , from about 10 μg to about 90 μg , from about 10 μg to about 80 μg , from about 10 μg to about 70 μg , from

about 10 µg to about 60 µg, from about 10 µg to about 50 µg, from about 10 µg to about 40 µg, from about 10 µg to about 30 µg, from about 10 µg to about 20 µg, from about 25 µg to about 100, from about 25 µg to about 90 µg, from about 25 µg to about 80 µg, from about 25 µg to about 70 µg, from about 25 µg to about 60 µg, from about 25 µg to about 50 µg, from about 25 µg to about 40 µg, from about 25 µg to about 35 µg, from about 25 µg to about 30 µg, from about 30 µg to about 45 µg, from about 35 µg to about 45 µg, from about 30 µg to about 40 µg, or from about 25 µg to about 45 µg. In some embodiments, the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered as a unit dose of about 10 µg, about 15 µg, about 20 µg, about 25 µg, about 30 µg, about 35 µg, about 40 µg, about 45 µg, about 50 µg, about 55 µg, about 60 µg, about 70 µg, about 75 µg, about 80 µg, about 85 µg, about 90 µg, about 95 µg, or about 100 µg. In some embodiments, the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered as a unit dose of less than about 100 µg, less than about 90 µg, less than about 80 µg, less than about 70 µg, less than about 60 µg, less than about 50 µg, less than about 40 µg, less than about 30 µg, less than about 20 µg, or less than about 10 µg. In some embodiments, the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered as a unit dose of about 10 µg, about 25 µg, about 30 µg, about 35 µg, about 40 µg, about 50 µg, about 75 µg, or about 100 µg. As discussed herein, the unit dose can be administered in many different manners. In some embodiments the unit dose is administered by a single nasal spray. In some embodiments the unit dose is administered by a single nasal spray using a single dose spray device requiring no priming. The single dose can be administered through a single actuation of a nasal spray device. An examples of spray device that does not require priming includes, but is not limited to, Aptar Unitdose Intranasal Systems. The spray device can, in some embodiments, deliver a volume of about 100 µl. In some embodiments, the volume is about 10, 20, 30, 40, 50, 60, 70, 80, or 90 µl. In some embodiments, the volume is from about 10-100, about 20-100, about 30-100, about 40-100, about 50-100, about 60-100, about 70-100, about 80-100, about 90-100 µl.

In any of the methods described herein, the method comprises having no effect or having minimal effect on blood pressure after administration. In some embodiments, there is no effect on blood pressure within the hour immediately after a compound described herein is administered. In some embodiments, there is only minimal effect on blood pressure within the hour immediately after a compound described herein is administered. In some embodiments, the resting mean arterial blood pressure of the mammal is not effected by more than about 5 mmHg, more than about 10 mmHg, more than about 15 mmHg, more than about 20 mmHg, more than

about 25 mmHg, or more than about 30 mmHg. The mean arterial blood pressure can be measured by any method known to one of skill in the art. In some embodiments, there is no or minimal effect on blood pressure after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof.

5 In any of the methods described herein, the method further comprises administering in simultaneous, alternating, or sequential combination to the human or mammal one or more additional therapeutic agents. The one or more additional therapeutic agents is chosen from an analgesic, such as an opioid analgesic (e.g. morphine, oxycodone, hydromorphone, etc.), a synthetic opioid-like analgesic (e.g. meperidine, fentanyl, pentazocine, butorphanol, etc.), or a
10 non-opioid analgesic (e.g. NSAIDs, ketamine, salicylates, steroids, etc.); a vitamin; a vasodilator; a benzodiazepine (e.g. clonazepam, alprazolam, lorazepam, etc.); a triptan (and other compounds for migraine headaches); an anti-convulsant (e.g. pregabalin, valproic acid, gabapentin, etc.); an anti-depressant (e.g. tricyclics such as amitriptyline, nortriptyline, etc.; serotonin and norepinephrine reuptake inhibitors such as duloxetine, fluoxetine, venlafaxine,
15 etc.); an anti-nausea medication (e.g. metoclopramide, prochlorperazine, ondansetron, granisetron, etc.); and an anti-hypertensive (e.g. beta blockers such as propranolol and calcium channel blockers such as verapamil, etc.).

The present invention also provides any one or more of the compositions described herein for treating pain in a mammal without significant sedation.

20 The present invention also provides any one or more of the compositions described herein for use in the manufacture of a medicament for treating pain in a mammal without significant sedation.

In any of the methods described herein, the dexmedetomidine, or pharmaceutically acceptable salt thereof, can be administered intranasally with a device. In some embodiments, the
25 device is a metered dose device. In some embodiments, the metered dose device is a multi-dose, unit dose, or bi-dose device.

In some embodiments, the device is suitable for intranasal administration. Any device that is suitable for intranasal administration can be used. In some embodiments, the device is a metered dose device. The metered dose device can deliver a specific dosage amount of the
30 composition. The metered dose device can be a unit-dose, bi-dose, or a multi-dose device. The pharmaceutically effective amount that can be administered using a metered dose device can be a unit dose device. The metered dose can, in some embodiments, be a device that can deliver a pharmaceutical composition intranasally. Examples of metered dose devices include, but are not limited to, devices that are pump devices, mechanical devices, pressurized devices, and/or

electromechanical devices. Examples of a metered dose device include, but are not limited to, a spray pump, a pre-compression nasal spray pump, a metered valve device, an actuated spray device, a side actuated spray device, a syringe nasal spray device (e.g. a syringe that has an atomizer to deliver a spray to the nasal cavity), a mucosal atomization device, an

5 electromechanical pump device (with and without a counter), and the like. Examples of metered dose devices also include, but are not limited to, devices manufactured by Aptar Pharma (Congers, NY) and are commercially available. Examples of metered dose devices also include, but are not limited to, UDS (Aptar Pharma), BDS (Aptar Pharma), eDevices (Aptar Pharma), Equadel (Aptar Pharma), Latitude (Aptar Pharma), DF30 (Aptar Pharma), VP7 (Aptar Pharma),
10 Classic Nasal Device (Aptar Pharma), MAD Nasal Drug Device (Wolf Tory Medical, Inc.), BD Accuspray SCF™ (Becton Dickinson), and the like. Another example includes, but is not limited to, an Aptar Unitdose Intranasal System.

Analgesic, intranasal formulations of dexmedetomidine, or a pharmaceutically acceptable salt or derivative thereof, can be administered in metered dosages so that a
15 predetermined amount of the active pharmaceutical ingredient is properly administered to the subject in a pharmaceutically effective amount. For example, the intranasal formulation may be packaged as a bulk liquid containing multiple doses in a pump spray system comprising a sealed container fitted with a metering pump. In some embodiments, a subject is treated by intranasal self-administration, such as by one or more actuations from a spray pump. An advantage of
20 intranasal delivery examples herein is the ability to titrate subjects by single doses as supplied by single, discrete actuations. This advantage is typically absent from other forms of drug delivery (e.g., patches, lozenges, tablets, and suppositories) in which a one-size-fits-all dosage is administered in a standard regimen. Additional advantages of intranasal formulations include its ease of use, especially when self-administered absent an attending health care professional.

25 In some embodiments, the metered dose device is a spray delivery device, which includes a base unit, a discharge actuator, an orifice for the formulation to be release from the device, and a reservoir. The reservoir can be filled with dexmedetomidine, or pharmaceutically acceptable salt thereof, and optionally other excipients, such as those described throughout the present application, prior to dispensing to the patient, e.g., at the manufacturing site. The
30 reservoir can contain a measured amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, or derivative thereof, to be discharged upon activation. The reservoir body may be any acceptable material, for example, formed simply by a section of a cylindrical hollow of a plastic, steel, such as stainless steel, transparent material, or the like so that its production is very simple. An actuator, which is movable relative to the orifice for activating discharge, may be

provided on or with the device. In the course of the actuating movement, the reservoir opens, e.g. by puncturing, to administer a single dosage through an orifice. During a part of the actuating travel following the starting position an elevated pressure is built up. In a subsequent portion of the actuating movement continuing in the same direction, the medium may be relieved of the pressure at one of the sides and communicated to an orifice. In such a manner, the medium is pushed from the reservoir and through the orifice by the action of pressure.

In some embodiments, as the liquid formulation leaves the orifice, the liquid droplets follow a trajectory which is influenced by the orifice shape, as well as by pressure asserted. In some embodiments, the droplet size, spray geometry, and the spray pattern are dependent on the design of the pump and/or the properties of the formulation. In some embodiments, the orientation of the actuator, pump design, and the properties of the formulation will influence the spray symmetry and the shape. The spray pattern may also be optimized to disperse the droplets over a wider pathway thereby increasing the surface area through which the compound can be absorbed. The device may further be designed to facilitate ease of patient use and placement of the administered spray to specific regions of the nasal mucosa.

Pump action sprays can be characterized by the application of external pressure for actuation, for example, external manual, mechanical or electrically initiated pressure. This is in contrast to pressurized systems, e.g., propellant-driven aerosol or compressed gas sprays, where actuation is typically achieved by controlled release of pressure, such as by controlled opening of a valve. In some embodiments, pump sprays are used. Use of a pump spray with the formulations herein allows for the administration of droplets or particles having a small mean diameter and a controllable size distribution of droplets. In some embodiments, pressurized systems containing a reservoir of pressurized propellant gas (e.g., carbon dioxide, nitrogen, chlorofluorocarbons, hydrofluoroalkanes, etc.) may produce suitable particles or droplets. Liquid droplets or particles having a diameter that is too small have the potential to enter into the lungs of a subject upon administration. In some embodiments, the droplet size of the delivered formulations further provides for an increase in surface area by being sprayed intranasally as opposed to being placed in a nostril, for example, with a dropper. The size of the spray particles and shape of the spray pattern also may contribute to whether the active ingredient is absorbed into body systems in addition to the nasal mucosa (e.g., lungs).

As described herein, the spray pump device may be pre-metered or, alternately, the device may be device-metered. Pre-metered dose devices may contain previously measured doses or a dose fraction in some type of units (e.g., single unit dose amount of solution, single or multiple blisters or other cavities) that may be included in the device during manufacture or by

the patient before use. Typical device-metered units have a reservoir containing a formulation sufficient for multiple doses that are delivered as metered sprays by the device itself when activated by the patient. The device may be metered both in the amount of drug substance delivered (i.e., the dosage per actuation), as well as the length of time between each dosage.

- 5 Limiting the time between each dosage can prevent over-use by limiting how often a dosage can be delivered to the patient.

The embodiments of the devices described herein, is not intended as limiting. In some embodiments, the formulations containing dexmedetomidine may alternately or additionally be provided as other intranasal dosage forms. For example, the intranasal composition may be
10 provided as a liquid compatible with administration by a dropper or similar device. The intranasal formulation can also be provided as a powder to be administered into the nasal cavity. The formulations can be, for example, packaged in pharmaceutically acceptable unit dose ampules with snap-off tops to permit the opened ampule to be inserted into the patient's nasal cavity to dispense a single dose of the formulation.

- 15 In yet another embodiment, the compounds can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.*, 1987, 14, 201; Buchwald et al., *Surgery*, 1980, 88, 507 Saudek et al., *N. Engl. J. Med.*, 1989, 321, 574). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and
20 Ball (eds.), Wiley, New York (1984); Ranger et al., *J. Macromol. Sci. Rev. Macromol. Chem.*, 1983, 23, 61; see, also Levy et al., *Science*, 1985, 228, 190; During et al., *Ann. Neurol.*, 1989, 25, 351; Howard et al., *J. Neurosurg.*, 1989, 71, 105). Other controlled-release systems discussed in the review by Langer, *Science*, 1990, 249, 1527-1533 may be used and can be adapted for
25 intranasal administration.

- In some embodiments, the aqueous dexmedetomidine intranasal compositions may be administered as drops or as a fine mist. Administration as a fine mist can improve the reproducibility of dosing by facilitating even deposition of the composition on the nasal mucosa. In some embodiments, a pump device is used to generate a fine mist from the bulk nasal solution
30 composition. Unit-dose and bi-dose devices may be used for dexmedetomidine nasal spray compositions since these devices can limit the total dose and/or number of doses that can be delivered from a single device thus reducing the potential for over-dosing/abuse. Furthermore, the unit-dose and/or bi-dose devices may require less packaged volume to deliver the spray volume by reducing the required amount of solution lost to pump priming. In some

embodiments, multi-dose devices are used due to their lower cost of manufacturing and less packaging waste.

The present invention also provides metered dose devices comprising a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the metered dose device delivers a metered dose spray of the pharmaceutical composition intranasally that is analgesic in a mammal without significant sedation.

In some embodiments, the metered dose spray produced by the device comprises droplets comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, that have a Dv90 of less than about 150 μm . In some embodiments, the spray comprises droplets which have a Dv90 of less than about 125 μm . In some embodiments, the spray comprises droplets which have a Dv90 of less than about 100 μm . In some embodiments, the spray comprises droplets which have a Dv90 from about 60 μm to about 150 μm , from about 60 μm to about 125 μm , or from about 60 μm to about 100 μm .

In some embodiments, the metered dose spray produced by the device comprises a metered dose of dexmedetomidine, or a pharmaceutically acceptable salt thereof, from about 10 μg to about 100 μg , from about 10 μg to about 90 μg , from about 10 μg to about 80 μg , from about 10 μg to about 70 μg , from about 10 μg to about 60 μg , from about 10 μg to about 50 μg , from about 10 μg to about 40 μg , from about 10 μg to about 30 μg , from about 10 μg to about 20 μg , from about 25 μg to about 100, from about 25 μg to about 90 μg , from about 25 μg to about 80 μg , from about 25 μg to about 70 μg , from about 25 μg to about 60 μg , from about 25 μg to about 50 μg , from about 25 μg to about 40 μg , from about 25 μg to about 35 μg , from about 25 μg to about 30 μg , or from about 25 μg to about 45 μg . In some embodiments, the metered dose spray produced by the device comprises a metered dose of about 10 μg , about 15 μg , about 20 μg , about 25 μg , about 30 μg , about 35 μg , about 40 μg , about 50 μg , about 55 μg , about 60 μg , about 70 μg , about 75 μg , about 80 μg , about 85 μg , about 90 μg , about 95 μg , or about 100 μg . In some embodiments, the metered dose spray produced by the device comprises a metered dose of less than about 100 μg , less than about 90 μg , less than about 80 μg , less than about 70 μg , less than about 60 μg , less than about 50 μg , less than about 40 μg , less than about 30 μg , less than about 20 μg , or less than about 10 μg . In some embodiments, the metered dose spray produced by the device comprises a metered dose of about 10 μg , about 25 μg , about 35 μg , about 50 μg , about 75 μg , or about 100 μg .

In some embodiments, the metered dose spray produced by the device comprises a volume of less than about 150 μl , less than about 140 μl , less than about 130 μl , less than about

120 μ l, less than about 110 μ l, less than about 100 μ l, less than about 75 μ l, or less than about 50 μ l. In some embodiments, the metered dose spray produced by the device comprises a volume of about 150 μ l, about 140 μ l, about 130 μ l, about 120 μ l, about 110 μ l, about 100 μ l, about 75 μ l, or about 50 μ l.

5 In some embodiments, the metered dose spray produced by the device produces a C_{plasma} in the mammal of from about 0.09 ng/ml to about 0.11 ng/ml, from about 0.08 ng/ml to about 0.12 ng/ml, or about 0.1 ng/ml within about 12 minutes to about 30 minutes, from about 12 minutes to about 20 minutes, from about 15 minutes to about 20 minutes, or within about 15 minutes of administration and has an analgesic effect without significant sedation. In some
10 embodiments, the metered dose spray produced by the device produces a C_{plasma} in the mammal of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration.

In some embodiments, the metered dose spray produces an onset of pain relief less than about 60 minutes, less than about 55 minutes, less than about 50 minutes, less than about 45 minutes, less than about 40 minutes, less than about 35 minutes, less than about 30 minutes, less
15 than about 25 minutes, less than about 20 minutes, or about 15 minutes.

In some embodiments, the metered dose spray produced by the device does not produce significant sedation in an adult within a period of time of about two hours after administration and has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 1.5 hours after administration, but
20 yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 1.0 hours after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 45 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation
25 in the adult is not produced within a period of time from about 30 minutes to about of about 1.5 hours after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 40 minutes to about 75 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a
30 period of time from about 45 minutes to about 70 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 50 minutes to about 65 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 55 minutes to

about 60 minutes after administration, but yet has an analgesic effect within the period of time.

In some embodiments, the metered dose spray produced by the device produces a plasma $C_{\max}$ in the mammal from about 0.08 ng/ml to about 0.25 ng/ml, from about 0.08 ng/ml to about 0.2 ng/ml, from about 0.1 ng/ml to about 0.25 ng/ml, from about 0.1 ng/ml to about 0.2 ng/ml, from about 0.08 ng/ml to about 0.15 ng/ml, from about 0.1 ng/ml to about 0.15 ng/ml, from about 0.15 ng/ml to about 0.2 ng/ml, or from about 0.15 ng/ml to about 0.25 ng/ml. In some embodiments, the metered dose spray produced by the device produces a plasma $C_{\max}$ in the mammal of about 0.08 ng/ml to about 0.25 ng/ml. In some embodiments, the metered dose spray produced by the device produces a plasma $C_{\max}$ in the mammal of about 0.08 ng/ml to about 0.2 ng/ml. In some embodiments, the metered dose spray produced by the device produces a plasma $C_{\max}$ in the mammal of about 0.15 ng/ml. In some embodiments, the metered dose spray produced by the device produces a plasma $C_{\max}$ in the mammal of about 0.08 ng/ml, about 0.1 ng/ml, about 0.2 ng/ml, or about 0.25 ng/ml.

In some embodiments, the metered dose spray produced by the device produces a $T_{\max}$ in the mammal of less than about 60 minutes, less than about 50 minutes, less than about 40 minutes, less than about 35 minutes, or less than about 30 minutes. In some embodiments, the metered dose spray produced by the device produces a $T_{\max}$ in the mammal from about 20 minutes to about 60 minutes, from about 20 minutes to about 50 minutes, from about 20 minutes to about 40 minutes, from about 20 minutes to about 30 minutes, from about 30 minutes to about 60 minutes, from about 30 minutes to about 50 minutes, from about 30 minutes to about 40 minutes, from about 40 minutes to about 60 minutes, from about 40 minutes to about 50 minutes, or from about 50 minutes to about 60 minutes. In some embodiments, the metered dose spray produced by the device produces a $T_{\max}$ in the mammal of less than about 1 hour. In some embodiments, the metered dose spray produced by the device produces a $T_{\max}$ in the mammal of less than about 50 minutes.

In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 1, Level 2, or Level 3 on the Ramsay Sedation Scale. In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 3 on the Ramsay Sedation Scale. In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 2 on the Ramsay Sedation Scale.

In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 1 or Level 2 on the Stanford Sleepiness Scale. In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 2 on the Stanford Sleepiness Scale.

In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not less than Level 6 on the Modified Observer's Assessment Of Alertness/Sedation Scale.

In some embodiments, the metered dose spray produced by the device has no or minimal effect on the blood pressure of the mammal after administration. In some embodiments, the metered dose spray produced by the device has no effect on blood pressure within the hour immediately after a compound described herein is administered. In some embodiments, the metered dose spray produced by the device has only minimal effect on blood pressure within the hour immediately after a compound described herein is administered. In some embodiments, the resting mean arterial blood pressure of the mammal is not effected by more than about 5 mmHg, more than about 10 mmHg, more than about 15 mmHg, more than about 20 mmHg, more than about 25 mmHg, or more than about 30 mmHg.

In some embodiments, any of the compositions described herein can further comprise one or more other therapeutic agents. The one or more additional therapeutic agents is chosen from an analgesic, such as an opioid analgesic (e.g. morphine, oxycodone, hydromorphone, etc.), a synthetic opioid-like analgesic (e.g. meperidine, fentanyl, pentazocine, butorphanol, etc.), or a non-opioid analgesic (e.g. NSAIDs, ketamine, salicylates, steroids, etc.); a vitamin; a vasodilator; a benzodiazepine (e.g. clonazepam, alprazolam, lorazepam, etc.); a triptan (and other compounds for migraine headaches); an anti-convulsant (e.g. pregabalin, valproic acid, gabapentin, etc.); an anti-depressant (e.g. tricyclics such as amitriptyline, nortriptyline, etc.; serotonin and norepinephrine reuptake inhibitors such as duloxetine, fluoxetine, venlafaxine, etc.); an anti-nausea medication (e.g. metoclopramide, prochlorperazine, ondansetron, granisetron, etc.); and an anti-hypertensive (e.g. beta blockers such as propranolol and calcium channel blockers such as verapamil, etc.).

Examples of other analgesic agents include, but are not limited to, narcotics, NSAIDs, Cox-2 inhibitors, steroids, and the like. Other examples include, but are not limited to, aspirin, codeine, oxycodone, ibuprofen, butalbital, acetaminophen (APAP), caffeine, aspirin, hydrocodone, acetaminophen, propoxyphene n-apap, propoxyphene HCl, butorphanol tartrate, pentazocine-apap, pentazocine-naloxone, tramadol, tramadol extended release, fentanyl,

morphine, meperidine HCl, hydromorphone HCl, methadone, levorphanol tartrate, oxymorphone, buprenorphine, celecoxib, rofecoxib, naltrexone, naproxen, flurbiprofen, diclofenac, sulindac, oxaprozin, piroxicam, indomethacin, etodolac, meclofenamate, meloxicam, fenoprofen, ketoprofen, nabumetone, tolmetin, ketorolac tromethamine, salsalate, diflunisal, choline and magnesium salicylates, or any combination thereof. The compounds or salts thereof, and compositions comprising the same, described herein can be administered either alone or in combination (concurrently or serially) with the other pharmaceutical agents. In some embodiments, the compositions described herein can be administered with one or more other analgesic agents.

In some embodiments, the composition further comprises a carrier vehicle. In some embodiments, the pharmaceutical composition further comprises sodium phosphate and/or sodium citrate. In some embodiments, the pharmaceutical composition further comprises sodium citrate, citric acid, and sodium chloride. In some embodiments, the pharmaceutical composition further comprises about 0.2% to about 0.3% (w/w) sodium citrate and about 0.005% to about 0.015% (w/w) citric acid.

In some embodiments, the composition comprises a salt, such as a pharmaceutically acceptable salt. In some embodiments, the composition comprises sodium chloride, potassium chloride, or any combination thereof. In some embodiments, the composition comprises citric acid. In some embodiments, the composition comprises sodium citrate, citric acid, and a salt, including, but not limited to, sodium chloride. In some embodiments, the composition comprises about 0.1% to about 0.5%, from about 0.1% to about 0.4%, from about 0.2% to about 0.5%, from about 0.2% to about 0.4%, from about 0.2% to about 0.3 % (w/w) of sodium citrate. In some embodiments, the composition comprises from about 0.005% to about 0.015%, from about 0.005% to about 0.05%, from about 0.005% to about 0.004%, from about 0.005% to about 0.03%, from about 0.005% to about 0.02%, or from about 0.005% to about 0.0175 % (w/w) of citric acid.

In some embodiments, the pharmaceutical composition further comprises a chelator or stabilizer that can be used to enhance chemical stability where required. Suitable stabilizers include, but are not limited to, chelating agents or complexing agents, such as, for example, the calcium complexing agent ethylene diamine tetraacetic acid (EDTA), a salt of EDTA, citric acid, chitosan, sorbitol, and tartaric acid. For example, an appropriate amount of EDTA or a salt thereof, e.g., the disodium salt, can be included in the composition to complex excess calcium ions and prevent gel formation during storage. EDTA or a salt thereof can suitably be included in an amount of about 0.01% to about 0.5%. In those embodiments containing a preservative other

than EDTA, the EDTA or a salt thereof, more particularly disodium EDTA, can be present in an amount of about 0.025% to about 0.1% by weight. Without being bound by any theory, the chelating agents can prevent multivalent cationic degradation of dexmedetomidine or other components in the composition.

5 In some embodiments, the intranasal compositions described herein may optionally include a buffering system comprised of an acid/base pair that resists changes in pH. The pH of the compositions can be controlled to limit irritation of the nasal spray. In some embodiments, a solution pH of about 6.0 to about 6.5 can be used to be compatible with the pH of nasal secretions while maintaining the drug in solution. Pharmaceutically acceptable buffers that
10 provide a pH compatible with the nasal mucosa include citrate, phosphate, and the like. In some embodiments, the pH of the composition is less than 7, less than 6.9, less than 6.8, less than 6.7, less than 6.6, less than 6.5, less than 6.4, less than 6.2, or less than 6.1. In some embodiments, the pH of the composition is from about 6 to about 6.1, from about 6 to about 6.2, from about 6 to about 6.3, from about 6 to about 6.4, from about 6 to about 6.5, from about 6 to about 6.6,
15 from about 6 to about 6.7, from about 6 to about 6.8, from about 6 to about 6.9, or from about 6 to about 7.0. In some embodiments, the pH of the composition is such that the composition does not irritate the nasal cavity.

 In some embodiments, the pharmaceutical composition further comprises one or more anti-microbial preservatives. Examples of preservatives include, but are not limited to, mercury-containing substances such as phenylmercuric salts (e.g., phenylmercuric acetate, borate and
20 nitrate) and thimerosal; stabilized chlorine dioxide; quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride; imidazolidinyl urea; parabens such as methylparaben, ethylparaben, propylparaben and butylparaben, and salts thereof; phenoxyethanol; chlorophenoxyethanol; phenoxypropanol;
25 chlorobutanol; chlorocresol; phenylethyl alcohol; disodium EDTA; and sorbic acid and salts thereof. Preservatives may precipitate in the presence of other excipients in the composition. For example, benzalkonium chloride can precipitate. Thus, in some embodiments in which a preservative is present, the preservative is one that does not precipitate but remains in solution in the composition. A suitable preservative is phenylethyl alcohol. The one or more anti-microbial
30 preservatives can be included, for example, to suppress microbial and fungal growth in the final delivery systems.

 In some embodiments, the pharmaceutical composition further comprises one or more antioxidants. Suitable antioxidants may optionally be included in the nasal composition, for example, to stabilize the formulation against long term effects of oxidation. Examples of

antioxidants include, but are not limited to, Vitamin E (and derivatives thereof), Vitamin C (and derivatives thereof), BHT, BHA, propyl gallate, citric acid, erythorbic acid, monothioglycerol, a metabisulfite (sodium or potassium), propionic acid, sodium sulfite, and thymol.

In some embodiments, the pharmaceutical composition further comprises one or more
5 dose confirmation excipients, which help facilitate proper usage and/or avoid overdosage. For medications that are administered intranasally, it can be difficult for the subject to determine whether the medication has been properly administered. The inclusion of a dose confirmation excipient can provide positive feedback to the subject after administration, confirming that the dose has been administered intranasally. In some embodiments, the dose confirming excipient
10 has an odor that can allow the subject to confirm that the dose was administered and taken or deposited into the nose. Other feedback mechanisms can be used to confirm that the dose has been administered appropriately. Odor is one non limiting example. In some embodiments, the dose confirmation excipient is phenylethyl alcohol. Without being bound by theory, dose confirmation excipients provide sensory feedback to the patient to confirm that a dose has been
15 delivered, thereby increasing compliance with the prescribed dosing regimen and reducing the potential for overdosing. Phenylethyl alcohol has a distinct odor and may serve as both an antimicrobial and dose confirmation excipient in the compositions previously described.

In some embodiments, the pharmaceutical composition further comprises one or more humectants. Examples of humectants include, but are not limited to, glycerin, propylene glycol,
20 polyethylene glycol, and a sugar/sugar alcohol, or any combination thereof. Humectants can provide moisturizing effects and reduce nasal irritation.

In some embodiments, the pharmaceutical composition further comprises one or more osmolality adjusting agents. The osmolality of the intranasal composition can also be relevant to the uptake of the medication intranasally. Suitable osmolality adjusting agents include, but not
25 limited to, sodium chloride, dextrose, sugars, or any combination thereof. The osmolality adjusting agents can also be included in the composition to produce solutions that are less irritating to the nasal mucosa by aligning the osmolality of the administered solution with the nasal mucosa.

In some embodiments, the pharmaceutical composition is free of a viscosity enhancing
30 agent. Viscosity enhancing agents including, but not limited to, Methocel E4M can optionally be added to increase residence time of the instilled or spray solution with the nasal mucosa. However, in the case of dexmedetomidine, the use of a viscosity increasing agent may result in diminished dexmedetomidine plasma levels and may therefore be omitted under certain conditions, such as when the dexmedetomidine composition is intended for rapid uptake.

Therefore, it was surprisingly found that the viscosity of the intranasal composition can affect the uptake of the active ingredient. Thus, in some embodiments, an increase in viscosity can decrease the uptake of dexmedetomidine. Accordingly, in some embodiments, the composition is free of a polymer that increases the viscosity of a liquid vehicle or composition. In some
5 embodiments, the polymer is a water-soluble polymer. Examples of a soluble polymer include, but are not limited to, a cellulose ether (e.g. hydroxypropyl methylcellulose), other cellulose based polymers (methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc.), povidone, polyvinyl alcohol, gums (e.g. xanthum gum), polyethylene glycol (PEG), polyethylene oxide (PEO), hyaluronic acid (and derivatives and salts thereof), carrageenan, dextran, and
10 poloxamer. In some embodiments, the cellulose ether is hydroxypropyl methylcellulose (HPMC). Thus, in some embodiments, the composition is free of HPMC. In some embodiments, the viscosity of the intranasal composition is no greater than the viscosity of water.

In some embodiments, the viscosity of the intranasal composition is no greater than 110%, no greater than 120%, no greater than 130%, no greater than 140%, no greater than 150%,
15 no greater than 160%, no greater than 170%, no greater than 180%, no greater than 190%, or no greater than 200% of the viscosity of water. In some embodiments, the viscosity of the intranasal formulation is about 1 mPa*s, 2 mPa*s, 3 mPa*s, 4 mPa*s, or 5 mPa*s. In some embodiments, the viscosity of the intranasal formulation is less than about 1 mPa*s, 2 mPa*s, 3 mPa*s, 4
20 mPa*s, or 5 mPa*s. In some embodiments, the viscosity of the intranasal formulation is from about 1 mPa*s to about 2 mPa*s, from about 1 mPa*s to about 3 mPa*s, from about 1 mPa*s to about 4 mPa*s, from about 1 mPa*s to about 5 mPa*s, from about 1.5 mPa*s to about 2.5
mPa*s, from about 2 mPa*s to about 3 mPa*s, from about 2 mPa*s to about 4 mPa*s, or from about 2 mPa*s to about 5 mPa*s.

The viscosity of a composition can be calculated by various methods. The viscosity can
25 also be directly measured using various techniques. For example, the viscosity of a composition can be calculated according to the following equation. The equation expresses the illustrated approximate relationship between solution viscosity and polymer concentration is $\eta^{1/3} = (C \cdot \alpha) + 1$, where η is the solution viscosity in millipascal-seconds, C is the polymer concentration in solution (expressed in percent), and α is a constant specific to the molecular weight. For
30 example, the value of α can be calculated by substitution and may then be used to calculate the approximate viscosity at the desired concentration.

It is also known in the art that the compounds and compositions comprising the same can be contained in formulations with pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers,

buffers, humectants, moisturizers, solubilizers, preservatives and the like. In some embodiments, the compounds and compositions comprising the same can be contained in formulations that do not comprise pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. In some embodiments, the compounds and compositions comprising the same can be contained in formulations that do not comprise a surfactant. The pharmaceutical compositions can also comprise suitable solid or gel phase carriers or excipients. In addition to other excipients described herein, examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. In some embodiments, the compounds described herein can be used with agents including, but not limited to, topical analgesics (e.g., lidocaine), barrier devices (e.g., GelClair), or rinses (e.g., Caphosol).

In some embodiments, when administered to a human, the compounds can be sterile.

Water can be a suitable carrier when the compound is administered intranasally. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers. Suitable pharmaceutical carriers also include excipients such as, but not limited to, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The compositions described herein can take the form of a solution, suspension, emulsion, powder, sustained-release formulation, aerosol, spray, or any other form suitable for the uses described herein. Examples of suitable pharmaceutical carriers are described in

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In some embodiments, the compounds are formulated in accordance with routine procedures as a pharmaceutical composition adapted for administration to humans. In some embodiments, compounds are solutions in sterile isotonic aqueous buffer and, for example, with the other components described herein. Where necessary, the compositions can also include a solubilizing agent. Compositions may optionally include a local anesthetic such as lidocaine to ease pain at the site of the administration that can be due to, for example, irritation from the composition.

In some embodiments, the present invention also provides pharmaceutical packs or kits comprising one or more containers containing one or more compounds described herein.

Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration for treating a condition, disease, or disorder described herein. In some

5 embodiments, the kit contains more than one compound described herein. In some embodiments, the kit comprises a compound described herein in a single unit dosage form, such as a single dose within an intranasal administrable device such as a metered dose device that administers a spray or a powder to a nasal activity.

10 In some embodiments, the components described herein are supplied either separately or mixed together in unit dosage form, for example, the components can be combined to create an intranasal formulation. Examples of making the formulations are described herein and can be modified to yield any suitable intranasal formulation.

15 The pharmaceutical compositions can be in unit dosage form. In such form, the composition can be divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations. The dosage form can be any form including, but not limited to, the forms described herein.

20 In some embodiments, a composition of the present invention is in the form of a liquid wherein the active agent is present in solution, in suspension, as an emulsion, or as a solution/suspension. In some embodiments, the liquid composition is in the form of a gel. In other embodiments, the liquid composition is aqueous. In other embodiments, the composition is in the form of an ointment. The liquid composition can also be a spray.

25 The liquid vehicle refers to the liquid in which dexmedetomidine is suspended or dissolved. Examples of the liquid vehicles include, but are not limited to, water, saline, an aqueous solution, DMSO, and the like.

30 In some embodiments, the pharmaceutical composition comprises, in addition to dexmedetomidine, the following (all based on % w/w): about 0.245% anhydrous sodium citrate, about 0.01% anhydrous citric acid, about 0.7% sodium chloride, about 99.045% purified water, at an initial pH of 6.31 adjusted to a final pH of about 6.78 with 2N sodium hydroxide. In some embodiments, the pharmaceutical composition comprises, in addition to dexmedetomidine, the following (all based on % w/w): about 0.245% anhydrous sodium citrate, about 0.01% anhydrous citric acid, about 0.1% Methocel E4M, about 0.7% sodium chloride, about 98.945% purified water, at an initial pH of 6.36 adjusted to a final pH of about 6.83 with 2N sodium hydroxide. In some embodiments, the pharmaceutical composition comprises, in addition to

dexmedetomidine, the following (all based on % w/w): about 0.193% sodium phosphate monobasic (monohydrate), about 0.162% sodium phosphate dibasic (heptahydrate), about 0.7% sodium chloride, about 98.946% purified water, at an initial pH of 6.37 adjusted to a final pH of about 6.53 with 2N sodium hydroxide. In some embodiments, the pharmaceutical composition comprises, in addition to dexmedetomidine, the following (all based on % w/w): about 0.193% sodium phosphate monobasic (monohydrate), about 0.162% sodium phosphate dibasic (heptahydrate), about 0.75% sodium chloride, about 98.896% purified water, at an initial pH of 6.37 adjusted to a final pH of about 6.53 with 2N sodium hydroxide. In some embodiments, the pharmaceutical composition comprises, in addition to dexmedetomidine, the following (all based on % w/w): about 0.193% sodium phosphate monobasic (monohydrate), about 0.162% sodium phosphate dibasic (heptahydrate), about 0.25% phenylethyl alcohol, about 0.68% sodium chloride, about 98.616% purified water, at an initial pH of 6.15 adjusted to a final pH of about 6.51 with 2N sodium hydroxide. In some embodiments, the pharmaceutical composition comprises, in addition to dexmedetomidine, the following (all based on % w/w): about 0.226% anhydrous sodium citrate, about 0.024% anhydrous citric acid, about 0.25% phenylethyl alcohol, about 0.76% sodium chloride, about 98.64% purified water, at an initial pH of 5.68 adjusted to a final pH of about 6.04 with 2N sodium hydroxide.

The compositions comprising dexmedetomidine described herein are stable. For a 0.035% dexmedetomidine hydrochloride intranasal spray formulation, for example, the stability is at least 3 months, at least 6 months, at least 9 months, or at least one year wherein the storage conditions are 25°C at 60% relative humidity, and at least 1 month, at least 3 months, at least 6 months wherein the storage conditions are 40°C at 75% relative humidity.

Where dexmedetomidine, or a pharmaceutically acceptable salt thereof, is used in any method or device described herein, it is understood that any and all metabolites of dexmedetomidine, or a pharmaceutically acceptable salt thereof, can also be used likewise.

In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the invention in any manner.

Examples

Example 1: Preparation of Intranasal Formulations

To a container, purified water, USP was added. To the water, anhydrous citric acid, sodium citrate dihydrate, sodium chloride, phenylethyl alcohol, and disodium EDTA was mixed until dissolved. The pH of the solution was modified, if necessary, to be in the range of 6.0 and

6.5. With continued mixing, dexmedetomidine HCl was added until dissolved. Water was added to adjust the dexmedetomidine HCl to a final selected concentration.

Example 2: Intranasal Formulations of Dexmedetomidine

Nasal delivery of dexmedetomidine HCl (DEX) was evaluated from aqueous sprays to provide pharmacokinetic profiles that provide analgesia without significant sedation. The nasal route of delivery is often desired by patients in pain that may be unable or unwilling to tolerate the treatment by an oral route (e.g., buccal, sublingual, swallowing), by a rectal route (e.g. foams, suppositories, etc.), or an injection route. In addition to the aqueous nasal sprays initially developed for evaluation of intranasally administered DEX, the formulations can be modified to include dry powders, suspensions, and/or vapors as would be apparent from the description contained herein.

An initial screening of DEX aqueous nasal compositions administered as nasal drops was evaluated in a canine model. The influence of buffer species and viscosity was evaluated in the following base compositions.

Component	First Placebo Base Composition (% w/w)		
	Formulation 1	Formulation 2	Formulation 3
Sodium Citrate, Anhydrous	0.245	0.245	--
Citric Acid, Anhydrous	0.010	0.010	--
Methocel E4M	--	0.100	--
Sodium Phosphate Monobasic, Monohydrate	--	--	0.193
Sodium Phosphate Dibasic, Heptahydrate	--	--	0.162
Sodium Chloride	0.700	0.700	0.700
Purified Water	99.045	98.945	98.946
Total	100.000	100.000	100.000
Initial pH	6.31	6.36	6.37
Final pH ¹	6.78	6.83	6.53
¹ Adjusted with 2N Sodium Hydroxide.			

DEX was dissolved into the Placebo Base Compositions to prepare Formulation solutions that would deliver 50 µg DEX in 100 µL volume. The DEX compositions were expressed as follows.

Component	DEX Nasal Drop Composition (% w/v)		
	Formulation 1-DEX	Formulation 2-DEX	Formulation 3-DEX
Dexmedetomidine HCl	0.059	0.059	0.059
Formulation 1	99.941	--	--
Formulation 2	--	99.941	--
Formulation 3	--	--	99.941
Total	100.000	100.000	100.000

The density of the DEX nasal drop compositions was approximately 1 g/mL at room temperature and allowed for weight and volume to be used interchangeably. The three DEX Nasal Drop Compositions were administered to canines. Surprisingly, compositions without a cellulose ether, which is a viscosity enhancing agent, such as Formulation 1-Dex and Formulation 3-Dex, provided significant plasma levels in less than 15 minutes after administration. Also surprisingly, Formulation 2-Dex, which contained 0.1% Methocel E4M and had the highest solution viscosity, resulted in negligible plasma levels of DEX, indicating that increased solution viscosity diminished the effectiveness of DEX delivered intranasally. This result was unexpected.

The influence of additional formulation additives was further investigated from aqueous DEX solutions that were delivered as fine mists from multiple-use aqueous spray pumps. The following placebo base compositions were prepared.

Component	Second Placebo Base Composition (% w/w)		
	Formulation 4	Formulation 5	Formulation 6
Sodium Citrate, Anhydrous	--	--	0.226
Citric Acid, Anhydrous	--	--	0.024
Sodium Phosphate Monobasic, Monohydrate	0.193	0.193	--
Sodium Phosphate Dibasic, Heptahydrate	0.162	0.162	--
Phenylethyl Alcohol	--	0.250	0.250
Disodium Edetate Dihydrate	--	0.100	0.100
Sodium Chloride	0.750	0.680	0.760
Purified Water	98.896	98.616	98.640

Total	100.000	100.000	100.000
Initial pH	6.37	6.15	5.68
Final pH ¹	6.53	6.51	6.04
¹ Adjusted with 2N Sodium Hydroxide.			

DEX was dissolved into the second set of Placebo Base Compositions to prepare solutions that would deliver 50 µg DEX in 100 µL volume. The DEX compositions are expressed as follows.

Component	DEX Nasal Spray Composition (% w/v)		
	Formulation 4-Dex	Formulation 5-Dex	Formulation 6-Dex
Dexmedetomidine HCl	0.059	0.059	0.059
Formulation 4	99.941	--	--
Formulation 5	--	99.941	--
Formulation 6	--	--	99.941
Total	100.000	100.000	100.000
Calculated Osmolality (mOsm/kg)	288	368	306

5

The density of the DEX nasal spray compositions was approximately 1 g/mL at room temperature and allowed for weight and volume to be used interchangeably. The three DEX Nasal Spray Compositions were administered to canines using a manually actuated nasal pump. The results of the canine study indicated measurable plasma levels as early as 5 minutes and decreasing plasma levels according to Formulation 4-Dex > Formulation 5-Dex > Formulation 6-Dex.

10

An additional placebo base composition was prepared as defined below.

Component	Third Placebo Base Composition (% w/w)
	Formulation 7
Sodium Citrate, Anhydrous	0.230
Citric Acid, Anhydrous	0.020
Phenylethyl Alcohol	0.250
Disodium Edetate Dihydrate	0.100
Sodium Chloride	0.760
Purified Water	98.640

Total	100.000
Initial pH	5.79
Final pH ¹	6.27
¹ Adjusted with 2N Sodium Hydroxide.	

DEX was dissolved into the third Placebo Base Composition to prepare a solution that would deliver 25 µg DEX in 100 µL volume. The DEX composition is expressed as follows.

Component	DEX Nasal Spray Composition (% w/v)
	Formulation 7-Dex
Dexmedetomidine HCl	0.0295
Formulation 7	99.9705
Total	100.0000
Final pH	6.20

The density of the DEX nasal spray composition was approximately 1 g/mL at room temperature and allowed for weight and volume to be used interchangeably. The DEX nasal compositions were developed as an aqueous solution that could be delivered as nasal drops or as a fine mist from a nasal spray device. The DEX nasal compositions minimally contained DEX dissolved in purified water at a suitable concentration to deliver the intended DEX dose in 25 µL to 200 µL. Dose volumes less than 25 µL can result in variable delivery while dose volumes greater than 200 µL can result in excess run off from the nasal cavity. The aqueous nasal compositions can optionally contain additional materials to facilitate the intranasal delivery of DEX.

Example 3: Droplet Particle Size Determination

In vitro spray pump performance of the Drug Product (DEX-IN.02 50µg API/100 µL Intranasal Spray and DEX-IN.03 25µg API/50 µL Intranasal Spray) and Placebo (DEX-IN.02P 100 µL Intranasal Spray) was based on droplet size distribution as measured by laser diffraction using a Malvern Spraytec. The Malvern Spraytec operates based on a laser diffraction principle and is a commonly used technique to characterize droplet size distributions from nasal sprays. The droplet size distribution was characterized by the following metrics: volume distribution (Dv10, Dv50, Dv90), Span and percentage (%) less than 10 µm per the FDA CMC Guidance for Nasal Sprays (2002) and FDA Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, April 2003.

Example 4: Pharmacokinetic Study of Dexmedetomidine Formulations Following Intranasal or Sublingual Administration in Dogs

One objective of the present study was to compare the pharmacokinetics of multiple experimental dexmedetomidine formulations to the pharmacokinetics of a commercial formulation of dexmedetomidine when administered intranasally or sublingually in dogs. For each dosing event, five male dogs were dosed intranasally or sublingually with 50 µg of dexmedetomidine free-base (equivalent to 59 µg of dexmedetomidine HCl) in 100 µL of formulation, except for Formulation 7-Dex, where the dogs were dosed with 25 µg of dexmedetomidine free-base (equivalent to 29.5 µg of dexmedetomidine HCl) in 100 µL, and the PRECEDEX[®] formulation, which contained 50 µg dexmedetomidine base equivalent in 500 µL of solution. Dosing was performed in 10 dosing events in three segments with the formulations, with a minimum 2-day interval between the dosing events, as shown in the table below:

Segment	Dosing Event	Formulation	Dose Route
1	1	Formulation 1-Dex*	Intranasal
	2	Formulation 3-Dex*	Intranasal
	3	Formulation 2-Dex*	Intranasal
	4	PRECEDEX [®] *	Intranasal
2	5	Formulation 4-Dex*	Intranasal
	6	Formulation 5-Dex*	Intranasal
	7	Formulation 6-Dex*	Intranasal
3	8**	Formulation 6-Dex*	Intranasal
	9	Formulation 7-Dex***	Intranasal
	10	DEX-SL.01*	Sublingual

*Dose = 50 µg of dexmedetomidine free-base (equiv. to 59 µg of dexmedetomidine HCl).

**Redose of Formulation 6-Dex using a new sprayer.

***Dose = 25 µg of dexmedetomidine free-base (equiv. to 29.5 µg of dexmedetomidine HCl).

Mean pharmacokinetic parameters for dexmedetomidine are summarized below.

Formulation (Dosing Event)	T _{max} (hr)	t _{1/2} (hr)	C _{max} (ng/ml)	AUC _{last} (hr*ng/ml)	AUC _{0-∞} (hr*ng/ml)
Formulation 1-DEX (1)	0.7	0.93	8.88	7.72	7.18
Formulation 2-DEX (2)	0.7	NC1	16.9	12.3	NC1
Formulation 3-DEX (3)	0.42	0.43	1.30	1.10	1.16

PRECEDEX [®] (4)	0.38	0.52	12.2	6.68	6.69
Formulation 4-DEX (5)	0.4	0.47	1.35	1.12	0.984
Formulation 5-DEX (6)	0.80	0.50	2.46	2.44	2.62
Formulation 6-DEX (7)	0.42	0.56	9.05	6.57	2.18
Formulation 6-DEX (8)*	0.27	0.79	5.92	3.61	6.06
Formulation 7-DEX (9)	0.32	0.63	1.33	1.18	1.09
DEX-SL.01 (10)	0.60	1.72	2.15	2.27	4.75

NC1 = Value could not be calculated by WinNonlin due to insufficient data points for the elimination phase.

*Redose of Formulation 6-DEX using a new sprayer.

For intranasal administration (dose events 1 to 9), $T_{\max}$ and elimination half-life for dexmedetomidine were similar between the PRECEDEX[®] formulation and the experimental doses 1-3 and 5-9. The mean $T_{\max}$ for dexmedetomidine for the PRECEDEX[®] formulation was 0.38 hours, and the mean $T_{\max}$ for dexmedetomidine for the experimental formulations that were administered intranasally (doses 1-3, 5-9) ranged from 0.32 hours to 0.80 hours. The mean elimination half-life for dexmedetomidine for the PRECEDEX[®] formulation was 0.52 hours, and the mean elimination half-life for dexmedetomidine for the experimental formulations administered intranasally (doses 1-3, 5-9) ranged from 0.43 hours to 0.93 hours. For sublingual administration (dosing event 10, formulation DEX-SL.01), the mean $T_{\max}$ was 0.60 hours similar to the $T_{\max}$ obtained following intranasal administration of PRECEDEX[®] and experimental doses 1-9, while the mean elimination half-life for the DEX-SL.01 formulation was 1.72 hours, longer than the elimination half-life obtained following intranasal administration of PRECEDEX[®] and experimental doses 1-3 and 5-9.

Based on $C_{\max}$ and AUC_{last} , dexmedetomidine exposure following intranasal administration was highest for the Formulation 3-DEX formulation. The mean $C_{\max}$ for Formulation 3-DEX formulation was approximately 140% of the mean $C_{\max}$ for PRECEDEX[®], while mean AUC_{last} for the Formulation 3-DEX formulation was approximately 180% of the mean AUC_{last} for PRECEDEX[®]. The mean AUC_{last} for the Formulation 6-Dex and Formulation 1-DEX formulations were similar to that of PRECEDEX[®], while the mean $C_{\max}$ for these formulations were approximately 70% of the mean $C_{\max}$ for PRECEDEX[®]. The mean $C_{\max}$ and AUC_{last} for all other experimental formulations dosed intranasally were lower than that for PRECEDEX[®]. Dexmedetomidine exposure following intranasal administration was lowest for the Formulation 2-DEX and Formulation 7-DEX formulations. Surprisingly, dexmedetomidine exposure following sublingual administration of formulation DEX-SL.01 was substantially lower

than for intranasal administration of PRECEDEX[®]; the mean $C_{\max}$ for the DEX-SL.01 formulation was 18% of the mean $C_{\max}$ for PRECEDEX[®], and mean AUC_{last} for the DEX-SL.01 formulation was 34% of the mean AUC_{last} for PRECEDEX[®].

Formulation (Dosing Event)	$T_{\max}$ (hr)	$t_{1/2}$ (hr)	$C_{\max}$ (ng/mL)	AUC_{last} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)
Formulation 1-DEX (1)	1.75	NC ¹	0.272	0.355	NC ¹
Formulation 2-DEX (2)	1.80	NC ¹	0.291	0.386	NC ¹
Formulation 3-DEX (3)	0.65	NC ¹	0.285	0.203	NC ¹
PRECEDEX [®] (4)	1.55	NC ¹	0.248	0.358	NC ¹
Formulation 4-DEX (5)	1.00	NC ¹	0.0847	0.111	NC ¹
Formulation 5-DEX (6)	1.35	1.28	0.116	0.169	0.233
Formulation 6-DEX (7)	0.90	NC ¹	0.221	0.319	NC ¹
Formulation 6-DEX (8)*	1.15	7.29	0.168	0.265	2.38
Formulation 7-DEX (9)	1.25	8.70	0.0999	0.109	1.15
DEX-SL.01 (10)	1.80	NC ¹	0.152	0.204	NC ¹

NC1 = Value could not be calculated by WinNonlin due to insufficient data points for the

5 elimination phase. *Redose of Formulation 6-Dex using a sprayer.

For intranasal administration (dose events 1 to 9), the $T_{\max}$ for this table was generally similar between the PRECEDEX[®] formulation and the experimental doses 1-3 and 5-9. The mean $T_{\max}$ for the PRECEDEX[®] formulation was 1.55 hours, and the mean $T_{\max}$ for the experimental formulations administered intranasally (doses 1-3, 5-9) ranged from 0.65 hours to 1.80 hours. For most formulations, the elimination half-life was either not calculated or not reported due to insufficient data points for the elimination phase or poor goodness-of-fit ($R^2 < 0.8$) for the elimination phase. Where calculable, the half-life ranged from 1.3 hours to 8.7 hours. For sublingual administration (dosing event 10, formulation DEX-SL.01), the mean $T_{\max}$ was 1.80 hours, similar to the $T_{\max}$ obtained following intranasal administration of PRECEDEX[®] and the experimental doses 1-3 and 5-9.

Based on $C_{\max}$ and AUC_{last} , exposure following intranasal administration was highest for the Formulation 3-Dex formulation. The mean $C_{\max}$ for the Formulation 3-Dex formulation was approximately 117% of the mean $C_{\max}$ for PRECEDEX[®], while the mean AUC_{last} for the Formulation 3-Dex formulation was approximately 108% of the mean AUC_{last} for PRECEDEX[®]. Mean $C_{\max}$ and AUC_{last} for all other experimental formulations dosed intranasally were similar to that for PRECEDEX[®], except for Formulation 4-DEX and Formulation 7-DEX (the amount of dexmedetomidine dosed with Formulation 7-DEX was half that of the other formulations).

Exposure following sublingual administration of formulation DEX-SL.01 was lower than for intranasal administration of PRECEDEX[®]; mean $C_{\max}$ for the DEX-SL.01 formulation was approximately 61% of the mean $C_{\max}$ for PRECEDEX[®], and mean AUC_{last} for the DEX-SL.01 formulation was approximately 57% of the mean AUC_{last} for PRECEDEX[®].

5 The results presented herein, surprisingly show that when compared to the previously studied sublingually administered formulation DEX-SL.01, absorption occurs more quickly via the nasal route. Therefore, intranasal administration of DEX surprisingly may provide faster pain relief and/or prevention of pain in subjects as compared to sublingual or methods of administering DEX across the oral mucosa, without significant sedation, and with little or no effect on blood pressure.

Dosing

Doses 1-3 were administered intranasally with a micropipette with the head inverted for dosing. The dosage was 50 µg of dexmedetomidine free-base (equivalent to 59 µg of dexmedetomidine HCl) in 100 µL of formulation. Dose 4 was administered using a commercial nasal spray bottle. Spray doses were administered with the head upright, alternating nostrils for each spray. The head was inverted for 30 seconds to 1 minute after spray administration. The spray bottle administers 100 µL per spray, and five sprays were required to deliver the dosage of 50 µg of dexmedetomidine free-base (equivalent to 59 µg of dexmedetomidine HCl). The spray bottle was primed in an area remote from dosing prior to dose administration to prevent possible cross-contamination. Additionally, dosing was performed in an area remote from blood collection to prevent possible contamination of blood samples with aerosolized test article.

Doses 5-7 were administered using a commercial nasal spray bottle. Spray doses were administered with the head upright. The head was inverted for 30 seconds to 1 minute after spray administration. The spray bottle administers 100 µL per spray, and one spray was required to deliver the dosage of 50 µg of dexmedetomidine free base (equivalent to 59 µg of dexmedetomidine HCl). The spray bottle was primed using five spray actuations in an area remote from dosing prior to dose administration to prevent possible cross-contamination. Additionally, dosing was performed in an area remote from blood collection to prevent possible contamination of blood samples with aerosolized test article.

Dose 8 was administered using a commercial nasal spray bottle. Spray doses were administered with the head upright. The head was inverted for 30 seconds to 1 minute after spray administration. The spray bottle administered 100 µL per spray, and one spray was required to deliver the dosage of 50 µg of dexmedetomidine free base (equivalent to 59 µg of

dexmedetomidine HCl). The spray bottle was primed using five spray actuations in an area remote from dosing prior to dose administration to prevent possible cross-contamination. Additionally, dosing was performed in an area remote from blood collection to prevent possible contamination of blood samples with aerosolized test article.

- 5 Dose 9 was administered using a commercial nasal spray bottle. Spray doses were administered with the head upright. The head was inverted for 30 seconds to 1 minute after spray administration. The spray bottle administered 100 μ L per spray, and one spray was required to deliver the dosage of 25 μ g of dexmedetomidine free base (equivalent to 29.5 μ g of dexmedetomidine HCl). The spray bottle was primed using five spray actuations in an area
10 remote from dosing prior to dose administration to prevent possible cross-contamination. Additionally, dosing was performed in an area remote from blood collection to prevent possible contamination of blood samples with aerosolized test article.

- Dose 10 was administered sublingually with a micropipette. The dosage was 50 μ g of dexmedetomidine free base (equivalent to 59 μ g of dexmedetomidine HCl) in 100 μ L of
15 formulation.

For intranasal administrations, the formulations were administered intranasally. Following dosing, the dog's nares were held shut and the head inverted for approximately 1 minute. Each dosing event was separated by a minimum of 2 days to allow an appropriate washout.

- 20 After dosing, blood samples were obtained and tested for DEX plasma levels.

Example 5: Pharmacokinetics Of Intranasally Administered Dexmedetomidine in Humans

- Four different formulations of DEX were used. PRECEDEX[®] (Treatment A) at a dose of 25 μ g which was administered intravenously over 10 minutes and 3 different intranasal
25 dosages or formulations. Formulation B (35 μ g administered in 100 μ l in one nostril via 1 spray); Formulation C (35 μ g total administered via 2 nostrils); and Formulation D (17.5 μ g administered in 50 μ l in one nostril via 1 spray).

	Treatment A Precedex IV 25 μ g	Treatment B DEX- IN.01 35 μ g 100 μ l in one nostril	Treatment C DEX-IN.01 35 μ g 50 μ l in each nostril	Treatment D DEX-IN.01 17.5 μ g 50 μ l in one nostril
C _{max} (ng/ml)	0.61 (58.7%)	0.17 (21.7%)	0.14 (34.0%)	0.08 (31.9%)
AUC ₀₋₂₄ (hr ng/ml)	0.71 (27.7%)	0.83 (23.6%)	0.75 (22.5%)	0.38 (16.6%)
T _{max} (hrs)	0.17 (0.17, 0.25)	1.00 (0.33, 4.00) [†]	1.25 (0.33, 4.00)	1.13 (0.33, 2.00)
t _{1/2} (hrs)	2.04 $\pm$ 0.200 [‡]	2.43 $\pm$ 0.825 [§]	2.64 $\pm$ 0.777 [§]	1.60 (NA) [¥]

[1] Geometric means (CV%) for C_{max} and AUC₀₋₂₄ median (min, max) for T_{max}; and arithmetic mean $\pm$ SD

for t_{1/2}; [†] n=11; [‡] n=10; [§] n=4; [¥] n=1

The pharmacokinetics observed showed the surprising result that the administration of the dose in single spray to a single nostril (Treatment B) provided a better $C_{\max}$ and a shorter $T_{\max}$ as compared to the same total dose administered in two nostrils via 2 sprays (half the dose being administered into each nostril). This result could not have been predicted and is opposite of what would have been expected by the skilled artisan, in part, due to a surface area comparison. The mean plasma concentrations produced by Treatment B reached a minimum target concentration (0.1 ng/ml) within 20 minutes after dosing. This surprising result of administering to a single nostril can facilitate the more rapid onset of activity (*e.g.*, pain relief) in target patient populations. The rate of absorption observed in Treatment B was more rapid than previously studied non-IV formulations or routes of administration. This unexpected more rapid absorption can allow for the fast onset of analgesic effects. In fact, the analgesic effects can begin in less than 20 minutes. Plasma concentrations achieved with the 17.5 and 35 μg intranasal administration are provided in Figure 1.

Dosing

Healthy volunteers were administered the selected dose intranasally or, if indicated, another route of administration. A single nostril was administered to at a time with the untreated nostril covered by a finger. Blood samples were taken and measured for DEX concentrations as indicated.

Example 6: Phase 1, Two Period, Open Label, Multiple-Dose Evaluation of the Safety, Tolerability, and Pharmacokinetics of Intranasal Dexmedetomidine in Healthy Volunteers

The primary objective of this study was to evaluate the pharmacokinetic profile of multiple doses of intranasal dexmedetomidine in healthy male and female subjects. Secondary endpoints of this study were to evaluate the safety and tolerability of intranasal dexmedetomidine in healthy volunteers.

Methodology

This was a Phase 1, open-label, two period, repeated dose study in healthy subjects to investigate the safety, tolerability, and pharmacokinetics of intranasal dexmedetomidine. A total of 12 subjects (6 male and 6 female) were planned and enrolled. Healthy subjects between the ages of 18 and 50 years, inclusive, were screened for participation at one study site in the United States within 28 days before study drug administration. Medical history, physical examination, baseline laboratory testing, 12 lead electrocardiogram (ECG), pregnancy testing, vital sign measurements, and informed consent were completed during the screening visit.

All study doses were a 35 μg dose of DEX IN.01 administered as a single 100 μL spray

into the left nostril. DEX-IN.01 contained 35 µg dexmedetomidine in each 100 µL of solution, as well as excipients including: citric acid, sodium citrate, sodium chloride, phenylethyl alcohol, disodium EDTA, and purified water. Doses of DEX-IN.01 utilized a 100 µL spray nozzle for administration into the nostril according to the treatment assignment.

5 During Period 1, subjects received two doses of study medication, separated by six hours. During Period 2, study participants received seven doses of study medication administered at six hour intervals. Study Periods were separated by not less than 24 hours between the last dose in Period 1 and the first dose in Period 2.

10 During Period 1, subjects were confined from the evening before dosing (Day -1) to approximately 18 hours after Dose 2 (Day 2). During Period 2, subjects were confined from the evening before dosing (Day -1) to approximately 24 hours after the last study dose (Day 3). While confined, subjects received a standardized daily diet.

15 Serial blood samples were collected at defined intervals during each study period in order to evaluate the pharmacokinetic properties of intranasally administered dexmedetomidine, and its metabolite. Whole blood was collected in 6 mL evacuated collection tubes treated with K₂EDTA.

20 Plasma samples were to be collected within ±2 minutes of the scheduled post-dose time through 60 minutes after dosing, samples collected 75 minutes to 6 hours after dosing were able to be collected within ±5 minutes, and samples collected at and beyond 12 hours after dosing were able to be collected within ±15 minutes of scheduled post-dose time. Actual times were to be recorded for all events, and any deviation outside the specified ranges were required to be clearly documented in the subject's study records.

25 Immediately after the collection of each sample, the collection tube was to be gently inverted and then placed in wet ice. Within 30 minutes of withdrawal, the tubes were centrifuged at about 2,000 × gravity for 10-15 minutes to separate the cells from the plasma. No aids for separation were to be used. Two aliquots (≥0.5 mL each) of plasma were transferred from each sample with clean pipettes and placed in 2 polypropylene storage tubes in equal volumes. The storage tubes were labeled with the following information: protocol number, subject number, study day and relative time of sample (e.g., Period 1, Dose 1, 10 Minutes after dosing), and biologic matrix to be analyzed (e.g., plasma). Within 60 minutes of the collection time, the storage tubes were to be placed into a freezer at -20°C or below; they remained in the freezer until shipment for analysis.

30 For pharmacokinetic analyses in Period 1, up to 12 blood samples were collected from each subject prior to and following administration of each study dose. These were collected at

predose (Time 0) and at the following approximate times after each dose of study medication: 10, 20, 30, 45, 60, and 90 minutes and 2 and 4 hours; additional blood samples were collected at 6, 12 and 18 hours after Dose 2. In Period 2, up to 13 blood samples were collected from each subject prior to and following administration of Dose 1 and Dose 7. These were collected at predose (Time 0) and at the following approximate times after dosing with study medication: 10, 20, 30, 45, 60, and 90 minutes and 2 and 4 hours; additional blood samples were collected at 6, 12, 18 and 24 hours after Dose 7. Blood samples for Dose 2 through Dose 6 were collected at predose (Time 0) only.

A summary table of study visits, and the assigned time points, is provided for the overall study, Period 1, Period 2 Doses 1 and 7, and Period 2 Doses 2 through 6 in the table below.

Table: Summary of Study Visits

Study Event	Period 1				Washout	Period 2								
	Day -1	Day 1 (hr)				Day -1	Day 1 (hr)				Day 2 (hr)			Day 3 (hr)
		0	6	24			0	6	12	18	24	30	36	60
Confinement	<-----X- ----->					<----- X----- ----->								
Study Dosing		X	X				X	X	X	X	X	X	X	

Inclusion Criteria:

Subjects met the following criteria to participate in the study: 1) was a man or woman between 18 and 50 years of age, inclusive; 2) for female subjects of childbearing potential, be surgically sterile, use double-barrier contraception, practice abstinence (must agree to use double-barrier contraception in the event of sexual activity) or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA through completion of the study and have negative results on a serum pregnancy test done before administration of study medication, and have negative results on subsequent urine pregnancy tests (women who are postmenopausal [no menses for at least 2 years] are also eligible to participate); 3) had a body mass index (BMI) $\leq 32 \text{ kg/m}^2$ and a body weight between 50 and 95 kg, inclusive; and 4) was able to understand the study procedures, agree to participate in the study program, and voluntarily provide written informed consent.

Treatments Administered

Study personnel administered all doses of study medication according to the treatment schedule. Doses of dexmedetomidine were administered using the intranasal delivery device into

the left nostril. Doses were administered into the assigned nostril with the untreated nostril covered with a finger. The subject's head was held in an upright position with the spray applicator inserted approximately ½" into the treated nostril. The subject inhaled through the treated nostril as the pump was squeezed and the dose was delivered.

- 5 After administration of study medication, participants were allowed to move around the study facility, and perform non-strenuous activities. Subjects may have been required to remain seated for a period of time by the study investigator if it was deemed unsafe for the subject to move around the study site without the accompaniment of study personnel.

- 10 Doses were subsequently evaluated in a single dose study in healthy volunteers where DEX-IN was evaluated using single and paired spray administration at doses of 17.5 and 35 µg. Based on the observed pharmacokinetics, it was determined that the 35 µg dose level administered into a single nostril would be most appropriate to explore further to achieve the targeted plasma concentrations. Plasma concentrations achieved with the 17.5 and 35 µg intranasal doses are provided in Figure 1.

15 *Ramsay Sedation Scale*

- The investigator, or designee, used the Ramsay Sedation Scale to assess each subject's degree of sedation. For each subject at each time point, the degree of sedation was assessed according to the Ramsay rating categories. The Ramsay Sedation Scale was performed pre-dose (Time 0), and at 30, 60 and 90 minutes after each study dose. All scores returned to their baseline level (Score 2) within six hours after dosing. Although an RSS score of 5 was assigned to two subjects during the course of the study, the majority of subjects did not experience significant sedation. Subjects were administered study doses every six hours, and completed safety monitoring activities subsequent to each dose, around the clock for seven doses during Period 2; the confounding effect of this schedule is not addressed in the assessment tool/results.

25 *Criteria for evaluation:*

- Pharmacokinetic parameters for the concentrations of dexmedetomidine and its major metabolite (ORM-14305) in plasma were calculated for Dose 1 and 2 during Period 1, and for Dose 1 and 7 during Period 2. The calculated parameters included peak (maximum) observed plasma drug concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration time curve (AUC) from Time 0 to last sampling time (t) with a quantifiable plasma drug concentration (AUC_{0-t}), AUC from Time 0 to 6 hours after dosing (AUC_{0-6}), AUC from Time 0 to infinity ($AUC_{0-\infty}$, for Period 1 Dose 2, and Period 2 Dose 7), and terminal phase elimination half life ($t_{1/2}$, for Period 1 Dose 2, and Period 2 Dose 7).

Results:

Observed pharmacokinetic parameters, $C_{\max}$, $T_{\max}$, and AUC_{0-6} of dexmedetomidine are presented in the table below.

Pharmacokinetic Parameters of Dexmedetomidine

Parameters [1]	Period 1 Dose 1	Period 1 Dose 2	Period 2 Dose 1	Period 2 Dose 7
$C_{\max}$ (ng/mL)	0.09 (30.6) [†]	0.16 (22.8) [†]	0.12 (35.8) [‡]	0.13 (31.3) [‡]
$T_{\max}$ (hrs)	1.26 (0.33, 4.00) [†]	0.88 (0.33, 2.02) [†]	1.01 (0.50, 2.00) [‡]	1.50 (0.33, 2.00) [‡]
AUC_{0-6}	0.39 (31.7) [†]	0.61 (19.2) [†]	0.47 (32.6) [‡]	0.50 (31.1) [‡]
AUC_{last} (hr·ng/mL)	0.38 (35.2) [†]	0.63 (22.2) [†]	0.47 (32.6) [‡]	0.51 (55.0) [‡]
[1] Geometric means (CV%) for $C_{\max}$, AUC_{0-6} , and AUC_{last} ; median (min, mix) for $T_{\max}$ [†] n=12; [‡] n=10				

5

Comparison of Pharmacokinetic Parameters Between Doses

Doses	$C_{\max}$ (ng/mL)	AUC_{last} (hr·ng/mL)	AUC_{0-6} (hr·ng/mL)
Period 1 Dose 2: Period 1 Dose 1	164.1 (138.0, 195.0)	164.2 (134.1, 201.0)	156.9 (134.7, 182.8)
Period 2 Dose 7: Period 2 Dose 1	106.3 (82.5, 136.9)	108.4 (77.8, 151.0)	105.5 (81.1, 137.3)
Period 2 Dose 1: Period 1 Dose 1	127.7 (112.4, 145.2)	125.1 (105.4, 148.6)	122.8 (106.5, 141.7)
Period 2 Dose 7: Period 1 Dose 2	86.8 (71.0, 106.1)	84.4 (66.5, 107.2)	85.2 (72.0, 100.9)

Data presented is Ratio % (90% CI)

Observed Mean Dexmedetomidine Plasma Concentrations (ng/mL)

Time Post-Dose	Period 1 (N=12)		Period 2 (N=10)	
	Dose 1	Dose 2	Dose 1	Dose 7
0 min	0	0.033 ± 0.014	0	0.037 ± 0.016
10 min	0.008 ± 0.014	0.077 ± 0.033	0.028 ± 0.035	0.059 ± 0.028
20 min	0.060 ± 0.028	0.118 ± 0.054	0.073 ± 0.050	0.091 ± 0.033
30 min	0.059 ± 0.020	0.134 ± 0.044	0.085 ± 0.041	0.101 ± 0.034
45 min	0.083 ± 0.028	0.145 ± 0.040	0.112 ± 0.046	0.113 ± 0.032
60 min	0.088 ± 0.024	0.145 ± 0.023	0.116 ± 0.041	0.119 ± 0.031
90 min	0.090 ± 0.025	0.134 ± 0.014	0.116 ± 0.036	0.119 ± 0.031
2 hrs	0.092 ± 0.026	0.135 ± 0.019	0.117 ± 0.039	0.126 ± 0.033
4 hrs	0.067 ± 0.024	0.090 ± 0.023	0.073 ± 0.026	0.072 ± 0.072
6 hrs	0.036 ± 0.010	0.050 ± 0.018	0.037 ± 0.012	0.048 ± 0.013
12 hrs		0.022 ± 0		0.024 ± 0
18 hrs		0		0
24 hrs				0

Observed Mean ORM-14305 Plasma Concentrations (ng/mL)

Time Post-Dose	Period 1 (N=12)		Period 2 (N=10)	
	Dose 1	Dose 2	Dose 1	Dose 7
0 min	0	0.032 ± 0.019	0	0.085 ± 0.037
10 min	0	0.032 ± 0.019	0	0.085 ± 0.036
20 min	0	0.035 ± 0.015	0	0.083 ± 0.036
30 min	0	0.042 ± 0.013	0	0.081 ± 0.032
45 min	0	0.039 ± 0.014	0	0.078 ± 0.029
60 min	0	0.042 ± 0.013	0	0.084 ± 0.034
90 min	0	0.045 ± 0.014	0.002 ± 0.006	0.080 ± 0.034
2 hrs	0.010 ± 0.013	0.053 ± 0.014	0.017 ± 0.015	0.088 ± 0.038
4 hrs	0.032 ± 0.019	0.064 ± 0.019	0.039 ± 0.014	0.087 ± 0.035
6 hrs	0.038 ± 0.013	0.062 ± 0.021	0.043 ± 0.016	0.079 ± 0.035
12 hrs		0.048 ± 0.011		0.061 ± 0.027
18 hrs		0.032 ± 0.011		0.045 ± 0.021
24 hrs				0.031 ± 0.011

These results are illustrated in Figure 2.

This study supported the safety and tolerability of repeated dosing with intranasal

5 administration. When administered at the six hour dosing interval, there was little evidence of

accumulation of dexmedetomidine when comparing the AUC for Dose 1 to Dose 7. DEX-IN.01 was demonstrated to be well tolerated upon repeated dosing with up to seven doses administered on a six hour interval. There was no apparent increase in adverse events, changes in vital signs, or nasal irritation severity with repeated dosing. When administered as an initial 35 µg dose, DEX-IN.01 reached peak plasma concentrations after 1.01-1.26 hours (median) with an average C_{max} of 0.09-0.12 ng/mL. No significant sedation was observed in subjects at various time points during the study.

Example 7: A Randomized, Double-Blind, Placebo-Controlled, Three Period Crossover

Evaluation of the Efficacy, Safety, and Pharmacokinetics of Intranasal Dexmedetomidine in Chronic Low Back Pain Subjects

A study was performed to to evaluate the efficacy, safety, and pharmacokinetics of two dose levels of intranasal dexmedetomidine (DEX-IN.02 and DEX-IN.03) compared with placebo in subjects with chronic low back pain.

Methods: Adult subjects with chronic low back pain symptoms present for greater than three months, and a baseline 24-hour pain intensity ≥ 4 (0-10 scale) were eligible to participate. Subjects were randomly assigned to a treatment sequence with DEX-IN.02 (50 µg; 50 µg/100 µL), DEX-IN.03 (25 µg; 25 µg/50 µL) and matching placebo. Study doses were administered as an intranasal spray using a single dose spray device requiring no priming. Doses were administered to a single nostril. Dosing devices were filled with the appropriate volume of drug solution to deliver the designated 25 or 50 µg dose of dexmedetomidine. Study doses were administered on consecutive days, with a minimum 24-hour washout between doses. Subjects with baseline chronic analgesic therapy were allowed to continue their regimen throughout study, but no doses were to be administered within 2 hours of study treatment (unless analgesic rescue was required). Rescue analgesia was available upon subject request according to the individual's baseline pain regimen.

Efficacy assessments included measures of pain intensity (PI), pain relief (PR), and global medication performance (GMP). Efficacy measures were used to calculate the pain intensity difference (PID), summed pain intensity difference (SPID) and total pain relief (TOTPAR) at multiple post-dose time points, and to determine the number of subjects with partial and complete responses to therapy. Safety assessments included collection of vital signs, nasal symptom assessment, sedation, and adverse events. Plasma samples were collected at intervals over the first 12 hours post-dose for pharmacokinetic analysis.

Results: The study enrolled and treated 24 subjects with DEX-IN.02, DEX-IN.03, and

placebo; all enrolled subjects completed all scheduled study doses. Subjects were primarily white (91.7%) and male (58.3%), with a mean age of 33.7 ± 10.19 years. Subjects had primarily visceral pain (91.7%) with a mean history of pain symptoms lasting 6.75 ± 6.85 years. One third of subjects utilized opioid analgesics for their pain symptoms.

- 5 Mean improvement in subject PID values were significantly greater for the 50 µg dose (DEX-IN.02) compared with placebo from 45 minutes through 2 hours post-dose (45 min: 2.2 vs. 1.2, $p=0.0291$; 1 hr: 2.2 vs. 0.8, $p=0.0082$; 1.5 hr: 2.2 vs. 0.7, $p=0.0028$; 2 hr: 2 vs. 0.9, $p=0.0126$). The mean SPID value was significantly greater for the 50 µg dose than placebo at 60 minutes after dose (7.1 vs. 3.6; $p=0.0352$). Mean TOTPAR was significantly higher for the 50
- 10 µg dose than placebo at both 45 and 60 minutes after dose (4.3 vs. 2.5; $p=0.0298$ and 6.2 vs. 3.3; $p=0.0097$, respectively). The results for the study are shown in the following tables.

Table: Summary of Mean±SD PID Values for All Post-Dose Time Points

Time Point	Placebo (N=24)	DEX-IN.03 (N=24)	DEX-IN.02 (N=24)
10 min	0.2 ± 0.48	0.3 ± 0.53	0.5 ± 0.93
15 min	0.6 ± 0.93	0.7 ± 1.09	0.8 ± 1.18
20 min	1.0 ± 1.33	0.9 ± 1.25	1.5 ± 1.32
30 min	1.0 ± 1.44	1.3 ± 1.36	1.9 ± 1.85
45 min	1.2 ± 1.63	1.4 ± 1.44	2.2 [§] ± 1.72
60 min	0.8 ± 1.49	1.5 ± 1.47	2.2 [¥] ± 1.82
90 min	0.7 ± 1.16	1.4 ± 1.41	2.2 [¥] ± 1.81
2 hours	0.9 ± 1.28	1.3 ± 1.23	2.0 [§] ± 1.76
4 hours	1.1 ± 1.75	1.5 ± 1.38	1.8 ± 1.81
6 hours	1.5 ± 1.56	1.5 ± 1.10	1.6 ± 1.71

§ $p < 0.05$; ¥ $p < 0.01$

Table: Summary of Mean±SE SPID Values

Time Point	Placebo (N=24)	DEX-IN.03 (N=24)	DEX-IN.02 (N=24)
15 min	0.6 ± 0.19	0.7 ± 0.22	0.8 ± 0.24
30 min	1.6 ± 0.47	1.9 ± 0.48	2.7 ± 0.59
45 min	2.8 ± 0.78	3.3 ± 0.75	4.9 ± 0.90
60 min	3.6 ± 1.05	4.8 ± 1.03	7.1* ± 1.24

* $p = 0.0352$

Table: Summary of Mean $\pm$ SE TOTPAR Values

Time Point	Placebo (N=24)	DEX-IN.03 (N=24)	DEX-IN.02 (N=24)
15 min	0.6 $\pm$ 0.15	0.5 $\pm$ 0.15	0.8 $\pm$ 0.20
30 min	1.5 $\pm$ 0.35	1.3 $\pm$ 0.32	2.4 $\pm$ 0.39
45 min	2.5 $\pm$ 0.56	2.4 $\pm$ 0.48	4.3 [§] $\pm$ 0.59
60 min	3.3 $\pm$ 0.74	3.5 $\pm$ 0.68	6.2 [¥] $\pm$ 0.81

§ p < 0.05; ¥ p < 0.01

Mean GMP scores were similar among all 3 treatment groups during both 30- and 60-minute post-dose time points. The 50 μ g dexmedetomidine treated group had more subjects with improvement $\geq$ 33% and $\geq$ 50% at all time points after 15 minutes post dose; 11 DEX-IN.02 treated subjects reported $\geq$ 50% improvement at 90 minutes (95% CI, 1.02-7.44) and 10 subjects at 2 hours (95% CI, 1.05-10.63), compared with 4 subjects at 90 minutes and 3 subjects at 2 hours in placebo group. No subjects in any of the treatment groups required rescue medications.

Adverse reactions were generally mild in DEX-IN treated subjects, with 5 events determined to be moderate in severity (2 BP decreased, 1 dizziness, 1 somnolence and 1 hypotension). No SAEs, deaths, or withdrawals due to an AE occurred during the conduct of the study. Changes in systolic and diastolic blood pressure (SBP and DBP respectively) were greater with DEX-IN.02 treated subjects than DEX-IN.03 and placebo treated subjects. Changes in heart rate (HR) were similar following DEX-IN.03 and placebo, while DEX-IN.02 treated subjects had a greater decrease in heart rate; the greatest mean percent change below baseline was -1% for placebo and -9% for DEX-IN.02, while the mean HRs for DEX-IN.03 never decreased below baseline. Results of the nasal assessment of nasal irritation were similar among all treatment groups at all time points with the mean score not exceeding 1 in DEX-IN.02 treated subjects at one hour post-dose (scale of 0-10). Subjects in the DEX-IN.02 treatment group experienced the highest Stanford Sleepiness Scale values 60 minutes post-dose with 17 subjects reporting a score $\geq$ 5.

A single dose of DEX-IN.03 (25 μ g) yielded a mean $C_{\max}$ of 0.11 ng/mL with a median $T_{\max}$ of 0.75 hrs, while a single dose of DEX-IN.02 (50 μ g) yielded a mean $C_{\max}$ of 0.25 ng/mL with a median $T_{\max}$ of 0.51 hrs. The following tables summarize these results

Table: Observed Mean Dexmedetomidine Plasma Concentrations (ng/mL)

Time Post-Dose	DEX-IN.03 (25 µg)	DEX-IN.02 (50 µg)
0 min	0	0
10 min	0.047	0.098
15 min	0.081	0.182
20 min	0.096	0.215
30 min	0.111	0.212
45 min	0.110	0.228
60 min	0.102	0.196
75 min	0.094	0.183
90 min	0.085	0.169
2 hrs	0.077	0.149
4 hrs	0.048	0.101
6 hrs	0.030	0.050
12 hrs	0	0.027

Table: Observed Pharmacokinetic Properties of Dexmedetomidine

Parameter	DEX-IN.03 (25 µg)	DEX-IN.02 (50 µg)
C _{max} (ng/mL)	0.11 (71.4)	0.25 (38.3)
T _{max} (hrs)	0.75 (0.25, 4.00)	0.51 (0.25, 4.00)
AUC _{inf} (hr·ng/mL)	0.48 (13.7)	0.92 (26.0)
AUC ₀₋₁ (hr·ng/mL)	0.08 (110.4)	0.16 (64.1)
AUC _{last} (hr·ng/mL)	0.24 (182.4)	0.75 (21.6)
t _{1/2} (hrs)	2.24 (1.60, 2.45)	2.05 (1.52, 3.07)

[1] Geometric means (CV%) for C_{max}, AUC₀₋₁, AUC_{last}, and AUC_{inf}, median (min, mix) for T_{max}; and arithmetic mean ± SD for t_{1/2}

- 5 This study shows that the intranasal route is a viable non-invasive means of administering dexmedetomidine. Dosing with DEX-IN.02 and DEX-IN.03 produced more rapid absorption with higher dexmedetomidine peak plasma concentrations than previously explored formulations. Analysis of SPID and TOTPAR values demonstrates the significant analgesic effects of a 50 µg dose of intranasal dexmedetomidine compared with a 25 µg dose or placebo in

subjects with CLBP starting 45 minutes post dose. Overall, DEX-IN was well tolerated; the AEs reported were generally mild in severity, while no SAEs were reported.

What is Claimed Is:

1. A method of treating or preventing pain without significant sedation in a mammal comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal whereby the intranasally effective
5 amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation.
2. A method of treating or preventing pain without significant sedation in an adult human
10 comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the adult human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult within a period of time of about two hours after administration and has an analgesic effect within the period of time.
15
3. A method of treating or preventing pain without significant sedation in a human comprising intranasally administering dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the human.
- 20 4. A method of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying in the mammal a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .
- 25 5. The method of any one of claims 1 to 4 wherein the plasma C_{max} of dexmedetomidine is about 0.08 ng/ml to about 0.2 ng/ml.
6. The method of any one of claims 1 to 4 wherein the plasma C_{max} of dexmedetomidine is about 0.15 ng/ml.
30
7. The method of any one of claims 1 to 4 wherein the plasma C_{max} of dexmedetomidine is about 0.2 ng/ml.

8. The method of any one of claims 1 to 7 wherein the $T_{\max}$ of dexmedetomidine is less than about 1 hour.

9. The method of any one of claims 1 to 7 wherein the $T_{\max}$ is less than about 50 minutes.

5

10. The method of any one of claims 1 to 9 wherein the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered as a unit dose of about 10 μg , about 25 μg , about 35 μg , about 40 μg , about 50 μg , about 75 μg , or about 100 μg .

10 11. The method of any one of claims 1 to 10 wherein during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 2 on the Ramsay Sedation Scale.

15 12. The method of any one of claims 1 to 11 wherein during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 1 on the Stanford Sleepiness Scale.

20 13. The method of any one of claims 1 to 12 wherein during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not less than Level 6 on the Modified Observer's Assessment Of Alertness/Sedation Scale.

25 14. The method of any one of claims 1 to 13 wherein there is no or minimal effect on blood pressure after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof.

30 15. The method of any one of claims 1 to 14 further comprising administering to the human or mammal one or more additional therapeutic agents.

16. The method of claim 15 wherein the one or more additional therapeutic agents is chosen from an opioid analgesic, a synthetic opioid-like analgesic, a non-opioid analgesic, a vitamin, a vasodilator, a benzodiazepine, a triptan, an anti-convulsant, an anti-depressant, an anti-nausea

medication, and an anti-hypertensive.

17. The method of any one of claims 1 to 16 wherein the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered about every 6 hours.

18. The method of any one of claims 1 to 17 wherein the pain is idiopathic pain.

19. The method of claim 18 wherein the idiopathic pain is neuralgia, myalgia, hyperalgia, hyperpathia, neuritis, or neuropathy.

20. The method of any one of claims 1 to 17 wherein the pain is associated with or caused by cancer, viral infection, physical trauma, arthritis, headache, migraine, or lower back pain.

21. The method of claim 20 wherein the physical trauma is associated with or caused by surgery, a burn, or blunt force trauma.

22. The method of any one of claims 1 to 21 wherein the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered intranasally with a metered dose device.

23. The method of claim 22 wherein the metered dose device is a multi-dose, unit dose, or bi-dose device.

24. A metered dose device comprising a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the metered dose device delivers a metered dose spray of the pharmaceutical composition intranasally that is analgesic in a mammal without significant sedation.

25. The metered dose device of claim 24 wherein the metered dose spray produced by the device comprises droplets comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, that have a Dv90 of less than about 150 μm .

26. The metered dose device of claim 24 or claim 25 wherein the metered dose spray produced by the device comprises a metered dose of about 10 μg , about 25 μg , about 35 μg , about 50 μg , about 75 μg , or about 100 μg of dexmedetomidine, or a pharmaceutically

acceptable salt thereof.

27. The metered dose device of any one of claims 24 to 26 wherein the metered dose spray produced by the device comprises a volume of less than about 150 μl , less than about 140 μl , less than about 130 μl , less than about 120 μl , less than about 110 μl , less than about 100 μl , less than about 75 μl , or less than about 50 μl .

28. The metered dose device of any one of claims 24 to 27 wherein the metered dose spray produced by the device produces a C_{plasma} in the mammal of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration.

29. The metered dose device of any one of claims 24 to 28 wherein the metered dose spray produced by the device does not produce significant sedation in an adult within a period of time of about two hours after administration and has an analgesic effect within the period of time.

30. The metered dose device of any one of claims 24 to 29 wherein the metered dose spray produced by the device produces a plasma C_{max} in the mammal of about 0.08 ng/ml to about 0.2 ng/ml.

31. The metered dose device of any one of claims 24 to 29 wherein the metered dose spray produced by the device produces a plasma C_{max} in the mammal of about 0.15 ng/ml.

32. The metered dose device of any one of claims 24 to 29 wherein the metered dose spray produced by the device produces a plasma C_{max} in the mammal of about 0.2 ng/ml.

33. The metered dose device of any one of claims 24 to 32 wherein the metered dose spray produced by the device produces a T_{max} in the mammal of less than about 1 hour.

34. The metered dose device of any one of claims 24 to 32 wherein the metered dose spray produced by the device produces a T_{max} in the mammal of less than about 50 minutes.

35. The metered dose device of any one of claims 24 to 34 wherein the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 3 on the Ramsay Sedation Scale.

36. The metered dose device of any one of claims 24 to 35 wherein the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 2 on the Stanford Sleepiness Scale.
- 5 37. The metered dose device of any one of claims 24 to 36 wherein the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not less than Level 6 on the Modified Observer's Assessment Of Alertness/Sedation Scale.
- 10 38. The metered dose device of any one of claims 24 to 37 wherein the metered dose spray produced by the device has no or minimal effect on the blood pressure of the mammal after administration.
39. The metered dose device of any one of claims 24 to 38 wherein the pharmaceutical
15 composition further comprises one or more other therapeutic agents.
40. The metered dose device of claim 39 wherein the one or more additional therapeutic agents is chosen from an opioid analgesic, a synthetic opioid-like analgesic, a non-opioid analgesic, a vitamin, a vasodilator, a benzodiazepine, a triptan, an anti-convulsant, an anti-
20 depressant, an anti-nausea medication, and an anti-hypertensive.
41. The metered dose device of any one of claims 24 to 40 which is a multi-dose, unit dose, or bi-dose device.
- 25 42. The metered dose device of any one of claims 24 to 41 wherein the pharmaceutical composition further comprises a carrier vehicle.
43. The metered dose device of any one of claims 24 to 42 wherein the pharmaceutical composition further comprises sodium phosphate and/or sodium citrate.
30
44. The metered dose device of any one of claims 24 to 43 wherein the pharmaceutical composition further comprises a chelator.

45. The metered dose device of any one of claims 24 to 44 wherein the pharmaceutical composition is free of a viscosity enhancing agent.

46. The metered dose device of any one of claims 24 to 45 wherein the pharmaceutical composition further comprises sodium citrate, citric acid, and sodium chloride.

47. The metered dose device of claim 46 wherein the pharmaceutical composition further comprises about 0.2% to about 0.3% (w/w) sodium citrate and about 0.005% to about 0.015% (w/w) citric acid.

48. The metered dose device of any one of claims 24 to 47 wherein the pH of the pharmaceutical composition is from about 6 to about 6.5.

49. The metered dose device of any one of claims 24 to 48 wherein the pharmaceutical composition further comprises one or more anti-microbial preservatives.

50. The metered dose device of claim 49 wherein the preservative is phenylethyl alcohol.

51. The metered dose device of any one of claims 24 to 50 wherein the pharmaceutical composition further comprises one or more antioxidants.

52. The metered dose device of any one of claims 24 to 51 wherein the pharmaceutical composition further comprises one or more dose confirmation excipients.

53. The metered dose device of claim 52 wherein the one or more dose confirmation excipients is phenylethyl alcohol.

54. The metered dose device of any one of claims 24 to 53 wherein the pharmaceutical composition further comprises one or more humectants.

55. The metered dose device of claim 54 wherein the one or more humectants is glycerin, propylene glycol, polyethylene glycol, or a sugar/sugar alcohol, or any combination thereof.

56. The metered dose device of any one of claims 24 to 55 wherein the pharmaceutical composition further comprises one or more osmolality adjusting agents.

57. The metered dose device of claim 56 wherein the one or more osmolality adjusting
5 agents is sodium chloride, dextrose, or another sugar, or any combination thereof.

Figure 1:

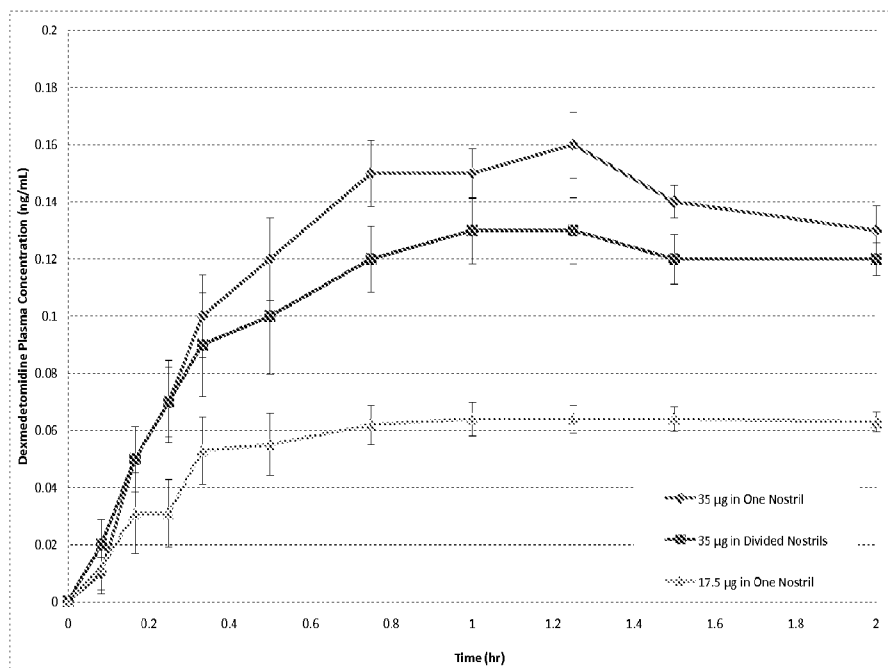
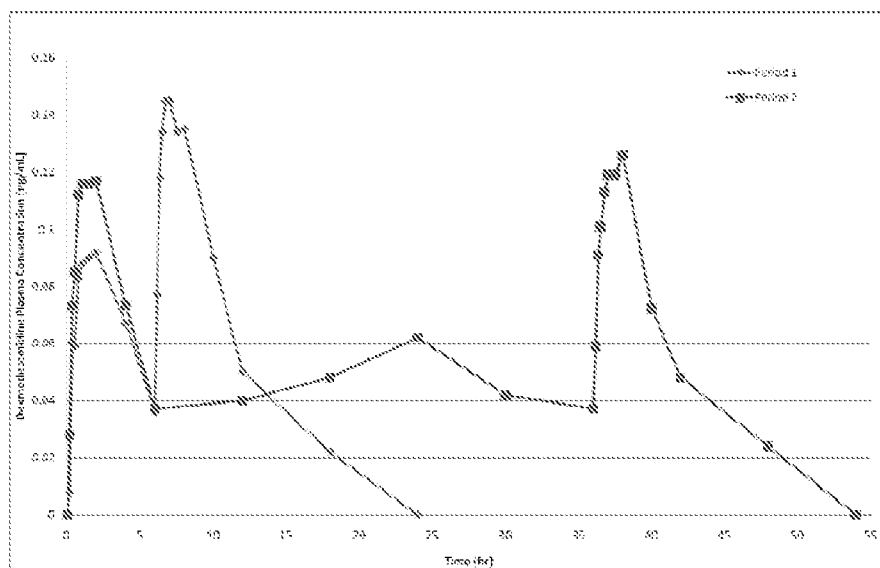


Figure 2



PATENT COOPERATION TREATY

FEB 25 2013

From the INTERNATIONAL SEARCHING AUTHORITY

DUE DATE _____
MAX DATE _____
PCT CHECKED BY *[Signature]*

To: PAUL K. LEGAARD
PEPPER HAMILTON LLP
400 BERWYN PARK
899 CASSATT ROAD
BERWYN, PA 19312
Act 19 Due 4/22/13
Demand/Resp to
WO Due 10/11/13
File IDS IN Related Appln
3/11/13 (2wk)
3/27/13 (30d)
5/22/13 (3m)

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year) 22 FEB 2013

Applicant's or agent's file reference
13761700402

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US 12/68988

International filing date
(day/month/year) 11 December 2012 (11.12.2012)

Applicant RECRO PHARMA, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see PCT Applicant's Guide, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to any protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the PCT Applicant's Guide, National Chapters.

Name and mailing address of the ISA/
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer
Lee W. Young
PCT Helpdesk: 571-272-4300
Telephone No. PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 13761700402	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US 12/68988	International filing date (<i>day/month/year</i>) 11 December 2012 (11.12.2012)	(Earliest) Priority Date (<i>day/month/year</i>) 11 December 2011 (11.12.2011)
Applicant RECRO PHARMA, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 9 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/68988

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 8-23 and 27-57
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/68988

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention provides intranasal formulations comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, that are analgesic but without significant sedation, methods of treating or preventing pain comprising administering the intranasal formulations to a mammal and metered dose devices for administering the intranasal formulation as a spray, wherein the droplets of the spray have a Dv90 of less than 150 μm .

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/68988

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/4174 (2013.01)

USPC - 514/396

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61K 31/4174 (2013.01)

USPC: 514/396 (text search)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/816; 424/400 (text search) Find search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (PGPB,USPT,USOC,EPAB,JPAB), Google Scholar, PatBase

dexmedetomidine, intranasal\$, nasal, nostril, composition, formulation, sedative, sedation, analgesic, pain, treat\$, alleviat\$, Dv90

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2011/085162 A2 (HENWOOD et al.) 14 July 2011 (14.07.2011) para [0005]-[0006], [0020], [0027]-[0039], [0060]	3, 24 and 26/24 1-2, 4-7, 25 and 26/25
Y	IIROLA et al. Bioavailability of dexmedetomidine after intranasal administration, Eur J Clin Pharmacol, 2011, Vol.67, pp 825-831. Published online: 12 February 2011, [Retrieved from the internet on 01 February 2013 from the URL: <http://link.springer.com/article/10.1007%2Fs00228-011-1002-y>]. Abstract; pg 826, col 2, para 2-para 3; pg 827, col 2, para 4; Table 1; Fig 1; pg 830, col 2, para 2	1-2 and (5-7)/(1-3)
Y	US 2008/0004305 A1 (WERMELING) 03 January 2008 (03.01.2008) para [0011]-[0012], [0066]-[0069]	4, (5-7)/4, 25 and 26/25
A	US 2011/0021588 A1 (HENWOOD et al.) 27 January 2011 (27.01.2011) para [0004]-[0008]	1-7 and 24-26
A	US 2011/0021426 A1 (TOLL et al.) 27 January 2011 (27.01.2011) para [0011]-[0013], [0041]-[0045], [0082]	1-7 and 24-26

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

01 February 2013 (01.02.2013)

Date of mailing of the international search report

22 FEB 2013

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

Authorized officer:

Lee W. Young

Intranasal Dexmedetomidine Compositions And Methods Of Use Thereof

Field Of The Invention

The present invention is directed, in part, to intranasal formulations of
5 dexmedetomidine, or a pharmaceutically acceptable salt thereof, that are analgesic but without
significant sedation, as well as methods of use thereof.

Background

Dexmedetomidine, 5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole, is a non-
10 narcotic α_2 -adrenoceptor agonist with sedative and analgesic properties. Currently,
dexmedetomidine is only commercially available as an injectable formulation indicated for
sedation of initially intubated and mechanically ventilated patients during treatment in an
intensive care setting and sedation of non-intubated patients prior to and/or during surgical and
other procedures, and it must be administered intravenously by an experienced and licensed
15 health care professional. Although dexmedetomidine has analgesic properties, an intranasal
formulation useful as an analgesic without sedation, however, is not commercially available.
Moreover, for a variety of reasons, the commercially available injectable formulation is not
suitable for use as an analgesic that can be self-administered. A continuing and unmet need exists
for a dexmedetomidine-based analgesic medicine that, for example, may be self-administered by
20 the patient intranasally to produce analgesia (or otherwise treat or prevent pain) without
significant sedation.

Brief Description of Drawings:

Figure 1 shows intranasal dexmedetomidine pharmacokinetics for some embodiments.
25 Figure 2 shows mean dexmedetomidine plasma concentrations (ng/mL) for some
embodiments.

Summary of the Invention

The present invention provides methods of treating or preventing pain without
30 significant sedation in a mammal comprising intranasally administering an intranasally effective
amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal
whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable
salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of
administration and has an analgesic effect without significant sedation.

The present invention also provides methods of treating or preventing pain without significant sedation in an adult human comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the adult human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult within a period of time of about two hours after administration and has an analgesic effect within the period of time.

The present invention also provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally administering dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the mammal, particularly a human.

The present invention also provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying in the mammal a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the spray comprises droplets which have a Dv90 of less than about 150 μm .

The present invention also provides metered dose devices comprising a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the metered dose device delivers a metered dose spray of the pharmaceutical composition intranasally that is analgesic in a mammal without significant sedation.

Description Of Embodiments

Unless defined otherwise, all technical and scientific terms have the same meaning as is commonly understood by one of ordinary skill in the art to which the embodiments disclosed belongs.

As used herein, the terms “a” or “an” means that “at least one” or “one or more” unless the context clearly indicates otherwise.

As used herein, the term “about” means that the numerical value is approximate and small variations would not significantly affect the practice of the disclosed embodiments. Where a numerical limitation is used, unless indicated otherwise by the context, “about” means the numerical value can vary by $\pm 10\%$ and remain within the scope of the disclosed embodiments.

As used herein, the term “analgesia” refers to the alleviation (partial or complete) or elimination of the sensation of pain.

As used herein, the term “carrier” means a diluent, adjuvant, or excipient with which a compound is administered. Pharmaceutical carriers can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical carriers can also be saline, gum

acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents can be used.

As used herein, the term, “compound” means all stereoisomers, tautomers, and isotopes of the compounds, or pharmaceutically acceptable salts thereof, including any and all metabolites described herein.

As used herein, the terms “comprising” (and any form of comprising, such as “comprise”, “comprises”, and “comprised”), “having” (and any form of having, such as “have” and “has”), “including” (and any form of including, such as “includes” and “include”), or “containing” (and any form of containing, such as “contains” and “contain”), are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

As used herein, the term “contacting” means bringing together of two elements in an *in vitro* system or an *in vivo* system. For example, “contacting” a compound or composition described herein with an individual or patient or cell includes the administration of the compound to an individual or patient, such as a human.

As used herein, the term “Dv90” means the value which represents the particle size below which 90% of the volume of a plurality of droplets exist (e.g., such as in a spray mist; in contrast to a nasal drop comprising one or two drops).

As used herein, the term “individual” or “patient,” used interchangeably, means any animal, including mammals, such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, such as humans.

As used herein, the phrase “in need thereof” means that the animal or mammal has been identified as having a need for the particular method or treatment. In some embodiments, the identification can be by any means of diagnosis. In any of the methods and treatments described herein, the animal or mammal can be in need thereof. In some embodiments, the animal or mammal is in an environment or will be traveling to an environment in which a particular disease, disorder, or condition is prevalent. For example, a mammal or animal may be in need of treatment or prevention of pain without sedation or without significant sedation.

As used herein, the phrase “metered dose device” refers to a device that provides a specified dose.

As used herein, the phrase “X to Y” means any number between X and Y and includes the endpoints. For example, the phrase “1 to 5” means 1, 2, 3, 4, or 5.

As used herein, “pain” refers to a wide range of clinical manifestations, and it has a broad meaning. Pain perception is highly subjective, and different individuals experience pain in different ways and with greatly different intensities. The International Association for the Study

of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” More simply stated, pain includes any sensory experience that causes suffering and is associated with an unpleasant awareness of one’s own body. Non-limiting types and causes of pain include neuralgia, myalgia, hyperalgesia, hyperpathia, neuritis, and neuropathy. Pain is often a symptom of an underlying physiological abnormality, such as cancer or arthritis. Some types of pain have no clearly identified causes, such as migraine headache pain. Pain may also be caused by physical trauma, such as burns or surgery. Viral infections, such as Herpes zoster (chicken pox and shingles), can also cause pain. Withdrawal from chemical dependence on alcohol or drugs of abuse is also often associated with pain symptoms. Accordingly, “pain” is understood herein to have a very broad meaning.

As used herein, the phrase “pharmaceutically acceptable” means those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with tissues of humans and animals. In some embodiments, “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

As used herein, the phrase “pharmaceutically acceptable salt(s),” includes, but is not limited to, salts of acidic or basic groups. Compounds that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. Acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions including, but not limited to, sulfuric, thiosulfuric, citric, maleic, acetic, oxalic, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, bisulfite, phosphate, acid phosphate, isonicotinate, borate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, bicarbonate, malonate, mesylate, esylate, napsydisylate, tosylate, besylate, orthophosphate, trifluoroacetate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include, but are not limited to, alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, ammonium,

sodium, lithium, zinc, potassium, and iron salts. The present invention can also include quaternary ammonium salts of the compounds.

As used herein, the terms “prevention” or “preventing” mean a reduction of the risk of acquiring a particular disease, condition, or disorder.

5 As used herein, the term “prodrug” means a derivative of a known direct acting drug, which derivative has enhanced delivery characteristics and therapeutic value as compared to the drug, and is transformed into the active drug by an enzymatic or chemical process.

As used herein, the term “sedation” means depressed consciousness in which a patient or subject retains the ability to independently and continuously maintain an open airway and a regular breathing pattern, and to respond appropriately and rationally to physical stimulation and verbal commands.

As used herein, the phrase “significant sedation” is consistent with a patient’s self-evaluation on the Stanford Sleepiness Scale, with Subject patients rating their degree of sedation as greater than or equal to Level 3, wherein: Level 1 = Feeling active, vital, alert, or wide awake; Level 2 = Functioning at high levels, but not at peak; able to concentrate; Level 3 = Awake, but relaxed; responsive but not fully alert; Level 4 = Somewhat foggy, let down; Level 5 = Foggy; losing interest in remaining awake; slowed down; Level 6 = Sleepy, woozy, fighting sleep; prefer to lie down; or Level 7 = No longer fighting sleep, sleep onset soon; having dream-like thoughts. “Significant sedation” also means that the patient or subject experiences sedation of Level 4 or greater on the Ramsay Sedation Scale, wherein: Level 1 = Patient is anxious and agitated or restless, or both; Level 2 = Patient is co-operative, oriented, and tranquil; Level 3 = Patient responds to commands only; Level 4 = Asleep; brisk response to light glabellar tap or loud auditory stimulus; Level 5 = asleep; sluggish response to light glabellar tap or loud auditory stimulus; Level 6 = asleep; no response to painful stimulus. “Significant sedation” also means that the patient or subject experiences sedation of Level 5 or less on the Modified Observer’s Assessment of Alertness/Sedation Scale, wherein: Level 6 = Appears alert and awake, responds readily to name spoken in normal tone; Level 5 = Appears asleep but responds readily to name spoken in normal tone; Level 4 = lethargic response to name spoken in normal tone; Level 3 = responds only after name is called loudly or repeatedly; Level 2 = responds only after mild prodding or shaking; Level 1 = does not respond to mild prodding or shaking; and Level 0 = does not respond to noxious stimulus.

As used herein, the phrase “solubilizing agent” means agents that result in formation of a micellar solution or a true solution of the drug.

As used herein, the term “solution/suspension” means a liquid composition wherein a first portion of the active agent is present in solution and a second portion of the active agent is present in particulate form, in suspension in a liquid matrix.

As used herein, the phrase “substantially isolated” means a compound that is at least
5 partially or substantially separated from the environment in which it is formed or detected.

As used herein, the phrase “therapeutically effective amount” generally means the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician. The therapeutic effect is dependent upon the
10 disorder being treated or the biological effect desired. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disorder and/or inhibition (partial or complete) of progression of the disorder, or improved treatment, healing, prevention or elimination of a disorder, or side-effects. The amount needed to elicit the therapeutic response can be determined based on the age, health, size and sex of the subject. Optimal amounts can
15 also be determined based on monitoring of the subject’s response to treatment. In some embodiments, the therapeutically effective amount is a specific amount or range described herein.

As used herein, the terms “treat,” “treated,” or “treating” mean both therapeutic treatment or prophylactic or preventative measures wherein the object is to prevent or slow down
20 (lessen) an undesired physiological condition, disorder or disease, or obtain beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of extent of condition, disorder or disease; stabilized (i.e., not worsening) state of condition, disorder or disease; delay in onset or slowing of condition, disorder or disease progression; amelioration of the condition, disorder or
25 disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder or disease. Treatment includes eliciting a clinically significant analgesic response without excessive levels of side effects, such as, but not limited to, significant sedation. Thus, “treatment of pain” or “treating pain” means an
30 activity that prevents, alleviates or ameliorates any of the primary phenomena or secondary symptoms associated with pain.

As used herein “without significant sedation” means that the patient experiences a level of sedation not greater than Level 3 on the Ramsay Sedation Scale, not greater than Level 2 on the Stanford Sleepiness Scale, and/or not less than Level 6 on the Modified Observer’s

Assessment Of Alertness/Sedation Scale.

It is further appreciated that certain features described herein, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

Dexmedetomidine is a specific alpha-2-adrenergic receptor agonist that causes sedation, anesthesia, and analgesia in mammals. In humans, dexmedetomidine is commercially available for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting, as well as sedation of non-intubated patients prior to or during surgical and other procedures. See, e.g., U.S. Patent Nos. 6,716,867 and 6,313,311, each of which are hereby incorporated by reference in their entirety.

Dexmedetomidine contains a basic nitrogen atom capable of forming a pharmaceutically acceptable salt with a pharmaceutically acceptable acid. Pharmaceutically acceptable salts, in this respect, refers to the relatively non-toxic, inorganic, and organic acid addition salts of dexmedetomidine. These salts may be prepared *in situ* during final isolation and purification of dexmedetomidine or by separately reacting purified dexmedetomidine in its free base form with a suitable organic or inorganic acid, and thereafter isolating the salt thus formed. Furthermore, the salt may be formed during a manufacturing process to produce the spray formulation. Representative pharmaceutically acceptable salts include, but are not limited to, the hydrohalide (including hydrobromide and hydrochloride), sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphylate, mesylate, glucoheptonate, lactobionate, 2-hydroxyethylsulfonate, and laurylsulphonate salts, and the like. See, e.g., "Pharmaceutical Salts," Berge et al., J. Pharm. Sci., 1977, 66, 1-19. Dexmedetomidine hydrochloride is an example of a pharmaceutically acceptable salt. Use of dexmedetomidine hydrochloride may be used, in part because, in some cases, the hydrochloride salt has greater water solubility and stability against oxidation by ambient oxygen.

Dexmedetomidine derivatives include covalent modifications that create a prodrug. Upon administration, the prodrug derivative undergoes chemical modification by the mammal that yields dexmedetomidine. Prodrugs may be used to favorably alter the biodistribution or the pharmacokinetics of dexmedetomidine or to produce other desirable characteristics. For example, a reactive nitrogen of dexmedetomidine may be derivatized with a functional group that is cleaved, enzymatically or non-enzymatically, reductively, oxidatively, or hydrolytically, to reveal the active pharmaceutical ingredient. Uses of certain types of prodrugs are known (see,

e.g., R. B. Silverman, 1992, "The Organic Chemistry of Drug Design and Drug Action," Academic Press, Chp. 8). For example, prodrugs may be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free base form with a suitable derivatizing agent.

5 The present disclosure describes the surprising and unexpected result(s) that an intranasal formulation of dexmedetomidine, or a pharmaceutically acceptable salt thereof, can be developed for the treatment of pain that has a reduced time to the onset of pain relief corresponding to C_{plasma} , a C_{max} , and a reduced time to T_{max} , that can lead to pain relief or prevention without sedation or significant sedation in a mammal.

10 The present invention provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal. The dexmedetomidine, or a pharmaceutically acceptable salt thereof, or compositions comprising the same, can be administered in any conventional manner such that the composition is administered
15 intranasally. That is, the composition is contacted with the nasal cavity. The compositions can also be administered, for example, by implanting the composition so that it is absorbed intranasally.

 In some embodiments, the dexmedetomidine, or pharmaceutically acceptable salt thereof, is absorbed through the nasal mucosa. In some embodiments, at least 10%, at least 20%,
20 at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% of the composition is absorbed through the nasal mucosa. In some embodiments, dexmedetomidine, or a pharmaceutically acceptable salt thereof, is not absorbed through the oral mucosa.

 In some embodiments, the method comprises treating or preventing pain relief without
25 sedation or significant sedation. In some embodiments, the level of sedation is no greater than Level 1 on the Ramsay Sedation Scale. In some embodiments, the level of sedation is no greater than Level 2 on the Ramsay Sedation Scale. In some embodiments, the level of sedation is no greater than Level 3 on the Ramsay Sedation Scale. In some embodiments, the level of sedation is no greater than Level 1 on the Stanford Sleepiness Scale. In some embodiments, the level of
30 sedation is no greater than Level 2 on the Stanford Sleepiness Scale. In some embodiments, the level of sedation is no less than Level 6 on the Modified Observer's Assessment of Alertness/Sedation Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 3 on the Ramsay Sedation

Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 2 on the Ramsay Sedation Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 1 on the Ramsay Sedation Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 2 on the Stanford Sleepiness Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 1 on the Stanford Sleepiness Scale. In some embodiments, during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not less than Level 6 on the Modified Observer's Assessment Of Alertness/Sedation Scale.

In some embodiments, the pain is idiopathic pain. In some embodiments, the idiopathic pain is neuralgia, myalgia, hyperalgia, hyperpathia, neuritis, or neuropathy. In some embodiments, the pain is associated with or caused by cancer, viral infection, physical trauma, arthritis, headache, migraine, or lower back pain. In some embodiments, the physical trauma is associated with or caused by surgery, a burn, blunt force trauma, or other trauma that can cause pain, such as being in an accident.

In some embodiments, the means and methods of administering the compositions described herein are known. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance (see, for example, Modern Pharmaceutics, Banker & Rhodes, Marcel Dekker, Inc. (1979); and Goodman & Gilman's The Pharmaceutical Basis of Therapeutics, 6th Edition, MacMillan Publishing Co., New York (1980)).

In some embodiments, the amount of compound to be administered is that amount which is therapeutically effective or intranasally effective. The dosage to be administered can depend on the characteristics of the subject being treated, e.g., the particular animal treated, age, weight, health, types of concurrent treatment, if any, and frequency of treatments, and can be easily determined by one of skill in the art (e.g., by the clinician). The selection of the specific dose regimen can be selected or adjusted or titrated by the clinician according to methods known to the clinician to obtain the desired clinical response or as they are described herein. Further, the

amount of a compound described herein that will be effective in the treatment and/or prevention of a particular disease, condition, or disorder will depend on the nature and extent of the disease, condition, or disorder, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The dosages can be, for example, the doses described herein.

The compounds, or composition comprising the same, can be administered in various dosage forms suitable for intranasal administration. The dosage amount present in the dosage form can be a pharmaceutically or intranasally effective amount. In some embodiments, the effective amount is an amount sufficient to treat or prevent pain. In some embodiments, the effective amount is an amount that does not produce sedation. In some embodiments, the effective amount does not produce significant sedation. In some embodiments, the effective amount is an amount sufficient to treat or prevent pain, yet does not produce sedation or significant sedation.

C_{plasma} is the concentration of dexmedetomidine in the plasma of a mammal or human at a particular time after administration. In some embodiments, the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation. Thus, in some embodiments, within about 15 minutes to about 20 minutes of administration of dexmedetomidine, or pharmaceutically acceptable salt thereof, to a mammal or human, the mammal or human will have a C_{plasma} of about 0.1 ng/ml. In some embodiments, the C_{plasma} is from about 0.09 ng/ml to about 0.11 ng/ml, from about 0.08 ng/ml to about 0.12 ng/ml, from about 0.06 ng/ml to about 0.09 ng/ml, from about 0.07 ng/ml to about 0.09 ng/ml, or from about 0.08 ng/ml to about 0.09 ng/ml. In some embodiments, the targeted C_{plasma} is reached within about 8 minutes to about 30 minutes, within about 10 minutes to about 30 minutes, within about 12 minutes to about 30 minutes, within about 8 minutes to about 20 minutes, within about 10 minutes to about 20 minutes, within about 12 minutes to about 20 minutes, within about 8 minutes to about 15 minutes, within about 10 minutes to about 15 minutes, within about 12 minutes to about 15 minutes, within about 8 minutes to about 10 minutes, within about 8 minutes to about 12 minutes, within about 15 minutes to about 20 minutes, within about 15 minutes to about 20 minutes, within about 15 minutes, within about 12 minutes, within about 10 minutes, or within about 8 minutes of administration and has an analgesic effect without significant sedation. This time point can reflect the onset of pain relief (i.e., an analgesic effect).

In some embodiments, the onset of pain relief is less than about 60 minutes, less than

about 55 minutes, less than about 50 minutes, less than about 45 minutes, less than about 40 minutes, less than about 35 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, less than about 12 minutes, less than about 10 minutes, about 15 minutes, about 12 minutes, about 10 minutes, or about 8 minutes. The onset of pain relief is the time when a mammal feels that the pain is less than prior to the administration of a compound or composition described herein. In some embodiments, the pain relief is complete and the mammal no longer feels the pain that was being relieved.

The present invention also provides methods of treating or preventing pain without significant sedation in an adult human comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the adult human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult within a period of time of about two hours after administration and has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 1.5 hours after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 1.0 hours after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 45 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 30 minutes to about 1.5 hours after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 40 minutes to about 75 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 45 minutes to about 70 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 50 minutes to about 65 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 55 minutes to about 60 minutes after administration, but yet has an analgesic effect within the period of time.

The present invention also provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally administering dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the mammal, particularly a human.

Administration to a single nostril means that the entire unit dose is administered to a single nostril as compared to a portion of the unit dose being administered to both nostrils. In some embodiments, the unit dose is only administered to a single nostril. That is, if a dosage is given every 4 hours, the dosage is administered to only a single nostril every 4 hours. The single nostril to which the compositions are administered may alternate between the two nostrils, however. In some embodiments, the methods comprise not administering dexmedetomidine or a pharmaceutically acceptable salt thereof or a composition described herein to more than one nostril (*e.g.*, two nostrils).

The present invention also provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying in the mammal a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm . In some embodiments, the spray comprises droplets which have a Dv_{90} of less than about 125 μm . In some embodiments, the spray comprises droplets which have a Dv_{90} of less than about 100 μm . In some embodiments, the spray comprises droplets which have a Dv_{90} from about 60 μm to about 150 μm , from about 60 μm to about 125 μm , or from about 60 μm to about 100 μm . In some embodiments, the spray comprises droplets which have a Dv_{90} of more than about 40 μm . In some embodiments, the spray comprises droplets which have a Dv_{90} of more than about 50 μm . In some embodiments, the spray comprises droplets which have a Dv_{90} of more than about 60 μm . In some embodiments, the spray comprises droplets which have a Dv_{90} of more than about 70 μm .

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation, and whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation within a period of time of about two hours after administration and has an analgesic effect within the period of time.

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof,

to a single nostril of the mammal, particularly a human, whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation.

5 In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20
10 minutes of administration and has an analgesic effect without significant sedation, and wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

 In some embodiments, the present invention also provides methods of treating or preventing pain without significant sedation in an adult human comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically
15 acceptable salt thereof, to a single nostril of the adult human, whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult within a period of time of about two hours after administration and has an analgesic effect within the period of time.

 In some embodiments, the present invention also provides methods of treating or preventing pain without significant sedation in an adult human comprising intranasally spraying an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the adult human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult within a period of time of about two hours after administration and has an analgesic effect within
20 the period of time, and wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

 In some embodiments, the present invention also provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the
30 mammal, particularly a human, wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

 In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a human comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof,

to a single nostril of the human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation, whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the human within a period of time of about two hours after administration and has an analgesic effect within the period of time.

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation, whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the mammal within a period of time of about two hours after administration and has an analgesic effect within the period of time, and wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a human comprising intranasally spraying an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation, wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In some embodiments, the present invention also provides methods of treating or preventing pain without significant sedation in a human comprising intranasally spraying an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the human within a period of time of about two hours after administration and has an analgesic effect within the period of time, wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In some embodiments, the present invention provides methods of treating or preventing pain without significant sedation in a human comprising intranasally spraying an intranasally

effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation, whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the human within a period of time of about two hours after administration and has an analgesic effect within the period of time, and wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .

In any of the methods described herein, the plasma C_{max} of dexmedetomidine is from about 0.08 ng/ml to about 0.25 ng/ml, about 0.08 ng/ml to about 0.2 ng/ml, from about 0.1 ng/ml to about 0.2 ng/ml, from about 0.08 ng/ml to about 0.15 ng/ml, from about 0.1 ng/ml to about 0.15 ng/ml, or from about 0.15 ng/ml to about 0.2 ng/ml. In some embodiments, the plasma C_{max} of dexmedetomidine is from about 0.08 ng/ml to about 0.2 ng/ml. In some embodiments, the plasma C_{max} of dexmedetomidine is about 0.15 ng/ml. In some embodiments, the plasma C_{max} of dexmedetomidine is about 0.2 ng/ml. In some embodiments, the plasma C_{max} of dexmedetomidine is about 0.25 ng/ml.

In any of the methods described herein, the T_{max} is less than about 60 minutes, less than about 50 minutes, less than about 40 minutes, less than about 35 minutes, or less than about 30 minutes. In some embodiments, the T_{max} is from about 20 minutes to about 60 minutes, from about 20 minutes to about 50 minutes, from about 20 minutes to about 40 minutes, from about 20 minutes to about 30 minutes, from about 30 minutes to about 60 minutes, from about 30 minutes to about 50 minutes, from about 30 minutes to about 40 minutes, from about 40 minutes to about 60 minutes, from about 40 minutes to about 50 minutes, or from about 50 minutes to about 60 minutes. In some embodiments, the T_{max} of dexmedetomidine is less than about 1 hour. In some embodiments, the T_{max} is less than about 50 minutes.

In any of the methods described herein, the compound or composition can be administered according to a specific schedule. In some embodiments, the composition is administered about every 2 hours, about every 4 hours, about every 6 hours, about every 8 hours, about every 10 hours, about every 12 hours, or about every 24 hours. The composition can also be administered as needed. In some embodiments, dexmedetomidine, or pharmaceutically acceptable salt thereof, or composition comprising the same, is administered about every 6 hours.

In any of the methods described herein, the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered as a unit dose of about 10 μg to about 100 μg , from about 10 μg to about 90 μg , from about 10 μg to about 80 μg , from about 10 μg to about 70 μg , from

about 10 µg to about 60 µg, from about 10 µg to about 50 µg, from about 10 µg to about 40 µg, from about 10 µg to about 30 µg, from about 10 µg to about 20 µg, from about 25 µg to about 100, from about 25 µg to about 90 µg, from about 25 µg to about 80 µg, from about 25 µg to about 70 µg, from about 25 µg to about 60 µg, from about 25 µg to about 50 µg, from about 25 µg to about 40 µg, from about 25 µg to about 35 µg, from about 25 µg to about 30 µg, from about 30 µg to about 45 µg, from about 35 µg to about 45 µg, from about 30 µg to about 40 µg, or from about 25 µg to about 45 µg. In some embodiments, the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered as a unit dose of about 10 µg, about 15 µg, about 20 µg, about 25 µg, about 30 µg, about 35 µg, about 40 µg, about 45 µg, about 50 µg, about 55 µg, about 60 µg, about 70 µg, about 75 µg, about 80 µg, about 85 µg, about 90 µg, about 95 µg, or about 100 µg. In some embodiments, the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered as a unit dose of less than about 100 µg, less than about 90 µg, less than about 80 µg, less than about 70 µg, less than about 60 µg, less than about 50 µg, less than about 40 µg, less than about 30 µg, less than about 20 µg, or less than about 10 µg. In some embodiments, the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered as a unit dose of about 10 µg, about 25 µg, about 30 µg, about 35 µg, about 40 µg, about 50 µg, about 75 µg, or about 100 µg. As discussed herein, the unit dose can be administered in many different manners. In some embodiments the unit dose is administered by a single nasal spray. In some embodiments the unit dose is administered by a single nasal spray using a single dose spray device requiring no priming. The single dose can be administered through a single actuation of a nasal spray device. An examples of spray device that does not require priming includes, but is not limited to, Aptar Unitdose Intranasal Systems. The spray device can, in some embodiments, deliver a volume of about 100 µl. In some embodiments, the volume is about 10, 20, 30, 40, 50, 60, 70, 80, or 90 µl. In some embodiments, the volume is from about 10-100, about 20-100, about 30-100, about 40-100, about 50-100, about 60-100, about 70-100, about 80-100, about 90-100 µl.

In any of the methods described herein, the method comprises having no effect or having minimal effect on blood pressure after administration. In some embodiments, there is no effect on blood pressure within the hour immediately after a compound described herein is administered. In some embodiments, there is only minimal effect on blood pressure within the hour immediately after a compound described herein is administered. In some embodiments, the resting mean arterial blood pressure of the mammal is not effected by more than about 5 mmHg, more than about 10 mmHg, more than about 15 mmHg, more than about 20 mmHg, more than

about 25 mmHg, or more than about 30 mmHg. The mean arterial blood pressure can be measured by any method known to one of skill in the art. In some embodiments, there is no or minimal effect on blood pressure after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof.

5 In any of the methods described herein, the method further comprises administering in simultaneous, alternating, or sequential combination to the human or mammal one or more additional therapeutic agents. The one or more additional therapeutic agents is chosen from an analgesic, such as an opioid analgesic (e.g. morphine, oxycodone, hydromorphone, etc.), a synthetic opioid-like analgesic (e.g. meperidine, fentanyl, pentazocine, butorphanol, etc.), or a
10 non-opioid analgesic (e.g. NSAIDs, ketamine, salicylates, steroids, etc.); a vitamin; a vasodilator; a benzodiazepine (e.g. clonazepam, alprazolam, lorazepam, etc.); a triptan (and other compounds for migraine headaches); an anti-convulsant (e.g. pregabalin, valproic acid, gabapentin, etc.); an anti-depressant (e.g. tricyclics such as amitriptyline, nortriptyline, etc.; serotonin and norepinephrine reuptake inhibitors such as duloxetine, fluoxetine, venlafaxine,
15 etc.); an anti-nausea medication (e.g. metoclopramide, prochlorperazine, ondansetron, granisetron, etc.); and an anti-hypertensive (e.g. beta blockers such as propranolol and calcium channel blockers such as verapamil, etc.).

The present invention also provides any one or more of the compositions described herein for treating pain in a mammal without significant sedation.

20 The present invention also provides any one or more of the compositions described herein for use in the manufacture of a medicament for treating pain in a mammal without significant sedation.

In any of the methods described herein, the dexmedetomidine, or pharmaceutically acceptable salt thereof, can be administered intranasally with a device. In some embodiments, the
25 device is a metered dose device. In some embodiments, the metered dose device is a multi-dose, unit dose, or bi-dose device.

In some embodiments, the device is suitable for intranasal administration. Any device that is suitable for intranasal administration can be used. In some embodiments, the device is a metered dose device. The metered dose device can deliver a specific dosage amount of the
30 composition. The metered dose device can be a unit-dose, bi-dose, or a multi-dose device. The pharmaceutically effective amount that can be administered using a metered dose device can be a unit dose device. The metered dose can, in some embodiments, be a device that can deliver a pharmaceutical composition intranasally. Examples of metered dose devices include, but are not limited to, devices that are pump devices, mechanical devices, pressurized devices, and/or

electromechanical devices. Examples of a metered dose device include, but are not limited to, a spray pump, a pre-compression nasal spray pump, a metered valve device, an actuated spray device, a side actuated spray device, a syringe nasal spray device (e.g. a syringe that has an atomizer to deliver a spray to the nasal cavity), a mucosal atomization device, an

5 electromechanical pump device (with and without a counter), and the like. Examples of metered dose devices also include, but are not limited to, devices manufactured by Aptar Pharma (Congers, NY) and are commercially available. Examples of metered dose devices also include, but are not limited to, UDS (Aptar Pharma), BDS (Aptar Pharma), eDevices (Aptar Pharma), Equadel (Aptar Pharma), Latitude (Aptar Pharma), DF30 (Aptar Pharma), VP7 (Aptar Pharma),

10 Classic Nasal Device (Aptar Pharma), MAD Nasal Drug Device (Wolf Tory Medical, Inc.), BD Accuspray SCF™ (Becton Dickinson), and the like. Another example includes, but is not limited to, an Aptar Unitdose Intranasal System.

Analgesic, intranasal formulations of dexmedetomidine, or a pharmaceutically acceptable salt or derivative thereof, can be administered in metered dosages so that a

15 predetermined amount of the active pharmaceutical ingredient is properly administered to the subject in a pharmaceutically effective amount. For example, the intranasal formulation may be packaged as a bulk liquid containing multiple doses in a pump spray system comprising a sealed container fitted with a metering pump. In some embodiments, a subject is treated by intranasal self-administration, such as by one or more actuations from a spray pump. An advantage of

20 intranasal delivery examples herein is the ability to titrate subjects by single doses as supplied by single, discrete actuations. This advantage is typically absent from other forms of drug delivery (e.g., patches, lozenges, tablets, and suppositories) in which a one-size-fits-all dosage is administered in a standard regimen. Additional advantages of intranasal formulations include its ease of use, especially when self-administered absent an attending health care professional.

25 In some embodiments, the metered dose device is a spray delivery device, which includes a base unit, a discharge actuator, an orifice for the formulation to be release from the device, and a reservoir. The reservoir can be filled with dexmedetomidine, or pharmaceutically acceptable salt thereof, and optionally other excipients, such as those described throughout the present application, prior to dispensing to the patient, e.g., at the manufacturing site. The

30 reservoir can contain a measured amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, or derivative thereof, to be discharged upon activation. The reservoir body may be any acceptable material, for example, formed simply by a section of a cylindrical hollow of a plastic, steel, such as stainless steel, transparent material, or the like so that its production is very simple. An actuator, which is movable relative to the orifice for activating discharge, may be

provided on or with the device. In the course of the actuating movement, the reservoir opens, e.g. by puncturing, to administer a single dosage through an orifice. During a part of the actuating travel following the starting position an elevated pressure is built up. In a subsequent portion of the actuating movement continuing in the same direction, the medium may be relieved of the pressure at one of the sides and communicated to an orifice. In such a manner, the medium is pushed from the reservoir and through the orifice by the action of pressure.

In some embodiments, as the liquid formulation leaves the orifice, the liquid droplets follow a trajectory which is influenced by the orifice shape, as well as by pressure asserted. In some embodiments, the droplet size, spray geometry, and the spray pattern are dependent on the design of the pump and/or the properties of the formulation. In some embodiments, the orientation of the actuator, pump design, and the properties of the formulation will influence the spray symmetry and the shape. The spray pattern may also be optimized to disperse the droplets over a wider pathway thereby increasing the surface area through which the compound can be absorbed. The device may further be designed to facilitate ease of patient use and placement of the administered spray to specific regions of the nasal mucosa.

Pump action sprays can be characterized by the application of external pressure for actuation, for example, external manual, mechanical or electrically initiated pressure. This is in contrast to pressurized systems, e.g., propellant-driven aerosol or compressed gas sprays, where actuation is typically achieved by controlled release of pressure, such as by controlled opening of a valve. In some embodiments, pump sprays are used. Use of a pump spray with the formulations herein allows for the administration of droplets or particles having a small mean diameter and a controllable size distribution of droplets. In some embodiments, pressurized systems containing a reservoir of pressurized propellant gas (e.g., carbon dioxide, nitrogen, chlorofluorocarbons, hydrofluoroalkanes, etc.) may produce suitable particles or droplets. Liquid droplets or particles having a diameter that is too small have the potential to enter into the lungs of a subject upon administration. In some embodiments, the droplet size of the delivered formulations further provides for an increase in surface area by being sprayed intranasally as opposed to being placed in a nostril, for example, with a dropper. The size of the spray particles and shape of the spray pattern also may contribute to whether the active ingredient is absorbed into body systems in addition to the nasal mucosa (e.g., lungs).

As described herein, the spray pump device may be pre-metered or, alternately, the device may be device-metered. Pre-metered dose devices may contain previously measured doses or a dose fraction in some type of units (e.g., single unit dose amount of solution, single or multiple blisters or other cavities) that may be included in the device during manufacture or by

the patient before use. Typical device-metered units have a reservoir containing a formulation sufficient for multiple doses that are delivered as metered sprays by the device itself when activated by the patient. The device may be metered both in the amount of drug substance delivered (i.e., the dosage per actuation), as well as the length of time between each dosage.

- 5 Limiting the time between each dosage can prevent over-use by limiting how often a dosage can be delivered to the patient.

The embodiments of the devices described herein, is not intended as limiting. In some embodiments, the formulations containing dexmedetomidine may alternately or additionally be provided as other intranasal dosage forms. For example, the intranasal composition may be provided as a liquid compatible with administration by a dropper or similar device. The intranasal formulation can also be provided as a powder to be administered into the nasal cavity. The formulations can be, for example, packaged in pharmaceutically acceptable unit dose ampules with snap-off tops to permit the opened ampule to be inserted into the patient's nasal cavity to dispense a single dose of the formulation.

- 15 In yet another embodiment, the compounds can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng., 1987, 14, 201; Buchwald et al., Surgery, 1980, 88, 507 Saudek et al., N. Engl. J. Med., 1989, 321, 574). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger et al., J. Macromol. Sci. Rev. Macromol. Chem., 1983, 23, 61; see, also Levy et al., Science, 1985, 228, 190; During et al., Ann. Neurol., 1989, 25, 351; Howard et al., J. Neurosurg., 1989, 71, 105). Other controlled-release systems discussed in the review by Langer, Science, 1990, 249, 1527-1533 may be used and can be adapted for intranasal administration.

- 25 In some embodiments, the aqueous dexmedetomidine intranasal compositions may be administered as drops or as a fine mist. Administration as a fine mist can improve the reproducibility of dosing by facilitating even deposition of the composition on the nasal mucosa. In some embodiments, a pump device is used to generate a fine mist from the bulk nasal solution composition. Unit-dose and bi-dose devices may be used for dexmedetomidine nasal spray compositions since these devices can limit the total dose and/or number of doses that can be delivered from a single device thus reducing the potential for over-dosing/abuse. Furthermore, the unit-dose and/or bi-dose devices may require less packaged volume to deliver the spray volume by reducing the required amount of solution lost to pump priming. In some

embodiments, multi-dose devices are used due to their lower cost of manufacturing and less packaging waste.

The present invention also provides metered dose devices comprising a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the metered dose device delivers a metered dose spray of the pharmaceutical composition intranasally that is analgesic in a mammal without significant sedation.

In some embodiments, the metered dose spray produced by the device comprises droplets comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, that have a Dv90 of less than about 150 μm . In some embodiments, the spray comprises droplets which have a Dv90 of less than about 125 μm . In some embodiments, the spray comprises droplets which have a Dv90 of less than about 100 μm . In some embodiments, the spray comprises droplets which have a Dv90 from about 60 μm to about 150 μm , from about 60 μm to about 125 μm , or from about 60 μm to about 100 μm .

In some embodiments, the metered dose spray produced by the device comprises a metered dose of dexmedetomidine, or a pharmaceutically acceptable salt thereof, from about 10 μg to about 100 μg , from about 10 μg to about 90 μg , from about 10 μg to about 80 μg , from about 10 μg to about 70 μg , from about 10 μg to about 60 μg , from about 10 μg to about 50 μg , from about 10 μg to about 40 μg , from about 10 μg to about 30 μg , from about 10 μg to about 20 μg , from about 25 μg to about 100, from about 25 μg to about 90 μg , from about 25 μg to about 80 μg , from about 25 μg to about 70 μg , from about 25 μg to about 60 μg , from about 25 μg to about 50 μg , from about 25 μg to about 40 μg , from about 25 μg to about 35 μg , from about 25 μg to about 30 μg , or from about 25 μg to about 45 μg . In some embodiments, the metered dose spray produced by the device comprises a metered dose of about 10 μg , about 15 μg , about 20 μg , about 25 μg , about 30 μg , about 35 μg , about 40 μg , about 50 μg , about 55 μg , about 60 μg , about 70 μg , about 75 μg , about 80 μg , about 85 μg , about 90 μg , about 95 μg , or about 100 μg . In some embodiments, the metered dose spray produced by the device comprises a metered dose of less than about 100 μg , less than about 90 μg , less than about 80 μg , less than about 70 μg , less than about 60 μg , less than about 50 μg , less than about 40 μg , less than about 30 μg , less than about 20 μg , or less than about 10 μg . In some embodiments, the metered dose spray produced by the device comprises a metered dose of about 10 μg , about 25 μg , about 35 μg , about 50 μg , about 75 μg , or about 100 μg .

In some embodiments, the metered dose spray produced by the device comprises a volume of less than about 150 μl , less than about 140 μl , less than about 130 μl , less than about

120 µl, less than about 110 µl, less than about 100 µl, less than about 75 µl, or less than about 50 µl. In some embodiments, the metered dose spray produced by the device comprises a volume of about 150 µl, about 140 µl, about 130 µl, about 120 µl, about 110 µl, about 100 µl, about 75 µl, or about 50 µl.

5 In some embodiments, the metered dose spray produced by the device produces a C_{plasma} in the mammal of from about 0.09 ng/ml to about 0.11 ng/ml, from about 0.08 ng/ml to about 0.12 ng/ml, or about 0.1 ng/ml within about 12 minutes to about 30 minutes, from about 12 minutes to about 20 minutes, from about 15 minutes to about 20 minutes, or within about 15 minutes of administration and has an analgesic effect without significant sedation. In some
10 embodiments, the metered dose spray produced by the device produces a C_{plasma} in the mammal of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration.

 In some embodiments, the metered dose spray produces an onset of pain relief less than about 60 minutes, less than about 55 minutes, less than about 50 minutes, less than about 45 minutes, less than about 40 minutes, less than about 35 minutes, less than about 30 minutes, less
15 than about 25 minutes, less than about 20 minutes, or about 15 minutes.

 In some embodiments, the metered dose spray produced by the device does not produce significant sedation in an adult within a period of time of about two hours after administration and has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 1.5 hours after administration, but
20 yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 1.0 hours after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time of about 45 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation
25 in the adult is not produced within a period of time from about 30 minutes to about of about 1.5 hours after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 40 minutes to about 75 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a
30 period of time from about 45 minutes to about 70 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 50 minutes to about 65 minutes after administration, but yet has an analgesic effect within the period of time. In some embodiments, significant sedation in the adult is not produced within a period of time from about 55 minutes to

about 60 minutes after administration, but yet has an analgesic effect within the period of time.

In some embodiments, the metered dose spray produced by the device produces a plasma $C_{\max}$ in the mammal from about 0.08 ng/ml to about 0.25 ng/ml, from about 0.08 ng/ml to about 0.2 ng/ml, from about 0.1 ng/ml to about 0.25 ng/ml, from about 0.1 ng/ml to about 0.2 ng/ml, from about 0.08 ng/ml to about 0.15 ng/ml, from about 0.1 ng/ml to about 0.15 ng/ml, from about 0.15 ng/ml to about 0.2 ng/ml, or from about 0.15 ng/ml to about 0.25 ng/ml. In some embodiments, the metered dose spray produced by the device produces a plasma $C_{\max}$ in the mammal of about 0.08 ng/ml to about 0.25 ng/ml. In some embodiments, the metered dose spray produced by the device produces a plasma $C_{\max}$ in the mammal of about 0.08 ng/ml to about 0.2 ng/ml. In some embodiments, the metered dose spray produced by the device produces a plasma $C_{\max}$ in the mammal of about 0.15 ng/ml. In some embodiments, the metered dose spray produced by the device produces a plasma $C_{\max}$ in the mammal of about 0.08 ng/ml, about 0.1 ng/ml, about 0.2 ng/ml, or about 0.25 ng/ml.

In some embodiments, the metered dose spray produced by the device produces a $T_{\max}$ in the mammal of less than about 60 minutes, less than about 50 minutes, less than about 40 minutes, less than about 35 minutes, or less than about 30 minutes. In some embodiments, the metered dose spray produced by the device produces a $T_{\max}$ in the mammal from about 20 minutes to about 60 minutes, from about 20 minutes to about 50 minutes, from about 20 minutes to about 40 minutes, from about 20 minutes to about 30 minutes, from about 30 minutes to about 60 minutes, from about 30 minutes to about 50 minutes, from about 30 minutes to about 40 minutes, from about 40 minutes to about 60 minutes, from about 40 minutes to about 50 minutes, or from about 50 minutes to about 60 minutes. In some embodiments, the metered dose spray produced by the device produces a $T_{\max}$ in the mammal of less than about 1 hour. In some embodiments, the metered dose spray produced by the device produces a $T_{\max}$ in the mammal of less than about 50 minutes.

In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 1, Level 2, or Level 3 on the Ramsay Sedation Scale. In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 3 on the Ramsay Sedation Scale. In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 2 on the Ramsay Sedation Scale.

In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 1 or Level 2 on the Stanford Sleepiness Scale. In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 2 on the Stanford Sleepiness Scale.

In some embodiments, the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not less than Level 6 on the Modified Observer's Assessment Of Alertness/Sedation Scale.

In some embodiments, the metered dose spray produced by the device has no or minimal effect on the blood pressure of the mammal after administration. In some embodiments, the metered dose spray produced by the device has no effect on blood pressure within the hour immediately after a compound described herein is administered. In some embodiments, the metered dose spray produced by the device has only minimal effect on blood pressure within the hour immediately after a compound described herein is administered. In some embodiments, the resting mean arterial blood pressure of the mammal is not effected by more than about 5 mmHg, more than about 10 mmHg, more than about 15 mmHg, more than about 20 mmHg, more than about 25 mmHg, or more than about 30 mmHg.

In some embodiments, any of the compositions described herein can further comprise one or more other therapeutic agents. The one or more additional therapeutic agents is chosen from an analgesic, such as an opioid analgesic (e.g. morphine, oxycodone, hydromorphone, etc.), a synthetic opioid-like analgesic (e.g. meperidine, fentanyl, pentazocine, butorphanol, etc.), or a non-opioid analgesic (e.g. NSAIDs, ketamine, salicylates, steroids, etc.); a vitamin; a vasodilator; a benzodiazepine (e.g. clonazepam, alprazolam, lorazepam, etc.); a triptan (and other compounds for migraine headaches); an anti-convulsant (e.g. pregabalin, valproic acid, gabapentin, etc.); an anti-depressant (e.g. tricyclics such as amitriptyline, nortriptyline, etc.; serotonin and norepinephrine reuptake inhibitors such as duloxetine, fluoxetine, venlafaxine, etc.); an anti-nausea medication (e.g. metoclopramide, prochlorperazine, ondansetron, granisetron, etc.); and an anti-hypertensive (e.g. beta blockers such as propranolol and calcium channel blockers such as verapamil, etc.).

Examples of other analgesic agents include, but are not limited to, narcotics, NSAIDs, Cox-2 inhibitors, steroids, and the like. Other examples include, but are not limited to, aspirin, codeine, oxycodone, ibuprofen, butalbital, acetaminophen (APAP), caffeine, aspirin, hydrocodone, acetaminophen, propoxyphene n-apap, propoxyphene HCl, butorphanol tartrate, pentazocine-apap, pentazocine-naloxone, tramadol, tramadol extended release, fentanyl,

morphine, meperidine HCl, hydromorphone HCl, methadone, levorphanol tartrate, oxymorphone, buprenorphine, celecoxib, rofecoxib, naltrexone, naproxen, flurbiprofen, diclofenac, sulindac, oxaprozin, piroxicam, indomethacin, etodolac, meclufenamate, meloxicam, fenoprofen, ketoprofen, nabumetone, tolmetin, ketorolac tromethamine, salsalate, diflunisal, choline and magnesium salicylates, or any combination thereof. The compounds or salts thereof, and compositions comprising the same, described herein can be administered either alone or in combination (concurrently or serially) with the other pharmaceutical agents. In some embodiments, the compositions described herein can be administered with one or more other analgesic agents.

10 In some embodiments, the composition further comprises a carrier vehicle. In some embodiments, the pharmaceutical composition further comprises sodium phosphate and/or sodium citrate. In some embodiments, the pharmaceutical composition further comprises sodium citrate, citric acid, and sodium chloride. In some embodiments, the pharmaceutical composition further comprises about 0.2% to about 0.3% (w/w) sodium citrate and about 0.005% to about 15 0.015% (w/w) citric acid.

In some embodiments, the composition comprises a salt, such as a pharmaceutically acceptable salt. In some embodiments, the composition comprises sodium chloride, potassium chloride, or any combination thereof. In some embodiments, the composition comprises citric acid. In some embodiments, the composition comprises sodium citrate, citric acid, and a salt, including, but not limited to, sodium chloride. In some embodiments, the composition comprises about 0.1% to about 0.5%, from about 0.1% to about 0.4%, from about 0.2% to about 0.5%, from about 0.2% to about 0.4%, from about 0.2% to about 0.3 % (w/w) of sodium citrate. In some embodiments, the composition comprises from about 0.005% to about 0.015%, from about 0.005% to about 0.05%, from about 0.005% to about 0.004%, from about 0.005% to about 25 0.03%, from about 0.005% to about 0.02%, or from about 0.005% to about 0.0175 % (w/w) of citric acid.

In some embodiments, the pharmaceutical composition further comprises a chelator or stabilizer that can be used to enhance chemical stability where required. Suitable stabilizers include, but are not limited to, chelating agents or complexing agents, such as, for example, the calcium complexing agent ethylene diamine tetraacetic acid (EDTA), a salt of EDTA, citric acid, 30 chitosan, sorbitol, and tartaric acid. For example, an appropriate amount of EDTA or a salt thereof, e.g., the disodium salt, can be included in the composition to complex excess calcium ions and prevent gel formation during storage. EDTA or a salt thereof can suitably be included in an amount of about 0.01% to about 0.5%. In those embodiments containing a preservative other

than EDTA, the EDTA or a salt thereof, more particularly disodium EDTA, can be present in an amount of about 0.025% to about 0.1% by weight. Without being bound by any theory, the chelating agents can prevent multivalent cationic degradation of dexmedetomidine or other components in the composition.

5 In some embodiments, the intranasal compositions described herein may optionally include a buffering system comprised of an acid/base pair that resists changes in pH. The pH of the compositions can be controlled to limit irritation of the nasal spray. In some embodiments, a solution pH of about 6.0 to about 6.5 can be used to be compatible with the pH of nasal secretions while maintaining the drug in solution. Pharmaceutically acceptable buffers that
10 provide a pH compatible with the nasal mucosa include citrate, phosphate, and the like. In some embodiments, the pH of the composition is less than 7, less than 6.9, less than 6.8, less than 6.7, less than 6.6, less than 6.5, less than 6.4, less than 6.2, or less than 6.1. In some embodiments, the pH of the composition is from about 6 to about 6.1, from about 6 to about 6.2, from about 6 to about 6.3, from about 6 to about 6.4, from about 6 to about 6.5, from about 6 to about 6.6,
15 from about 6 to about 6.7, from about 6 to about 6.8, from about 6 to about 6.9, or from about 6 to about 7.0. In some embodiments, the pH of the composition is such that the composition does not irritate the nasal cavity.

 In some embodiments, the pharmaceutical composition further comprises one or more anti-microbial preservatives. Examples of preservatives include, but are not limited to, mercury-
20 containing substances such as phenylmercuric salts (e.g., phenylmercuric acetate, borate and nitrate) and thimerosal; stabilized chlorine dioxide; quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride; imidazolidinyl urea; parabens such as methylparaben, ethylparaben, propylparaben and butylparaben, and salts thereof; phenoxyethanol; chlorophenoxyethanol; phenoxypropanol;
25 chlorobutanol; chlorocresol; phenylethyl alcohol; disodium EDTA; and sorbic acid and salts thereof. Preservatives may precipitate in the presence of other excipients in the composition. For example, benzalkonium chloride can precipitate. Thus, in some embodiments in which a preservative is present, the preservative is one that does not precipitate but remains in solution in the composition. A suitable preservative is phenylethyl alcohol. The one or more anti-microbial
30 preservatives can be included, for example, to suppress microbial and fungal growth in the final delivery systems.

 In some embodiments, the pharmaceutical composition further comprises one or more antioxidants. Suitable antioxidants may optionally be included in the nasal composition, for example, to stabilize the formulation against long term effects of oxidation. Examples of

antioxidants include, but are not limited to, Vitamin E (and derivatives thereof), Vitamin C (and derivatives thereof), BHT, BHA, propyl gallate, citric acid, erythorbic acid, monothioglycerol, a metabisulfite (sodium or potassium), propionic acid, sodium sulfite, and thymol.

In some embodiments, the pharmaceutical composition further comprises one or more
5 dose confirmation excipients, which help facilitate proper usage and/or avoid overdosage. For medications that are administered intranasally, it can be difficult for the subject to determine whether the medication has been properly administered. The inclusion of a dose confirmation excipient can provide positive feedback to the subject after administration, confirming that the dose has been administered intranasally. In some embodiments, the dose confirming excipient
10 has an odor that can allow the subject to confirm that the dose was administered and taken or deposited into the nose. Other feedback mechanisms can be used to confirm that the dose has been administered appropriately. Odor is one non limiting example. In some embodiments, the dose confirmation excipient is phenylethyl alcohol. Without being bound by theory, dose confirmation excipients provide sensory feedback to the patient to confirm that a dose has been
15 delivered, thereby increasing compliance with the prescribed dosing regimen and reducing the potential for overdosing. Phenylethyl alcohol has a distinct odor and may serve as both an antimicrobial and dose confirmation excipient in the compositions previously described.

In some embodiments, the pharmaceutical composition further comprises one or more humectants. Examples of humectants include, but are not limited to, glycerin, propylene glycol,
20 polyethylene glycol, and a sugar/sugar alcohol, or any combination thereof. Humectants can provide moisturizing effects and reduce nasal irritation.

In some embodiments, the pharmaceutical composition further comprises one or more osmolality adjusting agents. The osmolality of the intranasal composition can also be relevant to the uptake of the medication intranasally. Suitable osmolality adjusting agents include, but not
25 limited to, sodium chloride, dextrose, sugars, or any combination thereof. The osmolality adjusting agents can also be included in the composition to produce solutions that are less irritating to the nasal mucosa by aligning the osmolality of the administered solution with the nasal mucosa.

In some embodiments, the pharmaceutical composition is free of a viscosity enhancing
30 agent. Viscosity enhancing agents including, but not limited to, Methocel E4M can optionally be added to increase residence time of the instilled or spray solution with the nasal mucosa. However, in the case of dexmedetomidine, the use of a viscosity increasing agent may result in diminished dexmedetomidine plasma levels and may therefore be omitted under certain conditions, such as when the dexmedetomidine composition is intended for rapid uptake.

Therefore, it was surprisingly found that the viscosity of the intranasal composition can affect the uptake of the active ingredient. Thus, in some embodiments, an increase in viscosity can decrease the uptake of dexmedetomidine. Accordingly, in some embodiments, the composition is free of a polymer that increases the viscosity of a liquid vehicle or composition. In some
5 embodiments, the polymer is a water-soluble polymer. Examples of a soluble polymer include, but are not limited to, a cellulose ether (e.g. hydroxypropyl methylcellulose), other cellulose based polymers (methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc.), povidone, polyvinyl alcohol, gums (e.g. xanthum gum), polyethylene glycol (PEG), polyethylene oxide (PEO), hyaluronic acid (and derivatives and salts thereof), carrageenan, dextran, and
10 poloxamer. In some embodiments, the cellulose ether is hydroxypropyl methylcellulose (HPMC). Thus, in some embodiments, the composition is free of HPMC. In some embodiments, the viscosity of the intranasal composition is no greater than the viscosity of water.

In some embodiments, the viscosity of the intranasal composition is no greater than 110%, no greater than 120%, no greater than 130%, no greater than 140%, no greater than 150%,
15 no greater than 160%, no greater than 170%, no greater than 180%, no greater than 190%, or no greater than 200% of the viscosity of water. In some embodiments, the viscosity of the intranasal formulation is about 1 mPa*s, 2 mPa*s, 3 mPa*s, 4 mPa*s, or 5 mPa*s. In some embodiments, the viscosity of the intranasal formulation is less than about 1 mPa*s, 2 mPa*s, 3 mPa*s, 4 mPa*s, or 5 mPa*s. In some embodiments, the viscosity of the intranasal formulation is from
20 about 1 mPa*s to about 2 mPa*s, from about 1 mPa*s to about 3 mPa*s, from about 1 mPa*s to about 4 mPa*s, from about 1 mPa*s to about 5 mPa*s, from about 1.5 mPa*s to about 2.5 mPa*s, from about 2 mPa*s to about 3 mPa*s, from about 2 mPa*s to about 4 mPa*s, or from about 2 mPa*s to about 5 mPa*s.

The viscosity of a composition can be calculated by various methods. The viscosity can
25 also be directly measured using various techniques. For example, the viscosity of a composition can be calculated according to the following equation. The equation expresses the illustrated approximate relationship between solution viscosity and polymer concentration is $\eta^{1/8} = (C \cdot \alpha) + 1$, where η is the solution viscosity in millipascal-seconds, C is the polymer concentration in solution (expressed in percent), and α is a constant specific to the molecular weight. For
30 example, the value of α can be calculated by substitution and may then be used to calculate the approximate viscosity at the desired concentration.

It is also known in the art that the compounds and compositions comprising the same can be contained in formulations with pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers,

5 buffers, humectants, moisturizers, solubilizers, preservatives and the like. In some embodiments, the compounds and compositions comprising the same can be contained in formulations that do not comprise pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. In some embodiments, the compounds and compositions comprising the same can be contained in formulations that do not comprise a surfactant. The pharmaceutical compositions can also comprise suitable solid or gel phase carriers or excipients. In addition to other excipients described herein, examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. In some embodiments, the compounds described herein can be used with agents including, but not limited to, topical analgesics (e.g., lidocaine), barrier devices (e.g., GelClair), or rinses (e.g., Caphosol).

15 In some embodiments, when administered to a human, the compounds can be sterile. Water can be a suitable carrier when the compound is administered intranasally. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers. Suitable pharmaceutical carriers also include excipients such as, but not limited to, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The compositions described herein can take the form of a solution, suspension, emulsion, powder, sustained-release formulation, aerosol, spray, or any other form suitable for the uses described herein. Examples of suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A.R. Gennaro (Editor) Mack Publishing Co.

25 In some embodiments, the compounds are formulated in accordance with routine procedures as a pharmaceutical composition adapted for administration to humans. In some embodiments, compounds are solutions in sterile isotonic aqueous buffer and, for example, with the other components described herein. Where necessary, the compositions can also include a solubilizing agent. Compositions may optionally include a local anesthetic such as lidocaine to ease pain at the site of the administration that can be due to, for example, irritation from the composition.

In some embodiments, the present invention also provides pharmaceutical packs or kits comprising one or more containers containing one or more compounds described herein.

Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration for treating a condition, disease, or disorder described herein. In some
5 embodiments, the kit contains more than one compound described herein. In some embodiments, the kit comprises a compound described herein in a single unit dosage form, such as a single dose within an intranasal administrable device such as a metered dose device that administers a spray or a powder to a nasal activity.

10 In some embodiments, the components described herein are supplied either separately or mixed together in unit dosage form, for example, the components can be combined to create an intranasal formulation. Examples of making the formulations are described herein and can be modified to yield any suitable intranasal formulation.

15 The pharmaceutical compositions can be in unit dosage form. In such form, the composition can be divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations. The dosage form can be any form including, but not limited to, the forms described herein.

20 In some embodiments, a composition of the present invention is in the form of a liquid wherein the active agent is present in solution, in suspension, as an emulsion, or as a solution/suspension. In some embodiments, the liquid composition is in the form of a gel. In other embodiments, the liquid composition is aqueous. In other embodiments, the composition is in the form of an ointment. The liquid composition can also be a spray.

25 The liquid vehicle refers to the liquid in which dexmedetomidine is suspended or dissolved. Examples of the liquid vehicles include, but are not limited to, water, saline, an aqueous solution, DMSO, and the like.

30 In some embodiments, the pharmaceutical composition comprises, in addition to dexmedetomidine, the following (all based on % w/w): about 0.245% anhydrous sodium citrate, about 0.01% anhydrous citric acid, about 0.7% sodium chloride, about 99.045% purified water, at an initial pH of 6.31 adjusted to a final pH of about 6.78 with 2N sodium hydroxide. In some
embodiments, the pharmaceutical composition comprises, in addition to dexmedetomidine, the following (all based on % w/w): about 0.245% anhydrous sodium citrate, about 0.01% anhydrous citric acid, about 0.1% Methocel E4M, about 0.7% sodium chloride, about 98.945% purified water, at an initial pH of 6.36 adjusted to a final pH of about 6.83 with 2N sodium hydroxide. In some embodiments, the pharmaceutical composition comprises, in addition to

dexmedetomidine, the following (all based on % w/w): about 0.193% sodium phosphate monobasic (monohydrate), about 0.162% sodium phosphate dibasic (heptahydrate), about 0.7% sodium chloride, about 98.946% purified water, at an initial pH of 6.37 adjusted to a final pH of about 6.53 with 2N sodium hydroxide. In some embodiments, the pharmaceutical composition comprises, in addition to dexmedetomidine, the following (all based on % w/w): about 0.193% sodium phosphate monobasic (monohydrate), about 0.162% sodium phosphate dibasic (heptahydrate), about 0.75% sodium chloride, about 98.896% purified water, at an initial pH of 6.37 adjusted to a final pH of about 6.53 with 2N sodium hydroxide. In some embodiments, the pharmaceutical composition comprises, in addition to dexmedetomidine, the following (all based on % w/w): about 0.193% sodium phosphate monobasic (monohydrate), about 0.162% sodium phosphate dibasic (heptahydrate), about 0.25% phenylethyl alcohol, about 0.68% sodium chloride, about 98.616% purified water, at an initial pH of 6.15 adjusted to a final pH of about 6.51 with 2N sodium hydroxide. In some embodiments, the pharmaceutical composition comprises, in addition to dexmedetomidine, the following (all based on % w/w): about 0.226% anhydrous sodium citrate, about 0.024% anhydrous citric acid, about 0.25% phenylethyl alcohol, about 0.76% sodium chloride, about 98.64% purified water, at an initial pH of 5.68 adjusted to a final pH of about 6.04 with 2N sodium hydroxide.

The compositions comprising dexmedetomidine described herein are stable. For a 0.035% dexmedetomidine hydrochloride intranasal spray formulation, for example, the stability is at least 3 months, at least 6 months, at least 9 months, or at least one year wherein the storage conditions are 25°C at 60% relative humidity, and at least 1 month, at least 3 months, at least 6 months wherein the storage conditions are 40°C at 75% relative humidity.

Where dexmedetomidine, or a pharmaceutically acceptable salt thereof, is used in any method or device described herein, it is understood that any and all metabolites of dexmedetomidine, or a pharmaceutically acceptable salt thereof, can also be used likewise.

In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the invention in any manner.

Examples

Example 1: Preparation of Intranasal Formulations

To a container, purified water, USP was added. To the water, anhydrous citric acid, sodium citrate dihydrate, sodium chloride, phenylethyl alcohol, and disodium EDTA was mixed until dissolved. The pH of the solution was modified, if necessary, to be in the range of 6.0 and

6.5. With continued mixing, dexmedetomidine HCl was added until dissolved. Water was added to adjust the dexmedetomidine HCl to a final selected concentration.

Example 2: Intranasal Formulations of Dexmedetomidine

5 Nasal delivery of dexmedetomidine HCl (DEX) was evaluated from aqueous sprays to provide pharmacokinetic profiles that provide analgesia without significant sedation. The nasal route of delivery is often desired by patients in pain that may be unable or unwilling to tolerate the treatment by an oral route (e.g., buccal, sublingual, swallowing), by a rectal route (e.g. foams, suppositories, etc.), or an injection route. In addition to the aqueous nasal sprays initially
10 developed for evaluation of intranasally administered DEX, the formulations can be modified to include dry powders, suspensions, and/or vapors as would be apparent from the description contained herein.

An initial screening of DEX aqueous nasal compositions administered as nasal drops was evaluated in a canine model. The influence of buffer species and viscosity was evaluated in
15 the following base compositions.

Component	First Placebo Base Composition (% w/w)		
	Formulation 1	Formulation 2	Formulation 3
Sodium Citrate, Anhydrous	0.245	0.245	--
Citric Acid, Anhydrous	0.010	0.010	--
Methocel E4M	--	0.100	--
Sodium Phosphate Monobasic, Monohydrate	--	--	0.193
Sodium Phosphate Dibasic, Heptahydrate	--	--	0.162
Sodium Chloride	0.700	0.700	0.700
Purified Water	99.045	98.945	98.946
Total	100.000	100.000	100.000
Initial pH	6.31	6.36	6.37
Final pH ¹	6.78	6.83	6.53
¹ Adjusted with 2N Sodium Hydroxide.			

DEX was dissolved into the Placebo Base Compositions to prepare Formulation solutions that would deliver 50 µg DEX in 100 µL volume. The DEX compositions were expressed as follows.

Component	DEX Nasal Drop Composition (% w/v)		
	Formulation 1-DEX	Formulation 2-DEX	Formulation 3-DEX
Dexmedetomidine HCl	0.059	0.059	0.059
Formulation 1	99.941	--	--
Formulation 2	--	99.941	--
Formulation 3	--	--	99.941
Total	100.000	100.000	100.000

The density of the DEX nasal drop compositions was approximately 1 g/mL at room temperature and allowed for weight and volume to be used interchangeably. The three DEX Nasal Drop Compositions were administered to canines. Surprisingly, compositions without a cellulose ether, which is a viscosity enhancing agent, such as Formulation 1-Dex and Formulation 3-Dex, provided significant plasma levels in less than 15 minutes after administration. Also surprisingly, Formulation 2-Dex, which contained 0.1% Methocel E4M and had the highest solution viscosity, resulted in negligible plasma levels of DEX, indicating that increased solution viscosity diminished the effectiveness of DEX delivered intranasally. This result was unexpected.

The influence of additional formulation additives was further investigated from aqueous DEX solutions that were delivered as fine mists from multiple-use aqueous spray pumps. The following placebo base compositions were prepared.

Component	Second Placebo Base Composition (% w/w)		
	Formulation 4	Formulation 5	Formulation 6
Sodium Citrate, Anhydrous	--	--	0.226
Citric Acid, Anhydrous	--	--	0.024
Sodium Phosphate Monobasic, Monohydrate	0.193	0.193	--
Sodium Phosphate Dibasic, Heptahydrate	0.162	0.162	--
Phenylethyl Alcohol	--	0.250	0.250
Disodium Edetate Dihydrate	--	0.100	0.100
Sodium Chloride	0.750	0.680	0.760
Purified Water	98.896	98.616	98.640

Total	100.000	100.000	100.000
Initial pH	6.37	6.15	5.68
Final pH ¹	6.53	6.51	6.04
¹ Adjusted with 2N Sodium Hydroxide.			

DEX was dissolved into the second set of Placebo Base Compositions to prepare solutions that would deliver 50 µg DEX in 100 µL volume. The DEX compositions are expressed as follows.

Component	DEX Nasal Spray Composition (% w/v)		
	Formulation 4-Dex	Formulation 5-Dex	Formulation 6-Dex
Dexmedetomidine HCl	0.059	0.059	0.059
Formulation 4	99.941	--	--
Formulation 5	--	99.941	--
Formulation 6	--	--	99.941
Total	100.000	100.000	100.000
Calculated Osmolality (mOsm/kg)	288	368	306

5

The density of the DEX nasal spray compositions was approximately 1 g/mL at room temperature and allowed for weight and volume to be used interchangeably. The three DEX Nasal Spray Compositions were administered to canines using a manually actuated nasal pump. The results of the canine study indicated measurable plasma levels as early as 5 minutes and decreasing plasma levels according to Formulation 4-Dex > Formulation 5-Dex > Formulation 6-Dex.

10

An additional placebo base composition was prepared as defined below.

Component	Third Placebo Base Composition (% w/w)
	Formulation 7
Sodium Citrate, Anhydrous	0.230
Citric Acid, Anhydrous	0.020
Phenylethyl Alcohol	0.250
Disodium Edetate Dihydrate	0.100
Sodium Chloride	0.760
Purified Water	98.640

Total	100.000
Initial pH	5.79
Final pH ¹	6.27
¹ Adjusted with 2N Sodium Hydroxide.	

DEX was dissolved into the third Placebo Base Composition to prepare a solution that would deliver 25 µg DEX in 100 µL volume. The DEX composition is expressed as follows.

Component	DEX Nasal Spray Composition (% w/v)
	Formulation 7-Dex
Dexmedetomidine HCl	0.0295
Formulation 7	99.9705
Total	100.0000
Final pH	6.20

The density of the DEX nasal spray composition was approximately 1 g/mL at room temperature and allowed for weight and volume to be used interchangeably. The DEX nasal compositions were developed as an aqueous solution that could be delivered as nasal drops or as a fine mist from a nasal spray device. The DEX nasal compositions minimally contained DEX dissolved in purified water at a suitable concentration to deliver the intended DEX dose in 25 µL to 200 µL. Dose volumes less than 25 µL can result in variable delivery while dose volumes greater than 200 µL can result in excess run off from the nasal cavity. The aqueous nasal compositions can optionally contain additional materials to facilitate the intranasal delivery of DEX.

Example 3: Droplet Particle Size Determination

In vitro spray pump performance of the Drug Product (DEX-IN.02 50µg API/100 µL Intranasal Spray and DEX-IN.03 25µg API/50 µL Intranasal Spray) and Placebo (DEX-IN.02P 100 µL Intranasal Spray) was based on droplet size distribution as measured by laser diffraction using a Malvern Spraytec. The Malvern Spraytec operates based on a laser diffraction principle and is a commonly used technique to characterize droplet size distributions from nasal sprays. The droplet size distribution was characterized by the following metrics: volume distribution (Dv10, Dv50, Dv90), Span and percentage (%) less than 10 µm per the FDA CMC Guidance for Nasal Sprays (2002) and FDA Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, April 2003.

Example 4: Pharmacokinetic Study of Dexmedetomidine Formulations Following Intranasal or Sublingual Administration in Dogs

One objective of the present study was to compare the pharmacokinetics of multiple experimental dexmedetomidine formulations to the pharmacokinetics of a commercial formulation of dexmedetomidine when administered intranasally or sublingually in dogs. For each dosing event, five male dogs were dosed intranasally or sublingually with 50 µg of dexmedetomidine free-base (equivalent to 59 µg of dexmedetomidine HCl) in 100 µL of formulation, except for Formulation 7-Dex, where the dogs were dosed with 25 µg of dexmedetomidine free-base (equivalent to 29.5 µg of dexmedetomidine HCl) in 100 µL, and the PRECEDEX[®] formulation, which contained 50 µg dexmedetomidine base equivalent in 500 µL of solution. Dosing was performed in 10 dosing events in three segments with the formulations, with a minimum 2-day interval between the dosing events, as shown in the table below:

Segment	Dosing Event	Formulation	Dose Route
1	1	Formulation 1-Dex*	Intranasal
	2	Formulation 3-Dex*	Intranasal
	3	Formulation 2-Dex*	Intranasal
	4	PRECEDEX [®] *	Intranasal
2	5	Formulation 4-Dex*	Intranasal
	6	Formulation 5-Dex*	Intranasal
	7	Formulation 6-Dex*	Intranasal
3	8**	Formulation 6-Dex*	Intranasal
	9	Formulation 7-Dex***	Intranasal
	10	DEX-SL.01*	Sublingual

*Dose = 50 µg of dexmedetomidine free-base (equiv. to 59 µg of dexmedetomidine HCl).

**Redose of Formulation 6-Dex using a new sprayer.

***Dose = 25 µg of dexmedetomidine free-base (equiv. to 29.5 µg of dexmedetomidine HCl).

Mean pharmacokinetic parameters for dexmedetomidine are summarized below.

Formulation (Dosing Event)	T _{max} (hr)	t _{1/2} (hr)	C _{max} (ng/ml)	AUC _{last} (hr*ng/ml)	AUC _{0-∞} (hr*ng/ml)
Formulation 1-DEX (1)	0.7	0.93	8.88	7.72	7.18
Formulation 2-DEX (2)	0.7	NC1	16.9	12.3	NC1
Formulation 3-DEX (3)	0.42	0.43	1.30	1.10	1.16

PRECEDEX [®] (4)	0.38	0.52	12.2	6.68	6.69
Formulation 4-DEX (5)	0.4	0.47	1.35	1.12	0.984
Formulation 5-DEX (6)	0.80	0.50	2.46	2.44	2.62
Formulation 6-DEX (7)	0.42	0.56	9.05	6.57	2.18
Formulation 6-DEX (8)*	0.27	0.79	5.92	3.61	6.06
Formulation 7-DEX (9)	0.32	0.63	1.33	1.18	1.09
DEX-SL.01 (10)	0.60	1.72	2.15	2.27	4.75

NC1 = Value could not be calculated by WinNonlin due to insufficient data points for the elimination phase.

*Redose of Formulation 6-DEX using a new sprayer.

For intranasal administration (dose events 1 to 9), T_{max} and elimination half-life for dexmedetomidine were similar between the PRECEDEX[®] formulation and the experimental doses 1-3 and 5-9. The mean T_{max} for dexmedetomidine for the PRECEDEX[®] formulation was 0.38 hours, and the mean T_{max} for dexmedetomidine for the experimental formulations that were administered intranasally (doses 1-3, 5-9) ranged from 0.32 hours to 0.80 hours. The mean elimination half-life for dexmedetomidine for the PRECEDEX[®] formulation was 0.52 hours, and the mean elimination half-life for dexmedetomidine for the experimental formulations administered intranasally (doses 1-3, 5-9) ranged from 0.43 hours to 0.93 hours. For sublingual administration (dosing event 10, formulation DEX-SL.01), the mean T_{max} was 0.60 hours similar to the T_{max} obtained following intranasal administration of PRECEDEX[®] and experimental doses 1-9, while the mean elimination half-life for the DEX-SL.01 formulation was 1.72 hours, longer than the elimination half-life obtained following intranasal administration of PRECEDEX[®] and experimental doses 1-3 and 5-9.

Based on C_{max} and AUC_{last} , dexmedetomidine exposure following intranasal administration was highest for the Formulation 3-DEX formulation. The mean C_{max} for Formulation 3-DEX formulation was approximately 140% of the mean C_{max} for PRECEDEX[®], while mean AUC_{last} for the Formulation 3-DEX formulation was approximately 180% of the mean AUC_{last} for PRECEDEX[®]. The mean AUC_{last} for the Formulation 6-Dex and Formulation 1-DEX formulations were similar to that of PRECEDEX[®], while the mean C_{max} for these formulations were approximately 70% of the mean C_{max} for PRECEDEX[®]. The mean C_{max} and AUC_{last} for all other experimental formulations dosed intranasally were lower than that for PRECEDEX[®]. Dexmedetomidine exposure following intranasal administration was lowest for the Formulation 2-DEX and Formulation 7-DEX formulations. Surprisingly, dexmedetomidine exposure following sublingual administration of formulation DEX-SL.01 was substantially lower

than for intranasal administration of PRECEDEX[®]; the mean C_{max} for the DEX-SL.01 formulation was 18% of the mean C_{max} for PRECEDEX[®], and mean AUC_{last} for the DEX-SL.01 formulation was 34% of the mean AUC_{last} for PRECEDEX[®].

Formulation (Dosing Event)	T_{max} (hr)	$t_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)
Formulation 1-DEX (1)	1.75	NC ¹	0.272	0.355	NC ¹
Formulation 2-DEX (2)	1.80	NC ¹	0.291	0.386	NC ¹
Formulation 3-DEX (3)	0.65	NC ¹	0.285	0.203	NC ¹
PRECEDEX [®] (4)	1.55	NC ¹	0.248	0.358	NC ¹
Formulation 4-DEX (5)	1.00	NC ¹	0.0847	0.111	NC ¹
Formulation 5-DEX (6)	1.35	1.28	0.116	0.169	0.233
Formulation 6-DEX (7)	0.90	NC ¹	0.221	0.319	NC ¹
Formulation 6-DEX (8)*	1.15	7.29	0.168	0.265	2.38
Formulation 7-DEX (9)	1.25	8.70	0.0999	0.109	1.15
DEX-SL.01 (10)	1.80	NC ¹	0.152	0.204	NC ¹

NC1 = Value could not be calculated by WinNonlin due to insufficient data points for the

5 elimination phase. *Redose of Formulation 6-Dex using a sprayer.

For intranasal administration (dose events 1 to 9), the T_{max} for this table was generally similar between the PRECEDEX[®] formulation and the experimental doses 1-3 and 5-9. The mean T_{max} for the PRECEDEX[®] formulation was 1.55 hours, and the mean T_{max} for the experimental formulations administered intranasally (doses 1-3, 5-9) ranged from 0.65 hours to 1.80 hours. For most formulations, the elimination half-life was either not calculated or not reported due to insufficient data points for the elimination phase or poor goodness-of-fit ($R^2 < 0.8$) for the elimination phase. Where calculable, the half-life ranged from 1.3 hours to 8.7 hours. For sublingual administration (dosing event 10, formulation DEX-SL.01), the mean T_{max} was 1.80 hours, similar to the T_{max} obtained following intranasal administration of PRECEDEX[®] and the experimental doses 1-3 and 5-9.

Based on C_{max} and AUC_{last} , exposure following intranasal administration was highest for the Formulation 3-Dex formulation. The mean C_{max} for the Formulation 3-Dex formulation was approximately 117% of the mean C_{max} for PRECEDEX[®], while the mean AUC_{last} for the Formulation 3-Dex formulation was approximately 108% of the mean AUC_{last} for PRECEDEX[®]. Mean C_{max} and AUC_{last} for all other experimental formulations dosed intranasally were similar to that for PRECEDEX[®], except for Formulation 4-DEX and Formulation 7-DEX (the amount of dexmedetomidine dosed with Formulation 7-DEX was half that of the other formulations).

Exposure following sublingual administration of formulation DEX-SL.01 was lower than for intranasal administration of PRECEDEX[®]; mean C_{max} for the DEX-SL.01 formulation was approximately 61% of the mean C_{max} for PRECEDEX[®], and mean AUC_{last} for the DEX-SL.01 formulation was approximately 57% of the mean AUC_{last} for PRECEDEX[®].

5 The results presented herein, surprisingly show that when compared to the previously studied sublingually administered formulation DEX-SL.01, absorption occurs more quickly via the nasal route. Therefore, intranasal administration of DEX surprisingly may provide faster pain relief and/or prevention of pain in subjects as compared to sublingual or methods of administering DEX across the oral mucosa, without significant sedation, and with little or no
10 effect on blood pressure.

Dosing

Doses 1-3 were administered intranasally with a micropipette with the head inverted for dosing. The dosage was 50 μ g of dexmedetomidine free-base (equivalent to 59 μ g of dexmedetomidine HCl) in 100 μ L of formulation. Dose 4 was administered using a commercial
15 nasal spray bottle. Spray doses were administered with the head upright, alternating nostrils for each spray. The head was inverted for 30 seconds to 1 minute after spray administration. The spray bottle administers 100 μ L per spray, and five sprays were required to deliver the dosage of 50 μ g of dexmedetomidine free-base (equivalent to 59 μ g of dexmedetomidine HCl). The spray bottle was primed in an area remote from dosing prior to dose administration to prevent possible
20 cross-contamination. Additionally, dosing was performed in an area remote from blood collection to prevent possible contamination of blood samples with aerosolized test article.

Doses 5-7 were administered using a commercial nasal spray bottle. Spray doses were administered with the head upright. The head was inverted for 30 seconds to 1 minute after spray administration. The spray bottle administers 100 μ L per spray, and one spray was required to
25 deliver the dosage of 50 μ g of dexmedetomidine free base (equivalent to 59 μ g of dexmedetomidine HCl). The spray bottle was primed using five spray actuations in an area remote from dosing prior to dose administration to prevent possible cross-contamination. Additionally, dosing was performed in an area remote from blood collection to prevent possible contamination of blood samples with aerosolized test article.

30 Dose 8 was administered using a commercial nasal spray bottle. Spray doses were administered with the head upright. The head was inverted for 30 seconds to 1 minute after spray administration. The spray bottle administered 100 μ L per spray, and one spray was required to deliver the dosage of 50 μ g of dexmedetomidine free base (equivalent to 59 μ g of

dexmedetomidine HCl). The spray bottle was primed using five spray actuations in an area remote from dosing prior to dose administration to prevent possible cross-contamination. Additionally, dosing was performed in an area remote from blood collection to prevent possible contamination of blood samples with aerosolized test article.

5 Dose 9 was administered using a commercial nasal spray bottle. Spray doses were administered with the head upright. The head was inverted for 30 seconds to 1 minute after spray administration. The spray bottle administered 100 μ L per spray, and one spray was required to deliver the dosage of 25 μ g of dexmedetomidine free base (equivalent to 29.5 μ g of dexmedetomidine HCl). The spray bottle was primed using five spray actuations in an area
10 remote from dosing prior to dose administration to prevent possible cross-contamination. Additionally, dosing was performed in an area remote from blood collection to prevent possible contamination of blood samples with aerosolized test article.

Dose 10 was administered sublingually with a micropipette. The dosage was 50 μ g of dexmedetomidine free base (equivalent to 59 μ g of dexmedetomidine HCl) in 100 μ L of
15 formulation.

For intranasal administrations, the formulations were administered intranasally. Following dosing, the dog's nares were held shut and the head inverted for approximately 1 minute. Each dosing event was separated by a minimum of 2 days to allow an appropriate washout.

20 After dosing, blood samples were obtained and tested for DEX plasma levels.

Example 5: Pharmacokinetics Of Intranasally Administered Dexmedetomidine in Humans

Four different formulations of DEX were used. PRECEDEX[®] (Treatment A) at a dose of 25 μ g which was administered intravenously over 10 minutes and 3 different intranasal
25 dosages or formulations. Formulation B (35 μ g administered in 100 μ L in one nostril via 1 spray); Formulation C (35 μ g total administered via 2 nostrils); and Formulation D (17.5 μ g administered in 50 μ L in one nostril via 1 spray).

	Treatment A Precedex IV 25 μ g	Treatment B DEX- IN.01 35 μ g 100 μ L in one nostril	Treatment C DEX-IN.01 35 μ g 50 μ L in each nostril	Treatment D DEX-IN.01 17.5 μ g 50 μ L in one nostril
C _{max} (ng/ml)	0.61 (58.7%)	0.17 (21.7%)	0.14 (34.0%)	0.08 (31.9%)
AUC ₀₋₂₄ (hr ng/ml)	0.71 (27.7%)	0.83 (23.6%)	0.75 (22.5%)	0.38 (16.6%)
T _{max} (hrs)	0.17 (0.17, 0.25)	1.00 (0.33, 4.00) [†]	1.25 (0.33, 4.00)	1.13 (0.33, 2.00)
t _{1/2} (hrs)	2.04 $\pm$ 0.200 [‡]	2.43 $\pm$ 0.825 [§]	2.64 $\pm$ 0.777 [§]	1.60 (NA) [¥]

[1] Geometric means (CV%) for C_{max} and AUC₀₋₂₄ median (min, max) for T_{max}; and arithmetic mean $\pm$ SD for t_{1/2}; [†] n=11; [‡] n=10; [§] n=4; [¥] n=1

The pharmacokinetics observed showed the surprising result that the administration of the dose in single spray to a single nostril (Treatment B) provided a better $C_{\max}$ and a shorter $T_{\max}$ as compared to the same total dose administered in two nostrils via 2 sprays (half the dose being administered into each nostril). This result could not have been predicted and is opposite of what would have been expected by the skilled artisan, in part, due to a surface area comparison. The mean plasma concentrations produced by Treatment B reached a minimum target concentration (0.1 ng/ml) within 20 minutes after dosing. This surprising result of administering to a single nostril can facilitate the more rapid onset of activity (*e.g.*, pain relief) in target patient populations. The rate of absorption observed in Treatment B was more rapid than previously studied non-IV formulations or routes of administration. This unexpected more rapid absorption can allow for the fast onset of analgesic effects. In fact, the analgesic effects can begin in less than 20 minutes. Plasma concentrations achieved with the 17.5 and 35 μg intranasal administration are provided in Figure 1.

Dosing

Healthy volunteers were administered the selected dose intranasally or, if indicated, another route of administration. A single nostril was administered to at a time with the untreated nostril covered by a finger. Blood samples were taken and measured for DEX concentrations as indicated.

Example 6: Phase 1, Two Period, Open Label, Multiple-Dose Evaluation of the Safety, Tolerability, and Pharmacokinetics of Intranasal Dexmedetomidine in Healthy Volunteers

The primary objective of this study was to evaluate the pharmacokinetic profile of multiple doses of intranasal dexmedetomidine in healthy male and female subjects. Secondary endpoints of this study were to evaluate the safety and tolerability of intranasal dexmedetomidine in healthy volunteers.

Methodology

This was a Phase 1, open-label, two period, repeated dose study in healthy subjects to investigate the safety, tolerability, and pharmacokinetics of intranasal dexmedetomidine. A total of 12 subjects (6 male and 6 female) were planned and enrolled. Healthy subjects between the ages of 18 and 50 years, inclusive, were screened for participation at one study site in the United States within 28 days before study drug administration. Medical history, physical examination, baseline laboratory testing, 12 lead electrocardiogram (ECG), pregnancy testing, vital sign measurements, and informed consent were completed during the screening visit.

All study doses were a 35 μg dose of DEX IN.01 administered as a single 100 μL spray

into the left nostril. DEX-IN.01 contained 35 µg dexmedetomidine in each 100 µL of solution, as well as excipients including: citric acid, sodium citrate, sodium chloride, phenylethyl alcohol, disodium EDTA, and purified water. Doses of DEX-IN.01 utilized a 100 µL spray nozzle for administration into the nostril according to the treatment assignment.

5 During Period 1, subjects received two doses of study medication, separated by six hours. During Period 2, study participants received seven doses of study medication administered at six hour intervals. Study Periods were separated by not less than 24 hours between the last dose in Period 1 and the first dose in Period 2.

10 During Period 1, subjects were confined from the evening before dosing (Day -1) to approximately 18 hours after Dose 2 (Day 2). During Period 2, subjects were confined from the evening before dosing (Day -1) to approximately 24 hours after the last study dose (Day 3). While confined, subjects received a standardized daily diet.

Serial blood samples were collected at defined intervals during each study period in order to evaluate the pharmacokinetic properties of intranasally administered dexmedetomidine, 15 and its metabolite. Whole blood was collected in 6 mL evacuated collection tubes treated with K₂EDTA.

Plasma samples were to be collected within ±2 minutes of the scheduled post-dose time through 60 minutes after dosing, samples collected 75 minutes to 6 hours after dosing were able to be collected within ±5 minutes, and samples collected at and beyond 12 hours after dosing 20 were able to be collected within ±15 minutes of scheduled post-dose time. Actual times were to be recorded for all events, and any deviation outside the specified ranges were required to be clearly documented in the subject's study records.

Immediately after the collection of each sample, the collection tube was to be gently inverted and then placed in wet ice. Within 30 minutes of withdrawal, the tubes were 25 centrifuged at about 2,000 × gravity for 10-15 minutes to separate the cells from the plasma. No aids for separation were to be used. Two aliquots (≥0.5 mL each) of plasma were transferred from each sample with clean pipettes and placed in 2 polypropylene storage tubes in equal volumes. The storage tubes were labeled with the following information: protocol number, subject number, study day and relative time of sample (e.g., Period 1, Dose 1, 10 Minutes after 30 dosing), and biologic matrix to be analyzed (e.g., plasma). Within 60 minutes of the collection time, the storage tubes were to be placed into a freezer at -20°C or below; they remained in the freezer until shipment for analysis.

For pharmacokinetic analyses in Period 1, up to 12 blood samples were collected from each subject prior to and following administration of each study dose. These were collected at

predose (Time 0) and at the following approximate times after each dose of study medication: 10, 20, 30, 45, 60, and 90 minutes and 2 and 4 hours; additional blood samples were collected at 6, 12 and 18 hours after Dose 2. In Period 2, up to 13 blood samples were collected from each subject prior to and following administration of Dose 1 and Dose 7. These were collected at
 5 predose (Time 0) and at the following approximate times after dosing with study medication: 10, 20, 30, 45, 60, and 90 minutes and 2 and 4 hours; additional blood samples were collected at 6, 12, 18 and 24 hours after Dose 7. Blood samples for Dose 2 through Dose 6 were collected at predose (Time 0) only.

10 A summary table of study visits, and the assigned time points, is provided for the overall study, Period 1, Period 2 Doses 1 and 7, and Period 2 Doses 2 through 6 in the table below.

Table: Summary of Study Visits

Study Event	Period 1				Washout	Period 2								
	Day -1	Day 1 (hr)				Day -1	Day 1 (hr)				Day 2 (hr)			Day 3 (hr)
		0	6	24			0	6	12	18	24	30	36	60
Confinement	<-----X- ----->					<----- X----- ----->								
Study Dosing		X	X			X	X	X	X	X	X	X		

Inclusion Criteria:

15 Subjects met the following criteria to participate in the study: 1) was a man or woman between 18 and 50 years of age, inclusive; 2) for female subjects of childbearing potential, be surgically sterile, use double-barrier contraception, practice abstinence (must agree to use double-barrier contraception in the event of sexual activity) or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA through completion of the
 20 study and have negative results on a serum pregnancy test done before administration of study medication, and have negative results on subsequent urine pregnancy tests (women who are postmenopausal [no menses for at least 2 years] are also eligible to participate); 3) had a body mass index (BMI) $\leq 32 \text{ kg/m}^2$ and a body weight between 50 and 95 kg, inclusive; and 4) was able to understand the study procedures, agree to participate in the study program, and
 25 voluntarily provide written informed consent.

Treatments Administered

Study personnel administered all doses of study medication according to the treatment schedule. Doses of dexmedetomidine were administered using the intranasal delivery device into

the left nostril. Doses were administered into the assigned nostril with the untreated nostril covered with a finger. The subject's head was held in an upright position with the spray applicator inserted approximately ½" into the treated nostril. The subject inhaled through the treated nostril as the pump was squeezed and the dose was delivered.

5 After administration of study medication, participants were allowed to move around the study facility, and perform non-strenuous activities. Subjects may have been required to remain seated for a period of time by the study investigator if it was deemed unsafe for the subject to move around the study site without the accompaniment of study personnel.

Doses were subsequently evaluated in a single dose study in healthy volunteers where
10 DEX-IN was evaluated using single and paired spray administration at doses of 17.5 and 35 µg. Based on the observed pharmacokinetics, it was determined that the 35 µg dose level administered into a single nostril would be most appropriate to explore further to achieve the targeted plasma concentrations. Plasma concentrations achieved with the 17.5 and 35 µg intranasal doses are provided in Figure 1.

15 *Ramsay Sedation Scale*

The investigator, or designee, used the Ramsay Sedation Scale to assess each subject's degree of sedation. For each subject at each time point, the degree of sedation was assessed according to the Ramsay rating categories. The Ramsay Sedation Scale was performed pre-dose (Time 0), and at 30, 60 and 90 minutes after each study dose. All scores returned to their baseline
20 level (Score 2) within six hours after dosing. Although an RSS score of 5 was assigned to two subjects during the course of the study, the majority of subjects did not experience significant sedation. Subjects were administered study doses every six hours, and completed safety monitoring activities subsequent to each dose, around the clock for seven doses during Period 2; the confounding effect of this schedule is not addressed in the assessment tool/results.

25 *Criteria for evaluation:*

Pharmacokinetic parameters for the concentrations of dexmedetomidine and its major metabolite (ORM-14305) in plasma were calculated for Dose 1 and 2 during Period 1, and for Dose 1 and 7 during Period 2. The calculated parameters included peak (maximum) observed plasma drug concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration time curve
30 (AUC) from Time 0 to last sampling time (t) with a quantifiable plasma drug concentration (AUC_{0-t}), AUC from Time 0 to 6 hours after dosing (AUC_{0-6}), AUC from Time 0 to infinity ($AUC_{0-\infty}$, for Period 1 Dose 2, and Period 2 Dose 7), and terminal phase elimination half life ($t_{1/2}$, for Period 1 Dose 2, and Period 2 Dose 7).

Results:

Observed pharmacokinetic parameters, $C_{\max}$, $T_{\max}$, and AUC_{0-6} of dexmedetomidine are presented in the table below.

Pharmacokinetic Parameters of Dexmedetomidine

Parameters [1]	Period 1 Dose 1	Period 1 Dose 2	Period 2 Dose 1	Period 2 Dose 7
$C_{\max}$ (ng/mL)	0.09 (30.6) [†]	0.16 (22.8) [†]	0.12 (35.8) [‡]	0.13 (31.3) [‡]
$T_{\max}$ (hrs)	1.26 (0.33, 4.00) [†]	0.88 (0.33, 2.02) [†]	1.01 (0.50, 2.00) [‡]	1.50 (0.33, 2.00) [‡]
AUC_{0-6}	0.39 (31.7) [†]	0.61 (19.2) [†]	0.47 (32.6) [‡]	0.50 (31.1) [‡]
AUC_{last} (hr·ng/mL)	0.38 (35.2) [†]	0.63 (22.2) [†]	0.47 (32.6) [‡]	0.51 (55.0) [‡]
[1] Geometric means (CV%) for $C_{\max}$, AUC_{0-6} , and AUC_{last} ; median (min, mix) for $T_{\max}$ [†] n=12; [‡] n=10				

5

Comparison of Pharmacokinetic Parameters Between Doses

Doses	$C_{\max}$ (ng/mL)	AUC_{last} (hr·ng/mL)	AUC_{0-6} (hr·ng/mL)
Period 1 Dose 2: Period 1 Dose 1	164.1 (138.0, 195.0)	164.2 (134.1, 201.0)	156.9 (134.7, 182.8)
Period 2 Dose 7: Period 2 Dose 1	106.3 (82.5, 136.9)	108.4 (77.8, 151.0)	105.5 (81.1, 137.3)
Period 2 Dose 1: Period 1 Dose 1	127.7 (112.4, 145.2)	125.1 (105.4, 148.6)	122.8 (106.5, 141.7)
Period 2 Dose 7: Period 1 Dose 2	86.8 (71.0, 106.1)	84.4 (66.5, 107.2)	85.2 (72.0, 100.9)

Data presented is Ratio % (90% CI)

Observed Mean Dexmedetomidine Plasma Concentrations (ng/mL)

Time Post-Dose	Period 1 (N=12)		Period 2 (N=10)	
	Dose 1	Dose 2	Dose 1	Dose 7
0 min	0	0.033 ± 0.014	0	0.037 ± 0.016
10 min	0.008 ± 0.014	0.077 ± 0.033	0.028 ± 0.035	0.059 ± 0.028
20 min	0.060 ± 0.028	0.118 ± 0.054	0.073 ± 0.050	0.091 ± 0.033
30 min	0.059 ± 0.020	0.134 ± 0.044	0.085 ± 0.041	0.101 ± 0.034
45 min	0.083 ± 0.028	0.145 ± 0.040	0.112 ± 0.046	0.113 ± 0.032
60 min	0.088 ± 0.024	0.145 ± 0.023	0.116 ± 0.041	0.119 ± 0.031
90 min	0.090 ± 0.025	0.134 ± 0.014	0.116 ± 0.036	0.119 ± 0.031
2 hrs	0.092 ± 0.026	0.135 ± 0.019	0.117 ± 0.039	0.126 ± 0.033
4 hrs	0.067 ± 0.024	0.090 ± 0.023	0.073 ± 0.026	0.072 ± 0.072
6 hrs	0.036 ± 0.010	0.050 ± 0.018	0.037 ± 0.012	0.048 ± 0.013
12 hrs		0.022 ± 0		0.024 ± 0
18 hrs		0		0
24 hrs				0

Observed Mean ORM-14305 Plasma Concentrations (ng/mL)

Time Post-Dose	Period 1 (N=12)		Period 2 (N=10)	
	Dose 1	Dose 2	Dose 1	Dose 7
0 min	0	0.032 ± 0.019	0	0.085 ± 0.037
10 min	0	0.032 ± 0.019	0	0.085 ± 0.036
20 min	0	0.035 ± 0.015	0	0.083 ± 0.036
30 min	0	0.042 ± 0.013	0	0.081 ± 0.032
45 min	0	0.039 ± 0.014	0	0.078 ± 0.029
60 min	0	0.042 ± 0.013	0	0.084 ± 0.034
90 min	0	0.045 ± 0.014	0.002 ± 0.006	0.080 ± 0.034
2 hrs	0.010 ± 0.013	0.053 ± 0.014	0.017 ± 0.015	0.088 ± 0.038
4 hrs	0.032 ± 0.019	0.064 ± 0.019	0.039 ± 0.014	0.087 ± 0.035
6 hrs	0.038 ± 0.013	0.062 ± 0.021	0.043 ± 0.016	0.079 ± 0.035
12 hrs		0.048 ± 0.011		0.061 ± 0.027
18 hrs		0.032 ± 0.011		0.045 ± 0.021
24 hrs				0.031 ± 0.011

These results are illustrated in Figure 2.

This study supported the safety and tolerability of repeated dosing with intranasal administration. When administered at the six hour dosing interval, there was little evidence of

accumulation of dexmedetomidine when comparing the AUC for Dose 1 to Dose 7. DEX-IN.01 was demonstrated to be well tolerated upon repeated dosing with up to seven doses administered on a six hour interval. There was no apparent increase in adverse events, changes in vital signs, or nasal irritation severity with repeated dosing. When administered as an initial 35 µg dose, DEX-IN.01 reached peak plasma concentrations after 1.01-1.26 hours (median) with an average C_{max} of 0.09-0.12 ng/mL. No significant sedation was observed in subjects at various time points during the study.

Example 7: A Randomized, Double-Blind, Placebo-Controlled, Three Period Crossover Evaluation of the Efficacy, Safety, and Pharmacokinetics of Intranasal Dexmedetomidine in Chronic Low Back Pain Subjects

A study was performed to to evaluate the efficacy, safety, and pharmacokinetics of two dose levels of intranasal dexmedetomidine (DEX-IN.02 and DEX-IN.03) compared with placebo in subjects with chronic low back pain.

Methods: Adult subjects with chronic low back pain symptoms present for greater than three months, and a baseline 24-hour pain intensity ≥ 4 (0-10 scale) were eligible to participate. Subjects were randomly assigned to a treatment sequence with DEX-IN.02 (50 µg; 50 µg/100 µL), DEX-IN.03 (25 µg; 25 µg/50 µL) and matching placebo. Study doses were administered as an intranasal spray using a single dose spray device requiring no priming. Doses were administered to a single nostril. Dosing devices were filled with the appropriate volume of drug solution to deliver the designated 25 or 50 µg dose of dexmedetomidine. Study doses were administered on consecutive days, with a minimum 24-hour washout between doses. Subjects with baseline chronic analgesic therapy were allowed to continue their regimen throughout study, but no doses were to be administered within 2 hours of study treatment (unless analgesic rescue was required). Rescue analgesia was available upon subject request according to the individual's baseline pain regimen.

Efficacy assessments included measures of pain intensity (PI), pain relief (PR), and global medication performance (GMP). Efficacy measures were used to calculate the pain intensity difference (PID), summed pain intensity difference (SPID) and total pain relief (TOTPAR) at multiple post-dose time points, and to determine the number of subjects with partial and complete responses to therapy. Safety assessments included collection of vital signs, nasal symptom assessment, sedation, and adverse events. Plasma samples were collected at intervals over the first 12 hours post-dose for pharmacokinetic analysis.

Results: The study enrolled and treated 24 subjects with DEX-IN.02, DEX-IN.03, and

placebo; all enrolled subjects completed all scheduled study doses. Subjects were primarily white (91.7%) and male (58.3%), with a mean age of 33.7 ± 10.19 years. Subjects had primarily visceral pain (91.7%) with a mean history of pain symptoms lasting 6.75 ± 6.85 years. One third of subjects utilized opioid analgesics for their pain symptoms.

5 Mean improvement in subject PID values were significantly greater for the 50 µg dose (DEX-IN.02) compared with placebo from 45 minutes through 2 hours post-dose (45 min: 2.2 vs. 1.2, $p=0.0291$; 1 hr: 2.2 vs. 0.8, $p=0.0082$; 1.5 hr: 2.2 vs. 0.7, $p=0.0028$; 2 hr: 2 vs. 0.9, $p=0.0126$). The mean SPID value was significantly greater for the 50 µg dose than placebo at 60 minutes after dose (7.1 vs. 3.6; $p=0.0352$). Mean TOTPAR was significantly higher for the 50
10 µg dose than placebo at both 45 and 60 minutes after dose (4.3 vs. 2.5; $p=0.0298$ and 6.2 vs. 3.3; $p=0.0097$, respectively). The results for the study are shown in the following tables.

Table: Summary of Mean±SD PID Values for All Post-Dose Time Points

Time Point	Placebo (N=24)	DEX-IN.03 (N=24)	DEX-IN.02 (N=24)
10 min	0.2 ± 0.48	0.3 ± 0.53	0.5 ± 0.93
15 min	0.6 ± 0.93	0.7 ± 1.09	0.8 ± 1.18
20 min	1.0 ± 1.33	0.9 ± 1.25	1.5 ± 1.32
30 min	1.0 ± 1.44	1.3 ± 1.36	1.9 ± 1.85
45 min	1.2 ± 1.63	1.4 ± 1.44	2.2 [§] ± 1.72
60 min	0.8 ± 1.49	1.5 ± 1.47	2.2 [¥] ± 1.82
90 min	0.7 ± 1.16	1.4 ± 1.41	2.2 [¥] ± 1.81
2 hours	0.9 ± 1.28	1.3 ± 1.23	2.0 [§] ± 1.76
4 hours	1.1 ± 1.75	1.5 ± 1.38	1.8 ± 1.81
6 hours	1.5 ± 1.56	1.5 ± 1.10	1.6 ± 1.71

§ $p < 0.05$; ¥ $p < 0.01$

Table: Summary of Mean±SE SPID Values

Time Point	Placebo (N=24)	DEX-IN.03 (N=24)	DEX-IN.02 (N=24)
15 min	0.6 ± 0.19	0.7 ± 0.22	0.8 ± 0.24
30 min	1.6 ± 0.47	1.9 ± 0.48	2.7 ± 0.59
45 min	2.8 ± 0.78	3.3 ± 0.75	4.9 ± 0.90
60 min	3.6 ± 1.05	4.8 ± 1.03	7.1* ± 1.24

* $p = 0.0352$

Table: Summary of Mean $\pm$ SE TOTPAR Values

Time Point	Placebo (N=24)	DEX-IN.03 (N=24)	DEX-IN.02 (N=24)
15 min	0.6 $\pm$ 0.15	0.5 $\pm$ 0.15	0.8 $\pm$ 0.20
30 min	1.5 $\pm$ 0.35	1.3 $\pm$ 0.32	2.4 $\pm$ 0.39
45 min	2.5 $\pm$ 0.56	2.4 $\pm$ 0.48	4.3 [§] $\pm$ 0.59
60 min	3.3 $\pm$ 0.74	3.5 $\pm$ 0.68	6.2 [¥] $\pm$ 0.81

§ p < 0.05; ¥ p < 0.01

Mean GMP scores were similar among all 3 treatment groups during both 30- and 60-minute post-dose time points. The 50 μ g dexmedetomidine treated group had more subjects with improvement $\geq$ 33% and $\geq$ 50% at all time points after 15 minutes post dose; 11 DEX-IN.02 treated subjects reported $\geq$ 50% improvement at 90 minutes (95% CI, 1.02-7.44) and 10 subjects at 2 hours (95% CI, 1.05-10.63), compared with 4 subjects at 90 minutes and 3 subjects at 2 hours in placebo group. No subjects in any of the treatment groups required rescue medications.

Adverse reactions were generally mild in DEX-IN treated subjects, with 5 events determined to be moderate in severity (2 BP decreased, 1 dizziness, 1 somnolence and 1 hypotension). No SAEs, deaths, or withdrawals due to an AE occurred during the conduct of the study. Changes in systolic and diastolic blood pressure (SBP and DBP respectively) were greater with DEX-IN.02 treated subjects than DEX-IN.03 and placebo treated subjects. Changes in heart rate (HR) were similar following DEX-IN.03 and placebo, while DEX-IN.02 treated subjects had a greater decrease in heart rate; the greatest mean percent change below baseline was -1% for placebo and -9% for DEX-IN.02, while the mean HRs for DEX-IN.03 never decreased below baseline. Results of the nasal assessment of nasal irritation were similar among all treatment groups at all time points with the mean score not exceeding 1 in DEX-IN.02 treated subjects at one hour post-dose (scale of 0-10). Subjects in the DEX-IN.02 treatment group experienced the highest Stanford Sleepiness Scale values 60 minutes post-dose with 17 subjects reporting a score $\geq$ 5.

A single dose of DEX-IN.03 (25 μ g) yielded a mean C_{max} of 0.11 ng/mL with a median T_{max} of 0.75 hrs, while a single dose of DEX-IN.02 (50 μ g) yielded a mean C_{max} of 0.25 ng/mL with a median T_{max} of 0.51 hrs. The following tables summarize these results

Table: Observed Mean Dexmedetomidine Plasma Concentrations (ng/mL)

Time Post-Dose	DEX-IN.03 (25 µg)	DEX-IN.02 (50 µg)
0 min	0	0
10 min	0.047	0.098
15 min	0.081	0.182
20 min	0.096	0.215
30 min	0.111	0.212
45 min	0.110	0.228
60 min	0.102	0.196
75 min	0.094	0.183
90 min	0.085	0.169
2 hrs	0.077	0.149
4 hrs	0.048	0.101
6 hrs	0.030	0.050
12 hrs	0	0.027

Table: Observed Pharmacokinetic Properties of Dexmedetomidine

Parameter	DEX-IN.03 (25 µg)	DEX-IN.02 (50 µg)
C _{max} (ng/mL)	0.11 (71.4)	0.25 (38.3)
T _{max} (hrs)	0.75 (0.25, 4.00)	0.51 (0.25, 4.00)
AUC _{inf} (hr·ng/mL)	0.48 (13.7)	0.92 (26.0)
AUC ₀₋₁ (hr·ng/mL)	0.08 (110.4)	0.16 (64.1)
AUC _{last} (hr·ng/mL)	0.24 (182.4)	0.75 (21.6)
t _{1/2} (hrs)	2.24 (1.60, 2.45)	2.05 (1.52, 3.07)

[1] Geometric means (CV%) for C_{max}, AUC₀₋₁, AUC_{last}, and AUC_{inf}, median (min, mix) for T_{max}; and arithmetic mean ± SD for t_{1/2}

5 This study shows that the intranasal route is a viable non-invasive means of administering dexmedetomidine. Dosing with DEX-IN.02 and DEX-IN.03 produced more rapid absorption with higher dexmedetomidine peak plasma concentrations than previously explored formulations. Analysis of SPID and TOTPAR values demonstrates the significant analgesic effects of a 50 µg dose of intranasal dexmedetomidine compared with a 25 µg dose or placebo in

subjects with CLBP starting 45 minutes post dose. Overall, DEX-IN was well tolerated; the AEs reported were generally mild in severity, while no SAEs were reported.

What is Claimed Is:

1. A method of treating or preventing pain without significant sedation in a mammal comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the mammal whereby the intranasally effective
5 amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, produces a C_{plasma} of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration and has an analgesic effect without significant sedation.
2. A method of treating or preventing pain without significant sedation in an adult human
10 comprising intranasally administering an intranasally effective amount of dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the adult human whereby the intranasally effective amount of dexmedetomidine, or pharmaceutically acceptable salt thereof, does not produce significant sedation in the adult within a period of time of about two hours after administration and has an analgesic effect within the period of time.
- 15 3. A method of treating or preventing pain without significant sedation in a human comprising intranasally administering dexmedetomidine, or a pharmaceutically acceptable salt thereof, to a single nostril of the human.
- 20 4. A method of treating or preventing pain without significant sedation in a mammal comprising intranasally spraying in the mammal a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the spray comprises droplets which have a Dv_{90} of less than about 150 μm .
- 25 5. The method of any one of claims 1 to 4 wherein the plasma C_{max} of dexmedetomidine is about 0.08 ng/ml to about 0.2 ng/ml.
6. The method of any one of claims 1 to 4 wherein the plasma C_{max} of dexmedetomidine is about 0.15 ng/ml.
- 30 7. The method of any one of claims 1 to 4 wherein the plasma C_{max} of dexmedetomidine is about 0.2 ng/ml.

8. The method of any one of claims 1 to 7 wherein the $T_{\max}$ of dexmedetomidine is less than about 1 hour.
9. The method of any one of claims 1 to 7 wherein the $T_{\max}$ is less than about 50 minutes.
10. The method of any one of claims 1 to 9 wherein the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered as a unit dose of about 10 μg , about 25 μg , about 35 μg , about 40 μg , about 50 μg , about 75 μg , or about 100 μg .
11. The method of any one of claims 1 to 10 wherein during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 2 on the Ramsay Sedation Scale.
12. The method of any one of claims 1 to 11 wherein during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not greater than Level 1 on the Stanford Sleepiness Scale.
13. The method of any one of claims 1 to 12 wherein during the hour immediately after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof, to the mammal or human, the level of sedation is not less than Level 6 on the Modified Observer's Assessment Of Alertness/Sedation Scale.
14. The method of any one of claims 1 to 13 wherein there is no or minimal effect on blood pressure after administration of the dexmedetomidine, or pharmaceutically acceptable salt thereof.
15. The method of any one of claims 1 to 14 further comprising administering to the human or mammal one or more additional therapeutic agents.
16. The method of claim 15 wherein the one or more additional therapeutic agents is chosen from an opioid analgesic, a synthetic opioid-like analgesic, a non-opioid analgesic, a vitamin, a vasodilator, a benzodiazepine, a triptan, an anti-convulsant, an anti-depressant, an anti-nausea

medication, and an anti-hypertensive.

17. The method of any one of claims 1 to 16 wherein the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered about every 6 hours.

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18. The method of any one of claims 1 to 17 wherein the pain is idiopathic pain.

19. The method of claim 18 wherein the idiopathic pain is neuralgia, myalgia, hyperalgia, hyperpathia, neuritis, or neuropathy.

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20. The method of any one of claims 1 to 17 wherein the pain is associated with or caused by cancer, viral infection, physical trauma, arthritis, headache, migraine, or lower back pain.

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21. The method of claim 20 wherein the physical trauma is associated with or caused by surgery, a burn, or blunt force trauma.

22. The method of any one of claims 1 to 21 wherein the dexmedetomidine, or pharmaceutically acceptable salt thereof, is administered intranasally with a metered dose device.

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23. The method of claim 22 wherein the metered dose device is a multi-dose, unit dose, or bi-dose device.

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24. A metered dose device comprising a pharmaceutical composition comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the metered dose device delivers a metered dose spray of the pharmaceutical composition intranasally that is analgesic in a mammal without significant sedation.

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25. The metered dose device of claim 24 wherein the metered dose spray produced by the device comprises droplets comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, that have a Dv90 of less than about 150 μm .

26. The metered dose device of claim 24 or claim 25 wherein the metered dose spray produced by the device comprises a metered dose of about 10 μg , about 25 μg , about 35 μg , about 50 μg , about 75 μg , or about 100 μg of dexmedetomidine, or a pharmaceutically

acceptable salt thereof.

27. The metered dose device of any one of claims 24 to 26 wherein the metered dose spray produced by the device comprises a volume of less than about 150 μl , less than about 140 μl , less than about 130 μl , less than about 120 μl , less than about 110 μl , less than about 100 μl , less than about 75 μl , or less than about 50 μl .

28. The metered dose device of any one of claims 24 to 27 wherein the metered dose spray produced by the device produces a C_{plasma} in the mammal of about 0.1 ng/ml within about 15 minutes to about 20 minutes of administration.

29. The metered dose device of any one of claims 24 to 28 wherein the metered dose spray produced by the device does not produce significant sedation in an adult within a period of time of about two hours after administration and has an analgesic effect within the period of time.

30. The metered dose device of any one of claims 24 to 29 wherein the metered dose spray produced by the device produces a plasma C_{max} in the mammal of about 0.08 ng/ml to about 0.2 ng/ml.

31. The metered dose device of any one of claims 24 to 29 wherein the metered dose spray produced by the device produces a plasma C_{max} in the mammal of about 0.15 ng/ml.

32. The metered dose device of any one of claims 24 to 29 wherein the metered dose spray produced by the device produces a plasma C_{max} in the mammal of about 0.2 ng/ml.

33. The metered dose device of any one of claims 24 to 32 wherein the metered dose spray produced by the device produces a T_{max} in the mammal of less than about 1 hour.

34. The metered dose device of any one of claims 24 to 32 wherein the metered dose spray produced by the device produces a T_{max} in the mammal of less than about 50 minutes.

35. The metered dose device of any one of claims 24 to 34 wherein the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 3 on the Ramsay Sedation Scale.

36. The metered dose device of any one of claims 24 to 35 wherein the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not greater than Level 2 on the Stanford Sleepiness Scale.
- 5 37. The metered dose device of any one of claims 24 to 36 wherein the metered dose spray produced by the device during the hour immediately after administration to the mammal produces a level of sedation not less than Level 6 on the Modified Observer's Assessment Of Alertness/Sedation Scale.
- 10 38. The metered dose device of any one of claims 24 to 37 wherein the metered dose spray produced by the device has no or minimal effect on the blood pressure of the mammal after administration.
39. The metered dose device of any one of claims 24 to 38 wherein the pharmaceutical
15 composition further comprises one or more other therapeutic agents.
40. The metered dose device of claim 39 wherein the one or more additional therapeutic agents is chosen from an opioid analgesic, a synthetic opioid-like analgesic, a non-opioid analgesic, a vitamin, a vasodilator, a benzodiazepine, a triptan, an anti-convulsant, an anti-
20 depressant, an anti-nausea medication, and an anti-hypertensive.
41. The metered dose device of any one of claims 24 to 40 which is a multi-dose, unit dose, or bi-dose device.
- 25 42. The metered dose device of any one of claims 24 to 41 wherein the pharmaceutical composition further comprises a carrier vehicle.
43. The metered dose device of any one of claims 24 to 42 wherein the pharmaceutical composition further comprises sodium phosphate and/or sodium citrate.
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44. The metered dose device of any one of claims 24 to 43 wherein the pharmaceutical composition further comprises a chelator.

45. The metered dose device of any one of claims 24 to 44 wherein the pharmaceutical composition is free of a viscosity enhancing agent.
46. The metered dose device of any one of claims 24 to 45 wherein the pharmaceutical composition further comprises sodium citrate, citric acid, and sodium chloride.
47. The metered dose device of claim 46 wherein the pharmaceutical composition further comprises about 0.2% to about 0.3% (w/w) sodium citrate and about 0.005% to about 0.015% (w/w) citric acid.
48. The metered dose device of any one of claims 24 to 47 wherein the pH of the pharmaceutical composition is from about 6 to about 6.5.
49. The metered dose device of any one of claims 24 to 48 wherein the pharmaceutical composition further comprises one or more anti-microbial preservatives.
50. The metered dose device of claim 49 wherein the preservative is phenylethyl alcohol.
51. The metered dose device of any one of claims 24 to 50 wherein the pharmaceutical composition further comprises one or more antioxidants.
52. The metered dose device of any one of claims 24 to 51 wherein the pharmaceutical composition further comprises one or more dose confirmation excipients.
53. The metered dose device of claim 52 wherein the one or more dose confirmation excipients is phenylethyl alcohol.
54. The metered dose device of any one of claims 24 to 53 wherein the pharmaceutical composition further comprises one or more humectants.
55. The metered dose device of claim 54 wherein the one or more humectants is glycerin, propylene glycol, polyethylene glycol, or a sugar/sugar alcohol, or any combination thereof.

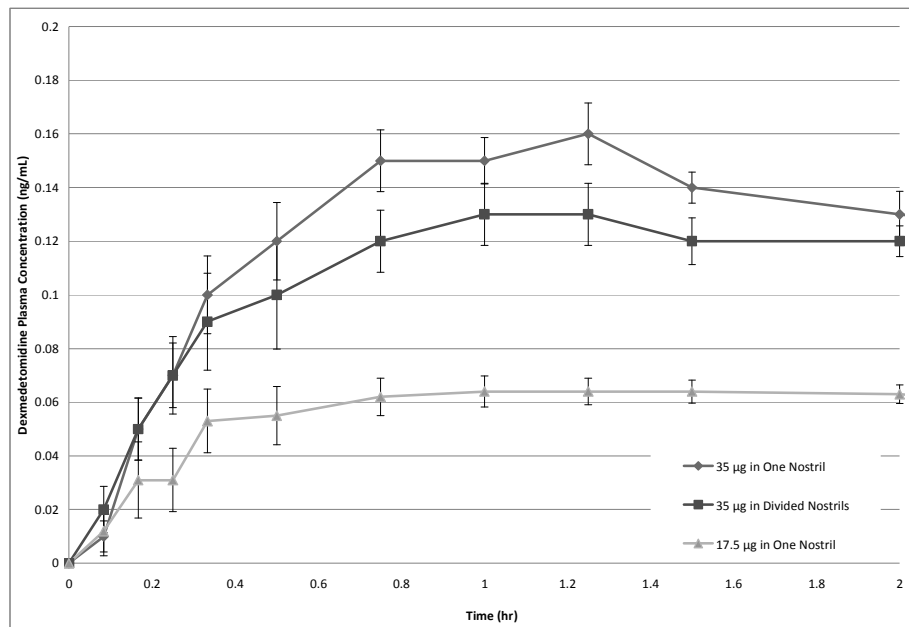
56. The metered dose device of any one of claims 24 to 55 wherein the pharmaceutical composition further comprises one or more osmolality adjusting agents.

57. The metered dose device of claim 56 wherein the one or more osmolality adjusting
5 agents is sodium chloride, dextrose, or another sugar, or any combination thereof.

Abstract

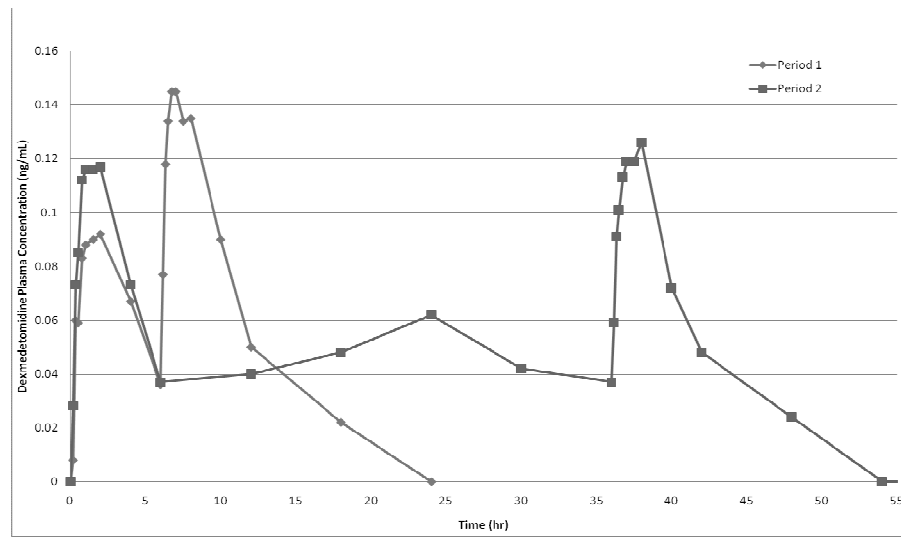
The present invention provides intranasal formulations comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, and uses thereof.

Figure 1:



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Figure 2



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
CONSULTA DE DOCUMENTOS

PAGINA SIN DIGITALIZAR

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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