

Bogotá, D.C., 16 de noviembre de 2016

Doctor

JOSE LUIS SALAZAR LÓPEZ

Director Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO -SIC-

E.

S.

D.

REF.: SOLICITANTE: OREXO AB.

**TÍTULO: "COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE
MICROPARTÍCULAS DE BUPRENORFINA Y
NALOXONA PARA EL TRATAMIENTO DE LA
DEPENDENCIA A OPIOIDES"**

EXPEDIENTE: 14045641

RESPUESTA AL EXAMEN DE FONDO OFICIO No. 8535

HELENA CAMARGO WILLIAMSON, mayor de edad y vecina de Bogotá D.C., identificada como aparece al pie de mi firma, en mi condición de apoderada de la empresa **OREXO AB**, respetuosamente me dirijo a usted con el fin de dar respuesta al examen de fondo dentro del término legal.

1. DE LA SOLICITUD DE PATENTE

1.1. Reivindicaciones

En respuesta a la objeción a la reivindicación 1 aclaramos que esta es concisa, se encuentra completamente definido el grupo de disgregantes y el estar definido como grupo implica que con cualquiera de los compuestos definidos, el efecto logrado es el mismo. Por lo tanto, la objeción se entiende por superada.

Adicionalmente, se ha modificado el capítulo reivindicatorio como se explica a continuación:

- (i) Se ha incluido la relación de dosis para buprenorfina:naloxona (calculada como las bases libres) de "aproximadamente 4:1" (soportado en la página 20, líneas 2 y 7, página 16, líneas 23 y 24 de la solicitud PCT), o "4:1 ($\pm$ 10%)" (soportado en la página 23, líneas 24 a 30, página 19, líneas 24 a 30 de la solicitud PCT); y

(ii) Se ha sustituido la frase "aditivo asociativo" por "las micropartículas [separadas] de buprenorfina y partículas de ácido cítrico están en contacto [íntimo] entre sí" (soportado en la página 10, línea 23 a página 11, línea 3).

Teniendo en cuenta que las modificaciones realizadas a las reivindicaciones superan las objeciones del examinador y cumplen con los parámetros establecidos en el artículo 34 de la Decisión 486 de la Comunidad Andina, solicito amablemente a ese Despacho se acepten las enmiendas efectuadas, toda vez que superan las objeciones efectuadas y no amplían el alcance de la divulgación original.

2. DETERMINACIÓN DEL ESTADO DE LA TECNICA

El examinador consideró que las reivindicaciones 1 a 10 de la solicitud de patente de invención no cumplen con el requisito de nivel inventivo, debido a las siguientes divulgaciones:

Ítem	Documento	Título	Fecha de Publicación	Reivindicaciones afectadas	Requisito que se afecta
D1	Suboxone Tablets 8mg/2mg	"Summary of product characteristics"	26/Septiembre/2006	1 a 10	Nivel Inventivo
D2	WO2008068471	""New non-abusable pharmaceutical composition comprising opioids"	12/Junio/2008	1 a 10	Nivel Inventivo

Después de realizar un análisis de cada una de las características de la reivindicación 1 de la presente invención frente a las de los documentos D1 y D2, el examinador concluyó que dichos documentos afectan el nivel inventivo de la reivindicación 1.

2.1. Argumentos a favor de la patentabilidad de la invención.

2.1.1. Invención reivindicada y Estado de la técnica anterior

Como se indica en la acción oficial, la reivindicación principal pendiente de la presente solicitud define una composición farmacéutica que comprende:

- (a) micropartículas de buprenorfina (en una cantidad específica en la forma de dosificación (comprimido));
- (b) donde las micropartículas de buprenorfina están en mezcla asociativa con partículas de ácido cítrico separadas;
- (c) naloxona (en una cantidad específica en la forma de dosificación); y

(d) un desintegrante seleccionado del grupo reducido: croscarmelosa sódica, almidón glicolato sódico y PVP reticulado.

El Examinador comienza su análisis con el resumen de las características del producto para comprimidos de Suboxone®, (**D1**), e indica que este documento describe todas las características que definen la invención reivindicada, excepto la característica (d).

El Examinador luego combina este documento con el documento WO 2008/068471 (**D2**), que describe un comprimido de disolución rápida que comprende opioides, afirmando que este documento cita la característica ausente en **D1** (es decir, la característica (d)).

Como se explica con más detalle a continuación, no estamos de acuerdo con la afirmación del Examinador donde manifiesta que los comprimidos a los que se hace referencia en el documento **D1** comprenden todas las características (a) a (c). **D1** es la información del producto emitida por, el entonces fabricante de tabletas Suboxone®, Reckitt Benckiser. Sobre el particular, se aclara que Suboxone® es una tableta combinada que comprende buprenorfina y naloxona.

D1 se emitió tras la aprobación de Suboxone® por la Agencia Europea del Medicamento (EMA) y contiene poca o ninguna información sobre la estructura de esos comprimidos. A la inversa, el documento adjunto "*Scientific Discussion Paper on Suboxone®*", que fue publicado por la EMA en 2006 (en adelante "**D3**"), contiene considerablemente más antecedentes e información sobre cómo se fabrica el producto.

2.1.2. *Antecedentes de la invención*

Como se indica en el documento D3, en la página 1 (segundo párrafo completo), la buprenorfina es un analgésico opioide que se conoce por su empleo en el tratamiento del dolor desde hace muchos años, pero también se aprobó más recientemente para el tratamiento de la dependencia de los opioides.

Como se confirma en la página 14, línea 31, a la página 15, línea 3 de la solicitud PCT correspondiente a la presente solicitud colombiana, la buprenorfina es un agonista parcial al receptor μ -opioide. Debido a que sus efectos agonistas opioides son menores que los efectos máximos de otros agonistas opioides, se produce un grado menor de dependencia física que con otros agonistas opioides, como la heroína, la morfina o la metadona. Por lo tanto, es particularmente útil en la terapia de sustitución de opioides.

Un problema perenne de los analgésicos opioides es la generación (a menudo sin intención) de dependencia física y, después de esto, el abuso por parte de personas dependientes de opioides. La OMS ha estimado que hay al menos 15 millones de personas adictas a los opioides en todo el mundo.

Como se indica en la solicitud (página 2, líneas 25 a 30, solicitud PCT página 2, líneas 20 a 24), se usan antagonistas opioides para revertir los efectos farmacológicos de los opioides. Los antagonistas opioides selectivos, como la naloxona, se usan para tratar una sobredosis de narcóticos o para diagnosticar la sospecha de adicción a los opioides.

Lo anterior se confirma en el último párrafo de la introducción de **D3**. La naloxona tiene una biodisponibilidad transmucosa deficiente, por lo tanto, si Suboxone® se toma por vía sublingual según las indicaciones, la pequeña cantidad de naloxona que se absorbe no interfiere con los efectos deseados de la buprenorfina.

Sin embargo, si un adicto disuelve y se inyecta Suboxona®, el aumento de la disponibilidad de naloxona a través de la vía parenteral trata de antagonizar los efectos de la buprenorfina, al mismo tiempo que precipita los síntomas desagradables de abstinencia de opioides en un individuo físicamente dependiente de los opioides. Como también se indica en el párrafo de referencia anterior de **D3**, la adición de naloxona a una formulación sublingual, que contiene buprenorfina, está destinada a hacer que el producto sea menos abusivo, al disuadir la inyección intravenosa.

Ahora bien, la solicitud (página 3, líneas 19 a 21, PCT página 3, líneas 8 a 18), cómo se ha informado con frecuencia, sobre el desvío y el uso ilícito de Suboxone®, especialmente en poblaciones ocultas, como los drogadictos en prisión y activos. Por ejemplo, un estudio publicado en 2009 mostró que el 100% de las personas que ingresaron al tratamiento de la adicción a los opioides con conocimiento de las tabletas de Suboxone® lo habían desviado (Monte et al, Journal of Addictive Diseases, 28, 226 (2009); se adjunta como **D4**).

De hecho, se estima que aproximadamente la mitad de las personas que toman Suboxone® lo obtienen por desviación. Por ejemplo, existen estudios que revelan que aproximadamente la mitad del uso de comprimidos de Suboxone®, en un plan de atención administrada, parece estar asociado con el uso de opioides sin receta (*Kaur et al, Journal of Managed Care Pharmacy 14, 186 (2008)*; se adjunta como **D5**). Por lo tanto, hay un gran mercado para la buprenorfina desviada.

Se entiende que la mayoría de los abusos relacionados con la buprenorfina provienen del Suboxone® desviado en lugar de la droga prescrita, y esto es un problema grave. Las tendencias en el abuso reportado de buprenorfina en los EEUU muestran que el 92,2% estaba involucrado con Suboxone® (ver *Smith et al, Journal of Addictive Diseases, 26, 107 (2007)*; adjunto como **D6**).

Adicionalmente, se predice que las tasas de abuso y desviación de Suboxone® aumentarán con el uso incrementado de la droga (ver, por ejemplo, *Stimmel, Journal of Addictive Diseases, 26, 1 (2007)*; adjunto como **D7**).

2.1.3. Ventajas de la presente invención

(1) Resultados sorprendentes- Biodisponibilidad mejorada de la Buprenorfina

Como se indica en la solicitud PCT (p.ej. página 20, líneas 6 a 15) las composiciones de la invención dan lugar sorprendentemente a una biodisponibilidad significativamente mejorada de la buprenorfina en comparación con las formulaciones disponibles comercialmente del estado de la técnica.

Esto se demuestra en el ensayo clínico descrito en el Ejemplo 2 de la presente solicitud, que es una comparación directa entre una composición de la invención, formulada de

acuerdo con las reivindicaciones, y comprimidos de Suboxone®. Se encontró que la formulación reivindicada logra una biodisponibilidad para la buprenorfina que es 1.66 veces mayor que la obtenida con Suboxone®.

Para ubicar este resultado en un contexto apropiado, debe tenerse en cuenta que la biodisponibilidad reportada de la buprenorfina, en una solución de etanol administrada por vía sublingual, es solo aproximadamente 1.5 veces mayor que para los comprimidos de Suboxone® (ver *Compton et al, Drug and Alcohol Dependence, 82, 25 (2006)*; adjunto como **D8**).

Por lo tanto, la biodisponibilidad relativa indicada en la presente solicitud para un comprimido sublingual sólido de la invención, fue incluso mayor que la reportada para una solución, donde las condiciones se optimizan teóricamente para una rápida absorción sobre la mucosa sublingual.

(2) Beneficios clínicos – Menos desviación que en el estado de la técnica

Además de ser un resultado sorprendente en sí mismo, esta biodisponibilidad mejorada da lugar a un verdadero beneficio clínico y social al proporcionar una solución al problema de la desviación, como se mencionó anteriormente.

En particular, permite la provisión de un comprimido, comercializado y aprobado por la FDA en los EEUU, que contiene una dosis de buprenorfina que es aproximadamente el 75% de la de la formulación de la técnica anterior (Zubsolv®; <http://orexo.com/en/productos/zubsolv/>). Esto representa una mejora significativa, dado que reduce la cantidad de opioide adictivo que está presente en la formulación.

Esta cantidad más baja no solo reduce la cantidad de opioides peligrosos que están en circulación, sino que también reduce inevitablemente la cantidad que un individuo adicto a los opioides puede colocar en una sola formulación del comprimido (es decir, su valor de "calle"). Como se indicó anteriormente y en **D3**, cuando los adictos abusan de estas formulaciones, a menudo se disuelven o dispersan para su administración por inyección. En tal situación, si un comprimido comprende el 75% de la dosis de opioide, el valor de "calle" se reduce:

- (i) en primer lugar, porque el comprimido simplemente no puede dar el mismo efecto eufórico que un comprimido con una dosis más alta; y
- (ii) en segundo lugar, porque, para lograr el mismo efecto, se requieren más comprimidos, lo que ciertamente es más inconveniente y potencialmente más costoso para el adicto.

Los comprimidos de la presente invención son, por lo tanto, menos susceptibles a ser desviados y a su abuso que las formulaciones de la técnica anterior, tales como Suboxone®.

(3) Resultados sorprendentes – Biodisponibilidad equivalente mejorada de Naloxona

El ensayo clínico, descrito en el Ejemplo 2 de la presente solicitud, muestra que en las composiciones de la invención se mejora inesperadamente no sólo la absorción de buprenorfina, sino también, de manera proporcional, la absorción de naloxona (véase también la página 20, líneas 17 a 28 de la solicitud PCT, originalmente presentada).

Es sorprendente en sí mismo que las composiciones de la invención cambien la biodisponibilidad tanto de la naloxona como de la buprenorfina, no solo de la misma manera, sino también en el mismo grado, cuando se toman según lo previsto (es decir, vía sublingual). Los dos compuestos tienen diferentes propiedades fisicoquímicas, como los valores de pKa y las solubilidades acuosas, y, por tanto, este no es un resultado que el experto pudiera esperar.

(4) Beneficios clínicos – Mantenimiento de la proporción de dosis 4:1

El aumento correspondiente en la biodisponibilidad para ambos ingredientes activos tiene un beneficio clínico, ya que se ha encontrado que las composiciones de la invención son inesperadamente capaces de mantener la proporción de 4:1 de buprenorfina:naloxona que está presente en Suboxone®.

La proporción 4:1 de la dosis a la que se llegó durante el desarrollo de Suboxone® representa la proporción óptima de buprenorfina/naloxona para evitar el abuso (consultar la página 20, líneas 22 a 28 de la solicitud PCT, y Mendelson y Jones, dependencia de drogas y alcohol, 70, 829 (2003); adjunto como **D9**).

La relación 4: 1 asegura que:

- (a) si se inyecta la formulación, se dispone de suficiente naloxona para contrarrestar los efectos de la buprenorfina;
- (b) cuando la formulación se administra por vía sublingual, según lo prescrito, la cantidad de naloxona que está presente no interfiere con los efectos deseados de la buprenorfina, y también evita eventos adversos, como la precipitación de la abstinencia de opioides, que puede dar lugar a elevaciones marcadas en ritmo cardíaco y presión arterial.

2.1.4. La presente invención es inventiva

(A) La combinación de D1 y D2 no conduce de forma obvia a la presente invención.

Si se parte de los comprimidos de Suboxone® a las que se hace referencia en el documento **D1** (o, más apropiadamente, la descripción más detallada del documento **D3**, que explica qué son esos comprimidos), como se mencionó anteriormente, la invención reivindicada proporciona una buprenorfina mejorada resistente al abuso y un comprimido sublingual que contiene naloxona que es útil en el tratamiento de, por ejemplo, dependencia a los opioides.

También es evidente, a partir de la discusión anterior y de la solicitud presentada, que este problema se ha resuelto en la presente invención mediante la mejora de la biodisponibilidad y una mejor resistencia a la desviación y/o abuso.

La presente solicitud enseña que este beneficio se logra cuando las micropartículas de buprenorfina se mezclan de manera asociativa con partículas de ácido cítrico, poniéndolas en contacto entre sí, cuando se presentan junto con los otros constituyentes definidos en la reivindicación principal.

El producto de referencia, como se describe en **D1** y **D3**, no comprende tal disposición espacial de partículas individuales específicas. En cambio, **D3** enseña que Suboxone® se produce a través de un proceso que incluye un paso de granulación húmeda (consultar la sección "Proceso de fabricación" al pie de la página 4).

El fabricante de Suboxone®, Reckitt Benckiser, publicó una solicitud de patente poco después de la publicación de **D3** (documento WO 2008/152347; adjunto como **D10**).

El **D10** brinda un poco más de detalle que el **D3** sobre el proceso que el fabricante de Suboxone® empleó para elaborar sus productos que contienen buprenorfina. Se puede ver que el proceso descrito en la página 8, líneas 10 a 22, de **D10**, que es el empleado para fabricar un producto comercial relacionado, Subutex®, contiene los mismos excipientes inertes que los enumerados en **D3** en la página 4.

En lugar de referirse a "*mezcla simple, granulación húmeda y compresión*" como en **D3**, **D10** proporciona más detalles, lo que hace que sea aún más claro que el proceso no puede garantizar que las micropartículas de buprenorfina se pongan en contacto con partículas que comprenden ácido cítrico en la formulación final.

En la página 8 de **D10** se indica que la etapa de granulación húmeda consiste en disolver clorhidrato de buprenorfina y ácido cítrico en una solución de agua-etanol, solución que luego se usa en el proceso de granulación húmeda.

Exactamente la misma etapa de co-disolución, en la que la buprenorfina se co-disuelve con ácido cítrico, también se emplea en el proceso de granulación húmeda (como se menciona en **D3**) mediante la cual se fabrican los comprimidos de Suboxone®.

Sostenemos que este paso de co-disolución da como resultado que la buprenorfina y el ácido cítrico estén en la misma partícula en la formulación final. Se deriva por tanto claramente que el proceso de **D10** no da lugar a micropartículas discretas de buprenorfina y partículas de ácido cítrico en contacto entre sí en la formulación final.

El producto obtenido en un proceso depende de la naturaleza de los ingredientes primarios que se utilizan y del proceso de fabricación de la formulación. Si no se parte de ingredientes particulados, y/o la naturaleza de esos ingredientes particulados no se conserva durante la fabricación, no habrá partículas relevantes en el producto.

En la presente solicitud, al experto se le sugiere que opere un proceso de mezcla asociativa para obtener un producto en el que exista una disposición espacial específica de partículas específicas en el producto en partículas definido, a saber, micropartículas de buprenorfina en contacto con partículas de ácido cítrico. Al experto, en **D1/D3**, no se le dice ni sugiere que haga esto y, por lo tanto, no llegaría de forma obvia a dicho producto.

En consecuencia, las características clave de las reivindicaciones de la presente invención no se mencionan en **D1/D3**, concluyendo que, su combinación con **D2**, donde únicamente se hace mención a los disgregantes, no llevaría en ningún caso a la invención reivindicada.

(B) La presente invención da lugar a ventajas inesperadas

Como hemos defendido anteriormente, la combinación reivindicada de las características individuales que forman la presente invención no está divulgada por la combinación de documentos citados por el Examinador, y precisamente es esta combinación de características las que juntas dan lugar a la biodisponibilidad mejorada discutida anteriormente.

Cuando el solicitante llevó a cabo la presente invención, no había disponible ninguna información sobre el alcance de la biodisponibilidad mejorada. Después de todo, como se mencionó anteriormente, el producto de referencia, Suboxone®, también incluía tanto buprenorfina como ácido cítrico.

La farmacocinética de la absorción de fármacos es un campo complejo de estudio. De hecho, se han escrito libros de texto completos sobre el tema, pero, en esencia, la "biodisponibilidad" de una sustancia farmacológica depende de múltiples factores, que a menudo compiten entre sí.

Un fármaco sólo puede ser absorbido a través de la superficie de la mucosa si está en solución y, en ese caso, influir en la velocidad de disolución puede tener un efecto. Sin embargo, la permeabilidad de una sustancia farmacológica a través de una superficie de la mucosa (en el presente caso, la mucosa sublingual) es igualmente importante, si no más.

La permeabilidad de una sustancia farmacológica puede verse afectada por múltiples factores, incluida la naturaleza de la propia molécula del fármaco (hidrofilicidad frente a lipofilicidad, tamaño de la molécula, etc.), el grado de ionización, la presencia de potenciadores de la permeación, el entorno local en el sitio de absorción (p. ej., pH, cantidad de líquido, la presencia de otros materiales químicos o enzimas), la unión del fármaco a los excipientes o tejidos de la formulación, el flujo sanguíneo local y otros.

En el caso de formulaciones sublinguales, como la de la presente invención, la situación es aún más complicada. Una vez que un medicamento se disuelve (y, por lo tanto, se presenta en la superficie de la mucosa sublingual en una forma adecuada para la absorción), puede tomar dos caminos. Se puede absorber localmente a través de la mucosa o se puede lavar con saliva y tragar. Estos son los dos procesos cinéticos competitivos esenciales que ocurren inevitablemente, y el equilibrio entre las tasas a las que ocurren estos procesos tiene un efecto directo (en última instancia) sobre la biodisponibilidad.

Si una sustancia farmacológica no se absorbe fácilmente a través de la mucosa sublingual, la deglución puede conducir a una reducción de la biodisponibilidad. En el caso de un medicamento como la buprenorfina, que tiene una biodisponibilidad deficiente cuando se administra por vía gastrointestinal, ya que sufre un metabolismo significativo de primer paso en el tracto gastrointestinal y en el hígado (ver, por ejemplo,

Cassidy et al, Journal of Controlled Release, 25, 21 (1993), primer párrafo de "Introducción"; copia adjunta como **D11**), conducirá a una reducción de la biodisponibilidad.

Algo que ilustra de manera muy efectiva el punto sobre los posibles procesos competitivos en el presente caso, es el hallazgo, mencionado anteriormente, de que la biodisponibilidad relativa para la invención reivindicada, un comprimido sublingual sólido, en el cual la disolución debe tener lugar después de la administración sublingual, en realidad fue más alta que el reportado para una solución (ver **D8**).

(C) La combinación de las características reivindicadas es contraintuitiva

Repetimos que las diferencias entre la invención reivindicada y el estado de la técnica citado y el documento **D1/D3** son que este último no revela:

- (a) micropartículas de buprenorfina
- (b) que las micropartículas se mezclan asociativamente (en contacto) con partículas que comprenden ácido cítrico;
- (c) Cualquiera de los disgregantes reclamados.

No hay nada en los documentos de la técnica anterior citados por el examinador, solos o en combinación, que sugieran la provisión de la combinación de características reivindicada, que dé lugar a las ventajas inesperadas mencionadas anteriormente.

También afirmamos que la combinación de características reivindicada no se sugiere en la técnica anterior (citada por el examinador o de otra manera) porque, en todo caso, se esperaría una combinación con una biodisponibilidad inferior.

Como se mencionó anteriormente, las limitaciones a la permeabilidad de la mucosa sublingual significarán que la presentación rápida de buprenorfina en estado disuelto debajo de la lengua aumentará la probabilidad de que se ingiera y se "*inactive*", en lugar de que se absorba.

Además, como se discutió en, por ejemplo, página 29 líneas 19 a 30 a página 30 líneas 1 a 6 (página 24, líneas 12 a 26 de la solicitud PCT tal como se presentó), se sabe que la buprenorfina es más soluble a pH más bajos. Por lo tanto, el experto esperaría que la reducción del pH con la inclusión de, por ejemplo, un ácido débil, como el ácido cítrico, resultara en una mayor disolución del fármaco debajo de la lengua, lo que podría exacerbar el problema mencionado anteriormente. Ciertamente, en ningún caso se esperaría que la absorción mejorara.

Más importante aún, con referencia a la discusión anterior sobre los factores que afectan la biodisponibilidad, la disminución del pH tendrá el efecto opuesto sobre la permeabilidad de la buprenorfina (es decir, el grado de absorción). Como se discutió en el párrafo mencionado anteriormente de la presente solicitud, disminuir el pH sirve para poner a la buprenorfina más en su estado ionizado, que es una forma en la que no es permeable. Claramente, si hay más buprenorfina en una forma en la que no será absorbida durante el corto tiempo en que se encuentra en el espacio sublingual, se tragará más, lo que dará como resultado una absorción aún menor.

Por lo tanto, no hay razón para combinar las enseñanzas del estado de la técnica acerca del uso de agentes reductores del pH, como el ácido cítrico, tal y como se describe en relación con el comprimido de buprenorfina sublingual Suboxone® (como se describe en **D1** y / o **D3**), con las enseñanzas relacionadas con un comprimido de rápida desintegración (como se describe, por ejemplo, en **D2**).

Por todos estos motivos, afirmamos que, en la fecha de prioridad de la presente solicitud, el experto en la materia esperaría que dicha combinación produjera una disminución de la biodisponibilidad de la buprenorfina debido al aumento de la deglución. Ciertamente, no hay una expectativa razonable de que tal combinación incremente exitosamente la biodisponibilidad, como se observó inesperadamente para la invención reivindicada.

(D) Posible explicación para los resultados inesperados de la presente invención.

Con referencia a lo anterior, afirmamos que es la disposición de las partículas de ácido cítrico y las partículas de buprenorfina entre sí, en combinación con otros ingredientes esenciales de la invención reivindicada, lo que contribuye al aumento de la biodisponibilidad. La mera presencia de ácido cítrico en una tableta de buprenorfina no explica nada (de lo contrario no habría una mejora en la biodisponibilidad respecto al Suboxone®, que también contiene buprenorfina y ácido cítrico).

La prueba descrita en el Ejemplo 5 de la presente solicitud fue diseñada por el solicitante después de haber realizado y probado clínicamente la invención reivindicada en seres humanos (ver Ejemplo 2). El solicitante hizo esto porque no tenía una explicación para la mejora de la biodisponibilidad que vio en su primer estudio farmacocinético.

En primer lugar, se realizó un experimento in vivo en el que se colocó una sonda de pH debajo de la lengua. Este experimento, que se describe en el Ejemplo 4 de la presente solicitud, controló el pH debajo de la lengua durante el corto período de tiempo de residencia en el que el comprimido estuvo en el espacio sublingual.

Se observó un perfil de pH distintivo para comprimidos de la invención reivindicada. Después de la administración, el pH sublingual primero bajó muy rápidamente a un cierto valor y luego se recuperó rápidamente a valores neutros por la capacidad natural de amortiguación de la saliva (consultar la Figura 4 de la presente solicitud).

Tras esta observación, la prueba in vitro del Ejemplo 5 se diseñó principalmente en un intento de imitar el entorno sublingual en el laboratorio. Los detalles del experimento se describen en el Ejemplo 5, pero se gotea esencialmente tampón fosfato con un pH de 6.8 (imitando la saliva) en una tableta colocada en un filtro sinterizado en un embudo de vidrio. Los cambios en el pH a la salida del embudo se midieron con el tiempo. La disolución de buprenorfina también se analizó durante el mismo período de tiempo.

Al realizar esta prueba in vitro en comprimidos de la invención reivindicada, el solicitante observó el mismo perfil de pH distintivo para los comprimidos de la invención reivindicada (ver Figuras 5 y 8 de la presente solicitud) que se había observado in vivo. Esto se puede ver comparando las curvas caracterizadas por

cuadrados blancos y cruces (resultados in vitro) con la línea discontinua (resultados in vivo) en la Figura 5.

Más importante aún, este perfil de pH fue completamente diferente al observado en la misma prueba para comprimidos Suboxone® (triángulos blancos en la Figura 5).

Con referencia a, por ejemplo, página 29 líneas 19 a 30 a página 30 líneas 1 a 6 (página 24, líneas 12 a 26 de la solicitud PCT tal como se presentó), tal como se presentó, y sin estar limitado por la teoría, se cree que este perfil de pH dinámico podría proporcionar una explicación de la mejora inesperada de la biodisponibilidad que se observó clínicamente en el Ejemplo 2.

En la farmacocinética, el flujo a través de la superficie de la mucosa está determinado, entre otras cosas, por:

- (a) la concentración de fármaco disuelto; y
- (b) La permeabilidad de ese medicamento en esa superficie

Se sabe que la buprenorfina es más soluble a pH más bajos y, por lo tanto, la caída inicial del pH da como resultado una mejor disolución del fármaco, lo que da como resultado una alta concentración de fármaco disuelto.

Sin embargo, este pH bajo también sirve para poner más buprenorfina en su estado ionizado, que es una forma en la que no es permeable. Es el rápido retorno del pH a valores casi neutros lo que pondrá estas altas concentraciones de fármaco en la mucosa sublingual en la forma no ionizada y permeable.

Se cree que es esta secuencia de eventos, que tiene lugar dentro de un corto período de tiempo (es decir, antes de que ocurra una ingestión significativa), lo que da como resultado una biodisponibilidad mejorada para la invención reivindicada.

El perfil de pH para Suboxone® es bastante diferente durante el mismo período de tiempo. Aquí, una menor caída en el pH resulta en una menor disolución (y por lo tanto una concentración más baja) de buprenorfina debajo de la lengua. Igualmente, no hay un cambio posterior en el pH que haga retroceder el equilibrio para favorecer la forma no ionizada, en la que la buprenorfina puede pasar a través de la membrana mucosa.

Aunque hay cierta absorción de buprenorfina a través de la mucosa sublingual de Suboxone®, se cree que su propio perfil de pH distintivo es lo que conduce a la biodisponibilidad inferior observada en comparación con la invención.

El solicitante cree, basándose en los resultados descritos en la presente solicitud, que es la presentación de la buprenorfina y el ácido cítrico en la misma partícula en la formulación del comprimido final, resultante del proceso de granulación húmeda descrito en **D3** y **D10**, lo que da lugar al perfil de absorción inferior en Suboxone®, en comparación con la invención reivindicada.

En conclusión, la Reivindicación 1, y todas las reivindicaciones que dependen de ésta, son claramente novedosas e inventivas a la luz del estado de la técnica citado.

En vista de los argumentos anteriormente expuestos, se concluye que la materia objeto de la presente solicitud **cumple con los requisitos de patentabilidad, en especial el de nivel inventivo.**

De otra parte, sea entonces oportuno indicar que el Tribunal de Apelaciones del Circuito Federal de los Estados Unidos ha confirmado recientemente la patentabilidad de las reivindicaciones presentadas en aquel país, que tienen esencialmente el mismo alcance que las reivindicaciones de la presente solicitud en Colombia.

3. Después de haber dado respuesta a las objeciones presentadas por la Superintendencia de Industria y Comercio solicito de manera respetuosa se otorgue el privilegio de patente de invención en este caso, teniendo en cuenta que esta cumple con los requisitos de patentabilidad establecidos en la Decisión 486.

Del Señor Director,

POSSE HERRERA RUIZ



HELENA CAMARGO WILLIAMSON
C.C 35.455.268 de Bogotá
T.P. 76.985

Anexos: Formulario Modificaciones
 Reivindicaciones en control de cambios
 Reivindicaciones en limpio
D3 - *Scientific Discussion Paper on Suboxone®*, EMEA (2006)
D4 - Monte *et al*, *Journal of Addictive Diseases*, **28**, 226 (2009)
D5 - Kaur *et al*, *Journal of Managed Care Pharmacy* **14**, 186 (2008)
D6 - Smith *et al*, *Journal of Addictive Diseases*, **26**, 107 (2007)
D7 - Stimmel, *Journal of Addictive Diseases*, **26**, 1 (2007)
D8 - Compton *et al*, *Drug and Alcohol Dependence*, **82**, 25 (2006)
D9 - Mendelson and Jones, *Drug and Alcohol Dependence*, **70**, 829 (2003)
D10 - WO 2008/152347
D11 - Cassidy *et al*, *Journal of Controlled Release*, **25**, 21 (1993)

DELEGATURA PROPIEDAD INDUSTRIAL
MODIFICACIONES Y/O CORRECCIONES A SOLICITUDES EN TRÁMITE

1. TIPO DE SOLICITUD

☒ **MODIFICACIÓN**

☐ **CORRECCIÓN**

1.1 IDENTIFICACIÓN DEL TRÁMITE

- ☒ Patente de invención/PCT
☐ Patente Modelo de Utilidad/PCT
☐ Diseño Industrial
☐ Esquema de Trazado Circuitos Integrados

2. DATOS DEL SOLICITANTE

☐ Persona Natural

☒ Persona Jurídica

OREXO AB.

NOMBRE O DENOMINACIÓN/NOMBRE O RAZÓN SOCIAL COMPLETA

DIRECCIÓN

No. TELÉFONO

CIUDAD

CORREO ELECTRÓNICO

DEPARTAMENTO/ESTADO Upsala

NACIONALIDAD O

PAÍS DE RESIDENCIA Suecia

LUGAR DE CONSTITUCIÓN

3. DATOS DEL APODERADO

APELLIDOS

NOMBRES

IDENTIFICACIÓN

CAMARGO WILLIAMSON

HELENA

C.C. 35.455.268 de Bogotá T.P. 76985

DIRECCIÓN Carrera 7 No. 71-52 Torre A, Piso 5

No. TELÉFONO 3257300

CIUDAD Bogotá D.C.

CORREO ELECTRÓNICO notipi@phrlegal.com

PAÍS Colombia

No. RADICACIÓN DE
PROTOCOLO DE
PODER GENERAL

4. MODIFICACIÓN Y/O CORRECCIÓN SOLICITADA

(Código actuación SIC - 608)

EXPEDIENTE No. **14045641**

- ☐ Capítulo Descriptivo
- ☒ Capítulo Reivindicatorio
- ☐ Resumen
- ☐ Modificación Título

5. MODIFICACIÓN Y/O CORRECCIÓN SOLICITADA

(Código actuación SIC - 587)

- ☐ Cesión/Cambio Solicitante ☐ Cambio de Nombre ☐ Cambio de Domicilio
- ☐ Cambio de Dirección ☐ Nombre Inventor ☐ Momento Publicación
- ☐ Otra: Especifique: _____

6. ANEXOS:

- ☐ Comprobante de pago de la tasa para la presentación de la modificación.
- ☐ Poder, si fuere el caso.
- ☐ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.
- ☒ Documento que contiene las modificaciones y/o correcciones

7. 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)



HELENA CAMARGO WILLIAMSON
APODERADO
C.C. 35.455.268 T.P. 76985

REIVINDICACIONES

1. Una composición farmacéutica que comprende micropartículas de buprenorfina, o una sal farmacéuticamente aceptable de la misma, en una cantidad en la composición comprendida entre 0.1 mg y 50 mg, ~~en mezcla asociativa con~~ partículas que comprenden ácido cítrico, naloxona, o una sal farmacéuticamente aceptable de la misma, en una cantidad en la composición comprendida entre 0.125 mg y 12.5 mg, y un disgregante seleccionado de croscarmelosa sódica, glicolato de almidón sódico, polivinilpirrolidona reticulada o una mezcla de los mismos, donde la proporción de la dosis de buprenorfina:naloxona es de aproximadamente 4:1 (calculada como bases libres) y donde las micropartículas de buprenorfina y las partículas que comprenden ácido cítrico están en contacto íntimo entre sí.
2. Una composición de acuerdo con la reivindicación 1, en la que las micropartículas de buprenorfina tienen un diámetro medio en base al peso inferior a 15 μm .
3. Una composición de acuerdo con una cualquiera de las reivindicaciones precedentes, que se presenta como una mezcla interactiva que comprende micropartículas de buprenorfina o una sal farmacéuticamente aceptable de la misma presentada sobre las superficies de partículas vehículo.
4. Una composición de acuerdo con la reivindicación 3, en la que las

partículas vehículo son de un tamaño que está entre 100 y 800 μm .

5. Una composición de acuerdo con la reivindicación 3 o la reivindicación 4, en la que las partículas vehículo son hidrosolubles.

5

6. Una composición de acuerdo con una cualquiera de las reivindicaciones 3 a 5, en la que las partículas vehículo comprenden manitol.

7. Una composición de acuerdo con una cualquiera de las reivindicaciones 3 a 6, en la que las partículas de ácido cítrico, se presentan y actúan como partículas vehículo.

8. Una composición de acuerdo con una cualquiera de las reivindicaciones precedentes, que está en forma de un comprimido adecuado para administración sublingual.

9. Un procedimiento para la preparación de una composición como se ha definido en una cualquiera de las reivindicaciones 3 a 8, que comprende mezclar en seco las partículas vehículo con buprenorfina o una sal de la misma.

10. Un procedimiento para la preparación de un comprimido sublingual como se ha definido en la reivindicación 8, que comprende comprimir o

compactar directamente una composición como se ha definido en una cualquiera de las reivindicaciones 1 a 7.

REIVINDICACIONES

1. Una composición farmacéutica que comprende micropartículas de buprenorfina, o una sal farmacéuticamente aceptable de la misma, en una
5 cantidad en la composición comprendida entre 0.1 mg y 50 mg, partículas que comprenden ácido cítrico, naloxona, o una sal farmacéuticamente aceptable de la misma, en una cantidad en la composición comprendida entre 0.125 mg y 12.5 mg, y un disgregante seleccionado de croscarmelosa sódica, glicolato de almidón sódico, polivinilpirrolidona reticulada o una mezcla de los mismos,
10 donde la proporción de la dosis de buprenorfina:naloxona es de aproximadamente 4:1 (calculada como bases libres) y donde las micropartículas de buprenorfina y las partículas que comprenden ácido cítrico están en contacto íntimo entre sí.
- 15 2. Una composición de acuerdo con la reivindicación 1, en la que las micropartículas de buprenorfina tienen un diámetro medio en base al peso inferior a 15 μm .
- 20 3. Una composición de acuerdo con una cualquiera de las reivindicaciones precedentes, que se presenta como una mezcla interactiva que comprende micropartículas de buprenorfina o una sal farmacéuticamente aceptable de la misma presentada sobre las superficies de partículas vehículo.
- 25 4. Una composición de acuerdo con la reivindicación 3, en la que las partículas vehículo son de un tamaño que está entre 100 y 800 μm .

5. Una composición de acuerdo con la reivindicación 3 o la reivindicación 4, en la que las partículas vehículo son hidrosolubles.

5 6. Una composición de acuerdo con una cualquiera de las reivindicaciones 3 a 5, en la que las partículas vehículo comprenden manitol.

7. Una composición de acuerdo con una cualquiera de las reivindicaciones 3 a 6, en la que las partículas de ácido cítrico, se presentan y
10 actúan como partículas vehículo.

8. Una composición de acuerdo con una cualquiera de las reivindicaciones precedentes, que está en forma de un comprimido adecuado para administración sublingual.
15

9. Un procedimiento para la preparación de una composición como se ha definido en una cualquiera de las reivindicaciones 3 a 8, que comprende mezclar en seco las partículas vehículo con buprenorfina o una sal de la misma.
20

10. Un procedimiento para la preparación de un comprimido sublingual como se ha definido en la reivindicación 8, que comprende comprimir o compactar directamente una composición como se ha definido en una cualquiera de las reivindicaciones 1 a 7.
25

SCIENTIFIC DISCUSSION

1. Introduction

Drug addiction is a worldwide problem of which opioid dependence, notably heroin addiction, is a major component. Most addicts inject drugs, quite often with dirty or shared syringes and needles and this behaviour is linked directly with the transmission of human immunodeficiency virus (HIV) and the hepatitis viruses. A key aim of treatment programs for opioid drug dependence is to stop the subjects from injecting drugs. Substitution is the treatment approach for opioid dependence in which street heroin of unknown strength and purity is replaced with a pharmaceutical grade opioid with a longer duration of action, such as buprenorphine.

Buprenorphine is a well-known substance available in several European countries for the treatment of severe pain. For the treatment of opioid dependence it was first approved in 1995 (France) and is currently available in most European countries. Buprenorphine has lower intrinsic activity than methadone and other full agonists, produces less sedation and cognitive impairment, and has a ceiling on potential depressant effects, even if injected, particularly on cardiac and respiratory functions. Sublingual buprenorphine (marketed as Buprenorphine alone) is an established substitution treatment for opiate abuse, but there has been some diversion to the intravenous route because buprenorphine produces a moderate opiate agonist effect. Thus, in the opinion of the applicant, there is a need for a formulation of buprenorphine that has low potential for intravenous misuse.

SUBOXONE is a fixed combination product for chronic substitution therapy in opiate dependence consisting of buprenorphine and naloxone formulated into a sublingual tablet containing buprenorphine and naloxone in the ratio 4:1 of the bases.

The claimed indication for SUBOXONE is **substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. As requested by the CHMP, treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.**

The product is intended as a “take home” medication presented in two strengths:

1. Buprenorphine 8 mg + naloxone 2 mg sublingual tablet
2. Buprenorphine 2 mg + naloxone 0.5 mg sublingual tablet.

The combination of an opioid antagonist with a potent μ -opioid analgesic is an established strategy for reducing the potential for intravenous misuse. Naloxone is a well-known opioid antagonist. As a mono-substance it is indicated for the treatment of opioid-overdosage or –intoxication. When administered in usual doses to patients who have not recently received opioids, naloxone exerts little or no pharmacologic effect. In patients who have received large doses of opioids, naloxone antagonises most of the effects of the opioid. The addition of naloxone to buprenorphine is intended to render the product less abusable by deterring intravenous injection.

2. Quality aspects

Introduction

Suboxone is presented as sublingual tablets containing a fixed dose combination of buprenorphine hydrochloride and naloxone hydrochloride dihydrate, at a ratio of 4:1, with respect to the free bases. Suboxone is available in two strengths:

- 2 mg / 0.5 mg tablets containing 2.16 mg buprenorphine hydrochloride (equivalent to 2 mg buprenorphine base) and 0.61 mg naloxone hydrochloride dihydrate (equivalent to 0.5 mg naloxone base).

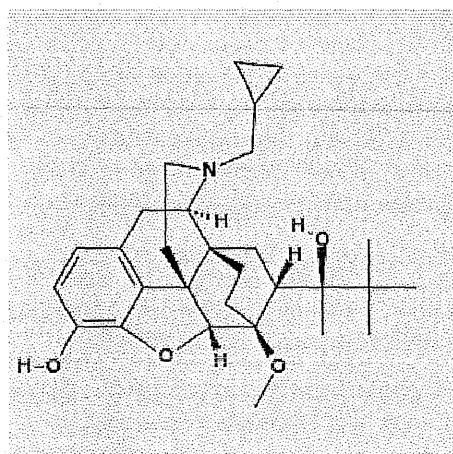
- 8 mg / 2 mg containing 8.64 mg buprenorphine hydrochloride (equivalent to 8 mg buprenorphine base) and 2.44 mg naloxone hydrochloride dihydrate (equivalent to 2 mg naloxone base).

The excipients used in this formulation are lactose monohydrate, mannitol, maize starch, povidone K30, citric acid anhydrous granular, sodium citrate, natural lemon and lime flavour, acesulfame potassium and magnesium stearate. Suboxone is administered via the sublingual route and is packed in nylon/aluminium/PVC blister packs containing either 7 or 28 tablets.

Active Substance 1. (Buprenorphine hydrochloride)

Buprenorphine hydrochloride is an established active substance and the subject of a monograph in the Ph. Eur.

Buprenorphine hydrochloride is designated chemically as (2S)-2-[17-Cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-6-methoxy-6 α ,14-ethano-14 α -morphinan-7 α -yl]-3,3-dimethylbutan-2-ol hydrochloride and its chemical structure is as follows:



Buprenorphine hydrochloride is a white or almost white, crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, practically insoluble in cyclohexane.

Buprenorphine has several chiral centres and it is therefore optically active.

The potential for polymorphism was investigated using powder X-Ray diffraction and Differential Scanning Calorimetry (DSC) techniques. The results showed that there is no evidence for polymorphism.

• Manufacture

Buprenorphine hydrochloride is synthesized from thebaine. The structure has been confirmed by elemental analysis, spectroscopic analysis (UV, IR, NMR and MS) and X-Ray crystallography. The stereochemistry of the intermediates and the final active substance was investigated using X-ray crystallography and NMR spectroscopy. The absolute configuration was confirmed at different stages during the synthesis.

• Specification

The specification of the active substance includes physical description, visual inspection of the appearance in solution, assay by titration and by HPLC, specific optical rotation, acidity or alkalinity and related substances (HPLC). Additional tests performed are as follows: control for water content using the Karl Fisher method and residue on ignition, residual solvent, ionic chloride and particle size.

The analytical methods used were those described in the PhEur. Monograph, one major exception being the determination of related substances. The HPLC method for determination of related impurities uses specific impurity markers. It allows detection and quantitation of the five major impurities specified, whereas using the method described in the Ph. Eur. only two of the impurities can be detected. In addition, the acceptance criteria set for each specified impurity is more stringent than the limits mentioned in Ph. Eur. monograph. The maximum limit for total related impurities is also

more stringent than that mentioned in the current Ph. Eur. Monograph. All analytical methods have been validated according to the ICH guideline on "Validation of Analytical methods".

Batch analysis data was provided for 23 batches of buprenorphine hydrochloride manufactured following the proposed synthetic method. The results showed that the active substance can be reproducibly manufactured.

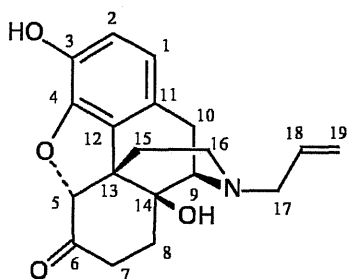
- **Stability**

The stability of buprenorphine hydrochloride was investigated in 3-production scale batches stored in the proposed packaging according to the ICH guideline. Stability studies were performed under long term and intermediate ICH conditions for 156 weeks, and accelerated ICH conditions for 52 weeks. An additional study was performed using a larger scale production batch. In this study the stability studies were performed under long-term and intermediate conditions for 52 weeks and accelerated conditions for 39 weeks. The results obtained demonstrate that buprenorphine hydrochloride remains physically and chemically stable for 52 week at long-term and intermediate conditions and 26 weeks at accelerated conditions.

The data provided is sufficient to confirm the proposed re-test period.

Active Substance 2. (Naloxone hydrochloride dihydrate)

Naloxone hydrochloride dihydrate is an established active substance and the subject of a monograph in the Ph. Eur. Naloxone hydrochloride dihydrate is designated chemically as Morphinan-6-one, 4,5-epoxy-3, 14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5 α)-dihydrate. Its chemical structure is as follows:



Naloxone hydrochloride dihydrate is a white or almost white crystalline powder, hygroscopic, soluble in water and alcohol, practically insoluble in ether. The pKa of Naloxone hydrochloride dihydrate is 7.94 at 20°C and the melting point is 200-205°C.

- **Manufacture**

Naloxone hydrochloride is synthesised from noroxymorphone. The assigned structure of naloxone hydrochloride dihydrate is supported by the evidence of IR spectrophotometry, and by ¹H-NMR and ¹³C-NMR spectrometry.

Naloxone hydrochloride dihydrate contains four chiral centres, all of which are already present in the starting material of the synthesis, noroxymorphone, which is derived from natural opiates.

The possibility of polymorphism was investigated by standard techniques. The results showed that all batches exhibited the same morphic form.

- **Specification**

Naloxone hydrochloride dihydrate is tested for compliance with both PhEur. and USP monographs by the active substance manufacturer. These tests include physical description, identification by IR, TLC and chloride, specific optical rotation, loss on drying, Noroxymorphone hydrochloride and other impurities by TLC, chloride content, appearance of solution, acidity or alkalinity, related substances by HPLC, water content, sulphated ash and assay by titration. The specification also includes some additional non-pharmacopoeial tests (a stability-indicating HPLC method for assay and related

substances, UV identification, sieve analysis and the melting range of naloxone base). The stability-indicating HPLC assay has been fully validated and was shown to have satisfactory linearity, precision, accuracy and ruggedness. The peak area of naloxone decreases and degradation products are observed in samples exposed to stress conditions, confirming that the assay is stability-indicating.

Five batches of naloxone hydrochloride were manufactured using the proposed synthetic method. The results indicate that every batch complied with the limits for related substances.

- **Stability**

The stability of naloxone hydrochloride was investigated in 12 batches stored in the proposed packaging according to the ICH guideline. Stability studies were performed under long term, intermediate and accelerated ICH conditions for up to 60 months. No marked evidence of instability was revealed under any of the storage conditions and the proposed re-test period appears to be justified on the basis of the stability data presented.

Medicinal Product

- **Pharmaceutical Development**

Suboxone was developed in order to deliver a similar dose of buprenorphine compared to buprenorphine alone tablets (medicinal product containing buprenorphine that is authorised in the EU for the treatment of opioid addiction), but reducing the potential for intravenous abuse. Naloxone, an opiate antagonist, has poor bioavailability when administered by the sublingual route and consequently when Suboxone is taken sublingually it shows only the required effects of buprenorphine and delivers the same performance as an equivalent dose of buprenorphine alone tablets. However, if abused intravenously by an opiate-dependent subject, the antagonist effects of naloxone become apparent first as intense withdrawal symptoms followed by the attenuated agonist effects of buprenorphine.

Therefore the Suboxone formulation is closely based on the formulation of buprenorphine alone sublingual tablets but with naloxone added to reduce the potential for abuse by the intravenous route. A buprenorphine to naloxone ratio of 4:1 contains sufficient naloxone to produce opiate antagonist effects following intra-venous administration, but does not impair the effectiveness of buprenorphine when the mixture is taken by the sublingual route.

The excipients used in Suboxone are qualitatively and quantitatively identical to those used in the existing buprenorphine alone sublingual tablets, i.e., lactose monohydrate, mannitol, maize starch, povidone K30, citric acid anhydrous, sodium citrate and magnesium stearate. Acesulfame potassium and natural lemon and lime flavour (sweetener and flavouring agents, respectively) were included to disguise the bitter taste of naloxone. The content of lactose monohydrate was reduced slightly in order to maintain identical compression weights. All excipients have been widely used in commercial pharmaceutical dosage forms or as food additives. Except for the natural lemon and lime flavour all excipients comply with the specification of the Ph. Eur. Natural lemon and lime flavour is a natural flavouring, which complies the requirements of directive 88/388/EEC (as amended) on flavourings for use in food. Certificates of analysis have been provided for all excipients.

- **Adventitious Agents**

Lactose monohydrate is the only excipient of animal origin. However, it is prepared from bovine milk suitable for human consumption, which is sourced from healthy animals. Magnesium stearate is of vegetable origin.

- **Manufacture of the Product**

The manufacturing process of the finished product comprises standard mixing, wet granulation and compression techniques. Process parameter ranges (sieve sizes, mixing times and speed, drying time and temperature) were described for each step of the manufacturing process. Validation studies involved the preparation of 3 full-scale batches of the tablet blend. Each of the batches was then subdivided into two sub-lots for the preparation of tablets of both strengths, i.e., 2 mg/0.5 mg tablets and 8 mg/2 mg tablets. An additional full-scale batch of each tablet strength was manufactured. All eight batches complied with final product specification. From the evidence of the process validation studies

provided, it can be concluded that the process is capable of consistently producing batches of the required quality.

- **Product Specification**

The product specifications include methods for appearance, identification (buprenorphine and naloxone) by HPLC and TLC, assay and content uniformity (buprenorphine and naloxone) by HPLC, dissolution of buprenorphine and dissolution of naloxone, disintegration time, buprenorphine degradation products, naloxone degradation products, water content and microbiological integrity.

The drug product specifications have been justified and all methods of analysis have been described and adequately validated.

- **Stability of the Product**

Stability data on three batches of each strength of Suboxone sublingual tablets (8 mg / 2 mg and 2 mg / 0.5 mg) packaged under a nitrogen atmosphere was provided. The studies were performed under long-term, intermediate, and accelerated conditions. The parameters evaluated during these studies were those mentioned in the shelf-life specification, except for two minor deviations. Analytical results up to 156 weeks were presented. All tests remained within specification for 156 weeks at 25°C/60% RH. The key shelf-life limiting parameter appeared to be disintegration time. There is evidence of a time-dependent increase but all samples stored at complied with the specification for 156 weeks.

Based on the available stability data, the proposed shelf life and storage conditions, as stated in the SPC, are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substances and drug product has been presented in a satisfactory manner. The results of test carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

3. Non-clinical aspects

- **Introduction**

Most of the preclinical studies were conducted in accordance with good laboratory practice regulations. Some studies have been performed prior to the introduction of GLP regulation and are not GLP-compliant. Since both of the active ingredients are established substances the documentation for pharmacology consists of published literature plus study reports with the combination of the active ingredients.

- **Pharmacology**

Buprenorphine is a semisynthetic, highly lipophilic opioid derived from thebaine with a 25 -30 fold higher analgesic potency as compared to morphine and a longer lasting effect. It is a partial agonist at the μ - and an antagonist at the κ -opioid receptor subtype. It dissociates very slowly from opioid receptors ($t_{1/2}$ 166 min vs. 7 min for fentanyl) and is, once bound, hardly displaced by naloxone, however, prior treatment with naloxone can prevent e.g. respiratory depression. It is able to substitute for other opioids such as heroin but provides only moderate opiate agonist effects and a low degree of physical dependence. Being a partial μ -receptor agonist it may cause symptoms of abstinence in patients treated with μ -receptor agonists (e.g. morphine) and restricts its own analgesic effects once a maximum is reached, resulting in a bell-shaped dose response curve. When treatment with buprenorphine is discontinued withdrawal signs are generally mild due to slow dissociation from the μ -receptor and concomitant adaptive processes.

Naloxone is the N-allyl derivative of oxymorphone. It has antagonistic effects at μ , δ - and κ -opioid receptors and is currently marketed in injectable form for the complete or partial reversal of opiate effects or for the suspected acute opiate overdose. When given alone, hardly any effect is observed

hinting at a low endogenous opioidergic tone. Because of its almost complete first pass metabolism, naloxone administered orally or sublingually is not expected to exert antagonistic activity. No documents dealing with the pharmacodynamics of naloxone were submitted.

Receptor Binding:

In the review presented in association with this application the receptor binding affinities of buprenorphine and naloxone for narcotic receptors are outlined in the following table.

Table: *In vitro* receptor-binding affinities for Buprenorphine and Naloxone.

Drug	K _i (nM)				
	Mu (μ)	Delta (δ)	Kappa (κ)	Sigma (σ)	Ratio (σ/κ)
Buprenorphine	0.77	2.2	1.1	>100000	>91000
Naloxone	1.2	19	12	>1000000	>83000

- Primary pharmacodynamics

In vivo studies have been carried out in order to examine the interaction of both substances as regards effects (antinociception), precipitation of withdrawal in morphine dependent rats, drug discrimination in rats and avoidance behaviour in monkeys.

Antinociceptive effects of buprenorphine and morphine given alone or in combination with naloxone (subcutaneous route) were measured in the rat tail pressure test: the results provided some evidence that buprenorphine is antagonised by naloxone, although less readily than morphine.

Buprenorphine and naloxone administered intraperitoneally to precipitate withdrawal signs in morphine-dependent rats suggest that buprenorphine did not affect the ability of naloxone to precipitate signs of opiate withdrawal.

To test whether buprenorphine plus naloxone mixtures are still perceived like buprenorphine alone, a drug discrimination study was performed. Male rats with about 300 g b.w. were trained to discriminate between subcutaneous (s.c.) injection of buprenorphine 0.03 mg/kg in an operant chamber with two levers, where repeated pressure of the correct lever (10x) resulted in the delivery of a food pellet. 30 min after application the pattern of lever pressing was recorded. No food reward was given during generalisation trials. Generalisation was considered to have occurred, if the percent responding on the relevant lever was 70 % or more. Responding to the buprenorphine-appropriate lever was 97 % following buprenorphine, 2 % following saline and 8 % following naloxone. Addition of naloxone 0.002, 0.01 and 0.02 mg/kg to buprenorphine resulted in 93 %, 59 % and 23 % buprenorphine lever pressing, respectively. It is concluded that buprenorphine combined with naloxone in a ratio 3:2 is not probable to be a narcotic cue to support opiate misuse.

Negative reinforcing properties of naloxone were studied in the non-dependent rhesus monkey: scheduled infusions of naloxone (1-100 μg/kg/inf.) and of buprenorphine (250 μg/kg/inf.) generated drug avoidance behavior in the non-dependent rhesus monkey under a continuous avoidance-escape paradigm. Pentazocine (1-100 μg/kg/inf.) codeine, (1-100 μg/kg/inf.) and tilidine (1-250 μg/kg/inf.) were ineffective. Addition of varying doses of naloxone to scheduled infusions of codeine, tilidine, and pentazocine generated avoidance behavior not present with scheduled infusions of these opioids alone. The naloxone doses necessary for generation of avoidance behavior were low with the agonists codeine and tilidine, higher with the weak antagonist pentazocine, and highest with the strong antagonist buprenorphine.

Monkeys were trained to avoid conditioned noxious stimuli. Subsequently, avoidance behaviour was extinguished and scheduled intravenous infusions of drugs were tested for their ability to re-introduce avoidance behaviour. Comparable to nalorphine, the opioid antagonist naloxone exerted negative reinforcing properties. The agonists codeine and tilidine had no effects on the behaviour of their own, as had the mixed agonist/antagonist pentazocine, while buprenorphine had a weak negative reinforcing effect only in the highest dose tested. Naloxone was added to equi-analgesic doses of the test compounds. Low doses were needed to induce negative reinforcement in the presence of codeine and tilidine, somewhat higher doses in the presence of pentazocine and high doses in the presence of buprenorphine.

Overall, where interaction between buprenorphine and naloxone was shown, the routes of administration used in the pharmacology studies may have limited relevance to the proposed clinical route of administration (sublingual) and the ratios chosen in these studies (3:1) do not reflect the proposed clinical ratio of 4:1. Thus 'proof of principle' that co-administration of naloxone will prevent intravenous misuse of buprenorphine has further to be derived from clinical studies and clinical evidence.

Buprenorphine and norbuprenorphine did not displace peripheral [^3H]PK 11195 binding and central [^3H]flunitrazepam binding, indicating lack of interaction with the GABA_A-receptors.

Diazepam and flunitrazepam have no significant affinity to human μ - and δ - opioid receptors and poor affinity to human κ -opioid receptors.

- **Secondary pharmacodynamics**

In order to look for blood compatibility (protein precipitating and haemolytic effects) of the combination of buprenorphine and naloxone 3: 2, the powdered product was dissolved in 5 % aqueous glucose or was diluted from a pre-prepared solution and added to citrated blood withdrawn from beagle dogs. The slight haemolysis observed with therapeutic concentration is not likely to be of clinical significance in the case that intravenous abuse of the product should occur.

- **Safety pharmacology programme**

No new studies were submitted. Due to the well-known pharmacology of the single substances and since no adverse interactions between these substances are expected this procedure is acceptable.

- **Pharmacodynamic drug interactions**

No unexpected pharmacodynamic drug interactions have been identified.

Pharmacokinetics

Pharmacokinetics of both buprenorphine and naloxone are well known. Buprenorphine is sufficiently absorbed following sublingual administration and is eliminated with a long half-life. Naloxone has a low oral bioavailability and is rapidly eliminated when given parenterally.

In a preclinical study it is shown, that co-administration of buprenorphine and naloxone had little or no effect on their individual pharmacokinetic profiles following administration by i.v. or i.m or by oral dosing.

Table. Results of single dose pharmacokinetic studies in rats and dogs with ³H-buprenorphine and ³H-naloxone alone or in combination with non-radiolabelled naloxone or buprenorphine respectively.

S P E C I E S	R O U T E	³ H-Buprenorphine			³ H Buprenorphine + Naloxone			³ H-Naloxone			³ H-Naloxone + Buprenorphine		
		C _{max} Plasma ng/g	AUC _(0-8 hr) ng/g h	C _{max} Brain ng/ equiv	C _{max} Plasma ng/g	AUC _(0-8 hr) ng/g h	C _{max} Brain ng/ equiv	C _{max} Plasma ng/g	AUC _(0-8 hr) ng/g h	C _{max} Brain ng/ equiv	C _{max} Plasma ng/g	AUC _(0-8 hr) ng/g h	C _{max} Brain ng/ equiv
Rat	i.v.	1442	1799	4763	1306	1653	3626	761	726	2141	574	690	1736
	i.m.	892	2248	1051	839	1453	760	865	908	1756	833	760	1850
	p.o.	571	188	1456	915	243	1564	313	48	8518	134	26	5853
Dog			Auc _(0-24 hr) ng/g h			Auc _(0-24 hr) ng/g h			Auc _(0-24 hr) ng/g h			Auc _(0-24 hr) ng/g h	
	i.v.	788	65	*	739	67	*	349	18	*	357	20	*
			Auc _(0-96 hr) ng/g h			Auc _(0-96 hr) ng/g h			Auc _(0-96 hr) ng/g h			Auc _(0-96 hr) ng/g h	
	i.m.	103	68.5	*	129	64	*	258	26	*	258	25.5	*
	p.o.	ND	ND	*	ND	ND	*	ND	8	*	ND	5.5	*

The only clinically relevant pharmacokinetic interaction detected is confined to inhibitors of CYP3A resulting in enhanced bioavailability of buprenorphine. Based on these studies inhibitors of CYP 3A enzyme can potentially increase the hepatic toxicity of buprenorphine. Patients concomitantly administered inhibitors of CYP 3A should be closely monitored for markers of liver toxicity. This is reflected in the clinical pharmacokinetics and is taken into account in the SPC.

Toxicology

- Single dose toxicity

Extensive acute toxicity studies employing different routes of administration (i.v., s.c. i.m. and oral) are presented in which the toxicity of buprenorphine and naloxone are compared with the toxicity of mixtures of these components. These studies demonstrate that there is no synergistic enhancement of toxicity when buprenorphine and naloxone are co-administered.

- Repeat dose toxicity (with toxicokinetics)

Dietary toxicity studies of 28 days and 13 weeks duration in rats were conducted using buprenorphine: naloxone at a ratio of 4:1 in terms of the bases (i.e. the ratio intended for human use).

The dietary route was selected for repeated dose toxicity evaluation of Suboxone since this route was relevant to the proposed sublingual route of human exposure. In addition to data on the dietary toxicity of Suboxone in rats, data on the toxicity of development formulations containing ratios of buprenorphine and naloxone of 1:1 and 3:2 for periods of up to 28 days in both the rat and the dog by a variety of enteral and parenteral routes of administration are presented.

Clinical observations were aggressive behaviour and excessive grooming. An analgesic effect (prolonged time to tail flick) has been observed in females of the 2000 ppm group. Bodyweight was significant lower throughout the study for males only. Food consumption and food utilisation was decreased in males also. A treatment-related increase in adrenal weight adjusted for body weight was recorded for males receiving Suboxone. The adrenals were histologically normal and this apparent weight change was not considered to be of toxicological importance. No other organ weight changes were apparent that were considered to be related to treatment and no treatment-related abnormalities were observed at autopsy. Histological examination revealed an increased incidence and severity of mononuclear cell infiltration of the Harderian gland in females of all groups receiving Suboxone and in males receiving ≥500 ppm. However, as there is no known clinical effect of insult to the Harderian gland, the toxicological importance of these findings remains unclear. No toxicological relevant target

organ toxicity was apparent apart from weight changes of the liver and histological effects on the kidneys, probably adaptive effects due to the high doses administered.

Safety margins based on AUC were calculated based on human data from Clinical Study CR97/007:

Table 7 Rat : human buprenorphine ratios based on AUC (ng·h/ml)

Dietary concentration of Suboxone (ppm)	Buprenorphine dose (mg)			
	4	8	16	24
100	7.3	4.4	2.5	2.0
500	28.2	17.1	9.7	7.6
1500	73.6	44.7	25.4	20.0
2000	93.9	57.0	32.4	25.5

Table 8 Rat : human naloxone ratios based on AUC (ng·h/ml)

Dietary concentration of Suboxone (ppm)	Naloxone dose (mg)			
	1	2	4	6
100	NC	NC	NC	NC
500	15.1	8.5	5.0	4.4
1500	231.8	130.8	76.1	68.0
2000	244.5	137.9	80.3	71.7

NC = Not calculated. Plasma concentration less than LLOQ (0.5 ng/ml).

The toxicokinetic data obtained in rats following dietary administration of buprenorphine: naloxone at a ratio of 4:1 also suggests that both rats and dogs receiving development formulations of buprenorphine: naloxone at a ratio of 1:1 by the oral route would have received toxicologically significant exposures to both of the active ingredients.

No novel toxicological aspects rose from the studies with a mixture of buprenorphine/naloxone in comparison with knowledge about the compounds alone. Based on toxicokinetic data raised from the dietary study with Suboxone, an exposure of animals sufficiently above the maximum therapeutic dose in humans has been reached. Clinical signs reflected the pharmacodynamics of the active ingredients.

- Genotoxicity

Standard in vitro and in vivo genotoxicity tests with buprenorphine and naloxone were negative indicating that both compounds are devoid of genotoxic properties.

A 7-day dietary palatability study in rats, a subacute 28 day dietary toxicity study in rats and associated mutagenicity studies have also been completed in order to investigate the potential toxicity and genotoxicity of synthesis impurities and degradants of Suboxone.

Synthesis impurity D (7,8-didehydronaloxone) present in naloxone was found clastogenic in vitro studies with human lymphocytes. The proposed specification limit of 7,8-didehydronaloxone will result in exposure below the Threshold of Toxicological Concern (TTC) of 1.5 µg/day which is recommended for setting acceptable daily intake limits of genotoxic impurities by the EU Draft Guideline on the Limits of Genotoxic Impurities (CHMP/SWP/5199/02).

A series of other synthesis impurities and degradants was reviewed for structure-activity relationship and were reported to be devoid of structural alerts. However, the process used to determine alerting structures was not fully clear and needed further clarification. The applicant further provided sufficient information about the approaches used (in house and at FDA) in assessing structural alerts as part of

the toxicological qualification of impurities and degradants. The applied approach for qualifying the impurities/degradants is acceptable.

- **Carcinogenicity**

A 2-year dietary carcinogenicity study with Suboxone was conducted in rats at doses of 7, 30 and 120 mg/kg/day, with estimated exposure multiples of 3 to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m² basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups.

A dose-related reduction in the incidence of adenomas in the pars distalis (male and female rats) and a decreased incidence of mammary hyperplasia were also observed. The reduced incidence of these findings were below internal as well as historical controls. Similar findings had been reported for Buprenorphine alone but at a lower incidence.

The Applicant supplied a number of possible explanations for the discrepancy between Suboxone and Buprenorphine alone regarding Leydig cell adenoma formation and proposed a mechanism for tumour formation, the modification of GnRH release could result in downstream effects on sexual hormone levels due to interference at the opiate receptors this would be responsible for the induction of Leydig cell adenomas in male rats and the accompanying hyperplasia. However, the mechanistic hypothesis was not accompanied by hormonal determinations.

To further elucidate the mechanism of induction of the Leydig cell tumours, the Applicant was asked to provide acceptable historical control data on the same strain of rat and, information on sexual hormone levels and buprenorphine and buprenorphine/naloxone administration and/or conducting a new study.

After consideration of new made available published data, an additional study in rats to investigate the hormonal effects of Suboxone appeared not longer justified.

This issue is taken into account in section 5.3 of the SPC.

- **Reproduction Toxicity**

Suboxone was evaluated in a fertility and early embryonic development study in the rat with dietary admixture of the test substance. Toxicokinetic data were obtained concomitantly with the fertility study. Embryotoxicity studies of development formulations (buprenorphine:naloxone 1:1 for oral or 3:2 for intramuscular administration, in terms of bases) were conducted in rats and rabbits by both, oral and intramuscular application. Studies were conducted according to GLP. No study on prenatal and postnatal development was performed. However, the applicant appropriately discussed and evaluated different studies, which investigated effects of buprenorphine or naloxone on the prenatal and postnatal development in the ARD.

In the fertility study, suboxone induced toxicity in the parental generation at all dose groups. At dose levels of 100 ppm or greater an increase in the incidence of non-pregnant females was observed. High pre-implantation losses were noticed at doses of 500 ppm or greater.

No teratogenic effects of the development formulations of buprenorphine and naloxone were noted in the embryotoxicity studies in rats and rabbits. However, treatment of pregnant rats and rabbits caused maternal toxicity. Reduced body weight gain, reduced food consumption and adverse clinical signs were frequently observed. In the rat, dose-related increases in the number of resorptions and decreases in the number of live fetuses were noticed after oral application of 10 mg/kg/day or greater. After i.m. administration in the rat, high post-implantation-losses, and consequently a reduced number of fetuses occurred at 30 mg/kg/day. In the rabbit, two dams receiving the highest oral dose (40 mg/kg/day) aborted and one dam receiving the highest i.m. dose (30 mg/kg/day) showed a total resorption of litter.

Despite the availability of toxicokinetic data in the fertility study in the rat, as part of the total package of reproductive and developmental toxicity studies, the applicant failed to discuss NOAEL levels and did not calculate any exposure margins in relation to human exposure. In the answers the applicant identified NOAEL levels for reproductive and developmental toxicity. Exposure margins were

calculated in an adequate manner. As far as toxicokinetic data were available, exposure margins were based on AUC otherwise exposure multiples were based on mg/m² comparisons. The calculated exposure margins replaced the mg/kg –details in section 5.3 of the SPC.

- **Local tolerance**

No specific local tolerance studies were conducted with Suboxone in animal models. The intended human sublingual route is not a practical route of administration in common laboratory animal species. Extensive data from human clinical trials indicate that Suboxone is well tolerated when administered by the sublingual route in man.

- **Other toxicity studies**

N.A.

Ecotoxicity/environmental risk assessment

The predicted environmental concentration (PEC) calculation initially provided by the applicant was incorrect.

The applicant has not provided an environmental risk assessment according to Phase II of the guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00). This would have been necessary because the concentration in the aquatic environment predicted according to Phase I of the guideline exceeds the trigger of 10 ng/l.

As the marketing authorization procedure for Suboxone started in October 2005, before the publication of the adopted guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00), it would be accepted an environmental risk assessment according to the draft of the guideline published in January 2005.

According to the draft of 2005 the trigger of 10 ng/l is exceeded and a phase II environmental risk assessment following this draft would be necessary.

In his response to the Day 180 LoOI, the applicant uses the guideline adopted in June 2006 for the environmental risk assessment of Suboxone. The default F_{pen} for the calculation of the predicted environmental concentration in surface water in Phase I of the guideline is 1 %. It is possible to refine the factor based on reasonably justified published data. The PEC-refinement based on published UN data on the prevalence of the abuse of opiates is agreed. However, the further refinement of F_{pen} conducted by the applicant is not acceptable. No valid data have been presented to justify the refinement based on market share and according to the guideline; the maximum daily dose is used for PEC-calculations in Phase I for all products. Using the F_{pen} of 0.43 %, the trigger of 10 ng/l is still exceeded. Therefore, a phase II environmental risk assessment is required. Besides that, the guideline of 2006 demands a Phase I pbt assessment for substances with a log K_{ow} >4.5 like Buprenorphine. This has been taken into account in the FUM, non- clinical.

Discussion on the non-clinical aspects

Where suboxone has been developed for long-term use in humans, the duration of repeated dose toxicity studies with the combination of the active ingredients does not meet the criteria of current guidelines.

However, taking into account that both sufficient chronic toxicity studies with buprenorphine alone, and data about naloxone from a 6- month repeated dose combination study with tilidine/naloxone are available, the non clinical programme on repeated dose toxicity is considered sufficient for the combination of the two substances which are established in clinical use.

4. Clinical aspects

Introduction

This is an application for a fixed combination. The new product is containing known active substances not used previously in combination (Article 10.1.(b)).

The Note for Guidance on fixed combination medicinal products describes some general rules for fixed combinations. Each substance of the fixed combination must have documented contribution within the combination and it will be necessary to show therapeutic advantages of the combination in the clinical situation against possible disadvantages. A simplification of therapy as the only justification will be acceptable in particular situations only.

The applicant justifies the development of Suboxone with the objective of having a similar sublingual effectiveness and safety profile as buprenorphine tablets, but with a lower intravenous misuse potential. From a regulatory point of view and after application of the Note for Guidance on fixed combination medicinal products the reduction of misuse potential is not a convincing justification for the application of a fixed combination with buprenorphine and naloxone.

However, in clinical view the advantages result, that on the one hand the medicinal product is not practical for misuse and on the other hand could be made available as take home medication. This fact contributes to a higher acceptance of the substitution therapy.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics

Suboxone is a fixed dose combination tablet of buprenorphine and naloxone in a 4:1 ratio. Most of pharmacokinetic studies of Suboxone and buprenorphine (as a reference) were undertaken in volunteers experienced in opiate use but not dependent on opiates.

The sublingual bioavailability of buprenorphine and naloxone from Suboxone was examined in five studies. In all studies a LC/MS/MS analysis was used for the determination of buprenorphine, norbuprenorphine and naloxone in human plasma and urine samples.

Pharmacokinetic parameters of buprenorphine and naloxone were determined from plasma concentration-time profiles. Statistical analyses were performed using the SAS Statistical analysis system program to compare treatments by analysis of variance (ANOVA).

- Absorption

The CR97/07 study was an open-label, dose-ascending, four-way crossover study to evaluate the pharmacokinetics and dose proportionality of buprenorphine, in the range of 4 to 24mg, when administered in sublingual tablets in combination with naloxone (at 4:1 dose ratio) in non-dependent opiate users.

The data from the analysis of 14 subjects indicated that both buprenorphine and naloxone were quickly absorbed following sublingual administration of the combination tablet of buprenorphine and naloxone. Mean peak plasma levels of buprenorphine (C_{max} 2.33, 3.53, 5.83 and 6.44 ng/ml) and naloxone (0.12, 0.25, 0.44 and 0.47 ng/ml) increased following 4 mg + 1 mg, 8 mg + 2 mg, 16 mg + 4 mg and 24 mg + 6 mg sublingual doses of Suboxone. Mean AUC_{0-t} values of buprenorphine (13.09, 23.23, 39.38 and 47.55 h.ng/ml) and naloxone (0.12, 0.30, 0.53 and 0.60 h.ng/ml) also increased with the sublingual dose of Suboxone. The mean elimination half-life of buprenorphine following sublingual dosing was 34 (14-116, N=53) hours, and that for naloxone was 1.24 (0.33-3.14, N=48) hours. Although linear, the increases in buprenorphine AUC were not proportional to the dose. There was a wide inter-patient variability in the sublingual absorption of buprenorphine.

The study results demonstrate a non-dose proportional increase of buprenorphine AUC.

Study CR96/023 had two objectives: to assess the relative and absolute bioavailability of a buprenorphine (8mg) and naloxone (2 mg) tablet when administered orally and sublingually, and to evaluate the subjective and physiologic effects of orally and sublingually administered buprenorphine and naloxone tablets. The study was an open label, balanced 3x3 Latin square crossover design. Results showed that absolute bioavailability of buprenorphine from the sublingually administered tablet was significantly greater than the bioavailability from the tablet administered orally (13.6 +/- 6.6 % compared to 6.0 +/- 4.1%). Naloxone was approximately 3% bioavailable sublingually while its bioavailability from the tablet taken orally was practically zero. Therefore, the AUC data indicate that sublingual administration yields 2.5 times more buprenorphine than oral and the bioavailability of naloxone after sublingual or oral administration is very low.

Study NIDA #01-1 was conducted to compare simultaneous administration of 4 tablets comprising a 20mg Suboxone dose (2 x 2 mg tablets plus 2 x 8 mg) with sequential administration of 2 x 8 mg tablets followed later by 2 x 2 mg tablets, after the first tablets had disintegrated. These were considered as supportive data. No absorption differences were observed between simultaneous or sequential administration of 4 Suboxone tablets.

Study CR96/012 was an open-label, single dose, four-period, dose-escalation study to evaluate whether plasma concentrations of buprenorphine increase proportionally to buprenorphine dose in the range of 4 to 24 mg administered as Buprenorphine alone sublingual tablets, and to evaluate the safety, and dose-response of subjective and physiological effects of buprenorphine. The study comprised four 3-day treatment periods separated by a washout period of at least ten days.

Examination of individual patient dose-response curves following 4 mg, 8 mg, 16 mg and 24 mg Buprenorphine alone showed that mean values of buprenorphine C_{max} were 1.99, 2.65, 4.42, and 5.41 ng/ml. Mean AUC_{0-72h} values were 9.37, 19.92, 34.94 and 48.81 h.ng/ml from the lowest to highest dose level respectively. Although linear, the increases in AUC were not proportional to the dose. There was a wide inter-patient variability in the sublingual absorption of buprenorphine.

In accordance with the above mentioned Suboxone study (CR97/07) the study results of CR96/012 demonstrate a non dose proportional pharmacokinetic of buprenorphine after administration of Buprenorphine alone. AUC, t_{max}, and C_{max} are comparable regarding different dose strengths in both studies. These results support the assumption that buprenorphine bioavailability is not influenced by sublingual administration of naloxone.

Study CR92/111 was designed to assess the treatment potential of sublingual buprenorphine (8mg) and naloxone (4mg and 8mg) combinations in subjects maintained on 8mg sublingual buprenorphine for 7 days. This was a double blind, double-placebo, 3x3 Latin square, within-subject study in which subjects were stabilised on 8mg buprenorphine sublingual solution and then challenged sublingually with three ratios of buprenorphine / naloxone.

The absolute bioavailability of 8 mg sublingual buprenorphine when given alone or in combination with 4 mg or 8 mg of naloxone was 42 ± 9%, 42 ± 12% and 40 ± 7%, respectively. The absolute bioavailability of 4 mg and 8 mg sublingual naloxone was 9 ± 6% and 7 ± 4% respectively. The mean elimination half-life of buprenorphine following intravenous dosing was 32 (16-55) hours, and that for naloxone was 1.0 (0.63-1.94) hours. The absolute bioavailability of buprenorphine was not influenced by simultaneous administration of naloxone, both given as sublingual solution. Therefore the bioavailability of buprenorphine in Buprenorphine alone or Suboxone is comparable and is not influenced by the presence of naloxone.

- **Bioequivalence**

The proof of bioequivalence for Buprenorphine in Suboxone and Buprenorphine alone was based on a crossover study (CR95/001). According to results analysis, bioequivalence in the sense of statistical significance could not be established. In fact, knowing that intra- and interindividual variability is high the planned number of subjects was too low and T-last interval at 48 hours was also too short. Then an extrapolation of AUC data is not recommended.

However, in connection with the data of the above mentioned bioavailability studies it can be concluded that the bioavailability of buprenorphine in Buprenorphine alone or Suboxone is comparable and is not influenced by the presence of naloxone.

Because of sublingual administration of Suboxone no additional studies were conducted regarding influence of food. This is acceptable.

- **Distribution**

Buprenorphine

Following sublingual absorption of buprenorphine, there is a rapid distribution phase. Buprenorphine is widely distributed within the body. The mean volume of distribution obtained following intravenous administration was 2,828 litres. Buprenorphine is also highly protein bound (96%), primarily to alpha and beta globulins. The long terminal elimination phase may be due in part to reappearance of buprenorphine from deep compartments, and in part due to enterohepatic cycling of the buprenorphine glucuronide metabolite.

Naloxone

In contrast, following sublingual administration, naloxone is rapidly eliminated (median terminal half-life 1.26 hours, 54 values). The mean (range) volume of distribution of naloxone following intravenous administration was 370 (133-770) litres, which agrees with the value of 375 (151-619) litres found by Aitkenhead et al (1984). Naloxone is 45% protein bound, primarily to albumin.

- **Metabolism and elimination**

Following sublingual administration of buprenorphine there is a very long terminal elimination phase: the median terminal half-life values of buprenorphine following Suboxone (27.41 from 113 values) and Buprenorphine alone (27.09 from 182 values) were similar (Table below). Naloxone is rapidly eliminated.

Table: Terminal elimination half-life values for buprenorphine and naloxone

	Suboxone	Buprenorphine alone	Suboxone
	Buprenorphine Half-Life	Buprenorphine Half-Life	Naloxone Half-Life
	All data (4 studies)	All data (3 studies)	All data (2 studies)
N	113	182	54
Mean	32.49h	28.67h	1.22h
SD	19.98	11.27	0.63
Median	27.41h	27.09h	1.26h
Min	8.98h	2.7h	0.33h
Max	161.16h	69.3h	3.14h

Buprenorphine

The metabolism of buprenorphine in humans is by 14-N-dealkylation and by conjugation of parent drug and the N-dealkyl metabolite, norbuprenorphine, to glucuronides. The principal route of excretion is via the faeces. This was demonstrated in a study in 6 subjects dosed intravenously with 3H-buprenorphine (CR94/006). Radioactivity was completely recovered over a 9-day period, 69% $\pm$ 11% in the faeces and 30% $\pm$ 7% in the urine. Most of the radioactivity was attributed to free and conjugated buprenorphine and norbuprenorphine. Two unidentified minor metabolites in urine accounted for 0.72% and 0.9% of the dose, respectively.

Naloxone

Two metabolites of naloxone, identified after hydrolysis and extraction of urine were 7,8-dihydro-14-hydroxy-normorphinone and N-allyl-7,8-dihydro-14-hydroxy-normorphinone (Weinstein et al, 1974). These results indicate that N-dealkylation, reduction of the 6-oxo group and glucuronidation occurs in man. The mean elimination half-life of naloxone following single sublingual doses of Suboxone was found to be 1.26 hours (54 values).

It can be concluded that the metabolism of buprenorphine is not influenced by the simultaneous administration of naloxone.

- Dose proportionality and time dependencies

The results of CR97/07 und CR96/12 regarding dose proportionality are presented above: dose proportionality could not be established. This is in accordance with the results of Buprenorphine alone studies.

As mentioned above additional multiple dose studies with Suboxone were not conducted. The kinetic data of the long term study CR96/014 demonstrate that accumulation will not occur. This is in accordance with Buprenorphine alone data.

- Special populations

Kinetic data of the target population was determined in study CR96/014 only. Different results between the target population and subjects in the short-term pharmacokinetic studies (subjects experienced in opiate use but not dependent) are not expected.

Renal elimination plays a relatively small role (less than 30% after IV administration) in the overall clearance of buprenorphine. No difference was observed in the pharmacokinetics of intravenous buprenorphine in nine subjects with end-stage renal failure compared with control subjects with normal renal function. However, plasma concentrations of the two inactive metabolites, norbuprenorphine and buprenorphine-3-glucuronide, were increased by 4 and 15 times, respectively in subjects with renal failure. No dose modification based on renal function is required. Based on the fact that the effects have been studied only under short-term dosing of buprenorphine, it is accepted to mention a precaution for use in subjects with severe renal impairment in the SPC.

Impaired hepatic function: buprenorphine is metabolised by both oxidation and glucuronidation and most of the elimination is biliary. The clearance of buprenorphine approaches hepatic blood flow. Population pharmacokinetic analysis indicated that clearance was reduced in subjects who had elevated ALT or elevated bilirubin. Therefore, the actions of buprenorphine may be prolonged in subjects with impaired hepatic function.

Buprenorphine is contraindicated in patients with severe hepatic impairment. This is also stated in section 4.3 of the SPC.

Gender, race and weight: A population pharmacokinetic assessment was undertaken using buprenorphine plasma concentration data from the Suboxone study (CR96/013 + CR96/014) and three other studies (CR94/001, CR95/001, CR97/007). The analysis showed that the pharmacokinetics of buprenorphine are described by either a one- or two-compartment disposition model with first-order absorption and an absorption lag time. The clearance of buprenorphine (>60 litres/hour) approached hepatic blood flow. The one-compartment NONMEM model predicted that increasing age and increasing AST or ALT levels were associated with at least a 20% decrease in clearance rate relative to the population standard value. Similarly, in the two-compartment model, the clearance rate of buprenorphine appeared to decrease with increased bilirubin, increased ALT and female gender.

The influence of gender, ethnicity, age and weight on buprenorphine C_{max} and AUC values were examined in the meta-analysis of PK parameters from single dose studies of Suboxone and Buprenorphine alone. With the exception of 'race' in the model results for AUC(0-72) of buprenorphine following the dosing of "volunteers, naltrexone block" subjects with Buprenorphine alone, no analysis found a statistically significant effect of the four demographic variables of gender, race weight and age. The statistical significance of 'race' may have been due to the large imbalance between the numbers of Caucasians in the analysis group, compared with other races.

Elderly: No pharmacokinetic studies were designed to be conducted with Suboxone in the elderly populations.

Children: No pharmacokinetic studies were designed to be conducted with Suboxone in children.

The pharmacokinetics of special population was evaluated in the development program of Buprenorphine alone. The results can be carried forward to Suboxone. No difference was observed in the pharmacokinetics of buprenorphine in subjects with normal renal function. Even if the concentration of metabolites were increased the dose may not be adjusted in patients with renal impairment. However, the company decided to include a statement of precaution for use in subjects with severe renal impairment in the SPC.

Suboxone should be contraindicated in subjects with severe impaired hepatic function. The influence of gender, ethnicity and weight was also evaluated in the Suboxone pharmacokinetic trials. No additional warnings regarding special populations are necessary.

- **Pharmacokinetic interaction studies**

Cytochrome P450 specificity studies have shown that CYP3A4 is responsible for the metabolic conversion of buprenorphine to norbuprenorphine. Therefore, potent inhibitors of CYP3A4 (e.g., protease inhibitors like ritonavir, nelfinavir, or indinavir, or azole antifungals such as ketoconazole or itraconazole) have the potential to increase plasma concentrations of buprenorphine. Similarly, inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) have the potential to reduce buprenorphine plasma concentrations because of increased metabolism of buprenorphine to norbuprenorphine.

An interaction study of buprenorphine with ketoconazole, has been undertaken (P01242). Subjects received 8 mg, 12 mg, or 16 mg Buprenorphine alone per day for two weeks, and ketoconazole 400 mg/day was added for six days. Ketoconazole administration resulted in clinically significant, 2-fold increases in both C_{max} and AUC of buprenorphine after sublingual administration of Buprenorphine alone. The SPC contains statements in Section 4.4 'Special warnings and special precautions for use', and Section 4.5 'Interaction with other medicinal products and other forms of interaction' relating to this interaction.

Pharmacodynamics

The rationale for developing Suboxone for use in treating opioid dependency is that it should be similar in efficacy to buprenorphine alone when taken sublingually, but should produce opiate withdrawal effects if misused intravenously by an opioid-dependent subject. This rationale is grounded on the fact that sublingual bioavailability of naloxone is poor. Naloxone is not expected to exert any pharmacological effect after sublingual administration of Suboxone. Therefore, pharmacodynamic and pharmacokinetic studies were conducted using the parenteral route and/or sublingual route of administration to investigate whether Suboxone complies with this rationale

- **Mechanism of action**

Buprenorphine is a potent opioid analgesic. It acts as a partial agonist at the μ -opiate receptor with high affinity to this receptor type and as an antagonist at the κ -receptor. Agonistic effects at μ -opiate receptors lead to euphoria, sedation, constipation, analgesia and respiratory depression. However as a partial agonist, buprenorphine has maximal opioid effects lower than those of full agonists, providing a wider safety margin. The analgesic potency of buprenorphine is 25-50 times higher (on a weight by weight basis) than that of morphine. Buprenorphine has been widely used for two decades and has proved to be a strong analgesic in relieving moderate to severe acute and chronic pain.

Naloxone hydrochloride is a semisynthetic opioid antagonist. When administered in usual doses to patients who have not recently received opioids, naloxone exerts little or no pharmacologic effect. In patients who have received large doses of opioids, naloxone antagonises most of the effects of the opioid. Because the duration of action of naloxone is generally shorter than that of the opioid, the effects of the opioid may return as the effects of naloxone dissipates.

However, 0.4 mg of naloxone administered iv or sc will precipitate potentially severe withdrawal symptoms in patients physically dependent on opioids or pentazocine. The precise mechanism of

action of the opioid antagonist effects of naloxone is not known. Naloxone is thought to act as a competitive antagonist at μ , K or σ opioid receptors in the central nervous system.

- Primary and Secondary pharmacology

The following studies provide information about the acute effects of buprenorphine + naloxone combinations on physiological parameters, and were all conducted in opioid-dependent subjects. Different subgroups were evaluated: heroin dependent subjects; subjects stabilized with morphine; patients in controlled methadone programs.

CR93/005 Study (*Low Dose Buprenorphine and Naloxone Interactions in Opioid Dependent Volunteers*) was an inpatient, double blind, double-placebo, within subject, 4x4 Latin square study to evaluate the physiological and subjective effects of intravenous buprenorphine (0.4mg) and naloxone (0.4mg), alone and in combination, in opiate-dependent subjects. On four separate occasions, at least five days apart, subjects were randomly administered: 0.4mg buprenorphine + 0.4mg naloxone, 0.4mg buprenorphine + placebo, placebo + 0.4mg naloxone, and placebo.

The opiate agonist effects of 0.4mg intravenous buprenorphine in heroin dependent subjects, measured by subjective and objective assessment, were very mild, and had a similar agonist profile to placebo at this dose. None of the subjects indicated they would pay money for this buprenorphine dose. The combination formulation acted more like an opiate antagonist than an opiate agonist on all physiological and subjective variables examined; intravenous administration of 0.4mg buprenorphine + 0.4mg naloxone gave similar pharmacological effects to 0.4mg naloxone. All the heroin dependent subjects perceived both treatments as dysphoric and unpleasant.

CR93/004 Study (*Intravenous Buprenorphine and Naloxone Interactions in Opiate-Dependent Volunteers*) was a double blind, placebo controlled, crossover study to evaluate the physiological and subjective effects of intravenous buprenorphine (2mg) and naloxone (2mg) alone and in combination in opiate-dependent subjects. Intravenous buprenorphine at a dose of 2mg gave typical opiate agonist effects in the heroin dependent subjects. Significant increases were noted in subjective ratings of global intoxication, on the opiate agonist scale and visual analogue scales for 'high', 'drug liking' and 'good drug' effect. However, as judged by the subjects' spontaneous comments, intravenous buprenorphine did not produce the same intense, immediate effect as intravenous heroin.

Intravenous injection of 2mg buprenorphine + 2mg naloxone produced short-lived but intense opiate withdrawal which was indistinguishable from the effects of naloxone alone. The combination significantly attenuated subjects' rating of global intoxication, 'drug liking' and 'good drug'. Qualitatively, naloxone effects were attenuated by buprenorphine. However during the antagonist phase immediately following injection, the buprenorphine + naloxone combination was perceived to be as dysphoric and unpleasant as naloxone alone. Therefore the buprenorphine and naloxone combination has a low abuse potential in opiate-dependent daily heroin users.

CR94/003 Study (*Buprenorphine and Naloxone Interactions in Morphine-Stabilised Opiate-Dependent Volunteers*) was a double blind, placebo-controlled, partially balanced, cross-over study. Subjects were admitted to an inpatient unit and for the first five days were stabilised on a dose of 60mg morphine per day given as four intramuscular doses of 15mg. Opiate agonist effects were substantial and similar in magnitude following 15 mg intramuscular morphine and 2mg intravenous buprenorphine administration. Combining naloxone with buprenorphine attenuated some of the pleasurable opiate agonist effects seen with buprenorphine alone: the 2:1 ratio diminished all opiate agonist measures as compared to buprenorphine alone; the 4:1 and 8:1 ratios decreased global intoxication and opiate agonist scale indices, but did not alter 'drug liking'.

Each of the three intravenously administered buprenorphine + naloxone combinations had measurable short-term opiate antagonist effects. All measures of opiate withdrawal were significantly increased by the 2:1 and 4:1 ratio combinations compared with buprenorphine alone, whereas only self-reports of global withdrawal were significantly increased with the 8:1 ratio. Antagonist effects peaked at five minutes then dissipated allowing opiate agonist effects to emerge but in a dose-dependent manner with the longest duration of antagonism produced by the 2:1 ratio.

All combination ratios significantly diminished the subject's estimated street value of buprenorphine and were generally reported by subjects as unattractive as agents for intoxication. Subjects were asked to estimate the US dollar value they would pay for the challenge dose if it were sold illicitly. Five minutes after the intramuscular challenge, subjects rated 15mg morphine the highest (\$12), followed

by 2mg buprenorphine (\$8). In contrast, the 8:1, 4:1 and 2:1 ratios of buprenorphine/naloxone had markedly lower peak dollar values of \$2, \$2 and \$0. The dollar value of the placebo was \$1. Intravenous administration of 2:1 and 4:1 buprenorphine/naloxone combinations reliably produced brief opiate withdrawal symptoms and was judged sufficiently unpleasant by opiate-dependent individuals to suggest a relatively low parenteral abuse liability by people using opiates regularly. Based on observations from this study, a 4:1 ratio of buprenorphine to naloxone was chosen for Suboxone tablet formulation development.

Bupp 4243 Study (*Effects of Buprenorphine and Naloxone in Morphine-Stabilised Opioid Addicts*)

This was a double blind, placebo-controlled randomised five-period crossover (two 5 x 5 Latin square) study, designed to evaluate the individual and combined effects of intravenously administered buprenorphine and naloxone. This dosage was continued throughout the study. Over a 14-18 day period following stabilisation, subjects received single intravenous challenge doses of placebo, 15mg morphine, 2mg buprenorphine, 2mg buprenorphine + 0.5mg naloxone (4:1 ratio), and 0.5mg naloxone challenges in random order at 48h to 72h intervals. Morphine produced significant 'good' effects as assessed on the VAS-G scale whereas 2mg buprenorphine in these patients was not significantly different from placebo. Similarly the 2mg buprenorphine + 0.5mg naloxone combination was no different from placebo on this scale. On the agonist effects checklist none of the challenges was associated with typical opioid-like effects.

Both naloxone and buprenorphine + naloxone were associated with significant withdrawal effects compared to placebo as assessed by the CINA scale measured during the first 25min and 60min periods. The effects produced by the buprenorphine + naloxone combination were not significantly different from those produced by naloxone.

A combination of buprenorphine + naloxone in a 4:1 ratio produced significant intravenous opiate antagonist effects similar to those produced by naloxone. This should limit its potential for intravenous abuse by opioid addicts.

This study supports the results of study CR94/03 described above.

CR92/110 Study (*Buprenorphine and Naloxone Interactions in Methadone Maintained Subjects*) was a double blind, placebo-controlled, randomised 4x4 Latin square crossover study to evaluate the physiological and subjective effects of intravenous buprenorphine (0.2mg) and naloxone (0.1mg), alone and in combination in opiate-dependent subjects. Subjects were randomly challenged on four separate occasions at least one day apart with intravenously administered 0.2mg buprenorphine, 0.1mg naloxone, 0.2mg buprenorphine + 0.1mg naloxone and placebo. The subjects were physically dependent opiate users who had been receiving 40-60 mg daily methadone maintenance for at least three months. Intravenous buprenorphine at a dose of 0.2mg generally produced only minimal opiate agonist effects that were no different from placebo. This was not surprising since the subjects were maintained on moderate doses of methadone.

The combination of buprenorphine + naloxone produced withdrawal as great or greater than naloxone alone and resulted in one subject precipitously leaving the study. Similarly buprenorphine + naloxone and naloxone alone produced opiate antagonist effects on heart rate and systolic and diastolic blood pressure.

Therefore the combination of buprenorphine 0.2mg + naloxone 0.1mg has a low abuse liability in methadone maintained subjects as it produces significant withdrawal symptoms in methadone-stabilized subjects after intravenous low dose administration.

Bupp 5257 Study (Buprenorphine/naloxone Combination Tablet: effects in Opioid Dependent Volunteers) was undertaken to assess the subjective, objective and physiological effects of buprenorphine/naloxone combinations and buprenorphine in opioid-dependent volunteers. On separate occasions, subjects received 5 dose levels of Suboxone sublingual tablets (buprenorphine/naloxone: 1/0.25mg, 2/0.5mg, 4/1mg, 8/2mg, and 16/4mg), 8mg taste-matched buprenorphine tablet, intramuscular 4:1 buprenorphine / naloxone injections (1/0.25mg, 2/0.5mg, 4/1mg, 8/2mg, and 16/4mg), 8mg intramuscular buprenorphine, 10mg intramuscular hydromorphone, and 0.25mg intramuscular naloxone. Intramuscular administration of 4:1 combinations of buprenorphine + naloxone (1/0.25mg, 2/0.5mg, 4/1mg, 8/2mg and 16/4mg) to 8 subjects stabilised on 40mg oral hydromorphone per day produced dose-related antagonist responses for observer rating of withdrawal, and subjective 'bad effects'. Significant withdrawal effects were observed only for intramuscular buprenorphine/naloxone 16/4mg. In contrast, intramuscular buprenorphine gave only

opioid agonist effects. Sublingual buprenorphine/naloxone was well tolerated in the opioid dependent subjects and neither precipitated withdrawal nor showed opioid agonist effects. The study results demonstrate that different sublingual doses of the buprenorphine/naloxone 4:1 produce opioid agonistic effects only. The intramuscular administration causes antagonistic effects as expected.

Bupp 3712 Study (Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans) had the primary purpose to determine whether any physical dependence resulting from chronic buprenorphine maintenance could be demonstrated using a precipitated withdrawal procedure with naloxone or naltrexone. After a 2-week outpatient buprenorphine induction and stabilisation period subjects were admitted onto a closed 14-bed behavioural pharmacology research unit for approximately 6 weeks. Subjects received 2, and 4 mg buprenorphine sublingual solution on Days 1 and 2, and 8 mg/day for the rest of the two-week stabilisation period. In the experimental unit they were maintained on 8 mg/day given at 08:00h each day. On challenge days they were given one of the following at 10:00h, ordered by Latin square and presented double blind and double-dummy: placebo, naloxone 0.3, 1, 3 and 10 mg /70kg i.m. and naltrexone 0.3, 1 and 3 mg /70kg orally separated by a least 72 hours. Behavioural and physiologic responses were measured over the following 12 hours. After the final challenge session the buprenorphine dose was tapered to zero over 4 days and the subjects received placebo for a further 5 days.

Both naloxone and naltrexone produced orderly dose-related and time-related effects on multiple variables assessing withdrawal. Generally, intramuscular doses of 3mg produced withdrawal effects.

High doses of intramuscular naloxone produce withdrawal effects in subjects stabilized on buprenorphine. The dose was 10 times greater than doses that precipitate withdrawal in subjects maintained on 30mg methadone. The applicant came to the conclusion that the need for higher doses is consistent with the presence of only a low level of physical dependence in buprenorphine maintained subjects.

The observed effect could be explained by the high affinity of buprenorphine (higher than the affinity of naloxone) to μ -receptors. Therefore naloxone is not suitable for the treatment of buprenorphine intoxication.

Relationship between plasma concentration and effect

The efficacy in relation to plasma concentration was evaluated in the Buprenorphine alone studies. The effects were not influenced by simultaneous sublingual administration of naloxone in doses up to 32/8mg Suboxone.

Pharmacodynamic interactions with other medicinal products or substances

Pharmacodynamic interactions were not evaluated for the fixed combination. Post marketing information regarding pharmacodynamic interactions will be provided.

Overall conclusions on pharmacodynamics

The rationale for developing Suboxone for use in treating opioid dependency is that it should be similar in efficacy to buprenorphine alone when taken sublingually, but should produce opiate withdrawal effects if misused intravenously by an opioid-dependent subject.

The intravenous or intramuscular administration of buprenorphine/naloxone causes withdrawal effects in heroin dependent subjects, and also in morphine- or methadone- stabilized subjects. Sublingual administration of the buprenorphine/naloxone 4:1 combination produces opioid agonistic effects only. High doses of intramuscular naloxone produce withdrawal effects in subjects stabilized on buprenorphine. The dose was 10 times greater than doses that precipitate withdrawal in subjects maintained on 30mg methadone. The applicant came to the conclusion that the need for higher doses is consistent with the presence of only a low level of physical dependence in buprenorphine maintained subjects.

It can be concluded from the results of the pharmacodynamic studies that the intravenous misuse potential for Suboxone is very low in comparison with buprenorphine alone. The intravenous or

intramuscular administration produces withdrawal effects in all opiate dependent subjects. Sublingual or oral administration of naloxone in doses up to 8mg has no pharmacodynamic effects.

Clinical efficacy

This Section reviews the studies that show the efficacy of Suboxone for the clinical indication of “Substitution treatment for major opioid drug dependence, within a comprehensive therapeutic monitoring framework of medical, social and psychological treatment”. Of the fully reported trials, one was conducted with Suboxone (CR96/013+CR96/014), and one with Buprenorphine alone (CR96/013). Three 52-week studies of Suboxone provide evidence for the long-term effectiveness of Suboxone (CR96/013+CR96/014, NIDA #1018, US08). Three double blind pilot studies of Suboxone provided dose-finding information prior to commencing study CR96/013+CR96/014, or provide information about less than daily dosing of Suboxone (CR95/002, Bupp 4729, Bupp 5113).

The main Suboxone efficacy studies are CR96/013 and CR96/014. All the other studies presented in the table are pilot efficacy studies or long term studies in different settings. Of those only NIDA#1018 and US08 will be presented and discussed as supportive studies.

Study ID	Design	Study Posology	Subjs by arm entered/ compl.	Duration	Diagnosis Incl. criteria	Primary Endpoint
CR96/013	randomised, placebo-controlled, double blind, parallel group	sublingual buprenorphine/ naloxone 16/4mg or buprenorphine 16mg or placebo	109 Bupr/nalox 105 Bupr 109 Placebo	4 weeks	Opiate dependence seeking for substitution therapy	opiate craving illicit drug use
CR96/014	open label, subjects from study 96/013 and patients from 4 new centres	flexible with buprenorphine/ naloxone doses of up to 24/6mg	472	48-52 weeks	Opiate dependence seeking for substitution therapy	illicit drug use
NID A#1018	open label with no randomisation	Suboxone 8/2mg up to 24/6mg	582	9-52 weeks	Opiate dependence seeking for substitution therapy	illicit drug use
US08	multi center randomized open parallel group study	Suboxone up to 24/6mg	93 randomised 28 completed 52 weeks	12-52 weeks	Opiate dependence seeking for substitution therapy	illicit drug use
CR95/002	randomised double blind parallel group	Suboxone up to 16/4mg	25 only seven completed	up to 21 weeks	Opiate dependence	illicit drug use
Bupp 4729	double blind triple cross over	Suboxone up to 16/4mg	47 only 14 completed	37 days	Opiate dependence	illicit drug use
Bupp 5113	double blind triple cross over	Suboxone up to 24/6mg	46 enrolled only 13 completed	11 weeks	Opiate dependence	illicit drug use

- Dose response studies

See Clinical Pharmacodynamics.

- Main studies

CR96/013 (and CR96/014): Phase III Multicenter Efficacy/Safety Study of Suboxone for the Treatment of Opiate Dependence

METHODS

CR96/013 was a randomised, placebo controlled, double blind study intended to demonstrate the safety and efficacy of four weeks treatment with Suboxone sublingual tablets.

Matched Buprenorphine alone (mono buprenorphine) tablets were included as an active control and matched placebo tablets as a non-active control. The study was designed to compare each active buprenorphine treatment against placebo. The 4-week study was the first part of a larger safety study that offered continued open label treatment of Suboxone for up to a total of 52 weeks, including at-home use. All subjects who completed the efficacy phase (CR96/013) were offered continued treatment in the safety phase, and additional subjects were recruited directly into the safety study (CR96/014).

Study Participants

All participants were opiate-dependent and had used heroin for a median duration of 84 months and about half of them had previously been treated with methadone or LAAM while the others were naive to treatment. 64.7% were men and 35.3% were women; mean age was 37.6 years.

Treatments

A total of 451 subjects were screened from which 326 were randomised to treatment: 110 subjects to Suboxone 16/4mg, 106 to taste-matched Buprenorphine alone 16mg, and 110 to taste-matched placebo. Three subjects, one in each group were not dosed. Therefore the intent-to-treat efficacy sample comprised 323 subjects, 109 receiving Suboxone, 105 receiving Buprenorphine alone, and 109 receiving placebo tablets.

It was decided not to use Suboxone for induction but to use the taste-matched Buprenorphine alone tablets, with the objective of achieving a rapid attainment of the target 16mg dose of buprenorphine, without the complication of withdrawal symptoms, which might have occurred during induction. Placebo group patients were inducted with matching placebo tablets and remained on this study medication throughout the 4-week trial.

Objectives

The main objective of the study was to demonstrate the safety and efficacy of four weeks treatment with Suboxone sublingual tablets versus placebo in reducing opiates misuse.

Outcomes/endpoints

There were two primary efficacy parameters: the number of opiate negative urine samples provided by the subjects, and opiate craving score values. It was hypothesized that buprenorphine treatment with Suboxone or Buprenorphine alone tablets would give rise to an increased number of opiate negative urine samples and would reduce opiate craving scores.

Secondary outcomes: Subject's global impression of his/her own status was reported using a 100-point scale where a score of 50 represented 'no change' and a score of 100 represented 'much better'.

Clinicians provided global impressions of their subjects' status from the perspective of the entire 4-week study period and relative to the previous clinic visit using a similar scale.

Sample size

A target sample size of 128 subjects per treatment group was chosen based on power calculations for the two primary efficacy variables, urine tests negative for opiates and opiate craving score, taking into consideration a potential 33% attrition rate.

In order to detect a difference of 10% in urine tests negative for opiates between the buprenorphine and placebo groups, with a Type I error of 0.05 and a power of 0.90, 84 subjects per treatment group would be required.

A sample size of 86 subjects per group would be sufficient to detect a 10-point difference between treatment groups in opiate craving with a Type I error rate of 0.05 and a power of 0.80.

Randomisation

A total of 451 subjects were screened from which 326 were randomised to treatment: 110 subjects to Suboxone, 106 to taste-matched Buprenorphine alone, and 110 to taste-matched placebo. Three subjects, one in each group were not dosed. Therefore the intent-to-treat efficacy sample comprised 323 subjects, 109 receiving Suboxone, 105 receiving Buprenorphine alone, and 109 receiving placebo tablets.

Blinding (masking)

Blinding was accomplished by using identically appearing and tasting tablets for all three treatment groups. Flavour was added to placebo and buprenorphine tablets to match the flavour of the combination of buprenorphine/naloxone tablet.

Statistical methods

In the protocol, pairwise normal approximation to the binomial (Z-test) was the proposed statistical test for analyzing the percentage of urine samples negative for opiates. In fact, the distribution of the percentage of urine samples negative for opiates was analyzed with the two-way ANOVA model containing the fixed effects of center and treatment and included a center by treatment interaction. The least squares means of the treatment groups were compared in pairs. The 95% confidence interval for the difference between combination therapy and monotherapy was calculated. The two-way ANOVA model was adjusted for center effect. Since the distribution of the percentage of clean urine samples was severely skewed, the data were also analyzed with the Wilcoxon test to compare each pair of treatment groups.

All statistical tests were performed as two-sided tests at the 5% level of significance. The baseline characteristics and primary efficacy variables in the efficacy study were to be analyzed using "intent-to-Treat methodology. For some of the efficacy parameters, some subsets of this sample were also planned, such as those subjects with complete data sets, however, these were not performed.

RESULTS

Recruitment

A total of 451 subjects were screened from which 326 were randomised to treatment: 110 subjects to Suboxone, 106 to taste-matched Buprenorphine alone, and 110 to taste-matched placebo. Three subjects, one in each group were not dosed. Therefore the intent-to-treat efficacy sample comprised 323 subjects, 109 receiving Suboxone, 105 receiving Buprenorphine alone, and 109 receiving placebo tablets. All subjects enrolled in the efficacy study were opiate-dependent and had used heroin for a median duration of 84 months (range 3 to 468 months) at the time of entry into the study. About half of the subjects had previously been treated with methadone or LAAM while the others were naive to treatment. The majority of subjects were white men in their mid-thirties. Of the 323 subjects in the efficacy study, 64.7% were men and 35.3% were women; mean age was 37.6 years. There were no statistically significant differences in any baseline characteristic between treatment groups.

Conduct of the study

The study terminated after significant statistical effects were shown between treatment and placebo groups. For the 296 subjects who were not affected by the early closure of the study, retention in the study was high; 243 subjects (82%) completed and 53 (18%) discontinued. Five of these subjects discontinued due to adverse events. Three of them had received Suboxone; their adverse events included nausea, vomiting, and withdrawal symptoms (1 subject); withdrawal symptoms alone (1 subject); and irritability, headache, and decreased appetite (1 subject). The remaining two subjects had received Buprenorphine alone and experienced nausea (1 subject) and sedation and dizziness (1 subject).

Baseline data

The study was conducted in the target population. Baseline data were comparable for the three treatment groups.

Numbers analysed

Of the 296 subjects who entered the dosing phase 243 completed the study. This is acceptable, as the retention in study was high. 85% combination therapy; 84% monotherapy, and 77% placebo.

Outcomes and estimation

Negative urine samples: Statistical analysis of the results showed that patients treated with Suboxone or Buprenorphine alone tablets had a significantly higher percentage of urine samples that were negative for opiates than patients treated with placebo tablets. There was a statistically significant effect of centre but the treatment-by-centre interaction was not significant. There was no significant effect of age, gender or ethnicity on the percentage of clean urine samples, and there was no significant interaction between these variables and treatment.

**Mean Percent (SE) Urine Samples Negative for Opiates by Treatment Group
for Subjects in the Efficacy Study**

Treatment Group	N	Mean Percent (SE)	P-value vs. Placebo [†]
Buprenorphine/naloxone	109	17.8 (2.3)	<0.0001
Buprenorphine	105	20.7 (2.8)	<0.0001
Placebo	109	5.8 (1.7)	-
Total	323	14.7 (1.4)	-

[†]Two-way ANOVA

Craving score: Upon entry into the efficacy study, opiate craving was moderate (mean scores 62.4 to 65.6) and reflect no apparent differences between treatment groups. Over the 4-week study period there was a steady decline in mean craving scores following treatment with both Suboxone and Buprenorphine alone: at Week 4 the mean score in the Suboxone group was 29.8, and was 33.0 in the Buprenorphine alone group and both were significantly lower than the change in opiate craving in the placebo-treated group, that had a mean Week 4 craving score of 55.1. Also, at each week after baseline, the craving scores in the Suboxone and Buprenorphine alone groups were significantly lower than in the placebo group. No significant interactions between treatment and centre, age, gender or ethnicity on craving scores were detected.

**Opiate Craving Score Adjusted Means (SE) by Treatment Group and Follow-up
Period for Subjects in the Efficacy Study**

Week	Combination Therapy		Monotherapy		Placebo	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Baseline	109	62.4 (2.6)	104	63.3 (2.7)	109	65.6 (2.4)
1	108	44.4 (2.2)	104	45.7 (2.3)	107	60.5 (2.2)
2	98	33.8 (2.4)	93	33.2 (2.6)	100	57.0 (2.3)
3	95	30.2 (2.6)	89	35.6 (2.8)	90	54.4 (2.6)
4	86	29.8 (2.8)	86	33.0 (3.0)	79	55.1 (2.8)

Combination therapy vs. Placebo: $p < 0.0001$, repeated measures ANOVA, verified with split-plot analysis
Monotherapy vs. Placebo: $p < 0.0001$, repeated measures ANOVA, verified with split-plot analysis

Secondary outcomes: Subject's global impression improved over the 4-week study period: the mean score for subjects treated with Suboxone increased from 64.1 to 75.7 and the mean score for subjects treated with Buprenorphine alone increased from 65.8 to 74.7. At each week, subjects who received Suboxone or Buprenorphine alone had significantly higher scores than those who received placebo. At Week 4, mean clinician's global impression scores were 69.2 and 66.5 for the Suboxone and Buprenorphine alone groups, respectively, compared to the placebo group mean score of 57.9. The scores in the Suboxone and Buprenorphine alone groups were statistically significantly higher than the placebo score at each week.

The chosen primary and secondary efficacy endpoints were acceptable and in accordance with those chosen for studies that lead to approval of Buprenorphine alone.

Compared with placebo treated subjects, those treated with Suboxone or Buprenorphine alone had statistical significant reduced heroin use, as judged by the higher percentages of urine samples that were negative for opiates. Subjects also had a marked reduction in craving for heroin.

There was no effect of age on the efficacy results and there were no meaningful differences between the genders or the different ethnic groups.

The study also showed that Buprenorphine alone treatment was similarly effective, and there were no obvious differences between Suboxone and Buprenorphine alone: 16 mg doses of both products produced similar mean increases in the numbers of opioid negative urine samples, and reduced opioid craving by similar amounts. A post-hoc statistical analysis of non-inferiority of Suboxone and Buprenorphine alone was undertaken but the study was found to be underpowered to provide a firm

conclusion, but it was not the intention to show non-inferiority of Suboxone to Buprenorphine alone in the context of this study. Although statistical significance was not established, the results indicate that Suboxone is as effective as Buprenorphine alone in the treatment of opiate dependency.

Ancillary analyses

NA

- Analysis performed across trials (pooled analyses and meta-analysis)

NA

- Clinical studies in special populations

All relevant studies were conducted in the target population. Studies in children, in the elderly or in patients with renal or hepatic impairment were not conducted with Suboxone.

- Supportive study(ies)

NIDA#1018

Open study of Suboxone tablets to investigate 'Best Practice' for use in an office-based setting

NIDA #1018 was an open study of Suboxone tablets to investigate 'Best Practice' for use in an office-based setting. The study was conducted in the USA. Physicians could each recruit up to ten opioid-dependent subjects. Treatment was for up to one year. A total of 582 (386 males) were enrolled in the study.

Suboxone was successfully used to initiate treatment. On the first day of treatment, most patients received 8 mg (190, 32.6%), 4 mg (126, 21.6%) or 16 mg (102, 17.5%) Suboxone.

During the remainder of the study, the doses of Suboxone were adjusted to meet individual patient's needs; the most frequent average daily doses were between 8 mg and 16 mg. A total of 189 patients completed the study protocol representing a retention rate of 32%. Overall retention rates (27-35%) were similar across all the treatment settings. Of the 189 patients, 162 (112 male and 50 female) received at least 47 weeks of Suboxone treatment.

Suboxone treatment was associated with reductions in the percentage of opiate-positive urine samples during the study. Overall after 3, 6 and 12 months of treatment, 29.6%, 23.65% and 19.0% of urine samples were positive for opiates compared with 90.5% at the start of treatment. Similar results were found for self-reporting of opiate use by patients. Non-opiate drug use was also reduced during treatment. Improvements were also noted in the Clinical Global Impression Scores recorded during treatment. Overall there was a good level of agreement between patients' and physicians' assessments, with most patients being scored as 'much improved'. Risk Assessment Battery (RAB) results showed marked and statistically significant reductions in 'Drug Risk' and 'RAB Scaled' scores following treatment. Addiction Severity Index results showed highly statistically significant reductions in severity of 'Drug-related Impairment' and 'Legal Status' scores and a smaller reduction in 'Family/Social (Interpersonal Functioning)' scores.

Overall there were 112,851 patient days of Suboxone dosing. The overall average daily dose of Suboxone was 15.8 mg, although there was significant use of higher and lower doses.

This study confirms the results of the randomised study CR96/013. Subjects who remained in the study exert reduced misuse of opiates. The low retention rate is typical for this patient group.

US08 Study (*Randomized comparison of the use of Suboxone for opioid dependence in three office based settings in the USA*) A 52-week study compared the use of Suboxone for opioid dependence in three office-based settings in the USA (US08). The study aims were: to document physicians' preferred prescribing practices, including induction, dose adjustment, maintenance, and take-home dosing; to document the ease or difficulty they encounter in delivering Suboxone in the three treatment settings; and to document the acceptance, compliance, response and necessary adjustments from the patients' perspective. The three treatment settings were: an office-based psychosocial treatment setting, using the Matrix Recovery / Relapse Prevention Model, within which buprenorphine treatment was introduced by making available the service of a physician; a private physician's office within which buprenorphine is prescribed and supplemented with relapse prevention delivered by an appropriately trained medical assistant; and a research clinic housed in a traditional opiate

maintenance treatment (methadone) clinic but with personnel experienced in the clinical use of buprenorphine.

A total of 128 patients were screened for participation in the study. Of these, 16 failed the screening process, two others who passed the screening process failed to show for randomization. The efficacy evaluable (EE) population comprised 93 patients and the intent to treat (ITT) population comprised 103 patients (EE population + 10 partners). The safety population comprised 104 patients (ITT population + a subject treated at two settings).

On the first day of treatment, patients saw the physician and received a 2, 4 or 8mg first dose of Suboxone taken sublingually at the clinic. Most (97) of the 103 patients were given 4mg Suboxone as their first dose of Suboxone. Of the other 6 patients, 4 received 2mg and 2 received 8mg Suboxone as their first dose. On the first day, patients could receive an additional Suboxone dose up to 8mg at the treating physician's discretion. Most patients were recorded as having taken 8mg Suboxone (50 patients) or were prescribed 8mg Suboxone (35 patients) as their total dose on Day 1. Twelve patients received just 4mg total dose of Suboxone on Day 1. The other patients received a higher total dose of Suboxone on Day 1. Patients were prescribed or dispensed enough medication to continue dosing until the next office visit. Patients made contact with the study physician on the following day and were seen by the physician at least one more time during the first study week for follow-up evaluation to include drug use, signs and symptoms of opiate withdrawal or over-medication, and any adverse effects. At that time, dosage could be adjusted by 8 mg/day increments, to a maximum of 24 mg buprenorphine.

During weeks 2-6 patients saw the study physician once weekly for evaluation of treatment progress, medication effects and side effects. A urine sample was obtained at each visit to screen for drugs of abuse. Additional visits were to be scheduled as medically indicated. After Week 6 the study physician reviewed and discussed treatment progress and options with the subject to determine whether to begin detoxification, continue further maintenance, or explore other treatment options. Buprenorphine treatment could continue for up to 52 weeks.

Urinary opiate results are not available from the study.

Retention of patients in treatment is an important indicator of treatment efficacy. Of the 104 patients, 28 completed the study, 26 of who completed at least 47 weeks of Suboxone treatment. Of the 76 patients who discontinued early, 47 failed to return to the clinic at some point in the study, and 14 patients requested early termination from the study. Three patients discontinued due to unwanted effects of the medication.

This study report provides limited efficacy information since urinary opiate results are not available.

Studies CR95/002, Bupp4729, and Bupp5113 were pilot studies. Only a few subjects completed the studies. No additional results were obtained to demonstrate efficacy.

- Discussion on clinical efficacy

Study CR96/013 demonstrates statistical significant superiority of Suboxone compared to placebo regarding all primary and secondary efficacy endpoints. The results also indicate that Suboxone is as effective as Buprenorphine alone in the treatment of opiate dependency.

This conclusion is endorsed by the results of the open Suboxone studies CR96/014, NIDA#018 and US08 including more than 1000 patients.

Successful detoxification can be obtained with Suboxone titrated downward to 2mg before termination of the therapy. However, in some patients it is necessary to titrate downward from 2mg in small steps of 0.4mg before termination of the therapy.

The CHMP was concerned, as for these patients a titration would be possible only with Buprenorphine alone. As Suboxone is indicated for substitution treatment for opioid dependence, be it acute detoxification or maintenance treatment, is clinically justified to have 0.4mg/0.1mg Suboxone tablets.

The Applicant argued that the efficacy and safety of Suboxone and Buprenorphine alone when used as directed are comparable. Therefore, it should be acceptable to patients to use the 0.4 mg Buprenorphine alone tablet for those exceptional circumstances when doses below 2 mg buprenorphine are required and, since detoxification of patients who are continuing to inject opioids is

not likely to be considered an appropriate course of treatment, the lack of a combination tablet in this dose range should not present a significant clinical issue.

Where it is not desirable to switch detoxification therapy from Suboxone to Buprenorphine alone (or any other buprenorphine that might be available for the treatment of opioid addiction in the future), the CHMP agreed with the applicant's position that the lack of a combination tablet in this dose range should not present a significant clinical issue. Therefore a follow up measure is adequate.

In conclusion detoxification with a switch from Suboxone to Buprenorphine alone will be monitored, as a part of the risk management plan.

Clinical safety

Suboxone is proposed for the treatment of opiate dependence. Buprenorphine alone (buprenorphine) is a well-established substitution treatment for opiate dependency as an alternative to methadone treatment. Buprenorphine has equal efficacy to other substitution treatments but has the added benefit of being safer in overdose as there is a ceiling effect on respiratory depression. Buprenorphine alone (buprenorphine alone) has been licensed in France since 1996. It became clear however that the diversion of Buprenorphine alone to the black-market and inappropriate use was occurring. There were deaths, due to respiratory depression and cardiovascular collapse in addicts who misused buprenorphine, especially with the concomitant use of benzodiazepines. The concept of combining buprenorphine and naloxone in a single tablet stemmed from the goal of deterring intravenous misuse of buprenorphine by opiate addicts.

- Patient exposure

The total exposure to Suboxone is **1631** patients. The total **long-term** exposure is **1158** patients. In CR96/013 and CR96/014 the 16mg and the 20mg/day doses were the most frequently administered. The 16 mg dose had the highest exposure

Study	Product	N. subjects	Men	Women	Duration
CR95/002	Suboxone	25	16	9	6-20 wks
CR96/013+CR96/014	Suboxone 4mg-24mg	472	327	145	52 weeks
US08	Suboxone 4mg-24mg	104	66	38	52 weeks
NIDA #1018	Suboxone 4mg-24mg	582	386	196	52 weeks
0600201	Suboxone 4mg	40	31	9	12 weeks
Bupp 4729	Suboxone 8mg	47	33	14	11 weeks
Bupp 5113	Suboxone 8mg	46	30	16	11 weeks
Bupp 6683 Australian Study	Suboxone 2mg-32mg	17	11	6	26 weeks
RC050175 Finnish Study	Suboxone 2mg-32mg	64	52	12	Up to 75 weeks
10.CTN-001 and CTN 002	Suboxone 1mg – 8mg	234	161	73	2 weeks

Table: Demographic characteristics of Patients in the long term Suboxone studies

Race	Total	Age range	Women	Age range	Men	Age range	% Male
White	754	(15-61)	252	(15-61)	502	(16-61)	66.6
Black	202	(18-65)	76	(18-60)	126	(22-65)	62.4
Hispanic	138	(21-66)	25	(21-52)	113	(21-66)	81.9
Other Hispanic	29	(33-65)	10	(33-45)	19	(34-65)	65.5
Asian/Pacific Islander	12	(21-56)	4	(23-41)	8	(21-56)	66.7
Native American	11	(24-60)	7	(24-47)	4	(36-60)	36.4
Asian	9	(19-39)	4	(19-36)	5	(28-39)	55.6
Other	3	(24-42)	1	24	2	(24-42)	66.7
Total	1158	(15-66)	379	(15-61)	778	(16-66)	67.3

Suboxone Doses used in Clinical Trials

When the number of dose levels to which each subject was exposed was counted, including induction and titration doses, the 16 mg/day and the 20 mg/day doses of Suboxone were the most frequently administered. The minimum and maximum Suboxone doses used for maintenance treatment were 4 mg/day and 24 mg/day, respectively. A 2 mg/day dose was used during dose-reduction at the end of the study.

Individual subjects attained a stable dose level of buprenorphine/naloxone and tended not to deviate from this dose during the study.

Overall, there was a total of 92,930 person-days exposure (average of 197 person-days per subject) among the 472 subjects in the safety study. The 16 mg Suboxone dose had the highest exposure (32,448 person-days), with an average of 82 person-days per subject

• Adverse events

A profile of adverse events relating to clinical use of Suboxone is obtained from the 52-week pivotal efficacy/safety study (CR96/013 + CR96/014) and from the 52-week Suboxone Safety/Best Practice study (NIDA #1018). Comparison of Suboxone, Buprenorphine alone and placebo is made from the 4-week efficacy study (CR96/013).

Common Adverse Events

Adverse Events Following Treatment with Suboxone, Buprenorphine alone and Placebo in Study CR96/013

Overall Adverse Events

Buprenorphine, whether administered alone or in combination with naloxone, was well tolerated. The most frequently reported events during the efficacy study (reported by at least 10% of subjects) were headache, withdrawal syndrome, pain, insomnia, nausea, and sweating. Of the more common events, headache, abdominal pain, and constipation were reported somewhat more frequently by the subjects in the buprenorphine groups compared to the placebo group. Placebo subjects reported a higher incidence of back pain, withdrawal syndrome, diarrhoea, and rhinitis than buprenorphine-treated subjects.

When adverse events most frequently reported by subjects treated with either buprenorphine formulation were examined, the frequency of adverse events was similar between the treatment groups in the vast majority of cases. Amongst events that were reported by fewer than 5% of the subjects, somnolence was somewhat more common amongst buprenorphine-treated subjects; no other trends were observed.

CR96/013: Adverse Events Reported by at Least 5% of Subjects Overall by Body System and Treatment Group

Adverse Event (COSTART Coded Term)	Suboxone (N = 107)	Buprenorphine alone (N = 103)	Placebo (N = 107)	All (N = 317)
Body As A Whole				
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)	19 (6.0%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)	24 (7.6%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)	93 (29.3%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)	25 (7.9%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)	63 (19.9%)
Pain Abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)	31 (9.8%)
Pain Back	4 (3.7%)	8 (7.8%)	12 (11.2%)	24 (7.6%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)	86 (27.1%)
Cardiovascular System				
Vasodilatation	10 (9.3%)	4 (3.9%)	7 (6.5%)	21 (6.6%)
Digestive System				
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)	24 (7.6%)
Diarrhoea	4 (3.7%)	5 (4.9%)	16 (15.0%)	25 (7.9%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)	42 (13.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)	21 (6.6%)
Nervous System				
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)	54 (17.0%)
Respiratory System				
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)	29 (9.1%)
Skin And Appendages				
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)	39 (12.3%)

Source data: Table 40 of CR96/013 + CR96/014 study report. Report located in Module 5, Section 5.3.5.1.1

Treatment Relationship and Severity

The most common adverse events that were judged by the investigators to have been at least possibly related to either of the buprenorphine treatments were headache (26.2% of Suboxone subjects, 18.4% of Buprenorphine alone subjects), insomnia (10.3%, 17.5%), nausea (13.1%, 9.7%), sweating (11.2%, 9.7%), and constipation (11.2%, 6.8%). The incidence of adverse events was comparable when buprenorphine was administered as monotherapy as compared to administration in combination with naloxone.

The majority of adverse events reported were either mild or moderate in severity. Headache, pain, and withdrawal syndrome were the most frequent events reported as being severe in intensity.

CR96/013: Adverse Events Classified as Severe in Intensity

Adverse Event (COSTART Coded Term)	Suboxone (N=107)	Buprenorphine alone (N=103)	Placebo (N=107)	All (N=317)
Body As A Whole				
Asthenia	1 (0.9%)	0	0	1 (0.3%)
Fever	1 (0.9%)	0	0	1 (0.3%)
Headache	5 (4.7%)	2 (1.9%)	2 (1.9%)	9 (2.8%)
Accidental Injury	0	0	2 (1.9%)	2 (0.6%)
Pain	2 (1.9%)	2 (1.9%)	1 (0.9%)	5 (1.6%)
Pain, Abdomen	1 (0.9%)	0	2 (1.9%)	3 (0.9%)
Pain, Back	0	1 (1.0%)	1 (0.9%)	2 (0.6%)
Withdrawal Syndrome	1 (0.9%)	1 (1.0%)	3 (2.8%)	5 (1.6%)
Cardiovascular System				
Syncope	0	0	1 (0.9%)	1 (0.3%)
Digestive System				
Constipation	2 (1.9%)	0	0	2 (0.6%)
Gastrointestinal Disorder	1 (0.9%)	0	0	1 (0.3%)
Nausea	0	1 (1.0%)	0	1 (0.3%)
Nausea/Vomiting	0	0	1 (0.9%)	1 (0.3%)
Stomatitis	1 (0.9%)	0	0	1 (0.3%)

Adverse Event (COSTART Coded Term)	Suboxone (N=107)	Buprenorphine alone (N=103)	Placebo (N=107)	All (N=317)
Tooth Disorder	1 (0.9%)	0	0	1 (0.3%)
Musculoskeletal System				
Myalgia	1 (0.9%)	0	0	1 (0.3%)
Nervous System				
Convulsions	1 (0.9%)	0	0	1 (0.3%)
Depression	1 (0.9%)	0	0	1 (0.3%)
Drug Dependence	0	0	1 (0.9%)	1 (0.3%)
Emotional Lability	1 (0.9%)	0	0	1 (0.3%)
Insomnia	0	0	2 (1.9%)	2 (0.6%)
Paresthesia	1 (0.9%)	0	0	1 (0.3%)
Respiratory System				
Rhinitis	0	0	1 (0.9%)	1 (0.3%)
Special Senses				
Conjunctivitis	0	1 (1.0%)	0	1 (0.3%)
Urogenital System				
Dysmenorrhea	1 (0.9%)	0	1 (0.9%)	2 (0.6%)
Urinary Tract Disorder	0	0	1 (0.9%)	1 (0.3%)

Source data: Table 42 of CR96/013 + CR96/014 study report. Report located in Module 5, Section 5.3.5.1.1

In study CR96/013, the more commonly reported adverse events (reported by 5% or more of the subjects overall) were reviewed for possible difference by gender, ethnicity, duration of heroin abuse, and baseline liver function.

Adverse Events Reported During Long-term Treatment with Suboxone

Adverse events following two 52-week studies of Suboxone have been reported from studies: CR96/013 /014 and NIDA #1018.

Adverse Effects

Of 472 subjects in Study CR96/014, 446 (94.5%) experienced a treatment-emergent adverse event at some time while on-treatment. Most of these reported events appear to be either events that are common in the general population, or would be expected in a population of illicit drug users. Among all subjects receiving the buprenorphine/naloxone tablet, the most frequently reported events were headache, pain, withdrawal syndrome, infection, insomnia, back pain, and constipation, each reported by more than 20% of subjects. Additionally, flu syndrome, abdominal pain, nausea, rhinitis, sweating, accidental injury, depression, anxiety, pharyngitis, vomiting, diarrhoea, and asthenia were each reported by more than 10% of subjects.

The incidence of adverse events appeared to increase with dose level; 89 of the 131 subjects (67.9%) taking the lowest dose (4mg Suboxone) reported adverse events whereas 46 of the 48 subjects (95.8%) taking the highest dose (24mg Suboxone) reported adverse events. At the most commonly prescribed dose level (16mg Suboxone), 339 of the 394 subjects (86.0%) reported adverse events. There were some events that appeared to occur with higher incidence as the dose increased. However, since the design of the study was titration with low doses and progressively increasing doses, there was also an increase in duration of exposure as the dose increased.

Adverse events reported by at least 5% of subjects in study CR96/013 + CR96/014 are summarized by body system in the Table below.

CR96/013+CR96/014: Adverse Events Reported by at Least 5% of Subjects

Adverse Event (COSTART Coded Term)	All Subjects (N = 472)
Body as a Whole	
Asthenia	48 (10.2%)
Chills	44 (9.3%)
Fever	36 (7.6%)
Flu Syndrome	89 (18.9%)
Headache	202 (42.8%)
Infection	149 (31.6%)
Accidental Injury	72 (15.3%)
Pain	197 (41.7%)
Pain Abdomen	77 (16.3%)
Pain, Back	132 (28.0%)
Withdrawal Syndrome	194 (41.1%)
Cardiovascular System	
Vasodilatation	29 (6.1%)
Digestive System	
Constipation	115 (24.4%)
Diarrhoea	50 (10.6%)
Dyspepsia	45 (9.5%)
Nausea	76 (16.1%)
Tooth Disorder	37 (7.8%)
Vomiting	61 (12.9%)
Metabolic and Nutritional	
Peripheral Oedema	24 (5.1%)
Musculoskeletal System	
Myalgia	31 (6.6%)
Nervous System	
Anxiety	65 (13.8%)
Depression	70 (14.8%)
Dizziness	33 (7.0%)
Insomnia	138 (29.2%)
Nervousness	42 (8.9%)
Paresthesia	28 (5.9%)
Somnolence	40 (8.5%)
Respiratory System	
Cough Increased	36 (7.6%)
Pharyngitis	64 (13.6%)
Rhinitis	75 (15.9%)
Skin and Appendages	
Sweating	74 (15.7%)

Source data: Table 66 of CR96/013 + CR96/014 study report. Report located in Module 5, Section 5.3.5.1.1

A subset of 261 subjects in the safety study were exposed to Suboxone for at least 6 months. There were no clear differences in the frequency of adverse events in this sample compared with the overall safety sample; frequently reported adverse events (reported by at least 20% of the subjects) had a somewhat higher incidence in subjects exposed for at least 6 months and included pain, headache, infection, withdrawal symptoms, back pain, insomnia, constipation, flu syndrome, depression, accidental injury, rhinitis, and pharyngitis. Anxiety, abdominal pain, nausea, vomiting, asthenia, sweating, diarrhoea, dyspepsia, tooth disorder, chills, fever, and paraesthesia were each reported by 10% or more of the subjects. In terms of evaluation by dose, the observations for subjects exposed to Suboxone for 6 months or more are similar to those observed for all subjects, where the apparent increase with dose level may equally relate to the increased duration of exposure.

Treatment Relationship and Severity

The most frequently reported adverse events that were judged by the investigator to have been at least possibly related to the study drug (Suboxone) were headache (30.3% of subjects), constipation (21.6% of subjects), insomnia (20.3% of subjects), withdrawal syndrome (15.7% of subjects), sweating (12.1% of subjects), and nausea (11.2% of subjects). Most of the adverse events reported in the study were mild or moderate in severity. For the treatment-related adverse events most frequently reported by all subjects, pain and back pain were the most frequently reported as being severe in 3.6% and 3.2% of subjects, respectively. Severe withdrawal syndrome was reported by 2.3% of subjects. For subjects exposed for at least 6 months, the same general trends were apparent; severe pain and severe back pain were reported for 5.4% and 5.0% of subjects, respectively. When looking at the dose distribution of severe adverse events, they tended to occur with the most frequently prescribed doses, 16mg and 20mg Suboxone per day.

- **Serious adverse event/deaths/other significant events**

In total, 367 non-fatal serious adverse events were reported during clinical trials of buprenorphine in the treatment of opioid dependence: 175 in subjects treated with Suboxone, 28 with Buprenorphine alone, 115 with buprenorphine solution, 25 with methadone, 12 with placebo, 7 with clonidine, 4 in undosed subjects and 1 not stated.

All Trials: Serious Adverse Event Counts by Body System

Body system	Cases
Application Site	3
Benign and Malignant Neoplasms	3
Body as a Whole	11
Cardiovascular	18
Central and Peripheral NS	11
Gastrointestinal	19
Immune System	4
Infection and infestation	41
Injury and Poisoning	31
Liver and Biliary	52
Metabolic and Nutritional	2
Musculo-Skeletal	11
Psychiatric	129
Renal and Urinary	5
Reproductive	3
Respiratory	17
Skin and Subcutaneous	7
TOTAL	367

The serious adverse event preferred term most commonly reported was Elevated Liver Function Tests (47 cases in the Liver and Biliary Body System); The next most commonly reported events were: depression (34), overdose (25), detoxification request leading to hospitalisation (23), abscess (17), chest pain (14), pneumonia (13), automobile accident (13), infection (9), suicide attempt (9), asthma (8), seizure (8), cellulitis (7), suicide ideation (7), anxiety (6), surgery (6), obstructive pulmonary disease (5), and fracture (4). The cases of overdose, depression, suicide attempt, and suicide ideation show the instability of the addict patient population and point to the need to regularly monitor progress during treatment.

Of the other less frequently reported serious adverse events reported in clinical trials, two cases of allergic reaction occurred just hours following the sublingual administration of the first dose of Buprenorphine alone. In one case the reaction was severe and life threatening while the other case was of moderate severity. Two cases of myocardial infarction occurred, both in 46-year-old male subjects being treated with Suboxone. One had a history of pulmonary disease, secondary to smoking and grain dust inhalation at work; this event was judged unrelated to study drug. The other subject had a history of smoking and hypertension; the Principal Investigator judged this event to be possibly

related to the study drug. Both cases were mild in severity. Other serious adverse events were those that would be expected in this patient group or the general population over the study periods.

Serious Adverse Events in Subjects Receiving Suboxone in Clinical Trials of Opioid Dependence

A total of 175 serious adverse events were reported in patients receiving Suboxone in five clinical trials.

Apart from detoxification requests that led to hospitalisation (34 subjects), the most common serious adverse events reported for Suboxone treated subjects were depression (14), elevations in liver function tests (protocol reports, 11), overdose (11), pneumonia (9), abscess (8), and chest pain (7 subjects).

Adverse Events Leading to Discontinuation from Treatment in Clinical Trials

Adverse Event Preferred Term	Suboxone	Buprenorphine alone	Bup Sol	Methadone	Total
Withdrawal syndrome	13	4	5		22
Nausea	9	2	1		12
Nausea and vomiting	2	1	3	2	8
Abdominal Pain	1	4	2		7
Dizziness	2	2	3		7
Vomiting	3		1	1	5
Anxiety	1		3		4
Headache		2	1		3
Hypertension	2	1			3
Suicide attempt		1	2		3
Accidental injury			1	1	2
Alcoholism			1	1	2
Allergic reaction		2			2
Depression			2		2
Hepatitis			1	1	2
Rash	1		1		2
Abscess			1		1
Agitation			1		1
AIDS				1	1
Anorexia			1		1
Arthralgia				1	1
Asthenia			1		1
Back pain			1		1
Chest pain			1		1
Confusion			1		1
Constipation	1				1
Cramps, leg			1		1
Edema, peripheral	1				1
Edema, peripheral and rash		1			1
Fatigue	1				1
Hair loss	1				1
Herniated disc			1		1
Hostility		1			1
Libido decreased			1		1
Malaise				1	1
Nervousness			1		1
Obstructive pulmonary disease			1		1
Overdose				1	1
Pain	1				1
Paresthesia			1		1
Peri-oral eczema	1				1
Pneumonia		1			1
Strangulated intestine			1		1
Suicide ideation			1		1
Sweating increased	1				1

Adverse Event Preferred Term	Suboxone	Buprenorphine alone	Bup Sol	Methadone	Total
Weight loss	1				1
TOTAL	42	22	42	10	116

Analysis of Adverse Events by Organ System or Syndrome

The serious adverse event preferred term most commonly reported was elevated liver function tests (47 cases in the Liver and Biliary Body System). A few serious cases of acute hepatic injury have been reported in subjects misusing buprenorphine by the intravenous route, and increases in liver enzymes have been reported in other patients receiving buprenorphine. This prompted a retrospective analysis of hepatic cases from clinical trials and from the marketing of Buprenorphine alone (Report RC020117). This analysis was undertaken on data from 1615 patients who took part in five clinical trials where there was a baseline measurement of hepatic parameters plus regular on-treatment measurements. Of these, 252 patients (15.6%) had liver function parameter levels greater than or equal to three times the higher limit of normal at some point during the studies. Generally, continued treatment with buprenorphine was not associated with a worsening of the condition and often was associated with a reduction or normalization of hepatic function parameters.

A large number of the serious adverse events related to the 'Psychiatric' body system: depression (34), overdose (25), detoxification request leading to hospitalisation (23), suicide attempt (9), suicide ideation (7), anxiety (6).

Another large group of adverse events, often resulting in discontinuation from treatment, relate to the 'Gastrointestinal' System and include nausea, nausea with vomiting and vomiting.

Withdrawal symptoms are the other main group of adverse events seen in clinical trials of buprenorphine, and are common to addicts undergoing transition from street opiate to pharmacological treatment.

Deaths in Clinical Studies

There have been 13 deaths that occurred in clinical trials of buprenorphine for the treatment of opioid dependence. Deaths Occurring in Buprenorphine Clinical Trials of Opioid Dependence, by Body System

Study	Treatment	Dose	Study day - onset	Adverse event leading to death				Study day - death
				Preferred term	Verbatim term	Relationship	Action indicated	
CTN-001	Suboxone	2-16 mg schedule over 13 days	~122	Vomiting and dehydration	Acetaminophen poisoning., respiratory failure and MI	Unrelated	Hospitalization	~123
NIDA #1018	Suboxone	24 mg	~110	Infection	Necrotizing fascitis IV heroin	Unrelated	Hospitalization	~122
NIDA #1018	Suboxone	6 mg	~383	Overdose	Temazepam Overdose	Unknown	None	~383
OASIS	Suboxone	20 mg	191	Infection	Infection	Possible	Hospitalization	?
NEPOD #10	Buprenorphine alone	32 mg on alternate days		Suicide	Carbon monoxide poisoning	Unrelated	None	
CR88/130	Buprenorphine solution	8 mg	37	Overdose	Drug Overdose	Unrelated	None	37
CR92/100	Buprenorphine solution	8 mg	147	Coronary thrombosis	Coronary thrombosis	Unrelated	Hospitalization	147
CR92/100	Buprenorphine solution	32 mg	265	Infection	Dehydration and sepsis	Unrelated	Hospitalization	265
CTN-001	Clonidine	~0.4 mg per day by patch for 3 days	~127	Endocarditis	Endocarditis secondary to staphylococcus aureus infection	Unrelated	Hospitalization	~127
CR88/130	Methadone	20 mg	7	Accidental injury	Multiple injuries	Unrelated	None	7
Bupp 3773	Methadone	30 mg	18	Stab wound	Multiple stab wounds	Unrelated	None	18
CR96/005	Methadone	35 mg	~548	Accidental injury	Slipped and fell from a window	Unrelated	None	~548
Bupp 3773	Not known		Post study	Cancer		Unknown	Hospitalization	Post study

- Laboratory findings

No remarkable laboratory findings. The hepatic vulnerability will be discussed in the following section.

- Safety in special populations

Patients with Hepatic Vulnerability

A retrospective evaluation of the potential for buprenorphine-induced hepatotoxicity was undertaken in 2002; this also examined the role of viral hepatitis in increasing vulnerability to hepatotoxicity (Report RC020117). With regard to *in vitro* and preclinical work, this showed that very high concentrations of buprenorphine are toxic to hepatic mitochondria. However, the concentrations used in these experiments far exceed tissue concentrations likely from therapeutic use of buprenorphine. In clinical trials, elevations in hepatic enzymes were observed in 12.3% of patients being treated. An elevation of liver enzyme levels was not unique to buprenorphine since similar rises were also observed following treatment with methadone and LAAM. Generally, continued treatment with buprenorphine was not associated with a worsening of the condition and often was associated with a reduction or normalization of hepatic function parameters. In 81.7% of hepatic cases treatment was associated with rises in liver enzymes. However, in 8.0% of cases there was a reduction of liver enzymes, and in the other 10.3% of cases there was no obvious change in already elevated hepatic parameters.

The more confounding / contributory factors a patient has, the more likely he or she is to have an exaggerated hepatic enzymes response to treatment with buprenorphine. Thus, patients with existing HCV and / or who are taking anti-AIDS drugs are more vulnerable when treated with buprenorphine (or methadone and LAAM). In a few cases, introduction of buprenorphine to patients with no previous history of hepatitis was associated with a large elevation of liver enzyme levels, and withdrawal of the drug was associated with an improvement. However, since most addict subjects have other confounding factors, not least chaotic life-style of intravenous misuse of drugs, and their pre-treatment hepatitis status is usually not laboratory based, it could not be concluded that buprenorphine, *per se*, causes hepatitis, but it still remained a possibility.

It can be concluded that patients with existing hepatitis and/or HCV infection are probably more likely to have greater increases in hepatic enzymes during treatment with buprenorphine (or methadone and LAAM) than others without these complications.

Differences in baseline liver functions (232 subjects in study CR96/013 had normal baseline liver function and 85 had abnormal baseline liver function) did not appear to be associated with any consistent trend in the incidence of adverse events.

Use of Suboxone in Pregnancy

Currently clinical information on the use of Suboxone tablets in pregnancy is from four women receiving the product who became pregnant during study CR96/013+CR96/014. Three of the pregnancies were aborted, one spontaneous and the other two elective; the other pregnancy went to term. The latter case was a 29-year-old woman with no noteworthy active medical problems aside from drug abuse; she was using a barrier contraceptive as her only form of birth control. She had a negative pregnancy test recorded at Week 12 and the next recorded test at Week 20 was positive, then reporting not using any form of birth control. She was terminated from the study at that time. The subject delivered a 'drug addicted' baby girl who had respiratory difficulties, and weighed slightly over 4 pounds. The baby recovered from the drug addiction and respiratory difficulties, and no birth defects or permanent abnormalities were noted. The baby was reported as doing well and gaining weight. Later she was placed in foster care.

Use of Buprenorphine alone in pregnant women

It is clear from post marketing adverse event reports that Buprenorphine alone is being used in pregnant women because a number of the most frequently reported events related to this use: Drug Exposure during Pregnancy (300 cases), Drug Withdrawal Syndrome Neonatal (212) and Tremor Neonatal (21). A number of foetal abnormalities and foetal deaths also were reported.

In some markets Buprenorphine alone is contraindicated in pregnancy and in others Buprenorphine alone use is based on evaluation by the physician of the risk of Buprenorphine alone use versus continued illicit heroin use. The cases of foetal death and deformities did not display any unusual pattern and were not specific to the use of buprenorphine. In neonates of opioid dependent mothers the following problems occur more often: small for gestational age, reduced weight and length, premature delivery, small head circumference, neonatal withdrawal, and later mental, emotional or behavioural problems.

- Safety related to drug-drug interactions and other interactions

Drug interaction profile in vitro and in vivo was described for buprenorphine alone and not for the fixed combination.

No information to interactions is present in the post marketing database. The SPC includes information regarding the interactions and the monosubstances *in section 4.5 and 4.9*.

- Discontinuation due to adverse events

In clinical trials of opioid dependence with buprenorphine there have been 116 cases of adverse events leading to discontinuation from treatment. Of the 1715 subjects who were treated with Suboxone in clinical studies, 42 (2.4%) discontinued due to adverse events. This percentage compares favourably with patients who discontinued due to adverse events being treated with Buprenorphine alone (5.9%), buprenorphine solution (4.4%), and methadone (1.8%).

Discontinuations from Treatment due to Adverse Events

Treatment	Total Patients	Number discontinuing due to adverse events	%
Suboxone	1715	42	2.4%
Buprenorphine alone	370	22	5.9%
Buprenorphine Solution	949	42	4.4%
Methadone	567	10	1.8%
TOTAL		116	

Most of the discontinuations were due to a withdrawal syndrome (19) or individual withdrawal symptoms, which are not unexpected in patients being stabilised from street opiates. Nausea (12), nausea with vomiting (8), and vomiting (5) are known side effects of buprenorphine treatment that affect some patients more than others. Dizziness (7) is a known side effect of buprenorphine.

The discontinuation rates of Suboxone or Buprenorphine alone treated subjects are comparable.

- Post marketing experience

Post marketing exposure to Suboxone

For Suboxone, in the period from launch in the USA in April 2003 until March 31, 2005, 21.1 million tablets (6.52 million 2mg, and 14.58 million 8mg tablets) were distributed for the treatment of opioid dependent patients. This is equivalent to 16.21 million doses of 8mg Suboxone or 8.11 million doses of 16mg Suboxone taken over the 23-month period, or 23,190 or 11,595 patients treated with 8mg or 16mg Suboxone per day, respectively.

Post Marketing Exposure to Suboxone and Buprenorphine alone

	Suboxone	Buprenorphine alone
	Launch (April 2003) to March 2005	Launch (February 1996) to March 2005
Dosage form	Millions of tablets	Millions of tablets
0.4 mg tablet	Product not available	70.22
2 mg tablet	6.52	307.99
8 mg tablet	14.58	198.99
Total tablets	21.32	577.2
Number of daily doses	8.11 million 16mg doses over 23 months	279.5 million 8mg doses over 10 years
Patients per year	11,595 patients (based on 16mg per day)	76,575 patients (based on 8mg per day)

Source data: 2005 PSUR (Report RC050324). Report located in Module 5, Section 5.3.6.2

Suboxone Post Marketing Adverse Events

In the period since the launch in the USA in April 2003 to March 31, 2005, there were 89 post marketing adverse events reported for Suboxone. The types of adverse events were similar to those reported for Buprenorphine alone.

Buprenorphine alone Post Marketing Adverse Events

Safety data pertaining to the buprenorphine tablet are available from marketed use in France since February 1996.

The profile of adverse events relating to Buprenorphine alone use has been similar year on year. Overdose deaths in addicts using Buprenorphine alone in combination with other psychoactive agents continue to be the most serious events. Neonatal withdrawal symptoms, usual not serious but frequent in number, relate to the continued safe use of Buprenorphine alone in pregnant opioid dependent women. Reports of hepatitis and elevations of hepatic enzymes continue to be reported at a low incidence. Usually, these occur in subjects already compromised with HCV infection, or who are taking other drugs known to have hepatic effects. Intravenous misuse is also a contributory risk factor for hepatic adverse events.

The adverse event profiles of Suboxone and Buprenorphine alone are comparable regarding post marketing exposure.

Retrospective collection of patient data in study RC050175 in Finland regarding patients switched from Buprenorphine alone to Suboxone treatment.

Data were collected from the records of 64 patients, 52 male and 12 female. Twenty of the patients had been treated with Suboxone for over a year at follow up.

During the 4 week observation period, there were approximately 1714 patient days of dosing with Suboxone, either alone or in combination with Buprenorphine alone. There were approximately 17883 patient days of dosing with Suboxone during both the 4 week study period and the follow up period. An average daily dose during the 4 week study period was calculated by each patient by summing the doses prescribed and dividing by the number of days the patient remains in the study. The estimated

overall average daily dose of Suboxone when not in combination with Buprenorphine alone was 22.9mg. Half of the patients were taking Suboxone at doses between 20mg and 28mg. There were no deaths or other serious adverse events reported for patients in the study. During the 4-week period 32 of 64 patients reported adverse events. During the follow up 19 of 61 patients reported adverse events.

- Discussion on clinical safety

Suboxone doses in clinical trials ranged from 2mg to 32mg. Sufficient safety data is available for doses up to 24mg daily in different age and ethnic groups.

In the European Union, Buprenorphine alone (Buprenorphine) was first approved for substitution treatment of opioid dependence in 1995 and has been marketed since 1996.

Suboxone (Buprenorphine+Naloxone) have been marketed in the USA since April 2003 and therefore safety data could be presented over a period of more than two years.

In Finland, Suboxone was made available in late 2003 under special license, which made it possible for a retrospective study to be conducted on subjects who switch from Buprenorphine alone to Suboxone, thereby allowing the evaluation of safety resulting from such a switch.

The three 52-week clinical trials of Suboxone (CR96/013+CR96/014, NIDA#1018, US08) provide the main safety database for Suboxone, supported by a number of smaller Suboxone studies and the above mentioned post marketing data. A second safety database is from Buprenorphine alone clinical trials, buprenorphine sublingual solution clinical trials, and from clinical pharmacology studies.

3034 patients (2054 male, 980 female) were exposed to buprenorphine in clinical trials.

The most frequently reported events during the efficacy study were headache, withdrawal syndrome, pain, insomnia, nausea and sweating. The incidence of adverse events was comparable when buprenorphine was administered as monotherapy as compared to administration in combination with naloxone. The majority of adverse events reported were either mild or moderate in severity. Headache, pain, and withdrawal syndrome were the most frequent events reported as being severe in intensity. When looking at the dose distribution of severe adverse events, they tended to occur with the most frequently prescribed doses, 16mg and 20mg Suboxone per day.

The serious event preferred term most commonly reported was elevated liver function test. This is not a normal category of serious adverse events reporting but was designated as such in the protocols of studies CR96/013+CR96/014. The large number of serious adverse events related to psychiatric body system is explainable by the instability of the addict patient population and lead to the conclusion that a regularly monitoring during treatment is needed. Adverse events relating to the gastrointestinal system occur very often after induction of an opioid treatment, particularly in opioid naïve patients. Therefore it's not surprising that these adverse events are common reasons for discontinuation. The number of deaths is not increased in Suboxone treated subjects.

It can be concluded that patients with existing hepatitis and/or HCV infection are probably more likely to have greater increases in hepatic enzymes during treatment with buprenorphine (or methadone and LAAM) than others without these complications.

Differences in baseline liver functions (232 subjects in study CR96/013 had normal baseline liver function and 85 had abnormal baseline liver function) did not appear to be associated with any consistent trend in the incidence of adverse events.

In some markets Buprenorphine alone is contraindicated in pregnancy and in others Buprenorphine alone use is based on evaluation by the physician of the risk of Buprenorphine alone use versus continued illicit heroin use. The cases of foetal death and deformities did not display any unusual pattern and were not specific to the use of buprenorphine. In neonates of opioid dependent mothers the following problems occur more often: small for gestational age, reduced weight and length, premature delivery, small head circumference, neonatal withdrawal, and later mental, emotional or behavioural problems. This will be discussed in the preclinical assessment report in more detail.

The adverse event profiles of Suboxone and Buprenorphine alone are comparable. This conclusion results from more than 3000 subjects in clinical trials and from post marketing data in the USA. No safety issues arise from switching the therapy from Buprenorphine alone to Suboxone.

The CHMP was concerned about spontaneous abortion with the use of Suboxone.

The applicant's deletion of this term was not agreed, as in the applicant's response there are no unequivocal data supporting causality. Pregnancy data of patients under Buprenorphine alone treatment from the literature are scarce. The applicant states that all spontaneous abortion cases in the latest PSUR covering the period 05 May 2005 to 04 Nov 2005 were from EU countries in which pregnancy is not an absolute contraindication. This would suggest a possible link with buprenorphine substitution treatment. It is accepted that polyabuse is a factor and this can be reflected in the SPC. Also in this period there were 6 cases of spontaneous abortion, 5 foetal deaths and 4 premature deaths in 93 pregnancy cases (Results of the Cumulative Prospective Pregnancy data). In the Cumulative Retrospective Pregnancy Data (119 Pregnancy Cases with 294 Pregnancies Reported) there were 11 spontaneous abortion in 10 mothers.

Neonatal drug withdrawal syndrome will be mentioned in section 4.8 of the SPC. In fact the use of Buprenorphine alone and Suboxone, whether by inappropriate diversion to pregnancy women or not, has occurred and results in a neonatal withdrawal syndrome that should be addressed appropriately. The most recently submitted PSUR describes 38 cases as the most common newborn event with symptoms compatible with drug withdrawal syndrome.

The applicant had no further information with which to address concerns relating to the use of Suboxone in pregnancy at the time of the procedure and proposed to address this issue within the Risk Management Plan.

The section 4.8 of the SPC has been adapted accordingly.

"Spontaneous abortion has been reported with both buprenorphine and buprenorphine-naloxone. It is not possible to establish a causal relationship since cases typically involve other drug use or risk factors for spontaneous abortion (see Section 4.6).

A neonatal abstinence syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. The syndrome may be milder and more protracted than that from short acting full mu-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (see Section 4.6)."

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

A detailed description of the company's pharmacovigilance system as required by the new legislation & provisions with this consolidated response documentation was presented, which included the statements of the MAH and the qualified person regarding their availability of means for the notifications of adverse reactions, the organisation and procedural aspects of global pharmacovigilance and European safety department activities within Shering-Plough.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table: Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Induction with Suboxone	The applicant commits to performing a prospective study	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.2
<u>Switch from Buprenorphine alone to Suboxone</u>	The applicant commits to conducting a prospective controlled study	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.4
Switch from Suboxone to Buprenorphine alone during detoxification	The therapy will be monitored. and reported with regard to the development of a low dose (0.4/0.1) tablet of Suboxone .	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.2
Spontaneous abortion	Annual Safety Reports and Periodic Safety Update	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.6.
Neonatal withdrawal syndrome, other newborn conditions	Annual Safety Reports and Periodic Safety Update	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.6.
Hepatitis, other liver abnormalities	Annual Safety Reports and Periodic Safety Update	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.4.
Intravenous misuse	Annual Safety Reports and Periodic Safety Update	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.4.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The pharmacovigilance plan included signalling reviews on events of interest: spontaneous abortion, neonatal withdrawal syndrome and other newborn conditions, hepatitis and other hepatic abnormalities, misuse, intravenous misuse, death, overdose, drug interaction, infections, psychiatric disorders, from Schering Plough and from WHO Adverse event database.

The risk minimization plan included sales force training to ensure safe and effective use and minimize the potential for diversion and misuse. Additional information packages for physicians, pharmacists, and patients should increase the awareness on the risks of drug abuse and should emphasize the importance of reporting the cases of abuse and AE's.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of test carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

Non-clinical pharmacology and toxicology

No novel toxicological aspects rose from the studies with a mixture of buprenorphine/naloxone in comparison with knowledge about the compounds alone. Based on toxicokinetic data raised from the dietary study with Suboxone, an exposure of animals sufficiently above the maximum therapeutic dose in humans has been reached. Clinical signs reflected the pharmacodynamics of the active ingredients.

Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups during a 2-year dietary carcinogenicity study in rats.

Based on the estimated exposure multiples of 3 to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m² basis, the clinical relevance of this findings remains limited.

Efficacy

The combination of an opioid antagonist with a potent μ -opioid analgesic is an established strategy for reducing the potential for intravenous misuse.

Concerning the pharmacokinetic programme, individual studies were not powered to demonstrate statistically comparable bioavailability of buprenorphine from Suboxone or Buprenorphine alone (buprenorphine alone). Nevertheless all the presented studies lead to consistently comparable pharmacokinetic results. The conclusion of comparable bioavailability of buprenorphine from Suboxone or Buprenorphine alone is therefore endorsed.

Based on the results of the pharmacodynamic studies the intravenous misuse potential for Suboxone is very low in comparison with buprenorphine alone.

The intravenous or intramuscular administration produces withdrawal effects in all opiate dependent subjects. At the same time, sublingual or oral administration of naloxone in doses up to 8 mg has no pharmacodynamic effects.

After 4 week of treatment patients treated with Suboxone had statistically significant reduced heroin use versus placebo, as judged by the higher percentages of urine samples that were negative for opiates (17.8% versus 5.8%). Patients on Suboxone also had a significant reduction in craving for heroin.

Results also indicate that Suboxone is as effective as Buprenorphine alone (buprenorphine alone) in the treatment of opiate dependency.

Finally, successful detoxification can be obtained with Suboxone titrated downward to 2 mg per/day before termination of the therapy. The switch to 0.4 mg of buprenorphine alone may be considered.

Safety

The adverse event profiles of Suboxone and Buprenorphine alone are comparable. This conclusion results from data of more than 3000 subjects in clinical trials and from post marketing data in the USA.

The most frequently reported events during the efficacy study (reported by at least 10% of subjects) were headache, withdrawal syndrome, pain, insomnia, nausea, and sweating. No safety issues arise from switching the therapy from Buprenorphine alone to Suboxone.

Patients with existing hepatitis and/or HCV infection are probably more likely to have greater increases in hepatic enzymes during treatment with buprenorphine than others without these complications.

Spontaneous abortion and neonatal withdrawal syndrome have consistently been reported in case of exposure during pregnancy,

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

It was ongoing at the time of assessment. It will be provided post-authorisation (see 2.7).

Risk-benefit assessment

SUBOXONE is a fixed combination product for chronic substitution therapy in opiate dependence consisting of buprenorphine and naloxone formulated into a sublingual tablet containing buprenorphine and naloxone in the ratio 4:1 of the bases.

The claimed indication is substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse.

Suboxone is intended as a "take home" medication and treatment is intended for use in adults and, as requested by the CHMP, adolescents over 15 years of age who have agreed to be treated for addiction.

Concerning efficacy, the clinical studies programme consistently demonstrated Suboxone is effective as substitution treatment for opioid drug dependence within a framework of medical, social and psychological treatment for addiction.

Concerning safety, Suboxone was studied over short and long term repeated administration and followed across substantial post marketing experience. The safety profile of Suboxone does not raise concerns with respect to the risk already known for buprenorphine alone.

A risk management plan was submitted.

The CHMP, having considered the data submitted, was of the opinion that in addition to the use of routine pharmacovigilance, the following follow-up measures were needed:

- to performing both a prospective study of induction with Suboxone, and a prospective controlled study of the switch from buprenorphine alone to Suboxone,
- the Applicant will provide all safety information from ongoing or planned studies
- the switch from Suboxone to buprenorphine alone in detoxification therapy will be monitored and should problems occur they will be reported and discussed with regard to the development of a low dose (0.4/0.1) tablet of Suboxone
- the following additional risk minimisation activities were required: physician awareness on the risk of spontaneous abortion, neonatal withdrawal syndrome and other neonatal conditions, hepatitis and other liver abnormalities, (intravenous) misuse and related severe adverse events

Buprenorphine is a substance scheduled in Schedule III of the UN convention on Psychotropic substances, which requires it to be classified as special medical prescription.

It is proposed that Suboxone is prescribed by physicians experienced in the treatment of addiction /opiate dependence.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Suboxone in the treatment is substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. As requested by the CHMP, treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction - was favourable and therefore recommended the granting of the marketing authorisation



Suboxone

buprenorphine / naloxone

[« Previous tab](#)

Changes since initial authorisation of medicine

Name	Language	First published	Last updated
<u>Suboxone : EPAR - Procedural steps taken and scientific information after authorisation</u>	(English only)	25/06/2009	10/09/2013

Initial marketing-authorisation documents

Name	Language	First published	Last updated
<u>Suboxone : EPAR - Procedural steps taken before authorisation</u>	(English only)	19/10/2006	
<u>Suboxone : EPAR - Scientific Discussion</u>	(English only)	19/10/2006	

Share
Loading

Diversion of Buprenorphine/Naloxone Coformulated Tablets in a Region with High Prescribing Prevalence

Andrew A. Monte, MD
Todd Mandell, MD
Bonnie B. Wilford, MS
Joseph Tennyson, MD
Edward W. Boyer, MD, PhD

ABSTRACT. The purpose of this article was to characterize practices of buprenorphine/naloxone (B/N) diversion in a region with a high prescribing prevalence. A cross-sectional, open-ended survey was administered to individuals entering opioid addiction treatment programs in two New England states. The authors obtained formative information about the knowledge, attitudes, beliefs, practices, and street economy of B/N diversion. The authors interviewed 51 individuals, 49 of which were aware of B/N medication. Of that number, 100% had diverted B/N to modulate opiate withdrawal symptoms arising from attempted “self-detoxification,” insufficient funds to purchase preferred illicit opioids, or inability to find a preferred source of drugs. Thirty of 49 (61%) participants obtained the illicit drug from an individual holding a legitimate prescription for B/N. A high proportion of individuals in the study locations who sought treatment for opioid addiction self-reported the purchase and use of diverted B/N. The diversion of B/N may be minimized by modifying educational, treatment, monitoring, and dispensing practices.

KEYWORDS. Buprenorphine/naloxone, Suboxone, diversion, opiate withdrawal, detoxification

INTRODUCTION

The Drug Addiction Treatment Act of 2000 originated from the recognition that insufficient numbers of drug treatment centers offered opioid replacement or detoxification services.¹ Under the Drug Addiction Treatment Act of 2000, eligible physicians may obtain a waiver from the separate registration requirements of the Narcotic Addict Treatment Act to treat opioid addic-

tion with Schedule III, IV, and V opioid medications or combinations of such medications that have been specifically approved by the Food and Drug Administration for that indication.¹ Importantly, under the Drug Addiction Treatment Act of 2000, individual states could not preclude waived practitioners from prescribing or dispensing eligible medications.¹ The consequence of the Drug Addiction Treatment Act of 2000 is that medications for the treatment of opioid

Andrew A. Monte, Joseph Tennyson, and Edward W. Boyer are affiliated with the University of Massachusetts Medical School, Worcester, MA.

Todd Mandell is affiliated with the Alcohol and Drug Abuse Programs, Vermont Department of Health, Montpelier, VT.

Bonnie B. Wilford is affiliated with the JBS International, Inc., Rockville, MD.

Address correspondence to: Andrew A. Monte, MD, Department of Emergency Medicine, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01655 (E-mail: monteaa@umhc.org).

addiction may be prescribed and dispensed on a Food and Drug Administration basis by any licensed physician who has obtained a federal waiver.¹

On October 8, 2002, the Food and Drug Administration approved two formulations that contained buprenorphine, Subutex (buprenorphine alone), and a coformulation of buprenorphine and naloxone (Suboxone) (B/N); concurrently, the Drug Addiction Treatment Act of 2000 was amended to include these drugs.¹ Buprenorphine has favorable pharmacologic features that lend itself to outpatient treatment of opioid addiction. Unlike full agonists such as methadone, buprenorphine is a partial μ -receptor agonist. As a partial agonist, buprenorphine demonstrates a plateau of its agonist effect at higher doses that enhances its safety profile compared to full agonists.^{2,3} This "ceiling effect" includes an upper limit on the severity of side effects associated with overdose, such as respiratory depression.^{4,5} Additionally, buprenorphine dissociates slowly from the μ -receptor, permitting alternate day dosing.^{6–10} Buprenorphine may also have positive effects in combating depression associated with the addiction treatment of multiple classes of medications other than opioids.

Although buprenorphine is the pharmacologic component in both products that modulates opioid withdrawal, naloxone is incorporated only in B/N as a protection against diversion, misuse, and abuse of drug.¹¹ Additional protections against diversion are derived from provider education, Drug Enforcement Agency registration of providers, and regulatory limitations on the number of patients that a physician may treat at any one time. Despite these efforts, diversion and illicit use of B/N are increasingly reported, especially in hidden populations such as the incarcerated and active drug users.^{12–14} Unfortunately, little is known about B/N diversion, the reasons for its illicit use, or sources of diverted drug.¹² To obtain formative information of B/N diversion, we conducted an ethnographic study of opioid abusers in rural and urban environments to ascertain knowledge, attitudes, beliefs, and practices related to diversion and illicit use of B/N.

METHODS

Study Design and Sample

We conducted a cross-sectional study of individuals seeking treatment for opioid abuse in Worcester, Massachusetts, and Montpelier, Vermont, between October 1, 2007, and March 31, 2008. During random time periods, we approached sequential persons with a history of opioid abuse presenting for care. Inclusion criteria were (1) a history of opioid abuse; (2) 18 years of age or older; (3) awareness of B/N as a medication; (4) the ability to speak English; and (5) the ability to provide verbal informed consent. Eligible individuals participated in an open-ended interviewer-administered survey. Domains of the 29-item survey included participant demographics, substance abuse history, drug treatment history, and knowledge, attitudes, beliefs, and practices related to B/N. To increase the internal validity of survey results, we asked participants to describe or recognize B/N tablets. Interviews were audio-taped and transcribed in batches to preserve participant anonymity. We abstracted participant quotations related to the diversion of B/N, removed all identifiers, and placed them in a random order prior to review. The University of Massachusetts Medical School Institutional Review Board approved this study.

Assessments and Outcome

The dataset used in this investigation was intended to obtain formative information about the reasons why B/N was diverted to illicit use. We analyzed the study variable using Kappa and descriptive statistics. We used a 49-item abstraction form to collect information about B/N diversion; by means of simple, dichotomous answers ("agree/disagree"), examiners assessed whether opioid abusers diverted B/N for medically indicated purposes. Masked versions were coded independently by two examiners trained in the use of the form. Working according to an instruction manual and blinded to the results, responses were coded and the degree of inter-observer agreement was determined using the Kappa statistic.

TABLE 1. Demographics of Survey Participants (n = 49)

Variable	Value
Age mean (SD), y	32 (11.332)
Male, no. (%)	34 (69.4)
Race, no. (%)	
White	47 (95.9)
Black/African American	1 (2.0)
Hispanic	1 (2.0)
Spanish	0 (0.0)
Latino	0 (0.0)
Education, No. (%)	
8th grade or less	2 (4.1)
Some high school	12 (24.5)
Vocational degree/some college	6 (12.2)
College	28 (57.1)
Professional/graduate degree	1 (2.0)
Town size of participant residence, No. (%)	
Rural, < 5,000 people	9 (18.4)
Small town, 5,001–50,000 people	16 (32.7)
Medium city, 50,001–200,000 people	22 (44.9)
Large city, >200,000 people	2 (4.1)
Town size in which abused substance was procured, No. (%)	
Rural, < 5,000 people	4 (8.2)
Small town, 5,001–50,000 people	15 (30.6)
Medium city, 50,001–200,000 people	22 (44.9)
Large city, >200,000 people	5 (10.2)
Not sure or refused to answer	3 (6.1)
Town size in which illicit B/N was procured, No. (%)	
Rural, < 5,000 people	3 (6.1)
Small town, 5,001–50,000 people	12 (24.5)
Medium city, 50,001–200,000 people	21 (42.9)
Large city, >200,000 people	3 (6.1)
Not sure or refused to answer	10 (20.4)

RESULTS

The demographic profile of study participants is presented in Table 1. Of the 51 individuals approached for participation in the study, 49 (96%) were aware of B/N as a medication. Of that number, 49 (100%) had themselves diverted B/N for one or more of the following reasons to avoid opioid withdrawal, for attempted self-management of opioid withdrawal, because the individual lacked sufficient funds to purchase preferred opioids of abuse, or because trusted sources of opioids were unavailable (e.g., a participant's dealer had been arrested or incarcerated). Only two of 49 participants described the diversion of B/N for exploratory purposes by

people who were not already opioid dependent, although neither had witnessed such episodes of abuse. Despite the subjective nature of the research question, there was high agreement between coders (Kappa = 0.81, $p < .0001$). We had originally intended to analyze data on B/N diversion from urban and rural populations separately, but a preliminary examination indicated comparable behaviors that allowed combination of these data for analysis. A substantial proportion of participants (30; 61%) obtained the drug from an individual holding a legitimate prescription for B/N written by a waived provider, either as a gift or by purchase. The remaining participants (19; 39%) purchased B/N from heroin dealers. Participants indicated that a common practice is for a patient undergoing B/N induction to inflate the severity of withdrawal symptoms, leading the treating physician to over-prescribe the drug. With a legitimate prescription in hand, these patients could sell the unneeded B/N or they could revert to heroin use because B/N is intended for outpatient drug treatment. In the latter case, patients would interrupt heroin use, returning long enough to B/N to defeat surveillance drug testing performed at follow up office visits. Many respondents (23; 47%) reported that insufficient legitimate access to B/N compelled them to seek illicit sources of the drug.

Many participants reported that illicit B/N had comparable or greater availability than heroin due to persistent law enforcement action against heroin dealers. In purchasing illicit B/N, participants reported the price per 8 mg tablet in the New England street economy was between \$5 in urban areas to \$40 in rural settings. Selected themes related to B/N diversion are presented in Table 2.

DISCUSSION

A high proportion of individuals in central Massachusetts and Vermont seeking treatment for opioid addiction self-reported the purchase and illicit use of diverted B/N. It was also a striking finding that only opioid addicts who had not used illicit B/N were those who were unaware of its existence. The most common reason for

TABLE 2. Quotations from Selected Survey Participants Regarding B/N

B/N beliefs and attitudes	"My friends who were using it said it was a miracle drug-no CTs [cold turkey] and no withdrawal."
Perceived risks of B/N	"...I want a prescription [for B/N] but there aren't enough docs who prescribe it." "...getting dope sick if you take too much, I'm petrified of that." "[If you] mix it with rum [you get] too [messed] up." "[If] mixed with alcohol [there may be] death, hallucinations, [and] increased crime."
Practices of B/N diversion	"I sell it at \$20 per 8mg tablet. It's cheaper than a day's dope. ... I get it from users who have a prescription but use only a part of it. They'll take maybe half and sell the other half." "[B/N is] easier to get than heroin" "You can buy it anywhere, it is easy to buy." "I have a prescription for 64 mg a day, I take 16 or 24mg and sell the rest." "[It has been] stolen from pharmacies."
Reasons why B/N is used	"First (I used it) to get high, then I didn't want to be sick, and eventually to get off the drugs" "[To] Feel normal, feel OK, have a clear head" "I used it because I couldn't get no dope. There was a period of time when I used it to stay clean. It is far better than going to detox or going to a clinic." It is unbelievably good if used in the right way." "To avoid methadone clinic." "People use it when they can't find their dealer." "When they run out of money for dope." "Sometimes to get high, [people] mix it with rum." "People use it to maintain life."
Experience while on B/N B/N street practice	"I didn't even feel like smoking [cigarettes]." "I've also used B/N and then shot up to get high. I thought I wouldn't get any dope [heroin] and then some came up. You have about an hour to use before you can't get high after B/N." "... Another person who was prescribed B/N never took it ... he sold the prescription and used heroin. He [switched back to] B/N approximately 5 days before his next clinic visit to beat drug tests." "[It is] easily misused for [the] wrong reasons. People who don't need it use [it] to get high. [Some] use B/N IV."

diversion among our study population is to avoid opioid withdrawal. In our study participants, however, opioid withdrawal arose in the context of either (1) "self-detoxification" from heroin or prescription opioid analgesic agents, (2) insufficient funds to purchase preferred illicit opioids, or (3) the inability to locate a preferred source of illicit opioids. Although some of our participants purchased illicit B/N with the intent of treating their addiction, a substantial proportion (37%) used it with the intent of resuming opioid abuse. These results suggest that diversion and unsupervised use of B/N may prolong the problematic use of illegal opioids by delaying entry into formal drug treatment programs.

Our results also provide formative data about the source, means of diversion, and street economy of illicit B/N. Although the source of diverted B/N has been a point of conjecture, we feel that individuals reselling legitimately prescribed B/N is a reasonable explanation.¹² For

example, our results indicate that a single person who convinces a treating clinician to over-prescribe B/N can divert the drug to as many as eight individuals. Furthermore, our results are consistent with the National Survey on Drug Use and Health results in which respondents reported receiving opioid analgesic medications most commonly from a single person holding a single prescription.¹⁵ Previous findings of B/N being the least diverted of all opioid analgesics contradicts our observations.¹⁶ Those results, published in 2005, identified an increase in buprenorphine diversion that occurred almost immediately after the release of buprenorphine products in the United States.¹⁶ Furthermore, we believe that B/N has now so deeply penetrated into hidden populations of injection drug users that its diversion and illicit use is widespread. The abuse and diversion patterns differ from those of other commonly diverted prescription opioids such as oxycodone.

Oxycodone abusers, composed predominantly of white men drawn from suburban and rural areas, are demographically similar to our study population but the similarities are superficial.¹⁶ Surveillance using key informant networks led to the hypothesis that greater wealth in suburban and rural residents favored abuse of more costly prescription drugs such as oxycodone over heroin.¹⁶ In contrast, many members of our study population illicitly used B/N only during periods of financial hardship; this finding, when coupled with anecdotal reports from Baltimore, Maryland, seems to suggest that rates of B/N diversion may increase during economic strife.^{17,18} Alternatively, the composition of our study population may simply reflect the general population of central Massachusetts and Vermont or disparities in the availability of drug treatment programs.

Interestingly, study participants reported dramatic differences in the street cost of B/N. The lower price in urban areas connotes greater availability of illicit B/N that, in turn, reflects the degree of B/N prescribing in city communities. Alternatively, the higher street cost of B/N reported in Vermont may indicate insufficient access to addiction treatment programs in this mountainous rural area; this finding supports the hypothesis that limited services may exacerbate drug diversion.^{12,19} Vermont has the highest number of prescriptions for B/N per capita in the country, indicating extraordinary demand for drug treatment services; the elevated street price for B/N indicates either the remoteness of the population relative to treatment locations or the need for increased treatment settings.¹²

Although it can potentially decrease injection drug use and, concomitantly, HIV transmission, diverted B/N does carry public health risks.^{12,20–23} For example, individuals who self-treat opioid withdrawal with B/N may develop decreased tolerance to opioids that places them at increased risk of death if they revert to injection drug use.²⁴ As with other opioid analgesics, the number of B/N prescriptions filled in a region appears to correlate with unintentional ingestions in young children in the same area.²⁵ Massachusetts ranked third in grams of buprenorphine distributed per 100,000 population and Boston reported more buprenorphine-related Emergency Department visits than any other

metropolitan area between 2003 and 2005.¹² Diverted B/N may represent greater risk to children than legitimately prescribed drug because the former may not be sold with child-resistant packaging. Unintentional ingestion by pediatric patients, some of which resulted in severe respiratory compromise, has been associated with diverted B/N carried loose in clothing.²⁶

The diversion of B/N may be minimized by modifying educational, treatment, monitoring, and dispensing practices. For example, B/N, which was originally intended for use in highly selective subpopulations, has been increasingly applied to the treatment of individuals with long histories of opioid addiction and multiple coexisting psychological, social, and legal difficulties.²⁷ As suggested for oxycodone, improved provider education and more sophisticated patient selection may limit the opportunity for diversion from prescribing to inappropriate groups.²⁸ Clinicians who oversee B/N induction may consider applying greater scrutiny to anyone who reports unexpected intensity of opioid abstinence symptoms while initiating B/N treatment. In addition to seeking objective findings of opioid withdrawal, prescribers should consider more frequent follow-up office visits, employing drug testing capable of detecting buprenorphine, and utilizing random patient call-ins for drug testing and pill counting. In addition, improved case management to ensure that patients receive psychosocial services that enhance the success of pharmacologic therapy may lessen diversion. The use of bubble packs for B/N dispensing could minimize the opportunity to restock prescribed tablets that had been diverted to illicit sale. Lastly, alerting probation officers and other law enforcement personnel that a patient is diverting B/N may dissuade diversion of B/N.

CONCLUSION

Diversion of B/N co-formulated tablets is highly prevalent among individuals entering drug treatment programs in central New England. Illicit B/N is widely available, inexpensive, and predominantly diverted from patients with legitimate prescriptions written by a waived B/N provider. The primary use of illicit B/N is to modulate symptoms of opioid

withdrawal, the Food and Drug Administration approved indication, although its illicit use in context of "self-detoxification" from opioids, inability to find trusted sources of heroin or prescription opioid analgesic agents, or insufficient funds to support ongoing opioid abuse is inconsistent with the Food and Drug Administration intention. The availability of diverted B/N may delay entry into formal drug treatment programs. Lack of access to waived B/N providers also may also contribute to B/N diversion. Clinicians should carefully review their prescribing and patient monitoring practices.

REFERENCES

1. <http://buprenorphine.samhsa.gov/fulllaw.html>
2. Ling W, Smith D. Buprenorphine: blending practice and research. *J Subst Abuse Treat*. 2002; 23:87-92.
3. Fiellin D, O'Connor P. Office-based treatment of opioid-dependent patients. *NEJM*. 2002; 347:817-23.
4. Walsh S, Preston K, Stitzer M, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther*. 1994; 55:569-80.
5. Liguori A, Morse W, Bergman J. Respiratory effects of opioid full and partial agonists in rhesus monkeys. *J Pharmacol Exp Ther*. 1996; 277:462-72.
6. Petry N, Bickel W, Badger G. Examining the limits of the buprenorphine interdosing interval; daily, every-third-day and every-fifth-day dosing regimens. *Addiction*. 2001; 96:823-34.
7. Johnson R, Eissenberg T, Stitzer M, Strain EC, Liebson IA, Bigelow GE. Buprenorphine treatment of opioid dependence: clinical trial of daily versus alternate-day dosing. *Drug Alcohol Depend*. 1995; 40:27-35.
8. Fudala P, Jaffe JH, Dax EM, Johnson RE. Use of buprenorphine in the treatment of opioid addiction. II. physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. *Clin Pharmacol Ther*. 1990; 47:525-34.
9. Megarbane B, Hreiche R, Pirnay S, Marie N, Baud F. Does high-dose buprenorphine cause respiratory depression?: possible mechanisms and therapeutic consequences. *Toxicol Rev*. 2006; 25:79-85.
10. Lufy K, Cowan A. Buprenorphine: a unique drug with complex pharmacology. *Curr Neuropsychopharmacol*. 2004; 2:395-402.
11. Smith M, Bailey J, Woody G, Kleber H. Abuse of buprenorphine in the United States: 2003-2005. *J Addict Dis*. 2007; 26:107-11.
12. Wilford BB, Maxwell JC. Diversion and abuse of buprenorphine: a brief assessment of emerging indicators. In: SAMHSA, ed. Division of pharmacologic therapies. Washington, DC: US Department of Health & Human Services, 2006:1-70.
13. Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. *Drug Alcohol Depend*. 2007; 88:75-8.
14. Stimmel B. Buprenorphine misuse, abuse, and diversion: when will we ever learn? *J Addict Dis*. 2007; 26:1-3.
15. Results from the 2007 national survey on drug use and health: national findings. In: SAMHSA, ed. 2008. Washington, DC: US Department of Health & Human Services.
16. Cicero T, Inciardi J, Munoz A. Trends in abuse of oxycontin and other opioid analgesics in the united states: 2002-2004. *J Pain*. 2005; 6:662-72.
17. Donovan D. Mixed progress for bupe. *The Baltimore Sun*. 2008; Jul 12.
18. Schulte F, Donovan D, Niedowski E. The buprenorphine experiment. *The Baltimore Sun*. 2007; Dec 16, 2007.
19. Roux P, Carrieri M, Villes V, Dellamonica P, Poizot-Martin I, Ravoux I, Spire B. The impact of methadone or buprenorphine treatment and ongoing injection on highly active antiretroviral therapy (HAART) adherence: evidence from the MANIF2000 cohort study. *Addiction*. 2008; 103(11):1828-36.
20. Sullivan L, Moore B, Chawarski M, Pantalon MV, Barry D, O'Connor PG, Schottenfeld RS, Fiellin DA. Buprenorphine/naloxone treatment in primary care is associated with decreased human immunodeficiency virus risk behaviors. *J Subst Abuse Treat*. 2008; 35:87-92.
21. Spire B, Lucas G, Carrieri M. Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST). *Int J Drug Policy*. 2007; 18:262-70.
22. Maher L, Jalaludin B, Wand H, Jayasuriya R, Dixon D, Kaldor J. Impact of reduction in heroin availability on patterns of drug use, risk behaviour and incidence of hepatitis C virus infection in injecting drug users in new south wales, australia. *Drug Alcohol Depend*. 2007; 89:244-50.
23. Todd C, Abed A, Strathdee S, Scott PT, Botros BA, Safi N, Earhart KC. HIV, hepatitis C, and hepatitis B infections and associated risk behaviour in injection drug users, kabul, afghanistan. *Emerg Infect Dis*. 2007; 13:1327-31.
24. Wines J, Saitz R, Horton N, Lloyd-Travaglini C, Samet J. Overdose after detoxification: a prospective study. *Drug Alcohol Depend*. 2006; 89:161-9.
25. Bailey J, Campagna E, Dart R. The underrecognized toll of prescription opioid abuse in young children. *Ann Emerg Med*. 2008; 53(4):419-24.
26. Geib A, Babu K, Ewald M, Boyer E. Adverse effects in children after unintentional buprenorphine exposure. *Pediatrics*. 2006; 118:1746-51.
27. Gonzalez G, Oliveto A, Kosten T. Combating opiate dependence: a comparison among the available pharmacologic options. *Expert Opin Pharmacother*. 2004; 5:713-25.
28. Wunsch M, Cropsey K, Campbell E, Knisely J. Oxycontin use and misuse in three populations: substance abuse patients, pain patients, and criminal justice participants. *J Opioid Manag*. 2008; 4:73-9.

Opioid Drug Utilization and Cost Outcomes Associated With the Use of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use

Aman Deep Kaur, PharmD; Angela McQueen, PharmD; and Saira Jan, MS, PharmD

ABSTRACT

BACKGROUND: Management of opioid dependence is associated with many challenges such as the misuse of prescribed treatment and lack of medication adherence that can affect the clinical outcome of the patient. Buprenorphine-naloxone was approved by the U.S. Food and Drug Administration in October 2002 as the first outpatient treatment indicated for opioid dependence. There is only 1 report in the literature on the effectiveness of buprenorphine-naloxone in a real-world setting and no reports on persistence and cost obtained from administrative claims data.

OBJECTIVES: To determine (1) the length and cost of therapy with oral buprenorphine-naloxone, and (2) the cost avoidance for opioid dependence as measured by opioid utilization and opioid drug cost obtained from pharmacy claim records.

METHODS: The patients for this drug use evaluation (DUE) were identified from a New Jersey managed care organization (MCO) with approximately 1.8 million members with pharmacy benefits who (a) were continuously enrolled from October 1, 2004, through September 30, 2006; (b) had their first buprenorphine-naloxone pharmacy claim during the fixed 6-month initiation period (April 1, 2005, through September 30, 2005); and (c) had at least 1 opioid pharmacy claim in the 6-month pre period preceding the 6-month initiation period. The outcome measures included the number of opioid pharmacy claims, daily dose, days supply, and cost defined as opioid ingredient cost. Member cost share and net plan cost (after subtraction of member cost share) were also measured. The measurement periods for opioid use and cost were the fixed calendar periods for 6 months from October 1, 2004, through March 31, 2005, and for 12 months from October 1, 2005, through September 30, 2006. Persistence in the 12-month follow-up period was defined as a gap of 30 days or less between depletion of the days supply for the preceding pharmacy claim for buprenorphine-naloxone and the date of service (refill date) for the succeeding pharmacy claim for buprenorphine-naloxone.

RESULTS: Of the 160 new buprenorphine-naloxone users with continuous pharmacy enrollment for the 2-year period ending September 30, 2006, 84 patients (52.5%) had at least 1 opioid pharmacy claim in the 6-month pre period from October 1, 2004, through March 31, 2005, and were included in this DUE. In the 12-month post period from October 1, 2005, through September 2006, the median length of therapy with buprenorphine-naloxone was 1 month, and the mean length of therapy was 3.5 months. Only 40 patients (47.6%) had a pharmacy claim for buprenorphine-naloxone at month 1 in the 12-month post period. Persistence was 27.4% (n=23) at 6 months (March 2006) and 20.2% (n=17) at 12 months (September 2006) in the post period. A total of 24 study patients (28.6%) had no opioid pharmacy claims other than buprenorphine-naloxone in the 12-month post period. Utilization of opioids decreased by 18.8%, from 1.49 opioid pharmacy claims per patient per month (PPPM) in the pre period to 1.21 claims PPPM in the post period ($P=0.031$). Excluding the 0.42 buprenorphine-naloxone claims PPPM, opioid utilization decreased by 47.0%, from 1.49 claims PPPM to 0.79 claims PPPM ($P<0.001$) in the

12-month post period. Before subtraction of member cost share, the actual drug cost of opioids including buprenorphine-naloxone appeared to be 26.9% lower (\$156.24 PPPM) in the post period compared with \$213.74 PPPM in the pre period, but the difference was not statistically significant ($P=0.254$). Excluding the cost of the buprenorphine-naloxone, actual opioid drug cost decreased 66.5% from \$213.74 PPPM pre period to \$71.65 PPPM post period ($P=0.047$).

CONCLUSIONS: Approximately one half of the patients who had a new claim for buprenorphine-naloxone were excluded from this study because there was no utilization of prescription opioids in the 6 months prior to initiation. For patients with documented use of prescription opioids prior to initiation, treatment with buprenorphine-naloxone was associated with a reduction in opioid utilization and cost in the first year of follow-up. Persistence was only 27% at 6 months and 20% at 12 months, and there were no drug cost savings in the follow-up period when the actual cost of the buprenorphine-naloxone therapy was included.

J Manag Care Pharm. 2008;14(2):186-94

Copyright© 2008, Academy of Managed Care Pharmacy. All rights reserved.

What is already known about this subject

- In a multicenter, double-blind, randomized placebo-controlled trial, 17.8% of urine samples for opiate-addicted persons were negative for opiates after 4 weeks of treatment with 16 mg of buprenorphine and 4 mg naloxone per day compared with 5.8% for placebo ($P<0.001$). The open-label follow-up safety study over 52 weeks found 35% to 67% of urine samples negative for opiates. Another randomized 24-week trial without placebo-control reported about 6 weeks as the mean maximum duration of continuous abstinence from illicit opioids and 40% to 44% opioid-negative urine samples.
- There are many clinical trials of the efficacy of buprenorphine and buprenorphine-naloxone, but there is no retrospective drug use evaluation observational study published in the peer-reviewed literature that evaluates the relationship of buprenorphine-naloxone use for opioid dependence and the utilization and costs of prescription opioids.

Note: An editorial on the subject of this article appears on pages 195-97 of this issue.

Opioid Drug Utilization and Cost Outcomes Associated With the Use of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use

Abstract Study Data

- New use of buprenorphine-naloxone was associated with a 47.0% decrease in opioids other than the intervention drug, as measured by pharmacy claims, from 1.49 claims per patient per month (PPPM) in the 6-month pre period to 0.79 claims PPPM in the 12-month post period ($P<0.001$). Including the intervention drug, there was an 18.8% decrease in total opioid claims, from 1.49 to 1.21 PPPM ($P=0.031$).
- Opioid drug ingredient cost associated with new use of buprenorphine-naloxone, before subtraction of member cost share, decreased by 66.5%, from \$213.74 PPPM in the 6-month pre period to \$71.65 PPPM in the 12-month post period ($P=0.047$). Including the cost of the intervention drug and before subtraction of member cost share, use of buprenorphine-naloxone was not associated with drug cost savings, \$213.74 PPPM in the pre period versus \$156.24 in the post period ($P=0.254$).
- In addition to the \$84.59 PPPM in direct drug cost of the buprenorphine-naloxone incurred in the fixed 12-month post period, \$40,176 in buprenorphine-naloxone direct costs was incurred during the fixed 6-month initiation period, or an average \$478 per patient and 59 days supply of buprenorphine-naloxone per member.
- Persistence with buprenorphine-naloxone, defined as a gap of no more than 30 days between depletion of the days supply for the preceding pharmacy claim for buprenorphine-naloxone and the date of service (refill date) for the succeeding pharmacy claim, was only 47.6% at 1 month after the initiation period, 27.4% at 6 months, and 20.2% at 12 months.

An estimated 5.2 million people aged 12 years or older abused pain relievers in 2006.¹ Insured members who are opioid abusers are associated with 8.7 times higher mean annual direct health care cost than non-abusers (\$15,884 versus \$1,830, respectively).² Since the implementation of the Drug Addiction Treatment Act of 2000 (DATA 2000), physicians have been able to treat opioid addiction in the outpatient setting.³ Methadone for treatment of opioid addiction is limited to certified opioid treatment programs (i.e., in designated "clinics") by federal regulations.^{3,4} The combination of buprenorphine and naloxone in a sublingual tablet (Suboxone) is indicated for the treatment of opioid dependence and is preferred as maintenance therapy for most patients.^{3,5}

Buprenorphine-naloxone may be used by certified physicians in the outpatient setting for maintenance therapy, whereas methadone when used for opioid addiction in detoxification or maintenance programs is limited to certified opioid treatment programs.^{4,5} When treating opioid addiction with buprenorphine, there are 3 stages for maintenance therapy: (1) the induction phase occurs in an observed setting 12 to 24 hours after the

patient has not used opioids; (2) the stabilization phase occurs when the patient experiences "no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has uncontrollable cravings for opioid agonists"; and (3) the maintenance phase refers to when the patient is on steady doses of a buprenorphine-containing regimen.³ The length of therapy for the maintenance phase is individualized and may be infinite.³

Buprenorphine is a partial agonist at the μ -opioid receptor, and its abuse potential is lower than that of a full agonist. Naloxone, a pure narcotic antagonist, has no clinically significant effects sublingually, but when administered intravenously, it produces an antagonist action.³ The combination of buprenorphine and naloxone is desirable in a population prone to abuse, because the presence of naloxone deters illicit use by injection of both buprenorphine and other opiates. To avoid precipitation of withdrawal, buprenorphine (Subutex) is preferred for use during initial therapy because it contains no naloxone. Following induction, buprenorphine-naloxone is preferred when its use includes unsupervised administration.³ Therefore, buprenorphine-naloxone, not buprenorphine, was chosen to include for this drug use evaluation (DUE) for maintenance therapy.

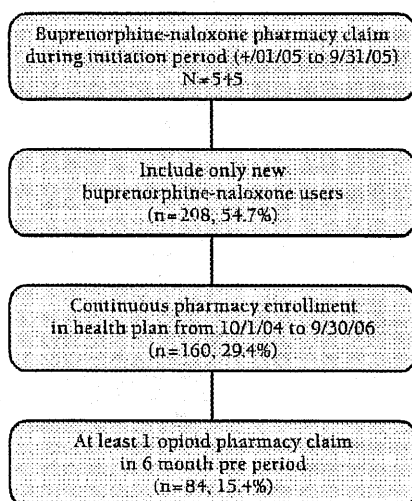
Under the federal Office of National Drug Control Policy Reauthorization Act of 2006 (OND CPRA),⁶ the limitation on the number of patients a physician may treat with buprenorphine-naloxone for opioid dependence increased from 30 patients per prescriber to 100 patients. DATA 2000 requires physicians to undergo a training session or be accredited as an addiction specialist in order to treat opioid dependence in the outpatient setting.³ With more physicians and patients gaining experience with buprenorphine-naloxone, post-marketing analyses are possible. The recommended target dose of buprenorphine per the prescribing information is 16 mg per day, with the range of 4 mg to 24 mg per day, depending on the individual.⁵ The wholesale acquisition cost (WAC) per tablet in 2007 was \$2.52 for the 2 mg to 0.5 mg buprenorphine-naloxone dose form and \$4.45 for the 8 mg to 2 mg dose form.

Clinical trials have shown that buprenorphine treatment is at least as effective as moderate doses of methadone and more effective than clonidine to treat opioid addiction.^{7,8,9,10} In a multicenter, double-blind, randomized placebo-controlled trial, 17.8% of urine samples for opiate-addicted persons were negative for opiates after 4 weeks of treatment with 16 mg of buprenorphine with 4 mg naloxone per day compared with 5.8% for placebo ($P<0.001$).¹¹ The open-label follow-up safety study ($n=461$, of whom 268 were from the double-blind trial) up to 52 weeks found 35% to 67% of urine samples negative for opiates. Another randomized 24-week trial without placebo control reported that the mean maximum duration of continuous abstinence from illicit opioids was about 6 weeks and 40% to 44% of opioid urine samples were negative.¹²

Although there are clinical trials of buprenorphine-naloxone, there has not been a published retrospective DUE of opioid

Opioid Drug Utilization and Cost Outcomes Associated With the Use of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use

FIGURE 1 Patient Inclusion Flow Chart
(From Health Plan of Approximately
1.8 million Commercial Members
With Pharmacy Benefits)



"New" users of buprenorphine-naloxone were defined as members without a pharmacy claim for buprenorphine-naloxone in the 6-month pre period from October 1, 2004, through March 31, 2005.

utilization associated with buprenorphine-naloxone intervention in a real-world setting. Clinical trials occur in a controlled environment, whereas a DUE can shed light on the use of drugs in the environment most important to clinicians and managed care health plans.

The objective of this retrospective DUE was to characterize the utilization patterns and associated costs of members using buprenorphine-naloxone for prescription opioid dependence by reporting (a) utilization defined as opioid pharmacy claims and opioid tablets dispensed, (b) savings defined as reduction in opioid pharmacy claims and opioid drug cost, and (c) persistence with therapy defined as a gap of no more than 1 month, starting from October 1, 2005. Review by an institutional review board was not sought because this DUE and the summary results involved no personal health information that was traceable to an individual health plan member.

Methods

Retrospective analysis identified members from a managed care organization with continuous commercial pharmacy benefit enrollment for 2 years (October 1, 2004, to September 30, 2006). The managed care organization is located in New Jersey and

during the study period had approximately 1.8 million commercial pharmacy members, including health maintenance organization, point-of-service, preferred provider organization, direct access, medical savings account, and traditional indemnity plans. Opioid pharmacy claims were identified using Medi-Span Generic Product Identifier codes beginning with 6510 (narcotic agonists), 6520 (narcotic partial agonists), 6540 (narcotic antagonists), and 6599 (narcotic combinations). A first pharmacy claim was defined as no use of buprenorphine-naloxone in the preceding 6 months. Members who had their first buprenorphine-naloxone claim during the initiation period (April 1, 2005, through September 30, 2005) and had at least 1 opioid pharmacy claim 6 months before initiation were included in the present study (Figure 1).

The follow-up analyses focused on (1) opioid utilization and cost 6 months before and 12 months after the 6-month initiation period, and (2) buprenorphine-naloxone persistence and dose 12 months after the initiation period. The following outcomes were calculated for opioid utilization pre and post index: number of pharmacy claims, days supply, and cost defined as total drug ingredient cost; member cost share; and net plan cost after subtraction of member cost share. The type of opioid product was also assessed, including the number of units (i.e., tablets, capsules, etc.) before and after initiation of buprenorphine-naloxone therapy.

Persistence was assessed for 12 months following the 6-month initiation period for buprenorphine-naloxone, defined as a gap of not more than 1 month in buprenorphine-naloxone therapy (i.e., the patient was defined as non-persistent when there was a gap of 30 days or more between the depletion of the days supply in the preceding claim and the date of service (fill date) of the following claim). Duration of therapy was counted as the number of months (claims) of buprenorphine-naloxone commencing in October 2006.

The dose of buprenorphine per day was calculated for each claim using the following formula: (number of tablets divided by days supply) multiplied by the strength of buprenorphine-naloxone filled. The statistical test used to calculate *P* values was a 1-tailed paired *t*-test. Because the 6-month pre period cannot be compared with the 12-months post period, statistical analyses were performed on the per-patient-per-month (PPPM) results.

Results

Of the 298 new users of buprenorphine-naloxone, 160 (53.7%) had continuous pharmacy benefit eligibility for the entire 2-year period of the study, and 84 (52.5%) of the 160 had prior use of an opioid pharmacy claim in the 6-month pre period (Figure 2). Of the 84 patients who met the inclusion and exclusion criteria, 62% were male, and 38% of patients were female. The mean age was 40.0 years ($n=84$, Figure 3).

The average ingredient cost of opioids decreased from \$213.74 PPPM in the 6 months prior to the initiation period to

Opioid Drug Utilization and Cost Outcomes Associated With the Use of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use

\$71.65 PPPM in the 12 months after the 6-month initiation period ($P=0.047$, Table 1). When the cost of buprenorphine-naloxone was included, the average drug cost (before member cost share) for opioid pharmacy claims was \$156.24 PPPM in the 12-month follow-up period, not significantly less than the pre period ($P=0.254$). The average number of opioid claims excluding buprenorphine-naloxone was lower in the follow-up period (0.79 PPPM) compared with the pre period (1.49 PPPM, $P<0.001$); when buprenorphine-naloxone is included in the comparison, the average number of opioid claims decreased after initiation of buprenorphine-naloxone (1.21 vs. 1.49 PPPM, $P=0.031$), but this lower opioid utilization did not translate into lower opioid drug cost (\$156.24 vs. \$213.74 PPPM, $P=0.254$).

The direct drug cost of the intervention, prior to subtraction of member cost share, was \$477.93 per patient during the 6-month initiation period from October 1, 2004, through March 31, 2005 (Table 2). Because initiation of buprenorphine-naloxone therapy could have commenced at any time during the 6-month initiation period, the total cost understates the actual cost of a 180-day treatment initiation period for all patients, and the cost per patient overstates an initiation pharmacy claim for buprenorphine-naloxone treatment. Members paid \$7,589 (18.7%) of the total allowed charge (i.e., managed care organization (MCO) cost+member cost) for buprenorphine-naloxone during the initiation period (Table 2).

There were 422 claims for buprenorphine-naloxone during the 12-months post period from October 1, 2005, through September 30, 2006, or 0.42 PPPM, of which 72% (304 claims) were for buprenorphine-naloxone 8 mg to 2 mg, while 118 claims were for the 2 mg to 0.5 mg strength (Table 3). Most members were within the recommended buprenorphine daily dose of 4 mg to 24 mg per day (Table 4).⁵ Of the total 281 claims written by prescribers with known medical specialty information in the database, 55.5% (156 claims) were from general/family practitioners or internal medicine, and 22.0% (62 claims) were from psychiatrists or physical medicine and rehabilitation specialists.

Excluding buprenorphine-naloxone use, there was an average 96.8 units PPPM of solid-dose opioid drug use in the 6 months in the pre period, which dropped by 43.9% to 54.3 units PPPM in the 12-months post period (Table 5). By opioid drug type, the largest reduction in use occurred with the fentanyl patch and oral transmucosal fentanyl (i.e., "lollipop").

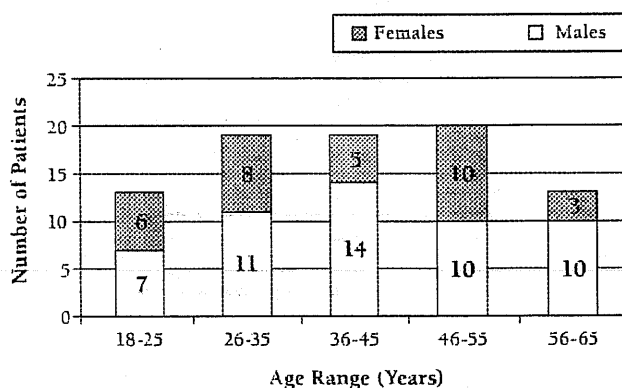
Of the 84 patients new to buprenorphine-naloxone therapy at some point in the 6-month period from October 1, 2004, through March 31, 2005, 59 patients (70.2%) had filled at least 1 pharmacy claim for buprenorphine-naloxone in the 12-months follow-up period from October 1, 2005, through September 30, 2006. Persistence, defined as a gap in therapy of no more than 30 days between exhaustion of the days supply and the actual subsequent refill date, was 47.6% ($n=40$) at month 1 of the 12-months follow-up period (Figure 4). Persistence, starting October 1, 2005, decreased to 27.4% ($n=23$) at month 6

FIGURE 2 Study Time Periods

Time	10/01/04 to 3/31/05	4/01/05 to 9/30/05	10/01/05 to 9/30/06
Analysis of opioid utilization and cost	6 months (pre period)	Initiation period	12 months (post period)
Analysis of buprenorphine-naloxone persistence and dosage			12 months (post period)

Members were included in this DUE if they received buprenorphine-naloxone during the initiation period from April 1, 2005, through September 30, 2005, and did not have a pharmacy claim for buprenorphine-naloxone in the 6 months preceding the initiation period, from October 1, 2004, through March 31, 2005. DUE = drug use evaluation.

FIGURE 3 Age Ranges by Gender ($n=84$)



(March 2006) and 20.2% ($n=17$) at 12 months (September 2006). The mean persistence over the follow-up period was 3.5 months, and the median length of therapy was 1 month.

Discussion

Almost one half of the new users, 76 of 160 (47.5%), of buprenorphine-naloxone did not have an outpatient pharmacy claim for an opioid drug in the 6 months preceding the initiation period. This suggests that the real-world use of buprenorphine-naloxone often involves treatment of opioid dependence for illicit drug use. Another retrospective chart review of 30 opioid-dependent patients treated with buprenorphine-naloxone induction as inpatient, found that 93% had a history of heroin use, 33% had used prescribed opioids, and 27% had used both.¹³ The use of buprenorphine-naloxone for detoxification from illicit opiates has implications for assessment of the potential cost savings associated with interventions with buprenorphine-naloxone because

**Opioid Drug Utilization and Cost Outcomes Associated With the Use
of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use**

TABLE 1 Opioid and Buprenorphine-Naloxone Utilization (n=84)

Outcomes	6-Month Pre Period ^a	12-Month Post Period Including Buprenorphine- Naloxone ^{b,c}	P Value ^d	12-Month Post Period Excluding Buprenorphine- Naloxone ^e	P Value ^d
Total					
Drug ingredient cost ^f	\$107,724	\$157,489		\$72,222	
Member cost share (copay)	\$14,351	\$26,846		\$12,134	
Net MCO paid amount	\$94,675	\$132,660		\$61,452	
Number of claims	753	1,216		794	
Days supply	11,654	22,565		11,943	
PPPM					
Drug ingredient cost ^f	\$213.74	\$156.24	0.254	\$71.65	0.047
Member cost share (copay)	\$28.47	\$26.63	0.395	\$12.04	0.016
Net MCO paid amount	\$187.85	\$131.61	0.257	\$60.96	0.065
Number of claims	1.49	1.21	0.031	0.79	<0.001
Days supply	23.13	22.39	0.491	11.85	<0.001

^a Pharmacy claims with dates of service between October 1, 2004, and March 31, 2005.

^b Including buprenorphine-naloxone for pharmacy claims with dates of service between October 1, 2005, and September 30, 2006.

^c 76 of 84 patients (90.5%) had at least 1 pharmacy claim for an opioid in the 12-month post period.

^d P value for the comparison to 6-month pre period PPPM calculated using a paired t-test.

^e 60 of 84 patients (71.4%) had at least 1 pharmacy claim for an opioid other than buprenorphine-naloxone in the 12-month post period (i.e., 28.6% had no opioid claims other than buprenorphine-naloxone).

^f drug ingredient cost+pharmacy dispense fee=allowed charge=member cost share+net MCO paid amount.

MCO=managed care organization; PPPM=per patient per month.

TABLE 2 Buprenorphine-Naloxone Utilization
In 6-Month Initiation Period (n=84)^a

Outcomes	Total	Per Patient
Drug ingredient cost ^b	\$40,146	\$477.93
Member cost share (copay)	\$7,589	\$90.35
Net MCO paid amount	\$32,960	\$392.38
Number of claims	246	2.93
Days supply	4,954	58.98

^a Pharmacy claims for buprenorphine-naloxone with dates of service between April 1, 2005, and September 30, 2005.

^b Drug ingredient cost+pharmacy dispense fee=allowed charge=member cost share+net MCO paid amount.

MCO=managed care organization.

TABLE 3 Buprenorphine-Naloxone Utilization
In 12-Months Post Period (n=84)^a

Outcomes	Total	PPPM
Drug ingredient cost ^b	\$85,267	\$84.59
Copay	\$14,712	\$14.60
MCO paid amount	\$71,208	\$70.64
Number of claims	422	0.42
Days supply	10622	10.54

^a 59 patients out of 84 (70.2%) received 1 or more buprenorphine-naloxone fills in the 12-month period from October 1, 2005, through September 30, 2006.

^b Drug ingredient cost+pharmacy dispense fee=allowed charge=member cost share+net MCO paid amount.

MCO=managed care organization; PPPM=per patient per month.

the costs of illicit opioids are not captured in administrative claims databases.

Initiation of treatment with buprenorphine-naloxone in a sample of patients with at least 1 opioid pharmacy claim in the prior 6 months was associated with a decrease in the number of opioid claims PPPM from 1.49 to 1.21, with a reduction of 43.9% in the number of solid dosage forms from pre index to post index. Furthermore, 28 of the 84 members did not fill any opioid medication claims during the 12 months after initiation, therefore not incurring direct opioid pharmacy costs. The average opioid

cost PPPM decreased by 66.5% in the 12-month period following new use of buprenorphine-naloxone, but these drug cost savings associated with reduced opioid utilization were not statistically significant after accounting for the direct drug cost of the intervention.

Persistence was low by our measure; the mean persistence was 3.5 months, and the median length of therapy was 1 month. One reason for the low numbers was that the persistence calculation did not account for gaps in therapy of more than 1 month. Patients with opioid addiction have frequent relapses.³ A patient

Opioid Drug Utilization and Cost Outcomes Associated With the Use of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use

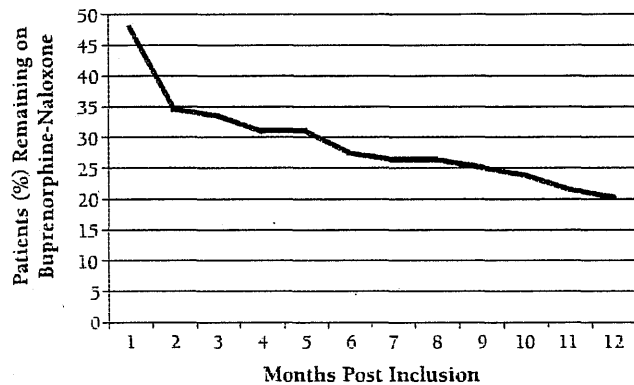
TABLE 4 Average Dose of Buprenorphine Per Day in 12-Months Post Period

Dose of Buprenorphine (mg per day) ^a	% of Total Pharmacy Claims ^b (no.)
≤ 4 mg	13.0% (55)
> 4 mg to ≤ 8 mg	31.8% (134)
> 8 mg to ≤ 16 mg	40.0% (169)
> 16 mg to ≤ 24 mg	11.8% (50)
> 24 mg to ≤ 32 mg	1.9% (8)
> 32 mg to ≤ 48 mg	1.4% (6)

^a The dose of buprenorphine per day for each pharmacy claim was calculated with the following formula: (# tablets divided by days supply) multiplied by the mg per tablet.

^b Buprenorphine-naloxone is supplied in 2 strengths in sublingual dose form: 2 mg-0.5 mg and 8 mg-2 mg; 304 (72%) of the 422 claims for buprenorphine-naloxone during the 12-month post period were the 8 mg-2 mg strength, and 118 claims were the 2 mg-0.5 mg strength. Of the 281 claims (66.6%) written by prescribers with known medical specialty information in the database, 55.5% (156) were in general/family practice or internal medicine, and 22.0% (62) were psychiatrists or physical medicine and rehabilitation specialties.

FIGURE 4 Persistence^a of Buprenorphine-Naloxone in 12-Months Post Period



^a Persistence was defined as no more than a 1-month gap in therapy in the fixed 12-months follow-up period from October 1, 2005, through September 30, 2006.

TABLE 5 PPPM Utilization In Units of Top Opioid Products^a 6-Months Pre Period and 12-Months Post Period (N=84)

Opioid Type	6-Month Pre Period PPPM Quantity	12-Month Post Period PPPM Quantity	% Change
Oxycodone-acetaminophen	36.0 tablets	17.1 tablets	-52.5%
Hydrocodone-acetaminophen	26.3 tablets	9.1 tablets	-65.4%
Oxycodone	15.4 tablets or capsules	13.2 tablets or capsules	-14.3%
Tramadol±acetaminophen	6.0 tablets	7.1 tablets	+18.3%
Hydrocodone-ibuprofen	2.5 tablets	2.6 tablets	+4.0%
Oral transmucosal fentanyl citrate	2.3 lozenges	0.03 lozenges	-98.7%
Methadone	1.8 tablets	1.8 tablets	0%
Buprenorphine oral ^b	1.1 tablets	1.3 tablets	+18.2%
Other opioids	5.4 tablets ^c	2.1 tablets ^d	-61.0%
Total solid dosage forms (tablets, capsules, lozenges)	96.8	54.3	-43.9%
Fentanyl patch	1.1 patches	0.03 patches	-97.3%
Buprenorphine ampule	0.06 mL	0 mL	-100.0%

^a Pharmacy claims for opioid drugs identified by Medi-Span Generic Product Identifier (codes beginning with 6510 (narcotic agonists), 6520 (narcotic partial agonists), 6540 (narcotic antagonists), and 6599 (narcotic combinations). A first pharmacy claim for buprenorphine-naloxone was defined as no use in the preceding 6 months.

^b Buprenorphine without naloxone.

^c Actual results included pharmacy claims for acetaminophen-codeine tablets, butalbital-acetaminophen-caffeine-codeine capsules, hydromorphone tablets, morphine capsules, oxycodone-aspirin tablets, and propoxyphene N-acetaminophen tablets.

^d Actual results included pharmacy claims for acetaminophen-codeine tablets, morphine capsules and tablets, oxycodone-ibuprofen tablets, propoxyphene N-acetaminophen tablets, butalbital-acetaminophen-caffeine-codeine capsules, hydromorphone tablets, meperidine tablets, oxycodone-aspirin tablets, pentazocine-acetaminophen tablets, and pentazocine-naloxone tablets.

PPPM=per patient per month.

Opioid Drug Utilization and Cost Outcomes Associated With the Use of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use

in the present study could be counted as "discontinued" by the persistence measure but later restart therapy with buprenorphine-naloxone during the 12-month follow-up period. In addition, if a patient had continuous fills for scripts after the first 30 days of October 2005, the persistence was 0 days. Caldiero et al. reported that, in a retrospective chart review, patients had an average of 3.4 prior substance use treatments before receiving inpatient induction of buprenorphine maintenance.¹³ There are no reports in the literature for the incidence of buprenorphine-naloxone relapses and restarts.

Most patients received the recommended 4 mg to 24 mg of buprenorphine per day, commonly prescribed as buprenorphine-naloxone (8 mg to 2 mg), 2 tablets per day. Very few patients had pharmacy claims for buprenorphine doses >32 mg per day. There was no dispensing limit placed on buprenorphine-naloxone during this study. Effective May 2007, a dose limit of 120 tablets per month was implemented at this MCO, allowing for a maximum dose of 32 mg of buprenorphine per day.

Because there are no retrospective, observational studies reported in the literature that evaluate the relationship of buprenorphine-naloxone use for opioid dependence and utilization and costs of prescription opioids, comparisons cannot be made between the results of the present study and other attempts to measure effectiveness of this intervention. In 2007, Mintzer et al. reported that 54% of 99 patients treated in 2 primary care clinics were "sober" after 6 months of therapy with buprenorphine-naloxone as determined by global assessment of the treating physician, including the results of periodic urine tests.¹⁴ These patients in 2 primary care clinics had demographic characteristics at baseline (mean age of 33 years and 64% males) that were similar to the present analysis. The average time in treatment was 105 days.

Compared with the 54% "success" rate reported by Mintzer et al. at 6 months of follow-up, we found that only 1 of 2 patients who received buprenorphine-naloxone as a new patient had a follow-up claim for the drug at 1 month following the initial treatment period, and only 27% were persistent at 6 months. In fact, 71.4% of the patients included in the DUE had filled at least 1 pharmacy claim for an opioid other than the study drug during the follow-up period after initiation of buprenorphine-naloxone. The results reported by Mintzer et al. pertained to hands-on primary care where the caregivers followed the patients and encouraged participation in psychological support groups.

Fudula et al. conducted a double-blind, randomized, placebo-controlled efficacy trial, with an open-label safety extension, involving opiate-dependent patients who were assigned to office-based treatment with sublingual buprenorphine 16 mg in combination with naloxone (4 mg) per day versus buprenorphine alone (16 mg per day) or placebo (initial randomized treatment for 4 weeks, followed by 48 to 52 weeks of open-label therapy). The authors reported that the percentage of urine samples during the open-label phase that were negative for opiates ranged

from 32.5% to 67.4% in multiple assessments conducted during 1 year of follow-up.¹¹ These results suggest that patients with opioid dependence have variable results depending on the time of measurements in this dynamic disease.

Bell et al. randomized 119 subjects seeking treatment for heroin addiction to observed or unobserved doses of buprenorphine-naloxone for heroin dependence in outpatient drug treatment centers.¹⁵ The mean retention in treatment did not differ between treatments ($P=0.84$), and mean reduction in days of self-reported heroin use in the preceding month did not differ between the unobserved group (18.5 days) versus the observed group (22.0 days, $P=0.13$). At 3 months, 52% of 92 interviewed patients reported no use of heroin in the last month. The mean cost per treatment episode, including cost of medication; medical, counseling, and dispensing costs; other health care costs like hospital admissions, etc.; travel costs; and travel time, in Australian dollars was AU\$1,663 in the unobserved group versus AU\$2,138 in the observed group.

Limitations

No causal relationship between buprenorphine-naloxone treatment and change in opioid use can be inferred from this study because it is an observational study without a control group. Second, it is not possible to determine the use of illicit substances from a pharmacy claims database. Although 24 of the 84 members did not fill pharmacy opioid claims other than buprenorphine-naloxone in the 12-month follow-up period, a DUE of this type, based on analysis of pharmacy administrative claims, cannot assess illicit opioid utilization. Our study results suggest that there was a decline in prescription opioid claims, but whether patients were sober or obtained opioids from illegal sources is unknown.

Third, no medical claims were examined in this study. Without access to medical claims, it was not possible to examine the relationship between buprenorphine-naloxone use and total medical costs. For example, patients may have been receiving psychiatric care, and its effect on drug efficacy cannot be measured with this DUE.

Fourth, we used an unusual study design based on fixed calendar periods rather than the customary approach of following each patient for a given number of months following the date of the first claim for the intervention. This method was intended to simulate a real-world situation for this health plan to determine the prescription opiate utilization for the patients after a 6-month initiation period. The shortcoming of this method is the creation of a follow-up period longer than 12 months from the date of the first buprenorphine-naloxone claim. For example, a patient could have started buprenorphine-naloxone as early as April 2005 and stopped treatment after 5 months (in September 2005), and this patient was considered nonpersistent, with no follow-up claim for buprenorphine-naloxone. In other words, the length of buprenorphine-naloxone therapy in the initiation period could

Opioid Drug Utilization and Cost Outcomes Associated With the Use of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use

have been as short as a few days or as long as 180 days prior to the start of the 12-month follow-up period. In fact, only 59 patients received buprenorphine-naloxone during follow-up. Therefore, our findings for mean utilization of and persistence with the intervention drug most likely understate what might be expected in an analysis that employed a running 12-month follow-up period following the first (initiation) buprenorphine-naloxone pharmacy claim.

Fifth, this study defined the initiation claim as the first claim for buprenorphine-naloxone during the calendar period from April 1, 2005, through September 30, 2005, with no prior use in the 6-month period from October 1, 2004, through March 31, 2005. However, some patients may have had utilization of buprenorphine alone, without naloxone. For the 84 patients included in the present study, utilization of buprenorphine alone was 1.1 tablets PPPM in the 6-month pre period and 1.3 tablets PMPM in the 12-month post period.

Sixth, the observed decrease in utilization of oral transmucosal fentanyl citrate contributed significantly to the lower total opioid cost in the post period. During the 24 months of study in this DUE, there was no prior authorization requirement for the use of oral transmucosal fentanyl citrate (e.g., use allowed for only the U.S. Food and Drug Administration-approved indication for cancer patients). A quantity limit of 120 transmucosal fentanyl "lollipops" per month was implemented prior to the study period on August 1, 2004, but this quantity limit would not have affected the pre versus post comparison in the present study.

Seventh, a dispensing (quantity) limit of 120 tablets per 30 days was placed on the following opioids in March 2005, the last month of the pre period: controlled-release oxycodone tablets, oxycodone-acetaminophen, tramadol, tramadol-acetaminophen, and hydrocodone-acetaminophen. The effect of this quantity limit on the use of these drugs has not been assessed but could have contributed to lower opioid utilization in the follow-up period from October 1, 2005, through September 30, 2006. However, the quantity limit imposed in March 2005 did not present a new limitation for Schedule II controlled substances such as controlled-release oxycodone, which were already subject to a dispensing limit of 120 dosage units or 30 days supply by New Jersey state regulations, except for patients with terminal illness, intractable pain, or residence in a long-term-care facility.¹⁶

Conclusions

About one-half of the utilization of buprenorphine-naloxone in this managed care plan appeared to be associated with nonprescription opioid use. Initiation of treatment with combination buprenorphine-naloxone in patients with a history of prescription opioid use was associated with reduced prescription opioid utilization, but not direct pharmacy cost, after 12 months of follow-up. Using a definition of persistence as a gap of no more

than 1 month between the date of exhaustion of the days supply and the next fill date, persistence with buprenorphine-naloxone was 27% at 6 months and 20% at 12 months of follow-up.

Authors

AMAN DEEP KAUR, PharmD, is a drug information scientist, Novo Nordisk Inc., Princeton. ANGELA MCQUEEN, PharmD, is a clinical pharmacy manager, Horizon Blue Cross Blue Shield of New Jersey, Newark. SAIRA JAN, MS, PharmD, is the director of clinical pharmacy management, Horizon Blue Cross Blue Shield of New Jersey, and an associate professor, Rutgers, the State University of New Jersey, Piscataway.

AUTHOR CORRESPONDENCE: Aman Deep Kaur, PharmD, Drug Information Scientist, Novo Nordisk Inc., 100 College Rd. West, Princeton, NJ 08540. Tel.: 609.919.7864; Fax: 973.466.4665; E-mail: AmandeepK@aol.com

DISCLOSURES

There was no external funding for this research, and the authors report no conflicts of interest related to the subject of this article. The content of this work was developed while Aman Kaur was employed at Horizon Blue Cross Blue Shield of New Jersey.

All authors contributed to the study concept and design. Kaur performed the data collection and data interpretation. Kaur did the majority of the writing of the manuscript, with assistance from McQueen and Jan; all authors contributed to the revision.

REFERENCES

1. Department of Health and Human Services. National Survey on Drug Use and Health: National Findings. Available at: <http://oas.samhsa.gov/11/6/469-79>. Accessed September 21, 2007.
2. White AG, Birnbaum HG, Mareva MN, et al. Direct costs of opioid abuse in an insured population in the United States. *J Manag Care Pharm*. 2005; 11(6):469-79. Available at: www.amcp.org/data/jmcp/3.pdf.
3. U.S. Department of Health and Human Services. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction: treatment improvement protocol (TIP) Series 40. 2004. Available at: <http://buprenorphine.samhsa.gov/bwns/Bup%20Guidelines.pdf>. Accessed January 4, 2007.
4. Roxane Laboratories, Inc. Methadone tablets package insert. Columbus, OH; 2006.
5. [Package insert] Reckitt Benckiser Pharmaceuticals, Inc. Suboxone. Richmond, VA; 2005.
6. U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration. Available at: www.buprenorphine.samhsa.gov/. Accessed January 22, 2006.
7. Strain EC, Stitzer ML, Liebson IA, et al. Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am J Psychiatry*. 1994;151:1025-30.
8. Johnson RE, Jaffe JH, and Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA*. 1992;267(20):2750-55.
9. Johnson RE, Chutuaape MA, Strain EC, et al. A comparison of levo-methadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med*. 2000;343:1290-97.

**Opioid Drug Utilization and Cost Outcomes Associated With the Use
of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use**

10. Marsch LA, Bickel WK, Badger GJ, et al. Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. *Arch Gen Psychiatry*. 2005;62:1157-64.
11. Fudala PJ, Bridge P, Herbert S, et al. Office-based treatment of opiate-addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003;349:1949-58.
12. Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med*. 2006;355:365-74.
13. Caldiero RM, Parran TV, Adelman CL, and Piche B. Inpatient initiation of buprenorphine maintenance vs. detoxification: can retention of opioid-dependent patients in outpatient counseling be improved? *Am J Addict*. 2006;15:1-7.
14. Mintzer LL, Eisenberg M, Terra M, et al. Treating opioid addiction with buprenorphine naloxone in community-based primary care setting. *Ann Fam Med*. 2007;5(2):146-50.
15. Bell J, Shanahan M, Mutch C, et al. A randomized trial of effectiveness and cost-effectiveness of observed versus unobserved administration of buprenorphine-naloxone for heroin dependence. *Addiction*. 2007;102:1899-1907.
16. New Jersey Board of Pharmacy. Office of the Attorney General: Department of Law & Public Safety. Available at: www.nj.gov/oag/ca/medical/pharmacy.htm. Accessed January 21, 2008.

RAPID COMMUNICATIONS

Abuse of Buprenorphine in the United States: 2003-2005

Meredith Y. Smith, PhD
J. Elise Bailey, MS
George E. Woody, MD
Herbert D. Kleber, MD

ABSTRACT. This study examines trends in the reported abuse of two sublingual buprenorphine products, Subutex® and Suboxone®, in the United States. Quarterly counts of abuse cases were obtained from 18 regional poison control centers (PCCS) for 2003-2005. Seventy-seven abuse cases were reported, of which 7.8 percent involved Subutex® and 92.2 percent involved Suboxone®. The average quarterly ratio of abuse cases per 1,000 prescriptions dispensed was 0.08 (SD $\pm$ 0.09) for Subutex®, and 0.16 (SD $\pm$ 0.08) for Suboxone®. Findings suggest that these sublingual buprenorphine formulations have a low rate of abuse based on toxico-surveillance data. doi:10.1300/J069v26n03_12 [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <http://www.HaworthPress.com> © 2007 by The Haworth Press, Inc. All rights reserved.]

KEYWORDS. Sublingual buprenorphine, Subutex®, Suboxone®, opioid analgesics, prescription drug abuse, opioid dependence, buprenorphine-naloxone, substitution therapy

INTRODUCTION

Buprenorphine, a partial μ opioid agonist, has been used as a pain medication for several

decades in the United States (U.S.).¹ In October 2002, two new sublingual buprenorphine formulations, Subutex® and Suboxone® (Reckitt Benckiser), were approved for the office-based

Meredith Y. Smith is affiliated with Purdue Pharma L.P., Stamford, CT.

J. Elise Bailey is affiliated with the Rocky Mountain Poison Control Center, 777 Bannock Street, Mail Code 0180, Denver, CO 80204.

George E. Woody, Treatment Research Institute, 600 Public Ledger Building, 150 South Independence Mall, West, Philadelphia, PA 19129.

Herbert D. Kleber is affiliated with the Columbia University, New York State Psychiatric Institute, Unit 66, 1051 Riverside Drive, New York, NY 10032.

Address correspondence to: Meredith Y. Smith, PhD, MPA, Director, Risk Management & Health Policy, Purdue Pharma L.P., One Stamford Forum, Stamford, CT 06901-3431 (E-mail: meredith.smith@pharma.com)

This work was supported by Purdue Pharma L.P., Stamford, Connecticut.

Journal of Addictive Diseases, Vol. 26(3) 2007

Available online at <http://jad.haworthpress.com>

© 2007 by The Haworth Press, Inc. All rights reserved.

doi:10.1300/J069v26n03_12

treatment of opioid dependence consistent with the Drug Addiction Treatment Act of 2000.² Subutex®, a single entity buprenorphine hydrochloride product, was intended for use during the initiation phase of substitution therapy while Suboxone®, a buprenorphine-naloxone combination drug, was intended for the maintenance phase.³

Buprenorphine's partial agonist properties, coupled with its slow rate of dissociation from the μ receptor after binding and ceiling effect at higher doses, contributed to its classification as a Schedule III drug with lower abuse potential than full μ opioid agonists.⁴ With the increased medical availability of buprenorphine, however, concerns have mounted regarding its abuse potential.¹ Internationally, cases of buprenorphine misuse and abuse-related morbidity and mortality have been documented in numerous countries where the drug has been approved for use in opioid dependence treatment.⁵⁻¹⁰ In Finland, where both single entity buprenorphine and buprenorphine-naloxone combination products are available for clinical use, intravenous abuse of these drugs has been reported among untreated intravenous users (IVs).¹¹

To date, however, little is known concerning the abuse of these sublingual buprenorphine products in the U.S. To address this issue, we assessed trends in the reported abuse of buprenorphine and buprenorphine-naloxone combination using data from regional toxicology surveillance systems.

METHODS

Study data consisted of calls received between 4th quarter, 2003 through 4th quarter, 2005 by 18 regional poison control centers (PCCs) covering a total of 103.1 million individuals in 20 different states. Call inclusion criteria specified that (a) the exposure resulted from an intentional improper or incorrect use of a substance with an attempt to get "high," produce euphoria, or other psychotropic effect (defined as "Abuse" per PCC rating criteria); and (b) the substance involved was Subutex® or Suboxone®. Each call was reviewed and classified by a Specialist in Poison Information (SPI), a professional trained in nursing and/or

pharmacology. Clinician review has shown good correspondence between PCC opioid analgesic cases categorized as "abuse" and standard nosological classifications of opioid abuse and dependence.¹² As a proxy for legitimate use, data were obtained on the estimated number of prescriptions dispensed for Subutex® and Suboxone® by retail pharmacies from IMS Health, Inc., a commercial vendor of healthcare data.¹³

Statistical Analysis

We tabulated the number of abuse cases and prescriptions dispensed for each drug by quarter for the nine quarter study period. We also calculated the mean number and standard deviation of abuse cases and the ratio of abuse cases to 1,000 prescriptions dispensed.

RESULTS

Table 1 presents the number of abuse cases and prescriptions dispensed for each drug by calendar quarter. Seventy-seven PCC abuse cases were reported for the two drugs combined. Of these, 7.8 percent involved Subutex®; and 92.2 percent involved Suboxone®. The mean number of abuse cases per quarter was 0.66 (standard deviation ± 0.71) for Subutex®,

TABLE 1. Number of abuse cases and estimated number of prescriptions dispensed on an outpatient basis for Suboxone® and Subutex® by quarter in the United States (US), 4th quarter 2003-4th quarter 2005.

	# Abuse Cases Subutex®	# Prescriptions Subutex®	# Abuse Cases Suboxone®	# Prescriptions Suboxone®
4Q03	0	3,239	1	14,568
1Q04	1	4,611	4	19,924
2Q04	0	6,259	1	27,946
3Q04	1	7,726	9	35,049
4Q04	1	8,722	6	43,313
1Q05	1	10,445	9	54,253
2Q05	0	11,239	19	66,655
3Q05	0	10,749	11	65,360
4Q05	2	11,696	11	73,106
Total	6	74,686	71	400,174

and 7.88 (standard deviation ± 5.68) for Suboxone®.

Of the estimated 474,860 prescriptions dispensed for the 2 drugs, 15.7 percent were for Subutex®; and 84.3 percent were for Suboxone®. The number of prescriptions dispensed for each product rose during the study period. The change was most pronounced for Suboxone®, which showed a 402 percent increase in the volume of prescriptions dispensed during the nine quarter period compared to a 261 percent increase for Subutex®.

Figure 1 presents the ratio of abuse cases to 1,000 prescriptions dispensed per quarter by drug. For Subutex®, the average quarterly ratio of abuse cases per 1,000 prescriptions dispensed was 0.08 (SD ± 0.090), while for Suboxone® the average quarterly ratio of abuse cases per 1,000 cases dispensed was 0.16 (SD ± 0.080).

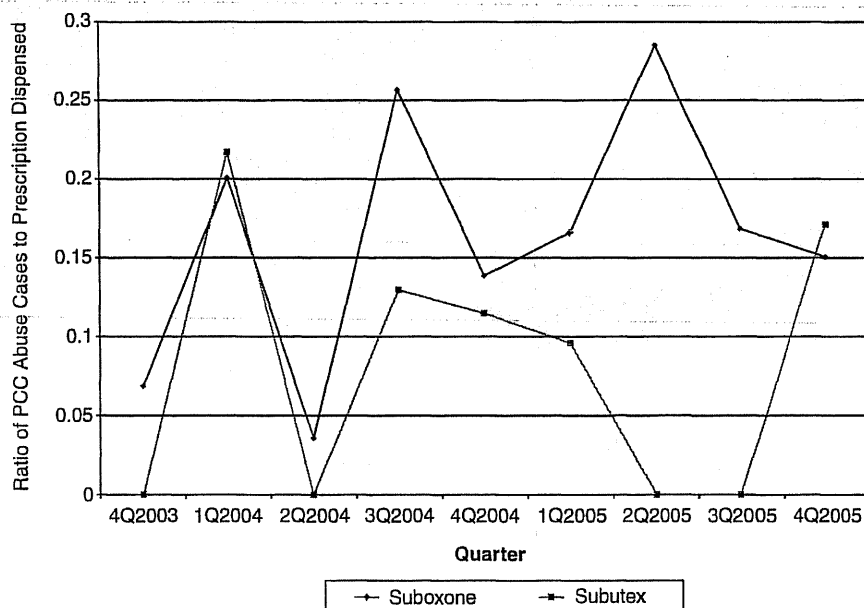
DISCUSSION

Our data indicate that the medical availability of both Suboxone® and Subutex® increased

steadily in the U.S. between 4th quarter, 2003 and 4th quarter, 2005. The rise was particularly marked for Suboxone® which accounted for approximately 84 percent of the total number of prescriptions dispensed for both drugs during this time period. Suboxone® also accounted for the majority (92 percent) of the 77 abuse cases reported in total for the two products combined.

After adjusting for differences in the degree of dispensing of these two drugs, the ratio of abuse cases was slightly higher on average for Suboxone® than for Subutex® (0.16 versus 0.08 abuse cases per 1,000 prescriptions dispensed, respectively). These ratios are low in comparison to similar data on opioid analgesic abuse. Zacny and colleagues calculated the ratio of drug-abuse related emergency department (ED) mentions per 1,000 prescriptions dispensed for five opioids for the period 1994-2001.¹⁴ Hydromorphone had the highest average ratio (1.80 ED mentions per 1,000 prescriptions dispensed), while fentanyl had the lowest (0.013 ED mentions per 1,000 prescriptions dispensed).

FIGURE 1. The ratio of Suboxone® and Subutex® abuse cases to 1,000 prescriptions dispensed as reported to participating poison control centers by quarter, 4th quarter, 2003-4th quarter 2005.



Our finding that Suboxone® had a higher abuse ratio than Subutex® is intriguing. One possible explanation is that the degree of patient exposure to Subutex is likely much lower than that for Suboxone. According to the product package insert, Subutex is preferred for use during induction, and the use of Subutex for unsupervised administration should be limited to those patients who cannot tolerate Suboxone.¹⁷ Suboxone®, in contrast, is recommended for use in all 3 phases of treatment, including long-term maintenance, and in a much broader array of patients.¹⁵

Information concerning the route of buprenorphine administration used by abusers would have aided us in interpreting our study results. Data show that, in non-dependent opioid abusers, the opioid agonist effects of sublingually administered Suboxone® closely resemble those seen for Subutex®.¹⁶ Similarly, it has been demonstrated that, when administered parenterally, naloxone's functional blockade of buprenorphine's action is only partial and short-lived in nature.¹⁷ A recent study of untreated intravenous abusers in Finland revealed that 68 percent reported abusing Suboxone intravenously.¹¹ Moreover, 66 percent of those who had abused the drug once admitted that they had abused it at least once subsequently, or even regularly thereafter, despite describing the effect as a "bad experience." Future research is needed to examine the characteristics of buprenorphine abusers in more detail and explore whether and to what extent route of administration varies by type of abuser.

In addition to lacking data on route of administration, our study was limited by the fact that the geographical coverage of participating PCCs was not nationally representative. It is important to note, however, that all major regions of the U.S. were included.

Our results suggest that while both Subutex® and Suboxone® are being abused in the post-marketing context, the level of such abuse is low relative to the number of prescriptions dispensed. These findings are especially noteworthy in light of the fact that both these products are prescribed for use in a population at high risk for drug abuse. Ongoing monitoring of these new products is vital in order to determine whether these trends will continue.

REFERENCES

1. Costa e Silva JA. Medicines and the drug control treaties: Is buprenorphine for opioid addiction at risk of being lost? *Hum Psychopharmacol Clin Exp* 2004; 19:215-224.
2. Drug Addiction Treatment Act of 2000, Public Law 106-310, Title XXXV (DATA, 2000). Federal Food, Drug, and Cosmetic Act. (Act) 21 U.S.C. § 360, Section 510.
3. U.S. Food and Drug Administration. FDA Talk Paper: Subutex® and Suboxone® approved to treat opioid dependence. T08-38; October, 8. 2002. Available at: <http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01165.hjtm1>. Last accessed: November 15, 2006.
4. Tzchenske TM. Behavioral pharmacology of buprenorphine with a focus on preclinical models of reward and addiction. *Psychopharmacology* 2002;161: 1-16.
5. Auriacombe M, Fatsea M, Dubernet J, Daulouede JP, Tignol J. French field experience with buprenorphine. *Am J Addict* 2001;13(Suppl. 1):S17-28.
6. Guichard A, Lert F, Calderon C, Gaigi H, Maguet O, Soletti J, Brodeur J-M, Richard L, Benigeri M, Zunzunegui M-V. Illicit drug use and injection practices among drug users on methadone and buprenorphine maintenance treatment in France. *Addiction* 2003; 98:1585-1597.
7. Jenkinson RA, Clark NC, Fry CL, Dobbin M. Buprenorphine diversion and injection in Melbourne, Australia: an emerging issue? *Addiction* 2005;100: 197-205.
8. Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti J-P. Injecting misuse of buprenorphine among French drug users. *Addiction* 2001; 96: 267-272.
9. Parfitt T. Designer drug Subutex takes its toll in Tbilisi. *Lancet* 2006; 368: 273-274.
10. Winslow M, Ng W-L, Mythily S, Song G, Yihong H-C. Socio-demographic profile and help-seeking behavior of buprenorphine abusers in Singapore. *Ann Acad Med Singapore* 2006;35:451-456.
11. Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. *Drug Alcohol Depend* 2006;22: 533-541.
12. Smith MY, Dart R, Hughes A, Geller A, Senay E, Woody G, Colucci S. Clinician validation of poison control center (PCC) intentional exposure cases involving prescription opioids. *Am J Drug Alcohol Abuse* 2006;32:465-478.
13. IMS Health Inc., Xponent Database-in retail pharmacies and mail order, 2003-2005.
14. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on problems of drug dependence taskforce on prescription opioid non-medical use and abuse: Position statement. *Drug Alcohol Depend* 2003;69:215-232.

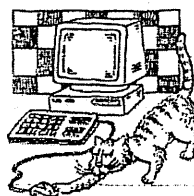
15. Substance Abuse and Mental Health Administration, Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) 40, 2004. Available at www.kap.samhsa.gov. (Last accessed, 04/13/07).

16. Strain EC, Stoller KM, Walsh SL, Bigelow GE. The effects of buprenorphine and buprenorphine/naloxone tablets in non-dependent opioid abusers. *Psychopharmacology* 2000;148:374-383.

17. Subutex®, Suboxone®. [package insert]. Reckitt-Benckiser Pharmaceuticals. Richmond, VA.

doi:10.1300/J069v26n03_12

**Get Articles *FAST* with
the Haworth Document
Delivery Service and Rightslink®**



To request single articles from Haworth, visit www.HaworthPress.com/journals/dds.asp. You can order single articles here directly from Haworth or through Rightslink®. We have over 40,000 articles ready for immediate delivery, and you can find articles by title, by author name, by keyword, and more!

RIGHTS LINK
Copyright Clearance Center

EDITORIAL



Buprenorphine Misuse, Abuse, and Diversion: When Will We Ever Learn?

Nearly 40 years ago, pentazocine (Talwin)—a narcotic antagonist with agonist activity—was made available as an analgesic for the relief of moderate to severe pain. Pentazocine was initially prescribed as a non-narcotic analgesic associated with a low risk of developing dependency. It was considered to be a partial agonist at the μ opioid receptor and an antagonist at the κ receptor. Therefore, it was classified as a Schedule IV drug with limited physical or psychological dependence and was authorized for prescription by practitioners.

However, the course of pentazocine abuse was soon quite clear. Contrary to initial expectations and promotion by pharmaceutical companies, many cases of pentazocine addiction have been reported in the literature since its approval in 1967. On the street, pentazocine became an effective alternative to heroin. Reports appearing soon after pentazocine became available described the intravenous injection of “Ts and blues.”^{1,2} Unfortunately, due to the lack of physician awareness about the potential for pentazocine abuse, physicians’ prescriptions became a major source of inappropriate use.³

At present, pentazocine has fallen out of favor in the medical armamentarium and is rarely used as a potent analgesic as a result of the myriad complications associated with its use.

Thanks to the wonders of modern chemistry, a new group of agonist-antagonists were developed decades later. These drugs are butorphenol (Stadol), buprenorphine (Buprenex, Subutex), and nalbuphine (Nubain). Of these, buprenorphine, which is 25 to 30 times as potent as morphine, is the most potent. As seen with pentazocine, the description of the action of buprenorphine was quite favorable: “Buprenorphine is a partial agonist at the μ opioid receptor and an antagonist at the κ receptor. It has very high affinity and low intrinsic activity at the μ receptor and will displace morphine, methadone, and other opioid agonists from the receptor. Its partial agonist effects imbue buprenorphine with several clinically desirable pharmacological properties: lower abuse potential, lower level of physical dependence (less withdrawal discomfort), a ceiling effect at higher doses, and greater safety in overdose compared with opioid full agonists.”⁴ Unfortu-

nately, for people dependent on heroin who were not aware of these qualities, it became an ideal drug for opioid addiction. Indeed, when buprenorphine was introduced in Europe, it quickly became a leading drug of abuse. Clinical studies revealed that heroin addicts using buprenorphine described mood-altering effects similar to those associated with heroin.⁵⁻⁸ Adverse events associated with buprenorphine use have been described as occurring more frequently than those associated with methadone.⁹

With the recognition that this drug could be abused, a second preparation of buprenorphine mixed with naloxone (Suboxone) in a 4:1 ratio was formulated. In 2002, both of these tablets were approved by the Food and Drug Administration for the treatment of opiate addiction. It was thought that while buprenorphine by itself could be abused and injected, the use of the combination tablet would reduce abuse potential when given to an opiate-dependent population. As stated in the guidelines, "[N]aloxone is approximately 10-20 times more potent by injection than by the sublingual route. Therefore, if the combination is taken sublingually, as directed, the small amount of naloxone available should not interfere with the desired effects of buprenorphine. If the combination form is dissolved and injected by an individual physically dependent on opioids, however, the increased bioavailability of naloxone via the parenteral route should precipitate an opioid withdrawal syndrome."⁴ This is also true of other antagonists, as stated more explicitly in NIDA Research Findings: "[Naltrexone] provides a safety net for patients because it blocks the euphoric effects they normally would feel if they slip and use heroin or any other opiate."¹⁰

The findings of Smith et al. in this issue of the *Journal* should be considered in relation to this expectation, which has been generally accepted by health care professionals providing addiction treatment. Studying trends in the reported abuse of both Subutex and Suboxone in the United States, Smith and her colleagues found that of 77 abuse cases reported to poison control centers, 7.8% involved Subutex and 92.2% involved Suboxone. This emphasizes the initial findings of Weinhold et al. that naloxone's functional blockade of buprenorphine is modest and short-lived, with an agonist effect similar to that produced by buprenorphine alone.¹¹

It is in fact notable that in a study by Alho et al. (and cited by Smith et al.), 68% of untreated intravenous abusers in Finland reported intravenous abuse of Suboxone, and that 66% of those who tried it once reported using it on more than one occasion even though they had had a "bad" experience with it.¹² Although Smith et al. conclude that there is an extremely low rate of abuse of both Subutex and Suboxone, it is suggested that in fact this is merely the proverbial tip of the iceberg and that as the use of these drugs becomes more prevalent, we will see rates of abuse and diversion similar to that seen in Europe. There is also no question that the number of people for whom buprenorphine is prescribed will increase, since as of December 2006, the number of patients a physician is allowed to treat with buprenorphine was increased more than threefold (from 30 to 100).

It should be emphasized that this is not to cast aspersions on the use of buprenorphine as a maintenance drug for heroin dependency, but rather to serve as a reminder that any mood-altering drug can be abused. Those who prescribe and use these medications should be fully aware of their potential for misuse, abuse, and addiction. Yet physicians, who should be among the most knowledgeable of these issues, have been historically uncritical in their approach to opiates and opioid antagonists.

Examples of this abound. In 1906, the American Medical Association (AMA) gave its approval to the use of heroin produced by the Bayer Pharmaceutical Company as a substitute for morphine addiction. It was not until 1920 that the hazards associated with heroin use caused the AMA to resolve that it be eliminated from medical practice.¹³ Propoxyphene (Darvon) was promoted in 1966 by stating that "when given in therapeutic doses, euphoria is not observed, tolerance does not occur, and physical dependence does not develop." Its use was so extensive that by 1997, the drug awareness network of the National Institute on Drug Abuse listed propoxyphene as a prominent drug of abuse. Reports from medical examiners' offices identified it as a drug involved in more overdose deaths than all nonbarbiturate sedatives and diazepam.¹⁴ Unfortunately, even today most physicians do not realize that propoxyphene is in fact an analog of methadone; when taken in sufficient doses, it can ex-

ert appreciable opioid effects subjectively and objectively.

There have been many instances in which pharmaceutical firms have provided misinformation that has been readily accepted by physicians. When oxycodone was first introduced, it was promoted as an ideal analgesic because it did not contain codeine. The more recent formulation of a long-acting tablet (OxyContin) was followed by cases of abuse and, in some instances, death. In May 2007, a combined fine of \$634.5 million was levied against Purdue Pharma, the manufacturer of OxyContin, and its executives for presenting misleading information about the drug that was accepted uncritically by many physicians.¹⁵

It is hoped that abuse and diversion of Suboxone and Subutex will be kept to a minimum as a result of the abundant literature on buprenorphine and the buprenorphine/naloxone combination and of the certification requirement for physicians who prescribe these drugs. However, this will only occur if the physicians responsible for dispensing this medication appraise its advantages and its potential for diversion and misuse.

Barry Stimmel, MD

REFERENCES

1. Sandoval RG, Wang RIH. Tolerance and dependence on pentazocine. *N Engl J Med.* 1969;280:1391-1392.
2. Bailey WJ. Nonmedical use of pentazocine: Letter to the editor. *JAMA.* 1979;242:2392.
3. O'Driscoll WG, Lindley, GR. Self administration of tripeleminamine by a narcotic addict. *N Engl J Med.* 1957;257:376.
4. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction: A Treatment Improvement Protocol [TIP 40]*. Rockville, MD. 2004.
5. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: A potential agent for treating narcotic addictions. *Arch Gen Psychiatry.* 1978;35:501-516.
6. Brady TM, Salvucci S, Sverdlow LS, Male A. Methadone dosage and retention: An examination of the 60mg/day threshold. *J Addict Dis.* 2005;24(3):23-47.
7. Obadia Y, Perrin V, Feroni I et al. Injecting misuse of buprenorphine among French drug users. *Addiction.* 2001;96:267-272.
8. Lavelle TL, Hammersley R, Forsyth A, Bain D. The use of buprenorphine and temazepam by drug injectors. *J Addict Dis.* 1991;10(3):5-14.
9. How safe are methadone, LAAM, buprenorphine? *Addiction Treatment Forum.* 2001;10(2):1.
10. Mathias R. New approaches seek to expand naltrexone use in heroin treatment. *NIDA Research Findings.* 2003;17:6.
11. Weinhold LL, Preston KL, Farre M, Liebson IA, Bigelow GE. Buprenorphine alone and in combination with naloxone in non-dependent humans. *Drug Alcohol Depend.* 1992;30:263-274.
12. Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. *Drug Alcohol Depend* 2006;22:533-541.
13. Report of the Committee on the Narcotic Drug Situation in the United States. *JAMA.* 1920;74:1318.
14. Drug Abuse Warning Network, IMS America. *Quarterly Report.* July-September 1977.
15. Meier B. Narcotic maker guilty of deceit over marketing. *The New York Times.* May 11, 2007.

doi:10.1300/J069v26n03_01

Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine

Peggy Compton^{a,*}, Walter Ling^b, David Moody^c, Nora Chiang^d

^a School of Nursing, University of California at Los Angeles, Factor Building 4-246, Box 956918, Los Angeles, CA 90095-6918, USA

^b Integrated Substance Abuse Programs, University of California at Los Angeles, 11075 Santa Monica Blvd, Suite 200, Los Angeles, CA 90095, USA

^c Center for Human Toxicology, University of Utah, Biomedical Polymers Building, Room 490, Salt Lake City, UT 84112, USA

^d Chemistry and Pharmaceutics Branch, Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse, 6001 Executive Boulevard, Room 4123, MSC 9551, Bethesda, MD 20892-9551, USA

Received 8 March 2005; received in revised form 5 August 2005; accepted 9 August 2005

Abstract

Aims: Two tablet formulations of buprenorphine (a buprenorphine mono-product, Subutex®, and a buprenorphine/naloxone combination product, Suboxone®) are available for use in the treatment of opioid addiction; however, the bulk of the clinical studies supporting its approval by the US Food and Drug Administration (FDA) were conducted with a sublingual liquid preparation. To assist the clinician in interpreting the relevant literature in establishing dosing parameters for prescription of tablet buprenorphine, this study was designed to compare the steady state: (1) pharmacokinetics and bioavailability, and (2) physiological, subjective and objective opiate effects of two 8 mg buprenorphine tablets (16 mg) to those of 1 ml (8 mg/ml) buprenorphine solution based upon early reports suggesting that the bioavailability of the tablet was approximately 50% of that of the liquid.

Design: Randomized, open-label, two-way crossover study.

Setting: Inpatient hospitalization for 21 days.

Participants: Twenty-four male and females in general good health and meeting DSM-IV criteria for opiate dependence.

Intervention: Subjects received one of the two buprenorphine formulations in the first 10-day period, and the other for the second 10-day period with no washout.

Measurements: Pharmacokinetic analyses, opiate effects and adverse events.

Findings: Drug steady state was reached by Day 7 of each 10-day period, area under the curve for 16 mg (two 8 mg) tablets was higher than the solution. The only non-kinetic statistically significant difference observed between the formulations was in changes in total opioid agonist score.

Conclusions: The serum concentration achieved by 16 mg of tablet buprenorphine is higher than that of the 8 mg solution, although differences between physiologic, subjective and objective opioid effects were not noted. The relative bioavailability of tablet versus solution is estimated to be 0.71; thus, with respect to dosing parameters for the tablet, clinicians should consider using less than 16 mg to achieve bioequivalence to the 8 mg solution.

© 2005 Elsevier Ireland Ltd. All rights reserved.

Keywords: Buprenorphine; Bioavailability; Pharmacokinetics

1. Introduction

The availability of buprenorphine for the outpatient treatment of opioid addiction (Resnick, 2003) represents a landmark event in the field of addiction treatment in the United States. Scheduled so that it may be dispensed by physicians in their private offices, buprenorphine is the first real alternative to the methadone clinic

available to patients seeking pharmacologic treatment for addiction to heroin or prescription opioids (Leshner, 2003; Ling and Smith, 2002). After nearly eight decades, US physicians are able to again use an opioid to treat patients with opioid addiction, despite buprenorphine for this indication having been available considerably longer in Australia and in Europe, most notably in France where it had been approved since 1995. Multiple carefully controlled clinical trials have established the dosing parameters, unique safety and good efficacy of buprenorphine (Barnett et al., 2001; Giacomuzzi et al., 2003; Ling and Wesson, 2003; West et al., 2000). Due to its partial agonist properties, a ceiling

* Corresponding author. Tel.: +1 310 206 2825; fax: +1 310 794 7482.

E-mail address: pcompton@sonnet.ucla.edu (P. Compton).

effect exists for its agonist properties, and unlike methadone or LAAM, it produces what appears to be a low level of physical dependence with minimal withdrawal symptoms (Walsh and Eissenberg, 2003).

As currently marketed, buprenorphine is formulated as a sublingual (SL) tablet in two forms, a mono-product (Subutex®) containing buprenorphine alone, and a combination product (Suboxone®) combined with naloxone to discourage parenteral misuse. Most of the studies conducted by European and Australian investigators had used the tablet mono-product Subutex® and most recent studies by US investigators had used the combination tablet Suboxone®. The bulk of the early investigations, mostly conducted in the US, and the pivotal clinical trials supporting buprenorphine's approval by the US Food and Drug Administration (FDA) were conducted using a SL solution, which is known to be not strictly bioequivalent to the tablet formulation (Walsh and Eissenberg, 2003).

Previous single-dose pharmacokinetic (PK) studies comparing buprenorphine sublingual tablets with solution formulations have shown that the extent of bioavailability of the tablet formulation (8 mg) was quantitatively less than that of the solution formulation (8 mg/ml) (Nath et al., 1999). The bioavailability of one 8 mg buprenorphine sublingual tablet was approximately 50% (range 24–74%) relative to 1 ml of 8 mg/ml buprenorphine sublingual solution, and unrelated to salivary pH. In comparison to the liquid, the tablet also produced significantly fewer opiate agonist effects, although the same degree of opioid antagonist effects. Similarly, in two studies using more chronic dosing paradigms, plasma concentrations of the 8 mg tablet were estimated to be 55% of those of the solution after 7 days of dosing (Schuh and Johanson, 1999), and 62% after 14 days of dosing (Strain et al., 2004).

The present study was designed to test the estimated 50% relative bioavailability for the tablet in comparison to the solution, as demonstrated in acute- and chronic-dose studies. Evaluated were the steady-state pharmacokinetics and bioavailability of buprenorphine following multiple administrations (10 days) of two 8 mg buprenorphine SL tablets in comparison to 1 ml of 8 mg/ml SL solution. Further, evidence of physiological, subjective and objective opioid agonist and antagonist responses to the tablets versus solution was documented.

2. Methods

2.1. Design

The study used an open-label, randomized, two-way crossover design and was conducted in an inpatient setting over 21 days. Twenty-four subjects were randomized to receive one of two treatments (two 8 mg tablets SL QD or 1 ml of 8 mg/ml solution SL QD) for the first 10-day period and the other treatment for the second 10-day period with no washout period between treatments. Plasma samples for PK analysis were taken prior to dosing Days 7–10 of each treatment period, and at specified intervals for 24 h following dosing on Day 10 of each treatment period. Subjective and physiologic effects were measured daily during both treatment periods, and again at spe-

cific time points following dosing on Day 10 of each treatment period.

2.2. Subjects

Subjects were recruited from the local community by referral and advertisement. Male and female adults 21–55 years of age who met DSM-IV criteria for opiate dependence were eligible to participate, provided they were not dependent on other substances (except caffeine and nicotine), and were in good general mental and physical health. All potential subjects entered the Institutional Review Board-approved study only after providing full informed consent. Female subjects were required to have a negative pregnancy test and to agree to use adequate birth control throughout the study.

Subjects were permitted to drop out of the study at any time if they so desired, or if the investigator felt to do so was clinically appropriate. Substitute subjects were enrolled for those who discharged early, keeping the sample size of completed subjects at 24. Data from discontinued subjects who received at least one dose of buprenorphine were retained and inspected for adverse events.

2.3. Materials and methods

The buprenorphine tablets (without naloxone) were manufactured by Reckitt and Colman (Hull, United Kingdom) and the buprenorphine solution (buprenorphine hydrochloride in 30% ethanol) was manufactured by Carolina Medical Products Company (Farmville, NC). Medication was supplied by Research Triangle Institute and shipped directly to the institutional pharmacy.

2.3.1. Measures

2.3.1.1. Pharmacokinetics. Blood samples for buprenorphine analyses were taken just prior to dosing on Days 7–10 and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h after dosing on Day 10 of both periods. Day 10 sampling took place via an intravenous catheter. Ten milliliters of blood was extracted at each time point, centrifuged within 15 min and the plasma was stored at –70 °C prior to analysis via liquid chromatography/tandem mass spectrometry (Moody et al., 2002).

2.3.1.2. Physiologic measures. Vital signs (heart rate, sitting blood pressure, temperature and respiration rate) and pupil diameter were measured daily during the study just prior to buprenorphine dosing, after the subject had sat quietly for 10 min, and had refrained from caffeine and nicotine for at least 30 min. On study Day 10, vital signs (0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h) and pupillary photographs (1, 3, 6, 12, 24) were collected for each treatment period following buprenorphine dosing. Also, prior to dosing, saliva was collected in a test tube to evaluate the effect of salivary pH on rate of tablet dissolution.

2.3.1.3. Opioid effects. Prior to dosing, and at specified time points following dosing on Day 10 (0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h), subjects were asked to rate their current

condition on four scales designed to measure opiate agonist and antagonist symptoms.

- *Global intoxication and withdrawal scale:* Subjects rated feelings of opioid intoxication and opiate withdrawal on scales of 0–100, where 0 indicated no effect and 100 the maximum effect experienced after using opiate drugs.
- *Opiate visual analog scale:* Subjects rated each of four drug effects (“good” drug effect, “bad” drug effect, drug liking and sickness) by making a vertical mark along a 100 mm line marked at opposite ends as “not at all” (0 mm) and “extreme” (100 mm).
- *Opiate agonist effects scale:* Subjects rated the degree to which they experienced each of 16 typical opiate-like effects (nodding, heavy or sluggish feeling, dry mouth, good mood, energetic, upset stomach, itchy skin, relaxed, coasting, talkative, pleasant sickness, drive, carefree, drunken, friendly, nervous) on a scale of 0 (not at all) to 4 (extremely), thus scores range between 0 and 64 points.
- *Opiate withdrawal scale:* Subjects rated the degree to which they experienced each of 21 typical opiate withdrawal symptoms (muscle cramps, flushing, painful joints, yawning, restless, watery eyes, runny nose, chills or gooseflesh, sick to stomach, sneezing, abdominal cramps, irritable, backache, tense and jittery, sweating, depressed, sleepy, shaky, tremulousness, hot or cold flashes, bothered by noise, skin clammy and damp) on a scale of 0 (not at all) to 4 (extremely). Scale scores range between 0 and 84 points.

A trained member of the research team concurrently evaluated the subject's symptoms on the opiate agonist effects scale and the opiate withdrawal scale, and also completed the:

- *Opiate withdrawal intensity scale:* The observer rated the presence and severity of six opiate withdrawal signs (lacrimation, rhinorrhea, yawning, perspiration, piloerection, restlessness) on a scale of 0 (not at all) to 4 (extremely). Scale scores range between 0 and 24.
- *Adverse effects:* Subjects were monitored for adverse events throughout the entire study period by trained study staff. The investigator or designated staff evaluated the intensity, seriousness and causal relationship to the study medication(s) of all adverse experiences.

2.3.2. Procedures

Subjects who appeared to be eligible to participate on the basis of a telephone interview underwent a screening visit following informed consent during which time they received a physical and psychiatric examination and clinical laboratory testing. A drug use history for the previous 6 months was also collected.

For study participation, subjects were admitted to the inpatient ward the morning of the day before their first buprenorphine dose, where they remained as inpatients until 24 h after the final dose. They were housed in a locked ward and were attended by a study staff member when not on the ward. Only

certain concomitant medications (Tylenol, Mylanta, Maalox, Milk of Magnesia, Immodium) were provided to subjects as needed and recorded in the study casebooks. They received a low fat breakfast each morning at 7:30 a.m. and received the study medication at 9:00 a.m. The first day of the first treatment period, all subjects received a half dose of the formulation to which they were assigned (1 ml of 4 mg/ml solution if assigned to liquid, one 8 mg tablet if assigned to tablet), and received a full dose for the remainder of the study. When receiving the solution medication, subjects were instructed to hold the sublingual medication under the tongue for 5 min and then swallow; for the sublingual tablets, subjects were instructed to keep the medication under the tongue until it completely dissolved or for 15 min, which ever occurred sooner, and then swallow.

2.4. Data analysis

To verify that steady state was attained, the predose plasma buprenorphine concentration (C_0) on Days 7, 8, 9 and 10 was examined. A repeated-measures ANOVA was used, with subject as the between-subject factor and treatment and day as the within-subject factors. Tests for a linear trend and multiple comparisons between days were performed. The bioequivalence analysis was performed on both the log-transformed and actual values of $AUC_{(0-24)}$, maximum concentration (C_{max}) and time to maximum concentration (T_{max}). A standard crossover model that included period and treatment as within-subject factors and sequence as a between-subject factor was used to analyze the PK parameters. Bioequivalence was assessed using two one-sided tests with 5% type I error. If the 90% confidence interval of the ratio of the log-transformed AUC or C_{max} for the two formulations was within the range of 0.80–1.25, the two formulations were considered to be bioequivalent.

The change from baseline (predose value on Day 10) for each physiologic measure collected following dosing on Day 10 of both periods was analyzed. Two change scores were calculated for both the subject and observer opiate effect measures: change from Day 1 to Day 10 of both periods, and change from predose Day 10 baseline and each measure collected following dosing. All change scores were analyzed with a repeated-measures ANOVA model that contained the effects of sequence, treatment, time and subject, and interactions between sequence and treatment, time and treatment, subjects and treatment, subject and time, and sequence, treatment and time. AUC analysis was also conducted on the total scores on the subject and observer opiate agonist effects scale and the opiate withdrawal scale. Differences between the formulations were compared. All adverse experiences reported by the subjects were coded using the COSTART dictionary and inspected for severity, frequency, body system and relationship to treatment. To describe the relationship between salivary pH and rate of tablet dissolution, data were examined with a *t*-test to determine if there was a difference in mean saliva pH for tablets which dissolved within 5 min or after 5 min.

3. Results

A total of 34 subjects enrolled in the study; of the 10 subjects who discontinued prematurely, 4 withdrew at their own request and 6 were discharged due to protocol non-compliance. Adverse event data were collected from the nine discharged subjects who had received at least one dose of buprenorphine. Demographic characteristics of 24 subjects who completed the study are summarized in Table 1.

3.1. Pharmacokinetic analysis

On Days 7–11 of both periods (where “Day 11” refers to the 24-h post-dose assessment on Day 10), the mean pre-dose concentration for the solution varied between 0.87 and 0.98 ng/ml, and the mean concentration for the tablet varied between 1.59 and 1.75 ng/ml. There were neither significant differences between days nor a significant linear trend, indicating that steady state was attained by Day 7. Mean plasma levels of buprenorphine on Day 10 of both periods are summarized by time and treatment in the Fig. 1. For both formulations, a second, small increase in blood level was noted approximately 8–12 h following dosing.

Descriptive statistics for the PK data for each formulation, and the 90% confidence intervals for the ratio of the two formulations with respect to AUC and $C_{\max}$ (analyzed on log-transformed or untransformed scales) are detailed in Table 2. No sequence effect or period effect was observed in any of the crossover analyses for AUC and $C_{\max}$. As can be seen, the upper limit of the 90% confidence interval for each of the four parameters is higher than 1.25, thus the two treatments are not bioequivalent.

Based upon these data, the relative bioavailability of an equal dose of 8 mg buprenorphine for the tablet versus solu-

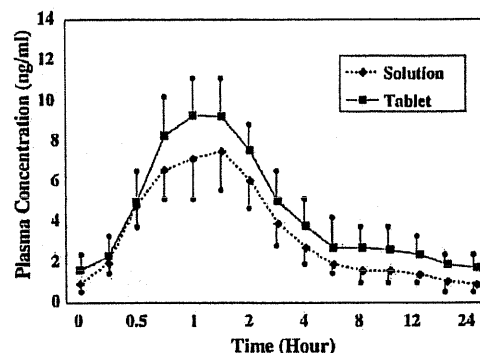


Fig. 1. Mean and standard deviation of plasma buprenorphine concentration (ng/ml) for subjects on 8 mg solution buprenorphine ($n=12$) and 16 mg tablet buprenorphine ($n=12$) on study Day 10.

tion was calculated. The 8 mg buprenorphine tablet contains 8.62 mg buprenorphine HCl; therefore, the adjusted blood concentrations for the tablet formulation were: adjusted Conc. = Conc. $\times 8/(8.62 \times 2)$. The crossover analysis was also performed on the adjusted AUC_(0–24) and $C_{\max}$ values. The estimated relative bioavailability of the 8 mg tablet versus 8 mg solution is 0.71, with 90% confidence intervals (0.64–0.79). The relative $C_{\max}$ of tablet versus solution is 0.63, with 90% confidence intervals (0.55–0.73). These estimates of bioavailability should be taken with caution; however, as the adjustment procedure used to obtain the estimates had an underlying assumption of dose proportionality.

3.2. Physiologic and opiate effects

Day 10 mean post-dose values for all physiologic measures in both periods were within normal range for both formulations, and all measures returned to their approximate predose values within 24 h after dosing. With both formulations, pupil diameter

Table 1
Demographic characteristics of study participants ($n=24$)

Characteristic	T-S ($n=12$)	S-T ($n=12$)
Gender		
Male	8	10
Female	4	2
Age (year)		
Mean	33.5	41.1
S.D.	6.5	28.4
Race		
White	7	7
Latino	5	4
Black	0	1
Height (in.)		
Mean	67.1	70.2
S.D.	3.2	3.3
Weight (lb)		
mean	146.8	150.3
S.D.	23.5	28.4

T-S, subjects crossing over from tablet to solution buprenorphine; S-T, subjects crossing over from solution to tablet buprenorphine. Crossover occurred at Day 10 with no washout period between treatments.

Table 2
Pharmacokinetic parameters for solution and tablet buprenorphine with 90% confidence intervals

	Solution			Tablet		
	AUC (ng/ml h)	$C_{\max}$ (ng/ml)	$T_{\max}$ (h)	AUC (ng/ml h)	$C_{\max}$ (ng/ml)	$T_{\max}$ (h)
Mean	46.37	7.87	1.22	70.32	10.38	1.24
S.D.	16.15	3.15	0.41	22.64	3.45	0.36
CV (%)	34.8	40.1	33.8	32.2	33.3	29.4
Minimum	23.26	2.40	0.50	43.16	4.12	0.50
Maximum	69.75	14.04	2.00	128.50	19.51	2.00
Estimated ratio (tablet/solution) 90% Confidence intervals						
Ln (AUC)	1.53			1.39–1.70		
Ln ($C_{\max}$)	1.36			1.18–1.57		
AUC	1.51			1.38–1.65		
$C_{\max}$	1.32			1.17–1.47		

Plasma samples for analyses were taken prior to dosing on Days 7–10 of each treatment period, and at specified intervals after dosing (0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h) following dosing on Day 10 of each treatment period.

and heart rate decreased slightly, systolic and diastolic blood pressure increased slightly, and respiratory rate and temperature showed little variance. The ANOVA showed that there were no significant effects of treatment on any of the physiologic measures.

For most of the subject-reported opiate effects, mean scores were low prior to dosing and did not change greatly after dosing on Day 10. In general, over the course of 24 h, slight increases in intoxication, “good drug effect” and “drug liking” peaked and a slight decrease in withdrawal ratings were noted 2–4 h post-dosing, while “bad drug effect”, “sickness” and withdrawal severity all increased 6–8 h post-dosing. The only non-kinetic measure on which a significant difference between treatment was noted was the total opiate agonist effects scale; for both formulations there was an initial increase effects followed by a decrease, which, in the case of the tablet, was larger and more stable than the solution ($p=0.039$).

Table 3
Summary of treatment-related adverse events reported by subjects during study period (subjects could have multiple responses in a given category)

Adverse event	Treatment group	
	Tablet (N=29)	Solution (N=28)
Body as a whole	11 (37.9%)	7 (25.0%)
Asthenia	1 (3.4%)	0 (0%)
Chill	5 (17.2%)	3 (10.7%)
Fever	1 (3.4%)	0 (0%)
Headache	7 (24.1%)	6 (21.4%)
Pain	2 (6.9%)	2 (7.1%)
Pain abdominal	2 (6.9%)	1 (3.6%)
Pain back	2 (6.9%)	1 (3.6%)
Cardiovascular system	4 (13.8%)	1 (3.6%)
Vasodilatation	4 (13.8%)	1 (3.6%)
Digestive system	3 (10.3%)	8 (28.6%)
Constipation	3 (10.3%)	3 (10.7%)
Diarrhea	0 (0%)	1 (3.6%)
Dyspepsia	0 (0%)	5 (17.9%)
Vomit	1 (3.4%)	0 (0%)
Hematologic and lymphatic system	1 (3.4%)	0 (0%)
Leukocytosis	1 (3.4%)	0 (0%)
Musculo-skeletal system	2 (6.9%)	3 (10.7%)
Arthralgia	0 (0%)	1 (3.6%)
Myalgia	3 (10.3%)	2 (7.1%)
Nervous system	5 (17.2%)	3 (10.7%)
Anxiety	2 (6.9%)	1 (3.6%)
Hypertonia	1 (3.4%)	0 (0%)
Insomnia	3 (10.3%)	2 (7.1%)
Nervousness	1 (3.4%)	1 (3.6%)
Somnolence	1 (3.4%)	0 (0%)
Respiratory system	4 (13.8%)	0 (0%)
Hiccup	1 (3.4%)	0 (0%)
Rhinitis	4 (13.8%)	0 (0%)
Skin and appendages	4 (13.8%)	5 (17.9%)
Acne	0 (0%)	1 (3.6%)
Rash	1 (3.4%)	2 (7.1%)
Sweat	3 (10.3%)	2 (7.1%)
Special senses	2 (6.9%)	2 (7.1%)
Lacrimation	1 (3.4%)	1 (3.6%)
Taste perversion	1 (3.4%)	1 (3.6%)

Opiate effects noted by the observer were similar in intensity and timing to those reported by the subjects on the total opiate effects and total opiate withdrawal scales; although not significantly different, observers tended to rate agonist effects higher than the subjects did, especially in subjects on solution buprenorphine. Maximal increases in observed withdrawal severity were noted 8–14 h after dosing, with a slight decrease in scores in the case of the tablet immediately following dosing.

3.3. Adverse events

Table 3 provides summary data on the treatment-related adverse events noted for each formulation. Percentages of treatment-related adverse effects were similar between the tablet (82.8%) and the solution (85.7%) formulations of buprenorphine, as were rates of those considered severe adverse events (tablet 62.1% versus solution 57.1%). Adverse events were predominately described as affecting the body as a whole, with headache being the most common symptom and considered to be treatment-related in 34.5% of subjects taking the tablet and 28.6% of the subjects taking solution. No serious adverse events occurred during the study.

3.4. Effects of salivary pH

No significant difference in salivary pH was noted between subjects whose tablets dissolved within 5 min (pH 6.40) and after 5 min (pH 6.50). Overall, 37% of the subjects had to swallow the un-dissolved pill after 15 min on between 3 and 7 occasions during the 10-day treatment.

4. Discussion

Although most of the early clinical studies of buprenorphine for the treatment of opioid addiction had been conducted by US investigators, its approval by the US Food and Drugs Administration (FDA) was slow. It literally took an act of congress in the form of the Narcotic Treatment Act of 2000 to make buprenorphine available to US clinicians. In Europe, notably in France and in Australia, buprenorphine for treatment of opioid addiction has been available considerably longer, and a number of clinical studies were conducted by European and Australian investigators using the mono-product Subutex®, while recent studies by US investigators have used the combination product Suboxone®. The bulk of the early research and the pivotal clinical trials providing critical data for its eventual approval by the FDA had used a liquid formulation of buprenorphine, which was known to have different bioavailability from the marketed tablets. To enable clinicians to properly interpret the body of research, it was necessary to determine the relative bioavailability of the tablet and the liquid formulations. The study results reported here was part of that effort.

An initial single-dose study had estimated the bioavailability of the tablet to be approximately 50% that of the liquid, and provided the rationale to compare the tablet formulation at twice the dose of the liquid so as to achieve comparable blood concentration in the two treatment groups, although subsequent studies

have shown that the blood concentration of the tablet formulation increased with repeated dosing. Data from the study reported here provide evidence for the lack of bioequivalence of 1 ml of 8 mg/ml buprenorphine and 16 mg (2 mg $\times$ 8 mg) buprenorphine tablets, as had been expected based upon the earlier studies. The tablet formulation at twice the dose of the solution achieved higher mean predose plasma concentration levels, a greater AUC (0–24), and a higher $C_{\max}$ than the solution, although the $T_{\max}$ was similar between the two formulations, as was the shape of 24 h plasma concentration curve. Despite higher plasma concentrations in the tablet condition, the percentages of adverse events were not different between the two formulations.

These data collected after 10 days of buprenorphine dosing are not unlike those reported by Strain et al. (2004) after 7 days of dosing, with respect to tablet versus solution AUC (64%) and peak plasma concentration (62%). These investigators did find that with a longer period of dosing (14 days), the bioavailability of the tablet increased with respect to the solution (AUC = 70%, $C_{\max}$ = 73%), primarily due to a decrease in the pharmacokinetic efficacy of the solution with the passage of time. Examination of buprenorphine plasma concentrations over Days 7–10 of each treatment period in the present study did not reveal a clear trend toward decreased values for the solution over time. Strain et al. (2004) suggest that an “adaptation of the buccal environment to the solution form relative to the tablets” (p. 41) may occur and be related to the alcohol used on the solution formulation, the concentration of which was higher in the Strain study (40%) than in the present work (30%), thus accounting for a lack of a time effect.

Despite the significant differences in bioavailability between the tablet and solution formulations, differences between physiologic, subjective and objective opioid effects were less distinct. Although observer and subject assessment was unblinded, no differences between treatments were noted in opiate effects over the course of the study; vital signs were normal and intoxication/withdrawal symptoms were minimal. The Day 10 measures showed small but predictable opiate agonist effects with both formulations on both physiologic and subjective indices, with agonist effects predominating in the first few hours after dosing and dysphoric and withdrawal symptoms following 6–8 h later. The general trend for a greater agonist effect on physiologic measures with the tablet is consistent with the higher blood concentration levels. The tablet significantly differed from the solution on the subjective total opiate agonist effects scale only, on which subjects on solution reported higher and more variable opiate agonist, despite the lower blood concentration achieved.

The physiologic measures are reassuring in that they showed little fluctuation between peak and trough concentrations, confirming the high safety profile of buprenorphine with chronic treatment, especially with regard to respiratory depression. These findings indicate that a steady state is achieved after about 7 days of dosing with the tablet attaining approximately 70% blood concentration of the equivalent liquid doses. This level is considerably higher than suggested by the results of the early single-dose studies, and consistent with subsequent findings from chronic dosing studies (i.e., Schuh and Johanson, 1999; Strain et al., 2004), that bioavailability of the two formulations

approach each other with chronic dosing. Thus, the initial suggestion that tablets need to be given at twice the milligram dose of the liquid is disputed.

This study was conducted before the development of the buprenorphine/naloxone combination tablet (Suboxone®). The tablets used in this study were provided by the manufacturer and were identical to the subsequently marketed mono-product tablet Subutex® (Chris Chapleo, Reckitt Benckiser, personal communication, 29 July 2005). The tablets were administered by instructing participants to hold the tablets under the tongue until they completely dissolved or until 15 min had elapsed before the participants were allowed to swallow. This was the practice subsequently adopted in the clinical dosing guidelines. While swallowing the small amount of residual tablets may have some minor effect on the total concentration achieved, it is reassuring to note that it would, if anything, further increase the blood concentration of the tablets and would not have altered the conclusions of the trial.

Acknowledgements

This work was supported by a medication development center grant from NIDA. Reckitt/Benckiser, manufacturer and owner of buprenorphine products provided the study material for this study. Walter Ling has served as consultant to Reckitt/Benckiser and Reckitt/Benckiser has given UCLA an unrestricted educational grant to support his work. The analytical work was performed under funding from the National Institutes on Drug Abuse, National Institutes of Health Contract No. N01DA-1-9205 and N01DA-7-8074.

References

- Barnett, P.G., Rodgers, J.H., Bloch, D.A., 2001. A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. *Addiction* 96, 683–690.
- Giacomuzzi, S.M., Ertl, M., Kemmler, G., Rossler, H., Hinterhuber, H., Kurz, M., 2003. Buprenorphine versus methadone maintenance treatment in an ambulant setting: a health-related quality of life assessment. *Addiction* 98, 693–702.
- Leshner, A., 2003. Accessing opiate dependence treatment medications: buprenorphine products in an office-based setting. *Drug Alcohol Depend.* 70, S103–S104.
- Ling, W., Smith, D., 2002. Buprenorphine: blending practice and research. *J. Subst. Abuse Treat.* 23, 87–92.
- Ling, W., Wesson, D., 2003. Clinical efficacy of buprenorphine: comparisons to methadone and placebo. *Drug Alcohol Depend.* 70, S49–S57.
- Moody, D.E., Slawson, M.H., Strain, E.C., Laycock, J.D., Spanbauer, A.C., Foltz, R.L., 2002. A liquid chromatographic-electrospray ionization-tandem mass spectrometric method for determination of buprenorphine, its metabolite, norbuprenorphine, and a co-formulant, Naloxone, that is suitable for in vivo and in vitro metabolism studies. *Anal. Biochem.* 306, 31–39.
- Nath, R.P., Upton, R.A., Everhart, T., Cheung, P., Shwonek, P., Jones, R.T., Mendelson, J.E., 1999. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. *J. Clin. Pharmacol.* 39, 619–623.
- Resnick, R.B., 2003. Food and Drug Administration approval of buprenorphine–naloxone for office treatment of addiction. *Ann. Intern. Med.* 138, 360–361.

- Schuh, K.J., Johanson, C.E., 1999. Pharmacokinetic comparison of the buprenorphine sublingual liquid and tablet. *Drug Alcohol Depend.* 56, 55–60.
- Strain, E.C., Moody, D.E., Stoller, K.B., Walsh, S.L., Bigelow, G.E., 2004. Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. *Drug Alcohol Depend.* 74, 37–43.
- Walsh, S.L., Eissenberg, T., 2003. The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. *Drug Alcohol Depend.* 70, S13–S27.
- West, S.L., O'Neal, K.K., Graham, C.W., 2000. A meta-analysis comparing the effectiveness of buprenorphine and methadone. *J. Subst. Abuse* 12, 405–415.

Review

Clinical and pharmacological evaluation of buprenorphine and naloxone combinations: why the 4:1 ratio for treatment?

John Mendelson*, Reese T. Jones

Drug Dependence Research Center, Langley Porter Psychiatric Institute, University of California, 401 Parnassus Avenue, San Francisco, CA 94143-0984, USA

Received 19 December 2002; accepted 4 February 2003

Abstract

Although only a partial μ -opiate agonist, buprenorphine can be abused and diverted from medical therapy to the illicit drug market. A combination of buprenorphine and naloxone for sublingual administration may discourage diversion and abuse by precipitating opiate withdrawal when taken parenterally. Because opiate-abusing populations are not homogeneous and have varying levels of opiate dependence, the efficacy of buprenorphine and naloxone in precipitating opiate withdrawal or in attenuating the pleasurable effects of buprenorphine may vary. This chapter describes the effects of sublingual and parenteral buprenorphine and naloxone combinations in several populations of opiate-dependent people. We conclude that buprenorphine and naloxone combinations should not diminish the efficacy of sublingual buprenorphine, but should have lower abuse liability than buprenorphine alone.

© 2003 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Opiate; Dependence; Treatment; Buprenorphine; Naloxone

1. Introduction

Initial reports suggested that buprenorphine would have a low abuse potential (Jasinski et al., 1978; Jasinski, 1979). However, like all potent μ -opiates, parenteral abuse and illicit diversion of buprenorphine has been reported worldwide (O'Connor et al., 1988; Singh et al., 1992; Robinson et al., 1993). The majority of the reported abuse occurs in heroin addicts who intravenously administer extracts of crushed tablets (Segui et al., 1991; Lavelle et al., 1991; San et al., 1993; Nigam et al., 1994). Injection drug abusers are at risk for serious bacterial and viral diseases, including HIV. Strategies which diminish the parenteral abuse liability of treatment medications will decrease transmission of infections between injection drug abusers; hence, the development of a formulation of buprenorphine less abusable by injection.

The efficacy of buprenorphine, alone or in combination with naloxone, for the treatment of opiate dependence is described in other chapters. Here we review the rationale for selecting a 4:1 ratio of buprenorphine to naloxone for marketed formulation and how the combination was assessed for safety and efficacy. We discuss the effects of both buprenorphine and naloxone in different populations of opiate abusers and nonabusers and use these findings to estimate abuse liability.

2. Requirements for a buprenorphine and naloxone combination

Buprenorphine and naloxone dose combinations should diminish the parenteral abuse liability of buprenorphine in opiate-dependent individuals by precipitating opiate withdrawal when taken parenterally but not sublingually. Naloxone in solution has a relatively low sublingual absorption of 8–10% (Weinberg et al., 1988; Preston et al., 1990; Harris et al., 2000), whereas buprenorphine in solution is better absorbed ($\approx$ 30–50%) and has significant pharmacologic activity when

* Corresponding author. Tel.: +1-415-476-7472; fax: +1-415-476-7690.

E-mail address: jsmmd@itsa.ucsf.edu (J. Mendelson).

given sublingually (Olley and Tiong, 1988; Weinberg et al., 1988; Jasinski et al., 1989; Mendelson et al., 1997a,b). The rapid and unpleasant effects of naloxone when administered intravenously to opiate-dependent people (O'Brien et al., 1978; Gilman et al., 1990; Mendelson et al., 1997a,b) suggested that it would be an ideal candidate for a combination formulation. The optimal combination formulation of buprenorphine and naloxone would preserve the therapeutic effects of buprenorphine and minimize opiate antagonist effects of naloxone when given sublingually. However, if the same combination was taken illicitly by a parenteral route, it would have the opposite effects, precipitating substantial opiate withdrawal.

This was an unusual requirement for a new drug formulation. In general, successful medications do not produce unpleasant effects and exhibit minimal inter-individual variability. However, the buprenorphine and naloxone combination needed to be aversive when administered parenterally but well tolerated when given sublingually. In addition, interindividual variability was desirable, with rapidly precipitated withdrawal in parenteral abusers but suppression of withdrawal (and illicit opiate use) in treated patients. Precipitated withdrawal can produce substantial sympathetic activation, with marked elevations in heart rate and blood pressure. Therefore, the combination should be as safe as possible. Because naloxone produces both desired aversive effects and potentially dangerous sympathetic activation, determining the lowest effective dose of naloxone required for precipitated withdrawal was important.

Precedents for combination agonist and antagonist opioid formulations include pentazocine and naloxone mixtures, which significantly reduced parenteral pentazocine abuse (Ghodse, 1987). A methadone and naloxone oral dose combination was tested but not widely prescribed (Nutt and Jasinski, 1974; Loimer et al., 1991). A survey of New Zealand opiate abusers suggested that a buprenorphine and naloxone combination marketed in that country appeared to decrease abuse liability for lower, analgesic buprenorphine doses (0.3–0.6 mg) (Robinson et al., 1993). However, sublingual buprenorphine doses in solution in the range of 4–32 mg per day are needed for opiate addiction treatment in most patients (Johnson et al., 1995; Ling et al., 1996; Strain et al., 1996; Schottenfeld et al., 1997; Eder et al., 1998; Ling et al., 1998), and the lowest effective dose is 2 mg (Johnson et al., 1992). Buprenorphine combinations with naloxone in this dose range had not been studied.

3. Efficacy of buprenorphine and naloxone in precipitating opiate withdrawal

Some buprenorphine likely will be diverted from therapeutic to illicit use. Effective deterrence will depend

to some extent on the magnitude and likelihood of adverse events. Because people already dependent on opiates are most likely to abuse an opiate drug, several studies have evaluated the efficacy of buprenorphine and naloxone combinations in precipitating opiate withdrawal. Complicating matters, opiate-abusing and dependent populations are not homogeneous. The varying levels of tolerance and dependence between infrequent users of opiates and patients on methadone maintenance mandated assessment of buprenorphine and naloxone combinations in a range of defined opiate-abusing and dependent populations. We and others have studied the effects of buprenorphine and naloxone in populations spanning a range of opiate abuse and dependence. Tables 1 and 2 summarize the results of human studies using various buprenorphine and naloxone combinations.

4. Buprenorphine and naloxone effects in opiate-dependent people

Quantification of the degree of opiate dependence can be difficult. No agreed upon definition exists distinguishing low, moderate, and high levels of opiate dependence. Substitution trials have used daily doses as large as 240 mg morphine (Fraser and Isbell, 1960) given in equal doses (60 mg s.c. doses every 6 h) to suppress withdrawal in highly dependent subjects. More recent substitution and challenge studies of partial agonists of morphine were conducted with volunteers dependent on 60 mg morphine sulfate given in four daily 15 mg s.c. or i.m. doses. At this dose, sufficient effects were produced to reliably suppress measured signs and symptoms of opiate withdrawal (Jasinski, 1977; Schuh et al., 1996). This dose of morphine was approximately equivalent to a 30 mg daily oral methadone dose, and is generally associated with moderate dependence.

Parenterally administered buprenorphine and naloxone reliably precipitate opiate withdrawal in people with high to moderate levels of opiate dependence. In two studies (Preston et al., 1988; Mendelson et al., 1997a,b), patients taking 30 mg or more of methadone per day had substantial precipitated withdrawal following fixed ratio (2:1, 1.5:1 and 1:1) low dose buprenorphine (0.2–0.3 mg) and naloxone (0.1–0.2 mg) combinations. These buprenorphine doses are in the analgesic dose range for opiate-naïve patients. The very small doses of naloxone required to precipitate substantial withdrawal (and a clear dislike for this combination) suggests a low abuse liability in people with moderate to high levels of opiate dependence.

In opiate-dependent daily heroin users, an i.v. dose of a 1:1 ratio of buprenorphine to naloxone (2 mg) produced opiate withdrawal and decreased the estimated illicit street value of the combination (Mendelson

Table 1
Effects of buprenorphine (B) and naloxone (B:N) combinations in opiate-naïve, experienced, or dependent populations

Study	Goal	N	Population	B:N Dose route	Results
Rolly et al., 1986	Examine efficacy and safety of B and B:N combo in post-surgical pain	30 B (9 M) 29 B:N (10 M)	Post-orthopedic or gynecological surgery	0.3 mg B and 0.2 mg N i.m. (3:2 B:N)	No difference in analgesic efficacy between B and B:N
Vanacker et al., 1986	Compare B and B:N combo efficacy in post-surgical pain	34 B (13 M) 36 B:N (16 M)	Abdominal surgery	0.3 mg B and 0.2 mg N i.m. (3:2 B:N)	No difference in analgesic efficacy between B and B:N
Preston et al., 1988	Determine abuse liability of B:N combo	6 M	Opiate-dependent, methadone maint (30 mg/day)	0.2 mg B and 0.2 mg N; 0.3 mg B and 0.2 mg N s.c. (1:1, 3:2 B:N)	B:N precipitated w/d less than N alone (using subjective, behavioral, and physiological measures)
Mendelson et al., 1989	Measure effects of non-B-induced prolactin release	6 M	Opiate-naïve	0.3 mg B and 0.15–0.6 mg N i.v. together (2:1, 4:1, 2:3, 1:2 B:N)	N suppressed B-induced prolactin release in a dose-dependent manner
Weinhold et al., 1992	Evaluate agonist effects of B:N combo	7 M	Opiate experienced, nondependent	0.4 mg B and 0.4–0.8 mg N, 0.8 mg B and 0.4–0.8 mg N i.m. together (1:1, 1:2, 2:1 B:N)	N attenuated agonist effects of B
Mendelson et al., 1996	Compare effects of B, N, B:N combo	8 M	Opiate-dependent (confirmed by N-induced w/d)	2 mg B and 2 mg N i.v. (1:1 B:N)	B:N induced substantial w/d; N diminished B agonist effects; B diminished N antagonist effects
Mendelson et al., 1997a,b	Compare effects of B, N, B:N combo	6 (5 M)	Opiate-dependent, methadone maint (49–60 mg/day)	0.2 mg B and 0.1 mg N i.v. (2:1 B:N)	B:N induced w/d using physiological and subjective measures
Fudala et al., 1998	Evaluate effects of B:N combo	10 M	Opiate-dependent morphine maint (15 mg i.m. q.i.d.)	2 mg B and 0.5 mg N i.v. together (4:1 B:N)	B:N precipitated w/d using subjective and observed measures
Mendelson et al., 1999	Evaluate effects of B:N combo	12 (11 M)	Opiate-dependent morphine maint (15 mg i.m. q.i.d.)	2.0 mg B and 0.25–2.0 mg N i.v. together (2:1, 4:1, 8:1 B:N)	N precipitated w/d, increased HR, BP, RR (8:1 only increased self-reported w/d; 2:1, 4:1) produced w/d using self-reported, observed and physiological measures
Strain et al., 2000	Evaluate abuse potential of sublingual B and B:N in non-dependent opiate abusers	7 M	Opiate abusers who were not physically dependent	B 4, 8, 16 mg s.l. B:N 1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg s.l.	Opiate agonist effects of B and B:N similar, suggesting that abuse can occur in nondependent abusers
Stoller et al., 2001	Assess abuse liability of B:N doses in the therapeutic range	10 (gender not specified)	Heroin addicts stabilized on oral hydromorphone 40 mg daily	B 8 mg i.m., s.l. N 0.25 i.m. B:N 1/0.25, 2/0.5, 4/1, 8/2, 16/4 i.m. and s.l. Hydro-morphone 10 mg i.m.	Dose-related precipitated withdrawal seen with i.m. B, s.l. B:N or B
Comer and Collins, 2002	Assess the reinforcing effects of B and B:N combinations in recently withdrawn heroin addicts	6 (5 M)	Heroin addicts withdrawn from heroin for 1–6 weeks	B 3 and 8 mg i.v. B:N 2/0.5 and 8/2 mg i.v. All compared with alternative reinforcer of \$20.00	All B containing doses had similar reinforcing properties. B:N attenuated measurable effects of B

B, Buprenorphine; N, Naloxone; w/d, withdrawal; i.v., intravenous; i.m., intramuscular; s.c., subcutaneous; s.l., sublingual; M, male.

Table 2
Effects of buprenorphine (B) and naloxone (B:N) combinations in buprenorphine maintained or abusing populations

Study	Goal	N	Population	B:N Dose route	Results
Kosten et al., 1990	Examine antagonist-induced w/d in B-maint subjects	15 (14 M, 1 F)	Opiate-dependent B-maint (2 mg or 3 mg s.l. solution) i.v. B users	1 mg naloxone p.o. given 16 h after last daily 8 mg B s.l. (n=10) or 0.5 mg/kg N i.v. given 40 h after last daily 8 mg B s.l. (n=5)	N but not naloxone significantly precipitated w/d using observed and physiological measures
Nigam et al., 1994	Examine N-induced w/d in B-dependent patients	7 M	i.v. B users	1.2 mg N i.v. 3–6 h after patient administered i.v. B (1.33±0.27 mg/day by self-report)	N precipitated w/d using subjective and observed measures
Eisenberg et al., 1996	Examine N-induced w/d in B-maint subjects	8 (6 M, 2 F)	Treatment seeking opiate-dependent B-maint (8 mg B s.l. sol'n q.i.d.)	0.3–3.0 mg/70 kg naloxone p.o.; or 0.3–10.0 mg/70 kg N i.m. 14 h after last daily 8 mg B s.l. sol'n	Both 3.0 and 10 mg N and 3.0 mg naloxone precipitated w/d using subjective, observed and physiological measures
Eisenberg et al., 1997	Assess opiate w/d during 72 h dose omission in B-maint patients	8 (6 M, 2 F)	Treatment seeking opiate-dependent B-maint (8 mg/day s.l. sol'n)	10 mg/70 kg N i.m. given 1 h before daily 8 mg B s.l. sol'n	N precipitated w/d using subjective and pupil size measures; w/d was only partially reversed by B
Harris et al., 2000	Compare B and B:N combo in B-maint subjects	9 (8 M, 1 F)	Opiate-dependent B-maint (8 mg/day s.l. sol'n)	8 mg B and 4 or 8 mg N s.l. solution together (2:1, 1:1 B:N); 4 mg B and 4 mg N i.v. (1:1 B:N)	B:N combos were as effective as B in ameliorating w/d using physiological and subjective measures

B, buprenorphine; N, Naloxone; w/d, withdrawal; i.v., intravenous; i.m., intramuscular; s.l., sublingual.

et al., 1996). Fig. 1 displays self-reports of opiate agonist and antagonist effects following this combination dose. Buprenorphine alone produced typical opioid agonist effects and was considered liable to abuse by these subjects. The buprenorphine and naloxone combination was very aversive and not substantially different from naloxone alone. Following the combination dose, opiate agonist effects did eventually emerge but they were always delayed and attenuated when compared to buprenorphine alone. Although some degree of opiate withdrawal was usually precipitated by parenteral administration of this buprenorphine and naloxone combination, there was considerable between-subject variability in withdrawal intensity. Some of this variability was probably due to differing self-administered opiate doses and resulting levels of dependence inherent in any group of untreated heroin injectors.

In subjects maintained on 40 mg/day of oral hydromorphone, parenteral doses of 1.0–16 mg of buprenorphine combined with 0.25–4 mg of naloxone (always in a 4:1 ratio) produced reliable dose-dependent precipitated withdrawal. Similar doses of sublingual buprenorphine and naloxone or buprenorphine alone did not precipitate withdrawal. Maximal cardiovascular responses in this highly dependent population were not excessive, suggesting that precipitated withdrawal will be relatively safe in typical heroin addicts (Stoller et al., 2001).

5. Comparisons of three different buprenorphine and naloxone dose ratios

Empirical evaluation of a range of dose combinations guided optimal formulation of a s.l. medication with low abuse liability for the treatment of opiate dependence. We tested the effects of three buprenorphine and naloxone combinations in opiate-dependent subjects where controlled doses of morphine were substituted for illicit heroin (Mendelson et al., 1999). The primary goals of this study were to determine the dose range over which i.v. naloxone, in combination with i.v. buprenorphine, would precipitate opiate withdrawal signs and symptoms and attenuate the pleasurable effects of buprenorphine in subjects with a moderate level of opiate dependence. To minimize variability due to differing degrees of opiate dependence, subjects were stabilized on parenteral morphine. With this paradigm, volunteers physically dependent on variable but always uncertain self-administered doses of illicit opiates are given known doses of morphine to achieve a stable level of dependence. Thus, when the experimental medication is substituted for morphine, opiate agonist and antagonist effects can be measured under controlled laboratory conditions. After stabilization for 5 days on a 60 mg daily dose of morphine given as four 15 mg i.m. doses,

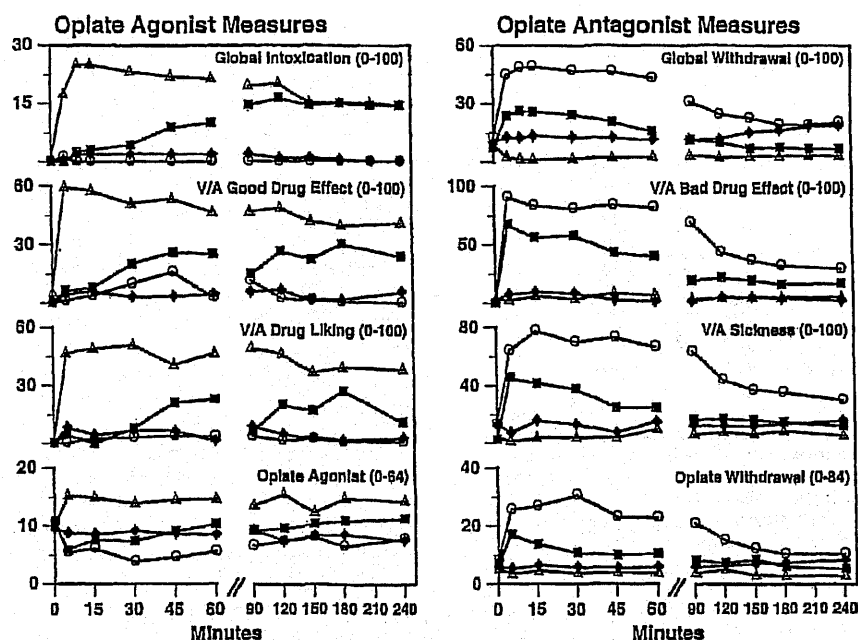


Fig. 1. Time course of opiate agonist and antagonist effects in untreated heroin addicts challenged with combinations of buprenorphine (2 mg) and naloxone (2 mg; 1:1 ratio). Buprenorphine (open triangles), buprenorphine and naloxone combination (solid squares), placebo (solid diamonds), and naloxone (open circles). Each data point represents mean values for eight subjects. VAS, Visual analog scale. (Mendelson et al., 1996) Reproduced with permission from the publisher.

subjects were challenged, under double-blind conditions, with a 2 mg i.v. dose of buprenorphine alone and in combination with 1, 0.5 and 0.25 mg naloxone (ratios of 2:1, 4:1 and 8:1). We knew naloxone at doses similar to those used in the study reliably precipitates opiate withdrawal in subjects maintained on 60 mg/day i.m. morphine (Schuh et al., 1996).

All three buprenorphine and naloxone combinations produced opiate antagonist effects when given intravenously. The naloxone in the combination dose produced dose-dependent precipitated withdrawal, with the 2:1 ratio (1 mg naloxone) producing the greatest and the 8:1 ratio (0.25 mg naloxone) the least opiate withdrawal (Fig. 2). All indices of opiate withdrawal were increased by the 2:1 and 4:1 ratios. With the 8:1 ratio, only self-reports of 'global' withdrawal were increased. Both subjective and physiologic withdrawal effects peaked within 5 min after injection of naloxone plus buprenorphine, then dissipated within 45 min for all combinations. The duration of withdrawal effects also depended on naloxone dose and lasted 30 min after the 2:1 ratio and 15 min after the 4:1 and 8:1 combinations. Buprenorphine-induced pupil constriction was significantly attenuated by the 2:1 and 4:1 buprenorphine and naloxone combinations, but not by the 8:1 ratio. In general, the 8:1 combination had a more variable

between-subject response and less overall effect. The 2:1 and 4:1 ratios were generally similar in the profile of antagonist effects. Although the 2:1 ratio could be distinguished from the 4:1 ratio on some withdrawal measures, both the 2:1 and 4:1 precipitated substantial withdrawal.

If buprenorphine was diverted from therapeutic to illicit use, our volunteer subjects would be typical potential purchasers. All subjects were regularly purchasing illicit heroin. They were qualified to judge the potential illicit street value of buprenorphine and naloxone combinations. They judged i.v. buprenorphine and morphine equivalent in dollar value (\$10 and 8, respectively). The estimated monetary value of all combination ratios was substantially less than buprenorphine or morphine. Although some subjects would be willing to pay small amounts for the 4:1 and 8:1 combination ratios (\$4), no one expressed any desire to pay for the 2:1 dose.

In a study similar to ours, opiate addicts were stabilized on the same daily dose of i.m. morphine sulfate (60 mg/day) and a single 4:1 dose ratio of buprenorphine and naloxone was evaluated (Fudala et al., 1998). Significant opiate withdrawal effects were produced by the i.v. dose of buprenorphine 2 mg and naloxone 0.5 mg, suggesting a decreased abuse potential

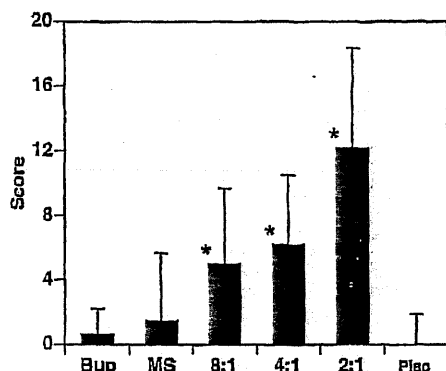


Fig. 2. Observer rating on the Clinical Institute Narcotic Assessment (CINA) Scale in opiate-dependent subjects stabilized on 60 mg/day i.m. morphine and challenged with three dose ratios of buprenorphine and naloxone. Change scores (mean $\pm$ S.D., $n = 12$) from baseline at 15 min postdose are shown. *, Significantly different from buprenorphine, morphine, and placebo ($P \leq 0.01$). Bup (buprenorphine, 2 mg), MS (morphine sulfate, 15 mg); 8:1 (buprenorphine, 2 mg; naloxone, 0.25 mg); 4:1 (buprenorphine, 2 mg; Naloxone, 0.5 mg); 2:1 (buprenorphine, 2 mg; naloxone, 1 mg); Plac (placebo). (Mendelson et al., 1996) Reproduced with permission from the publisher.

for this 4:1 dose ratio. Their findings are concordant with ours. The effects of higher or lower buprenorphine to naloxone ratios and doses were not examined.

The results of our study are also consistent with our earlier report of the effects of i.v. buprenorphine and naloxone combinations (2 mg; 1:1 ratio) in opiate-dependent daily heroin users not stabilized on morphine prior to challenge (Mendelson et al., 1996). When compared to the earlier study, the 2:1 combination produced more intense and less variable global withdrawal. The 4:1 ratio produced global withdrawal comparable to the 1:1 ratio in the earlier study. Although the pattern of self-ratings of antagonist effects (bad drug, sickness) was generally similar in both studies, more variability was evident in the unstabilized heroin addicts.

6. What about buprenorphine and naloxone in less dependent populations?

A substantial percentage of individuals abusing heroin or other opiates do not experience precipitated withdrawal after naloxone challenge (Kanof et al., 1991). Combination formulations might not be aversive in these individuals because naloxone-precipitated withdrawal would not occur. Therefore, in nondependent abusers an important additional feature of a combination would be attenuation of pleasurable and reinforcing effects of buprenorphine if the combination dose is taken parenterally. In our study of heroin-dependent

subjects, maximal opioid agonist effects were always smaller and delayed (for up to 3 h) following buprenorphine and naloxone combinations when compared with buprenorphine alone (Mendelson et al., 1996). The time course of effects was biphasic on self-ratings of global intoxication, with opiate antagonist-like effects dominating in the first 90 min and opioid agonist-like effects emerging only later in the second hour (Fig. 1). Comer and Collins (2002) also found that combinations of buprenorphine and naloxone (2 mg buprenorphine with 0.5 mg naloxone and 8 mg buprenorphine with 2 mg naloxone i.v.) attenuated the positive subjective effects of buprenorphine (2 and 8 mg, respectively) in recently detoxified heroin addicts. However, in this population of addicts who had only been off heroin for 1–6 weeks, both buprenorphine and the combination had similar reinforcing properties. Therefore, in people not currently in treatment, the combination of attenuated pleasurable effects (in both dependent and nondependent abusers) and precipitated opiate withdrawal (in dependent abusers) should decrease the illicit market value of buprenorphine.

In our study of three dose ratios of buprenorphine and naloxone, we assessed the ability of these combinations to attenuate opioid agonist effects. The opiate agonist effects of buprenorphine remained substantial following 5 days exposure to 60 mg/day of morphine. Buprenorphine 2 mg was equivalent to 15 mg of morphine on all opiate agonist measures (Mendelson et al., 1999). All three of the buprenorphine and naloxone combinations we tested diminished the opiate agonist effects of buprenorphine, with the 2:1 ratio decreasing all opiate agonist measures (Mendelson et al., 1999). The 4:1 and 8:1 ratios decreased global intoxication and opiate agonist scale indices but did not alter drug liking. All subjects rated all the intravenous buprenorphine and naloxone challenges as dysphoric, not euphoric. Our results are in agreement with reports from opiate abusers who were not physically dependent. Opiate agonist effects of lower buprenorphine doses were attenuated by concurrent naloxone at dose ratios of 1:2, 1:1 and 2:1 (Weinhold et al., 1992). Although not tested in this experiment, diminished pleasurable effects would be expected in nondependent opiate abusers administered buprenorphine and naloxone combinations similar to the ones we tested.

Strain evaluated the effects of sublingual buprenorphine and naloxone tablets (1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg) in opiate abusers with a low level of physical dependence. When compared to intramuscular hydromorphone (2 and 4 mg), the opiate agonist effects of buprenorphine doses greater than 4 mg were similar to hydromorphone. None of the sublingual buprenorphine and naloxone doses produced opiate withdrawal (Strain et al., 2000). These authors concluded that sublingual

buprenorphine and naloxone had a relatively low abuse liability in nondependent opiate abusers.

7. Buprenorphine and naloxone effects in buprenorphine-stabilized opiate addicts

Would the combination dose present a problem for patients taking buprenorphine regularly? In opiate-dependent subjects stabilized for 7 days on 8 mg/day of s.l. buprenorphine solution (Harris et al., 2000), s.l. 8 mg buprenorphine with 4 or 8 mg naloxone (2:1 and 1:1 ratios) did not precipitate opiate withdrawal. Buprenorphine abuse in patients treated with s.l. buprenorphine may also be limited by the partial agonist properties of buprenorphine with ceiling effects at higher doses (Walsh et al., 1994). Parenteral naloxone precipitates withdrawal in patients maintained on s.l. buprenorphine, but relatively large doses of naloxone are needed. For example, in patients taking 2–3 mg/day of s.l. buprenorphine solution, i.m. naloxone 35 mg (0.5 mg/kg) precipitated withdrawal (Kosten et al., 1990). Similarly, i.m. naloxone 3 mg/70 kg precipitated withdrawal in patients on 8 mg/day of s.l. buprenorphine solution (Eissenberg et al., 1996). In buprenorphine abusers injecting an average of 1.3 mg per day, naloxone 1.2 mg i.v. also precipitated withdrawal (Nigam et al., 1994). In contrast, patients maintained for 45–52 days on 8 mg of s.c. buprenorphine did not experience opiate withdrawal following 4 mg of s.c. naloxone (Jasinski et al., 1978).

8. Safety of buprenorphine and naloxone combinations

Buprenorphine and naloxone combinations appeared safe in our opiate-dependent subjects. Naloxone produced an expected dose-dependent sympathetic activation with statistically significant (but clinically and functionally insignificant) increases in heart rate, blood pressure, and respiratory rate. No subject developed unstable cardiovascular changes despite substantial subjective withdrawal. Therefore, although unpleasant, combination formulations are probably safe in otherwise healthy opiate-dependent individuals. Because most heroin overdose deaths are due to respiratory depression (Gilman et al., 1990), illicit administration of buprenorphine formulations containing naloxone are probably safer than continued heroin abuse. In non-opiate abusers, lower doses of buprenorphine and naloxone combinations retain analgesic efficacy (Rolly et al., 1986; Vanacker et al., 1986) and suppress buprenorphine-induced stimulation of prolactin (Mendelson et al., 1989).

9. Effects of buprenorphine on opiate withdrawal

Because buprenorphine is a partial μ -agonist and could displace full μ -agonists from receptor sites, in theory μ -opiate-dependent people could experience precipitated withdrawal after buprenorphine. Precipitated withdrawal was evident in morphine-dependent laboratory animals (Martin et al., 1976) and in methadone-maintained volunteers challenged with i.m. injections of 1 and 2 mg buprenorphine (but not 0.5, 4 or 8 mg) 20 h after the last methadone dose (Strain et al., 1995). In our studies, opiate withdrawal did not occur after buprenorphine given alone, consistent with the reports of others (Strain et al., 1992; Walsh et al., 1995; Schuh et al., 1996).

10. Conclusions

The abuse liability of buprenorphine in μ -opiate-dependent individuals can safely and effectively be diminished by the use of buprenorphine and naloxone combination formulations. Intravenous administration of buprenorphine and naloxone combinations containing more than 0.5 mg naloxone in a 2:1 or 4:1 ratio of buprenorphine to naloxone reliably precipitates opiate withdrawal. The combination dose is judged to have low illicit street value by parenteral opiate abusers. In addition to precipitating withdrawal, these combinations substantially diminish the rewarding effects of buprenorphine. At the doses of buprenorphine needed to treat opiate dependence, combination formulations with 2:1 or 4:1 ratios of buprenorphine to naloxone should have lower abuse liability than buprenorphine alone. The 4:1 ratio of buprenorphine to naloxone appears preferable to the 2:1 ratio because it provides a lower naloxone dose.

Several factors limit extrapolation of the data to all populations of opiate abusers. First, there are almost no data on the effects of buprenorphine and naloxone combinations in women. Buprenorphine is safe and effective for treatment of pregnant heroin addicts (Fischer et al., 2000; Johnson et al., 2001) and may become the standard pharmacotherapy in this group. Therefore, studies in this group are clearly needed. Second, although most abusers inject buprenorphine, some nonparenteral abuse occurs (San et al., 1993; Cracowski et al., 1999). The effects of intranasal buprenorphine and naloxone combinations in highly opiate-dependent people are not yet well defined (for example, we could find no reports of smoked buprenorphine). However, these alternate routes of administration are relatively uncommon. In the populations of opiate addicts most likely to abuse buprenorphine, the addition of naloxone should decrease abuse liability and illicit diversion.

Acknowledgements

The authors thank Nora Chiang Ph.D., our project officer at the NIDA Medication Development Division, for constructive advice regarding all of our buprenorphine experiments and the staff of the Drug Dependence Research Center at University of California, San Francisco. Supported by US Public Health Service grants DA12393 and DA00053 and contract No. N01DA-4-8306 from the National Institute on Drug Abuse, National Institutes of Health, and the General Clinical Research Center at University of California, San Francisco, with support of the Division of Research Resources, National Institutes of Health (RR-00079).

References

- Comer, S.D., Collins, E.D., 2002. Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. *J. Pharmacol. Exp. Ther.* 303, 695–703.
- Cracowski, J.L., Mallaret, M., Vanzeito, G., 1999. Myocardial infarction associated with buprenorphine (Ltr). *Ann. Inter. Med.* 130, 536 (discussion 536–537).
- Eder, H., Fischer, G., Gombas, W., Jagsch, R., Stuhlinger, G., Kasper, S., 1998. Comparison of buprenorphine and methadone maintenance in opiate addicts. *Subst. Use Misuse* 33, 3–7.
- Eisenberg, T., Greenward, M.K., Johnson, R.E., Liebson, I.A., Bigelow, G.E., Stitzer, M.L., 1996. Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans. *J. Pharmacol. Exp. Ther.* 276, 449–459.
- Eisenberg, T., Johnson, R.E., Bigelow, G.E., Walsh, S.L., Liebson, I.A., Strain, E.C., Stitzer, M.L., 1997. Controlled opioid withdrawal evaluation during 72 h dose omission in buprenorphine-maintained patients. *Drug Alcohol Depend.* 45, 81–91.
- Fischer, G., Johnson, R.E., Eder, H., Jagsch, R., Peterneil, A., Weninger, M., Langer, M., Aschauer, H.N., 2000. Treatment of opioid-dependent pregnant women with buprenorphine. *Addiction* 95, 239–244.
- Fraser, H.F., Isbell, H., 1960. Human pharmacology and addiction liabilities of phenazocine and levophenacetylmorphine. *Bull. Narcot.* 12, 15–23.
- Fudala, P.J., Yu, E., Macfadden, W., Boardman, C., Chiang, C.N., 1998. Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. *Drug Alcohol Depend.* 50, 1–8.
- Ghodes, A.H., 1987. Analysis of epidemiological data on agonist-antagonist analgesics. *Drug Alcohol Depend.* 20, 375–383.
- Gilman, A.G., Rail, T.W., Nies, A.S., Taylor, P., 1990. Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, eighth ed., Pergamon Press, New York.
- Harris, D.S., Jones, R.T., Weim, S., Upton, R.A., Lin, E., Mendelson, J., 2000. Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. *Drug Alcohol Depend.* 61, 85–94.
- Jasinski, D.R., 1977. Assessment of the abuse potential of morphine-like drugs (Methods used in man). In: Martin, W.R. (Ed.), *Drug Addiction I*. Berlin, Springer, Berlin.
- Jasinski, D.R., 1979. Human pharmacology of narcotic antagonists. *Br. J. Clin. Pharmacol.* 7 (Suppl. 3), 287S–290S.
- Jasinski, D.R., Fudala, P.J., Johnson, R.E., 1989. Sublingual versus subcutaneous buprenorphine in opiate abusers. *Clin. Pharmacol. Ther.* 45, 513–519.
- Jasinski, D.R., Pevnick, J.S., Griffith, J.D., 1978. Human pharmacology and abuse potential of the analgesic buprenorphine. *Arch. Gen. Psychiatry* 35, 501–516.
- Johnson, R.E., Eisenberg, T., Stitzer, M.L., Strain, E.C., Liebson, I.A., Bigelow, G.E., 1995. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend.* 40, 17–25.
- Johnson, R.E., Jaffe, J.H., Fudala, P.J., 1992. A controlled trial of buprenorphine treatment for opioid addiction. *J. Am. Med. Assn.* 267, 2750–2755.
- Johnson, R.E., Jones, H.E., Jasinski, D.R., Svika, D.S., Haug, N.A., Jansson, L.M., Kissin, W.B., Alpan, G., Lantz, M.E., Cone, E.J., Wilkins, D.G., Golden, A.S., Huggins, G.R., Lester, B.M., 2001. Buprenorphine treatment of pregnant opioid-dependent women: maternal and neonatal outcomes. *Drug Alcohol Depend.* 63, 97–103.
- Kanof, P.D., Aronson, M.J., Ness, R., Cochrane, K.J., Horvath, T.B., Handelsman, L., 1991. Levels of opioid physical dependence in heroin addicts. *Drug Alcohol Depend.* 27, 253–262.
- Kosten, T.R., Krystal, J.H., Charney, D.S., Price, L.H., Morgan, C.H., Kleber, H.D., 1990. Opioid antagonist challenges in buprenorphine maintained patients. *Drug Alcohol Depend.* 25, 73–78.
- Lavelle, T.L., Hammersley, R., Forsyth, A., 1991. The use of buprenorphine and temazepam by drug injectors. *J. Addict. Dis.* 10, 5–14.
- Ling, W., Charuvastra, C., Collins, J.F., Batki, S., Brown, L.S., Jr., Kintaudi, P., Weson, D.R., McNicholas, L., Tusel, D.J., Malmekker, U., Renner, J.A., Jr., Santos, E., Casadonte, P., Fye, C., Stina, S., Wang, R.L., Segal, D., 1998. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 93, 475–486.
- Ling, W., Weson, D.R., Charuvastra, C., Klett, C.J., 1996. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch. Gen. Psychiatry* 53, 401–407.
- Loimer, N., Presslich, O., Grunberger, J., Linzmayer, L., 1991. Combined naloxone/methadone preparations for opiate substitution therapy. *J. Subst. Abuse Treat.* 8, 157–160.
- Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E., Gilbert, P.E., 1976. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* 197, 517–532.
- Mendelson, J., Jones, R.T., Fernandez, L., Weim, S., Melby, A.K., Baggott, M.J., 1996. Buprenorphine and naloxone interactions in opiate-dependent volunteers. *Clin. Pharmacol. Ther.* 60, 105–114.
- Mendelson, J., Jones, R.T., Weim, S., Baggott, M., Fernandez, L., Melby, A.K., Nath, R.P., 1999. Buprenorphine and naloxone combinations: the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. *Psychopharmacology* 141, 37–46.
- Mendelson, J., Jones, R.T., Weim, S., Brown, J., Batki, S.L., 1997a. Buprenorphine and naloxone interactions in methadone maintenance patients. *Biol. Psychiatry* 41, 1095–1101.
- Mendelson, J., Upton, R.A., Everhart, E.T., Jacob, P., III, Jones, R.T., 1997b. Bioavailability of sublingual buprenorphine. *J. Clin. Pharmacol.* 37, 31–37.
- Mendelson, J.H., Mello, N.K., Teoh, S.K., Lloyd-Jones, J.G., Clifford, J.M., 1989. Naloxone suppresses buprenorphine stimulation of plasma prolactin. *J. Clin. Psychopharmacol.* 9, 105–109.
- Nigam, A.K., Srivastava, R.P., Saxena, S., Chavan, B.S., Sundaram, K.R., 1994. Naloxone-induced withdrawal in patients with buprenorphine dependence. *Addiction* 89, 317–320.
- Nutt, J.G., Jasinski, D.R., 1974. Methadone-naloxone mixtures for use in methadone maintenance programs. *Clin. Pharmacol. Ther.* 15, 156–166.
- O'Brien, C.P., Greenstein, R., Ternes, J., Woody, G.E., 1978. Clinical pharmacology of narcotic antagonists. *Ann. NY Acad. Sci.* 311, 232–239.

- O'Connor, J.J., Moloney, E., Travers, R., Campbell, A., 1988. Buprenorphine abuse among opiate addicts. *Br. J. Addict.* 83, 1085–1087.
- Olley, J.E., Tong, G.K., 1988. Plasma levels of opioid material in man following sublingual and intravenous administration of buprenorphine: exogenous/endogenous opioid interaction? *J. Pharm. Pharmacol.* 40, 666–667 (letter).
- Preston, K.L., Bigelow, G.E., Liebson, I.A., 1988. Buprenorphine and naloxone alone and in combination in opioid-dependent humans. *Psychopharmacology (Berl.)* 94, 484–490.
- Preston, K.L., Bigelow, G.E., Liebson, I.A., 1990. Effects of sublingually given naloxone in opioid-dependent human volunteers. *Drug Alcohol Depend.* 25, 27–34.
- Robinson, G.M., Dukes, P.D., Robinson, B.J., Cooke, R.R., Mahoney, G.N., 1993. The misuse of buprenorphine and a buprenorphine–naloxone combination in Wellington, New Zealand. *Drug Alcohol Depend.* 33, 81–86.
- Rolly, G., Poelaert, J., Mungroop, H., Paellack, H., 1986. A combination of buprenorphine and naloxone compared with buprenorphine administered intramuscularly in postoperative patients. *J. Int. Med. Res.* 14, 148–152.
- San, L., Torrens, M., Castillo, C., Porta, M., de la Torre, R., 1993. Consumption of buprenorphine and other drugs among heroin addicts under ambulatory treatment: results from cross-sectional studies in 1988 and 1990. *Addiction* 88, 1341–1349.
- Schottenfeld, R.S., Pakes, J.R., Oliveto, A., Ziedonis, D., Kosten, T.R., 1997. Buprenorphine versus methadone maintenance for concurrent opioid dependence and cocaine abuse. *Arch. Gen. Psychiatry* 54, 713–720 (see comments).
- Schuh, K.J., Walsh, S.L., Bigelow, G.E., Preston, K.L., Stitzer, M.L., 1996. Buprenorphine, morphine and naloxone effects during ascending morphine maintenance in humans. *J. Pharmacol. Exp. Ther.* 278, 836–846.
- Segui, J., Cascio, A., Aragon, C., Llovet, J.M., Soler, J.M., Salvador, L., 1991. The prevalence of buprenorphine consumption in a sample of outpatient drug abusers. *Rev. Clin. Esp.* 189, 14–17.
- Singh, R.A., Mattoo, S.K., Malhotra, A., Varma, V.K., 1992. Cases of buprenorphine abuse in India. *Acta Psychiatrica Scand.* 86, 46–48.
- Stoller, K.B., Bigelow, G.E., Walsh, S.L., Strain, E.C., 2001. Effects of buprenorphine/naloxone in opioid-dependent humans. *Psychopharmacology (Berl.)* 154, 230–242.
- Strain, E.C., Preston, K.L., Liebson, I.A., Bigelow, G.E., 1992. Acute effects of buprenorphine, hydromorphone and naloxone in methadone-maintained volunteers. *J. Pharmacol. Exp. Ther.* 261, 985–993.
- Strain, E.C., Preston, K.L., Liebson, I.A., Bigelow, G.E., 1995. Buprenorphine effects in methadone-maintained volunteers: effects at two hours after methadone. *J. Pharmacol. Exp. Ther.* 272, 628–638.
- Strain, E.C., Stitzer, M.L., Liebson, I.A., Bigelow, G.E., 1996. Buprenorphine versus methadone in the treatment of opioid-dependence: self-reports, urinalysis, and addiction severity index. *J. Clin. Psychopharmacol.* 16, 59–67.
- Strain, E.C., Stoller, K., Walsh, S.L., Bigelow, G.E., 2000. Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers. *Psychopharmacology (Berl.)* 148, 374–383.
- Vanacker, B., Vandermeersch, E., Tomassen, J., 1986. Comparison of intramuscular buprenorphine and a buprenorphine/naloxone combination in the treatment of post-operative pain. *Curr. Med. Res. Opin.* 10, 139–144.
- Walsh, S.L., June, H.L., Schuh, K.J., Preston, K.L., Bigelow, G.E., Stitzer, M.L., 1995. Effects of buprenorphine and methadone in methadone-maintained subjects. *Psychopharmacology (Berl.)* 119, 268–276.
- Walsh, S.L., Preston, K.L., Stitzer, M.L., Cone, E.J., Bigelow, G.E., 1994. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin. Pharmacol. Ther.* 55, 569–580.
- Weinberg, D.S., Inturrisi, C.E., Reidenberg, B., Moulin, D.E., Nip, T.J., Wallenstein, S., Houde, R.W., Foley, K.M., 1988. Sublingual absorption of selected opioid analgesics. *Clin. Pharmacol. Ther.* 44, 335–342.
- Weinhold, L.L., Preston, K.L., Farre, M., Liebson, I.A., Bigelow, G.E., 1992. Buprenorphine alone and in combination with naloxone in nondependent humans. *Drug Alcohol Depend.* 30, 263–274.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 December 2008 (18.12.2008)

PCT

(10) International Publication Number
WO 2008/152347 A2

(51) International Patent Classification:

A61J 1/03 (2006.01) *A61K 31/485* (2006.01)
A61K 9/00 (2006.01) *B65D 75/00* (2006.01)

(74) Agents: **HOLMES, Jeremy** et al.; Reckitt Benckiser
Corporate Services Limited, Legal Department - Patents
Group, Dansom Lane, Hull HU8 7DS (GB).

(21) International Application Number:

PCT/GB2008/001659

(22) International Filing Date: 14 May 2008 (14.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0711376.4 13 June 2007 (13.06.2007) GB

(71) Applicant (*for all designated States except US*):
**RECKITT BENCKISER HEALTHCARE (UK)
LIMITED** [GB/GB]; 103-105 Bath Road, Slough, Berk-
shire SL1 3UH (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **CAIRNS, Graham**
[GB/GB]; Reckitt Benckiser Healthcare (UK) Limited,
Dansom Lane, Hull HU8 7DS (GB). **DAVIS, John,
Alfred** [GB/GB]; Reckitt Benckiser Healthcare (UK)
Limited, Dansom Lane, Hull HU8 7DS (GB). **HYDE, Neil**
[GB/GB]; Reckitt Benckiser Healthcare (UK) Limited,
Dansom Lane, Hull HU8 7DS (GB).

(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
CH, 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, PG, PH,
PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV,
SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,
ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL,
NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished
upon receipt of that report*

(54) Title: PACK

(57) Abstract: A water- and oxygen-occlusive pack is described. The pack encloses an inert atmosphere containing medicinal tablets, wherein the tablets contain buprenorphine or a salt or ester thereof.



WO 2008/152347 A2

PACK

This invention relates to a pack of medicinal tablets, in particular to a pack of medicinal tablets containing
5 buprenorphine or a salt or ester thereof, as the, or an, active ingredient.

Existing products containing buprenorphine hydrochloride are TEMGESIC (trade mark), SUBUTEX (trademark) and
10 SUBOXONE (trade mark); products sold for the treatment of moderate to severe pain or for the treatment of opiate addiction. TEMGESIC and SUBUTEX contain buprenorphine hydrochloride as the sole active ingredient; SUBOXONE contains buprenorphine hydrochloride and naloxone, as co-
15 active ingredients.

It has been stated in WO 2005/117838 that buprenorphine hydrochloride shows degradation in acid or alkaline conditions and may be degraded by oxidation.

20

One attempt to stabilise buprenorphine is provided in US 6,365,596, which discloses pharmaceutical compositions containing buprenorphine and at least one antioxidant in a molar ratio, antioxidant to buprenorphine, in the range
25 1:1 to 3:1. It is also mentioned in US 6,365,596 that stability is improved by avoiding the presence of magnesium ions, and polyvinylpyrrolidone.

In the invention of WO 2005/117838 the improvement is to
30 stabilise buprenorphine by using a lower concentration of an antioxidant, compared with US 6,365,596 (preferably 1:1000-1:10, molar ratio, antioxidant: buprenorphine), and a chelating agent (preferably 0.01-5%, wt:wt).

We see an inherent undesirability in having to use a large amount of an antioxidant (per US 6,365,596), or an antioxidant and a chelating agent together (per WO 2005/117838), in order to stabilise buprenorphine and/or salts or esters thereof.

In accordance with a first aspect of the present invention there is provided a water- and oxygen-occlusive pack enclosing an inert atmosphere containing medicinal tablets, wherein the tablets contain buprenorphine or a salt or ester thereof.

Preferably the inert gas is nitrogen.

A traditional pack for tablets containing buprenorphine hydrochloride is a PVC/PVdC blister pack. PVC/PVdC is a laminate of polyvinyl chloride polyvinylidene chloride. It is generally accepted to be a good oxygen and moisture barrier, suitable for the packaging of many medicinal products. Nevertheless we have found that the stored tablets, and in particular the active ingredient buprenorphine hydrochloride, may be affected both by moisture and by oxygen, in such a pack.

In the present invention the use of a water- and oxygen-occlusive barrier material in combination with keeping the tablets under an inert atmosphere protects the active ingredient(s) from significant chemical decomposition.

The approach followed in the present invention is in contrast with the prior art methods of US 6,365,596 and WO 2005/117838, which both follow the approach of seeking

improvement in stability by chemical formulation improvement.

Preferably each tablet contains at least 0.2 mg
5 buprenorphine, preferably at least 0.4 mg.

Preferably each tablet contains up to 20 mg buprenorphine,
preferably up to 16 mg, preferably up to 12 mg, preferably
up to 10 mg, preferably up to 8 mg, preferably up to 4 mg,
10 preferably up to 2 mg.

These amounts referring to buprenorphine may be converted
to buprenorphine salts or esters, if such forms are
present, by simple arithmetical scaling.

15

Thus, when buprenorphine hydrochloride is present, each
tablet preferably contains at least 0.21 mg of
buprenorphine hydrochloride, preferably at least 0.43 mg;
and preferably up to 22 mg of buprenorphine hydrochloride,
20 preferably up to 18 mg, and more preferably up to 13 mg.
In especially preferred embodiments each tablet containing
buprenorphine hydrochloride contains up to 11 mg of
buprenorphine hydrochloride, preferably up to 9 mg,
preferably up to 4.5 mg, preferably up to 2.4 mg.

25

A co-active ingredient may be present. Naltrexone,
nalmeferene and, especially, naloxone are preferred.
Preferably the weight of such co-active ingredients (or of
co-active ingredients in total), does not exceed the
30 weight of buprenorphine; and preferably is not greater
than 50% wt/wt, of the weight of buprenorphine (non-salt,
non-ester compounds compared). The weight ratio in the
tablet of buprenorphine to such a co-active ingredient, or

of co-active ingredients in total, is preferably in the range 2:1 to 8:1, preferably 3:1 to 5:1.

In these and other definitions a weight of "buprenorphine" also denotes a weight of salt or ester, converted to buprenorphine content (i.e. the base). Should there be more than one buprenorphine compound (e.g. buprenorphine and buprenorphine hydrochloride) the total weight, converted to buprenorphine, is to be used in the definition.

Preferably the tablets comprise at least one monosaccharide or disaccharide or a mixture thereof.

When a monosaccharide is present it may suitably be a sugar, for example glucose, galactose, fructose or mannose, or a sugar alcohol, for example mannitol or sorbitol. Preferably the amount of monosaccharide, or of monosaccharides in total, is in the range 15-50 %wt/wt of composition, preferably 20-40 %wt/wt. Sugar alcohols are preferred monosaccharides, especially mannitol.

When a disaccharide is present it may suitably be a sugar, for example maltose, lactose or sucrose. Preferably the amount of disaccharide, or of disaccharides in total, is in the range 20-70 %wt/wt of composition, preferably 40-60 %wt/wt. Lactose is a preferred disaccharide.

Preferably the tablets comprise a disintegrant.

When a disintegrant is present it may suitably be sodium croscarmellose, maize starch or crospovidone. Preferably the amount of disintegrant, or of disintegrants in total,

is in the range 1-30 %wt/wt of composition, preferably 10-20 %wt/wt.

Preferably the tablets comprise a pressing aid, preferably
5 in an amount in the range 0.1 - 2 %wt/wt of composition.
A preferred pressing aid is magnesium stearate.

Preferably the tablets comprise a mixture of anhydrous
citric acid and sodium citrate, preferably in a weight
10 ratio of 2:1 to 1:1. Preferably the total amount of
anhydrous citric acid and sodium citrate is in the range
0.5 - 4 %wt/wt of composition.

Preferably the pack has a water- and oxygen-occlusive wall
15 material.

Preferably the pack is a blister pack having a plurality
of blister pockets, each containing one tablet and each
containing a charge of inert gas.

20

In a preferred embodiment the pack is of an aluminium or
aluminium-plastics laminate having a water-occlusive and
oxygen-occlusive wall material with each blister pocket
containing an inert atmosphere of nitrogen gas, and one
25 tablet.

A water-occlusive and oxygen-occlusive pack of this
invention has a wall or barrier member of water-occlusive
and oxygen-occlusive material. By water-occlusive and
30 oxygen-occlusive material, we mean a material which has a
higher degree of water and oxygen occlusivity under test
conditions, 25°C / 60% Relative Humidity (RH) and 40°C/75%
RH, than a traditional PVC/PVdC material.

In a PVC/PVdC material, the PVC is believed to be the "weak link". Preferably a blister pack of the invention comprises or is formed of a metallic material, for example aluminium or an aluminium alloy. Most preferably the base part, containing the pockets for tablets, may be of a cold-formable foil, comprising a metallic layer, over which a breachable-by-tablet metallic foil is laid, to close the pack. Especially preferred is a foil comprising a layer of a metallic material, for example aluminium or aluminium alloy, laminated to a layer of aliphatic polyamide and/or a layer of PVC. Especially preferred is a foil having a layer of aliphatic polyamide, 10-40 μm thick, then a metallic layer, 30-60 μm thick, then a layer of PVC, 40-80 μm thick, the latter being the product contact surface.

The pack may be packed with tablets and sealed, in an atmosphere of the inert gas.

Preferably the blister pack contains at least 6 tablets, more preferably at least 8 tablets. Preferably the blister pack contains up to 14 tablets, especially up to 12 tablets.

The protection provided by the present invention means that there is no need to add undesirable ingredients such as chemical stabilisers, for example chelating agents or antioxidants, to the formulation of the tablet in order to improve chemical stability.

30

Preferably the tablets do not contain a chelating agent which stabilizes the buprenorphine or acid or salt thereof.

Preferably the tablets do not contain an antioxidant to protect the buprenorphine or acid or salt thereof.

Preferably the tablets do not contain a chelating agent to
5 protect the buprenorphine or acid or salt thereof.

Preferably the tablets do not contain any component to protect the buprenorphine or acid or salt thereof.

10 The protection provided by the present invention means that there is no need to omit certain ingredients which have been implicated in causing chemical stability; for example magnesium ions or polyvinylpyrrolidone, according to US 6,365,596. There is no necessity to exclude such
15 compounds from the tablets in the pack of the present invention. Indeed magnesium stearate is a preferred component of the formulation for the tablets.

Preferably the pack of the invention has a use-by date at
20 least 18 months after its date of packing; more preferably at least 24 months. The use-by date may be recorded on the pack itself or on secondary packaging.

In accordance with a second aspect there is provided a
25 method of manufacturing a pack of the first aspect, wherein the tablets are enclosed in a water- and oxygen-occlusive material under an inert atmosphere.

In accordance with a third aspect of the present invention
30 there is provided a method of supplying and/or administering tablets from a water- and oxygen-occlusive pack of the first aspect.

The invention will now be further described, by way of example, with reference to the following example.

Medicament tablets were made, containing the following
5 ingredients.

Component	Quantity/tablet (mg)	Quantity/tablet (mg)
Buprenorphine hydrochloride	0.216	0.432
Lactose monohydrate	29.842	29.628
Mannitol	18.000	18.000
Maize starch	9.000	9.000
Povidone K30	1.200	1.200
Citric acid anhydrous granular	0.888	0.888
Magnesium stearate	0.450	0.450
Sodium citrate	0.404	0.404
TOTAL	60.0	60.0

The tablets were prepared as follows.

- 10 All the excipients were screened through a 20 mesh sieve screen. The lactose, starch, mannitol and povidone were thoroughly mixed together, wetted and granulated with a solution of buprenorphine hydrochloride, citric acid and sodium citrate previously dissolved in a mixture of the
15 purified water and ethanol by stirring. The resultant granules were dried at 42 - 48°C until a moisture content of 1 - 2% was attained. The granules were screened through a 20 mesh sieve screen and blended. Magnesium stearate was added to the sieved granules and mixed thoroughly. The
20 granules were sieved and re-blended. The mixture was tabletted using 7/32 inch (5.6mm) punches to a target weight of 60 mg.

The resulting tablets were packed into two types of blister pack: one in accordance with the present invention, which had a cold form aluminium foil tray, heat sealed by an aluminium breachable foil lid under an inert nitrogen atmosphere; the other a "250/60" PVC/PVdC tray (250 PVC, 60 PVdC), with an aluminium breachable foil lid. The blister packs contained seven tablets. Packing for the present invention was carried out in a dry nitrogen atmosphere in order that each blister pocket contained nitrogen gas. Packing in the PVC/PVdC blisters was carried out in dry air. Each tablet pocket was individually sealed, by the breachable aluminium foil lid. Tablets were packed into the blister trays and sealed immediately after their manufacture.

15

The cold-form aluminium foil tray was a laminate of 25 μm thickness aliphatic polyamide, 46 μm thickness aluminium and 60 μm thickness PVC (the product contact surface).

20 The aluminium breachable foil lid was a 50 g/m^2 lidding foil of 12 μm PET/25 μm aluminium/6-8 g/m^2 PVC/PVA lacquer (product contact surface).

The tablets were then stored under constant conditions of 25°C temperature and 60% Relative Humidity (RH) and 40°C/75% RH. Samples were studied at several scheduled time points under these conditions for buprenorphine content, content of the compound we identified as being the main degradant, and total related degradation products. The results for three batches of tablets containing 0.216 mg buprenorphine hydrochloride per tablet are tabulated below. This converts to 0.2 mg

buprenorphine and the tables which follow quote the buprenorphine level (i.e. 100% = 0.2 mg).

Buprenorphine Content (% Nominal) at 25°C / 60% RH						
Nominal = 0.2 mg/tablet						
Time	PVC/PVdC			Alu/N ₂		
(Months)	1	2	3	1	2	3
0	98.5	98.0	99.5	98.5	99.5	99.0
3	95.0	94.0	96.0	97.0	98.0	97.5
6	92.5	93.5	94.0	97.5	98.0	98.5
9	98.0	97.5	99.0	103.0	103.0	104.0
12	94.5	93.5	94.5	100.0	103.5	103.5
18	92.0	93.5	93.5	101.5	102.5	99.0
24	90.5	91.0	90.5	101.5	103.0	101.5
36	89.0	88.5	88.5	102.5	102.0	103.5
Buprenorphine Content (% Nominal) at 40°C / 75% RH						
Nominal = 0.2 mg/tablet						
Time	PVC/PVdC			Alu/N ₂		
(Months)	1	2	3	1	2	3
0	98.5	98.0	99.5	98.5	99.5	99.0
1	96.0	96.0	96.0	97.0	97.5	98.5
3	93.5	93.5	94.0	96.5	97.0	97.0
6	89.0	89.5	90.0	97.0	98.5	97.5
12	85.5	83.5	87.5	100.5	100.5	101.0

Main Degradant Compound (% w/w) at 25°C / 60% RH						
Nominal = 0.2 mg/tablet						
Time	PVC/PVdC			Alu/N ₂		
(Months)	1	2	3	1	2	3
0	0.9	1.0	0.6	1.2	1.4	0.7
3	1.9	1.7	1.3	0.9	0.9	0.3
6	3.1	3.1	2.6	1.1	1.2	0.5
9	4.5	4.4	3.9	1.2	1.3	0.6
12	5.2	5.1	4.6	1.3	1.4	0.6
18	6.7	6.6	6.1	1.4	1.4	0.6
24	7.9	7.8	7.3	1.4	1.5	0.7
36	9.8	9.6	9.3	1.4	1.4	0.7

Main Degradant Compound (% w/w) at 40°C / 75% RH						
Nominal = 0.2 mg/tablet						
Time	PVC/PVdC			Alu/N ₂		
(Months)	1	2	3	1	2	3
0	0.9	1.0	0.6	1.2	1.4	0.7
1	2.8	2.7	2.4	1.4	1.4	0.7
3	3.5	3.8	3.3	1.1	1.1	0.6
6	6.3	6.4	5.8	1.3	1.3	0.7
12	13.8	13.5	12.7	1.6	1.5	0.9

Total Related Degradation Products (% w/w) at 25°C / 60% RH						
Nominal = 0.2 mg/tablet						
Time	PVC/PVdC			Alu/N ₂		
(Months)	1	2	3	1	2	3
0	2.4	2.6	1.8	2.7	3.0	1.7
3	3.4	3.2	2.7	1.8	1.7	0.9
6	6.2	6.2	5.6	2.6	2.7	1.5
9	8.8	8.5	7.9	2.9	3.0	1.8
12	9.7	9.4	8.9	2.9	3.1	1.8
18	12.2	12.2	11.6	3.1	3.1	1.9
24	14.5	14.4	13.6	3.4	3.5	2.3
36	17.3	17.0	16.6	3.1	3.1	2.2

Total Related Degradation Products (% w/w) at 40°C / 75% RH						
Nominal = 0.2 mg/tablet						
Time	PVC/PVdC			Alu/N ₂		
(Months)	1	2	3	1	2	3
0	2.4	2.6	1.8	2.7	3.0	1.7
1	3.9	3.8	3.5	2.3	2.2	1.4
3	5.1	5.4	4.8	2.2	2.1	1.3
6	9.1	9.2	8.4	2.6	2.6	1.7
12	18.7	17.9	16.9	2.6	2.5	1.8

The results for the tablets packed in the PVC/PVdC blister pack show clear evidence of chemical decomposition (or oxidation) of the active ingredient, buprenorphine. There is a clear time and temperature-dependent decrease in buprenorphine content upon storage. Moreover, there are corresponding time and temperature-dependent increases in the levels of the main degradant compound and of total buprenorphine-related degradation products.

The results for the tablets packed in aluminium blisters under nitrogen gas do not demonstrate any clear evidence of chemical decomposition (or oxidation) of the active ingredient upon storage for 36 months at 25°C/60%RH or for 12 months at 40°C/75%RH. There is no time or temperature-dependent decrease in buprenorphine content and no time or temperature-dependent increase in levels of degradation products.

Chemical decomposition of the active ingredient is clearly shown in the tablets of the PVC/PVdC pack, but not in the tablets of the Alu/N₂ pack.

The protection for chemical decomposition provided by the present invention means that there is no need to add undesirable ingredients such as chemical stabilisers or antioxidants to the formulation of the tablet in order to improve chemical stability.

CLAIMS

1. A water- and oxygen-occlusive pack enclosing an inert atmosphere containing medicinal tablets, wherein the tablets contain buprenorphine or a salt or ester thereof.
2. A water- and oxygen-occlusive pack wherein the tablets comprise from 0.2 to 20 mg of buprenorphine or a scaled amount of a salt or ester thereof.
3. A water- and oxygen-occlusive pack as claimed in claim 1 or 2 wherein each tablet thereof contains from 0.21mg to 22mg of buprenorphine hydrochloride.
4. A water- and oxygen-occlusive pack as claimed in any preceding claim wherein the tablets have a use-by date at least 18 months after their packing under an inert nitrogen atmosphere into the water and oxygen-occlusive pack.
5. A water- and oxygen-occlusive pack as claimed in any preceding claim, being a blister pack.
6. A water- and oxygen-occlusive pack as claimed in any preceding claim wherein the pack comprises wall material having a metallic layer.
7. A water- and oxygen-occlusive pack as claimed in any preceding claim wherein the tablets include a monosaccharide or a disaccharide or a mixture thereof.
8. A water and oxygen-occlusive pack as claimed in any preceding claim wherein the tablets comprise lactose.

9. A water and oxygen-occlusive pack as claimed in any preceding claim wherein the tablets comprise mannitol.

10. A water and oxygen-occlusive pack as claimed in any preceding claim wherein the tablets comprise a disintegrant.

11. A water and oxygen-occlusive pack as claimed in any preceding claim wherein the tablets comprise magnesium stearate.

12. A water and oxygen-occlusive pack as claimed in any preceding claim wherein the tablets do not comprise an antioxidant to protect the buprenorphine or salt or ester thereof.

13. A water and oxygen-occlusive pack as claimed in any preceding claim wherein the tablets do not comprise a chelating agent to protect the buprenorphine or salt or ester thereof.

14. A water and oxygen-occlusive pack as claimed in any preceding claim wherein the tablets comprise a mixture of anhydrous citric acid and sodium citrate.

15. A method of manufacturing a pack as claimed in any preceding claim wherein tablets are enclosed in said water- and oxygen-occlusive material under an inert atmosphere.

16. A method of supplying and/or administering tablets from a water- and oxygen-occlusive pack as claimed in any of claims 1 to 14.

COREL 00811

Controlled buccal delivery of buprenorphine

J.P. Cassidy, N.M. Landzert and E. Quadros

Ciba-Geigy Corporation, Ardsley, New York, USA

(Received 7 October 1992; accepted in revised form 13 November 1992)

Buprenorphine is a potent opiate agonist-antagonist used in the treatment of both acute and chronic pain. Like many opiates, it has low oral bioavailability due to both presystemic metabolism in the wall of the gastrointestinal tract and extensive first pass metabolism. Controlled delivery of analgesics results in good pain relief and a lower total requirement for the drug. Buccal delivery offers advantages in terms of accessibility, avoidance of first pass metabolism and the ability to provide controlled delivery for extended periods of time. Buccal permeation of buprenorphine was measured in vitro and in vivo in the dog model using prototype non-woven and hydrogel systems. The fluxes of drug were identical from solutions and from non-woven systems in vitro, providing a reliable way of applying a drug solution to the mucosa without leaking. A model is described that permits screening of potential buccal systems in vitro to select a system for in vivo use. In vivo, steady-state plasma levels were obtained using both non-woven and hydrogel systems. Steady state was attained in 1 to 1.5 h and was maintained during the time of application of the system. Assuming that the flux in man is similar to that in the dog, controlled buccal delivery of buprenorphine would provide adequate analgesia over an extended period of time.

Key words: Buccal; Buprenorphine; Analgesia; Controlled delivery; Hydrogels

Introduction

Buprenorphine, an opiate agonist-antagonist with 20 to 40 times the potency of morphine [1], is used in the treatment of both acute and chronic pain [2,3]. Like many opiates, it is extensively metabolized in both the gastrointestinal (GI) tract and the liver [4,5] and is therefore a poor candidate for oral delivery. It is currently administered as repeated intravenous or intramuscular injections and as a sublingual tablet. In the control of pain, it has been reported that administration of an analgesic at a constant rate results in

both optimal patient comfort and a reduced total amount of analgesic [6]. Controlled delivery of buprenorphine may therefore, offer advantages in pain management.

The buccal route offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic metabolism in the GI tract are avoided. The area is obviously very accessible for placement and removal of a delivery device. Polymeric systems with an impermeable backing could deliver drug in a unidirectional fashion to the mucosa and avoid loss due to swallowing. The ultimate aim would be to develop a small, thin, flexible device

Correspondence to: E. Quadros, Ciba-Geigy Corporation, 444 Saw Mill River Road, Ardsley, NY 10502, USA.

that would adhere to the mucosa during normal activities, including eating and drinking. Buccal delivery also offers the advantage of rapid absorption, which would obviously be necessary in the control of pain, and buprenorphine is known to be efficacious as a sublingual tablet [7]. The use of a device that provides rapid, long-lasting and adequate pain control by noninvasive means could offer considerable advantages in pain management.

In the present study, the buccal absorption of buprenorphine was assessed *in vitro* in modified Ussing chambers [8]. Three different prototype systems, one non-woven and two hydrogels of varying water content, were assessed *in vitro* and *in vivo* in the dog. Hydrogels have previously been used for the buccal delivery of diclofenac sodium in both the dog and man [9,10], and similar fluxes were measured in both species. Preliminary results of the current studies have been presented [11,12].

Materials and Methods

Materials

Buprenorphine hydrochloride was obtained from Diosynth (Bensenville, IL) and was used without further purification. Radioimmunoassay (RIA) kits were purchased from Diagnostic Products Corporation (Los Angeles, CA). *t*-Butyl peroctoate was from Pennwalt, Buffalo, NY. 2-hydroxyethyl methacrylate (HEMA, Lot #64622) was obtained from Polysciences, Inc., Warrington, PA, and monomer:macromer mix was kindly supplied by Dr. K. F. Mueller of Central Research, Ciba-Geigy Corporation, Ardsley, NY. All other reagents were of HPLC or analytical grade and were used as purchased.

Methods

Analytical methodology

HPLC. Buprenorphine was quantitated by reverse phase high performance liquid chromatography (HPLC) on a C-18 column (3 cm, 3 μ m particle size; Perkin-Elmer, Norwalk, CT) with

fluorescence detection using an excitation wavelength of 213 nm and a 360 nm emission cut-off filter. The mobile phase (60/40 acetonitrile / 0.01M KH_2PO_4 , 0.01% TEA, adjusted to pH 3 with phosphoric acid) was pumped isocratically at a flow rate of 1.5 ml/min. Standards were made up in the same solution as the samples being assayed. The standard curve was linear over the concentration range 25 ng/ml to 20 μ g/ml, using an injection volume of 15 μ l.

RIA. Buprenorphine in Tris-phosphate saline [13] was measured using a modification of a commercially available kit. Briefly, 50 μ l of sample (or standard) was incubated with 100 μ l of [^{125}I]buprenorphine and 100 μ l of antiserum at room temperature for 1 h. Separation of antibody-bound from free buprenorphine was accomplished by the addition of a second antibody (goat anti-rabbit gamma-globulin), and centrifugation at 25°C (1500 $\times$ g for 30 min). The pellet, containing antibody-bound material, was counted using a gamma counter (Minaxi Gamma Model 5000, Packard Instrument Company, Downers Grove, IL). The amount of buprenorphine was calculated from the standard curve which ranged from 0.05 to 15 ng/ml. Samples were assayed undiluted or at a dilution of 1:5 or 1:20. The assay was validated at all dilutions studied and stability of buprenorphine was confirmed in buffer stored at -70°C for up to 21 days prior to analysis.

Solubility of buprenorphine hydrochloride

The solubility of buprenorphine HCl was determined by the addition of excess drug to either phosphate buffers [14,15] or physiological buffer (Tris-phosphate saline) with initial pH values between 4 and 8. The vials were capped, vortexed and placed in a shaking water bath at 25°C for 24 h. 1.5 ml of solution was removed, centrifuged in a microfuge (Model 235B, Fisher Scientific, Springfield, NJ) at 15000 $\times$ g for 2 min at room temperature and diluted for determination of buprenorphine by HPLC. The pH of the solutions was measured to give the final pH of the solutions.

Buprenorphine flux across buccal mucosa in vitro

Male New Zealand White rabbits (2–4 kg) were sacrificed by carbon dioxide inhalation and beagle dogs of either sex (7–11 kg) were sacrificed by an intravenous overdose of Nembutal® and exsanguination. All animal experimentation was performed according to protocols approved by Ciba-Geigy's Animal Care Committee. Buccal tissue was removed by blunt dissection, separated from underlying muscle, rinsed in buffer and mounted in modified Ussing chambers (WPI, Sarasota, FL). Equilibration was in 10 ml Krebs-Henseleit buffer [16], containing 10 mM glucose. The pH was maintained at 7.4 by bubbling with 95% O₂/5% CO₂ and the temperature was maintained at 37°C by water-jacketing. The tissue was equilibrated for 30–60 min before drug donor solution was added to the mucosal side and fresh buffer was added to the serosal side. Samples (0.5 ml) were taken at intervals from the serosal side and the volume replaced with buffer. Samples were assayed for buprenorphine content by RIA or HPLC. Due to the low solubility of buprenorphine at neutral pH, some flux studies were performed at pH 4 using Tris-phosphate saline buffer. To monitor tissue viability, transepithelial potential difference and short-circuit current were measured by salt bridges of 2% agar in Krebs-Henseleit buffer in contact with Ag/AgCl electrodes connected to a voltage current clamp (DVC-1000, WPI, Sarasota, FL) via a preamplifier.

Preparation of hydrogel discs

The hydrogels were prepared by copolymerization of HEMA with a macromer synthesized by the reaction of polytetramethylene glycol (Polymeg®) with isophorone diisocyanate in a 1:2 ratio [17]. Both 90:10 (monomer:macromer, wt/wt) and 80:20 hydrogel systems were assessed. 90:10 and 80:20 hydrogels were prepared by the addition of HEMA to a 70:30 monomer:macromer mixture. After degassing for 30 min, 0.2 wt% of *t*-butyl peroctoate was added as initiator. The solution was placed between two Mylar®-covered glass plates with the appropriate Teflon® spacer around the perimeter. The polymer was crosslinked by placing the

mold at 80°C for 1 h. After cooling, the polymer was removed and washed with 5 changes of 8 l of distilled water. Discs were punched from the water-washed polymer, and remaining monomer was removed by Soxhlet extraction in ethanol overnight. The extracted discs were dried in a vacuum oven at 45°C for 24 h.

For drug loading, the dried discs were weighed, placed in a solution of buprenorphine HCl (15 wt% in 70% ethanol/30% 0.01 M KH₂PO₄, pH 4) and stirred at 45°C for 72 h. The loaded systems were removed, rinsed briefly in 70% ethanol and dried for 48 h at room temperature in a vacuum desiccator. Before use, the systems were placed in a 95% humidity chamber for 48 h at room temperature.

Dissolution testing

The release profiles of the systems were determined using dried discs in a standard dissolution apparatus with stainless steel baskets (Vanderkamp 600, Van-Kel Industries, Chatham, NJ). Dissolution was determined in 500 ml of distilled water at 32°C. At various time intervals, 0.8 ml of the solution was withdrawn from the reservoir and assayed for buprenorphine content by HPLC.

Systems application in vitro

The fluxes of buprenorphine across canine buccal mucosa were measured from both non-woven and hydrogel discs in vitro. Buprenorphine (220 µl of 10 mg/ml buprenorphine hydrochloride in 10 mM KH₂PO₄) was pipetted onto the surface of the non-woven material. The system was applied to the buccal mucosa and mounted in the Ussing chamber. Hydrogel discs, prepared as described above, were applied to the mucosal surface, backed with Parafilm® and mounted in the Ussing chamber. In all experiments, the total exposed surface area was 1 cm².

Buccal absorption in vivo

Beagles (7–11 kg) of either sex were fasted overnight and had free access to water until the time of experimentation. They were anesthetized with sodium pentobarbital (approximately 25 mg/kg) via a 22 G Abbocath® in the cephalic

vein and additional doses were administered to maintain anesthesia during the course of the experiment. Cannula patency was maintained with an i.v. drip of sterile lactated Ringers (1 ml/min). Blood samples (3 ml) were drawn into heparinized Monoject® syringes and plasma, obtained following centrifugation ($2000 \times g$ for 10 min), was placed in microfuge tubes and frozen in a dry ice-ethanol bath. Samples were stored for up to 3 weeks at -70°C .

To determine the i.v. pharmacokinetics of buprenorphine, a 0.30 mg bolus of buprenorphine HCl in 1.5 ml of lactated Ringers solution was injected through a second catheter placed in the saphenous vein. The bolus was followed by 5 ml of lactated Ringers to insure injection of the total dose. Plasma samples were obtained over a 4 h period and assayed for buprenorphine content by RIA. The fit of the plasma profile to a biexponential equation was modelled using R-Strip (Micromath, Inc.) with a y^2 weighting, and pharmacokinetic parameters were determined for each animal.

To determine buccal delivery of buprenorphine, beagles were anesthetized as described above, and a zero time blood sample was taken. The inner cheek was blotted dry with gauze, the appropriate device(s) was placed on the cheek and the area covered by an impermeable backing membrane held in place by a peripheral adhesive (Super Polygrip, Dentco, Inc., Jersey City, NJ). The device was left in position for 2 to 4 h. Blood samples were taken at intervals during the application of the device and after its removal. All plasma samples were assayed for buprenorphine content by RIA. Results are expressed as the mean ± 1 SEM.

Results

Solubility of buprenorphine hydrochloride

At the end of the 24 h incubation period all vials contained undissolved material which was removed by centrifugation. The solubility of buprenorphine was highly pH dependent with the highest solubility seen at low pH (17.3 mg/ml at

pH 4.2). The solubility at neutral pH was considerably lower ($52 \mu\text{g/ml}$ at pH 7.3) (Fig. 1). Essentially, similar solubilities were measured in USP, phosphate, and physiological (TPS) buffers, except at pH 4.2 when the solubility was considerably lower in TPS (4.2 mg/ml).

Buprenorphine flux across buccal mucosa in vitro

The flux of buprenorphine in vitro was measured across buccal mucosa obtained from both rabbit and dog. The donor solutions were at saturation (4.3 mg/ml) in TPS buffer, adjusted to pH 4 with isotonic citric acid. Steady-state fluxes were calculated by linear regression using the asymptotic region of the cumulative amount/time curve and the time lag (to steady-state) was determined from the intercept on the abscissa. The steady-state fluxes and time lags were $4.2 \pm 0.6 \mu\text{g/cm}^2/\text{h}$ and $2.7 \pm 0.1 \text{ h}$ ($n=6$) in the rabbit and $22.3 \pm 6.0 \mu\text{g/cm}^2/\text{h}$ and $1.6 \pm 0.4 \text{ h}$ ($n=4$) in the dog, respectively. In the rabbit, steady-state flux was linearly related to donor concentration over the range 0.04 to 4.3 mg/ml (Fig. 2, $r=0.998$). The addition of sodium azide (10 mM), a metabolic inhibitor, to the mucosal solution at the same time as the drug caused the abolition of the transepithelial potential difference and an approximately 10-fold increase in the flux of buprenorphine, with no attainment of steady-state within the experimental time period.

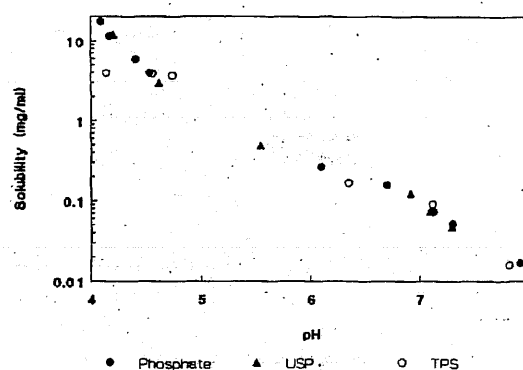


Fig. 1. Solubility of buprenorphine hydrochloride in phosphate, USP phosphate and physiological (TPS) buffers.

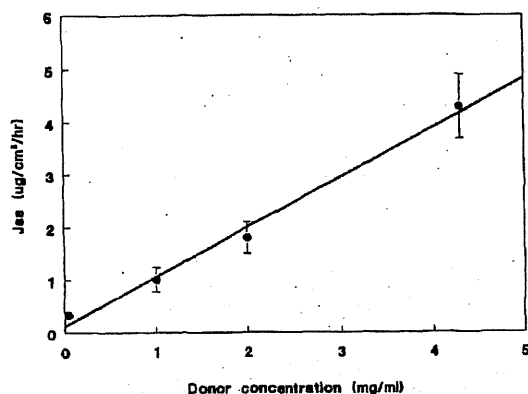


Fig. 2. Relationship between donor concentration and steady-state flux of buprenorphine across rabbit buccal mucosa in vitro. The number of experiments was between 4 and 6.

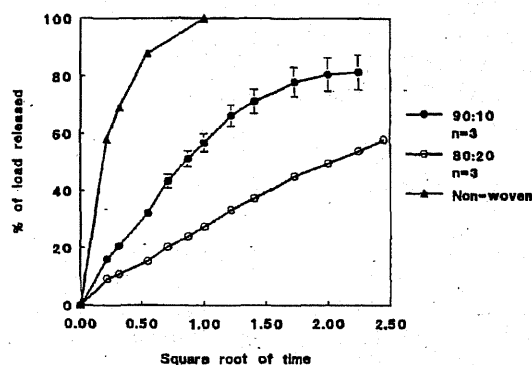


Fig. 3. Dissolution of buprenorphine from non-woven and hydrogel systems as a function of the square root of time in hours.

Dissolution of buprenorphine from systems

The hydrogel discs were 1.9 cm^2 and 0.138 mm thick. The release profiles of buprenorphine from 90:10 and 80:20 hydrogel discs were linear with the square root of time for 1 and 2 h, respectively (Fig. 3). The release rates were 432 ± 25 and $173 \pm 5 \text{ } \mu\text{g}/\text{cm}^2/\text{h}^{-1/2}$ for the 90:10 and 80:20 discs, respectively ($n=3$, for each system).

Drug release from these monoliths that are initially swelled with water may be described by the equation:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8 \exp(-D[2n+1]^2 \pi^2 t/L^2)}{(2n+1)^2 \pi^2} \quad (18)$$

where: M_t = total amount of drug released at time t , M_∞ = total drug loaded into hydrogel, D = drug diffusion coefficient, and L = thickness of hydrogel.

The diffusion coefficient for buprenorphine can be calculated using an early time approximation of the above equation:

$$\frac{M_t}{M_\infty} = 4 \frac{(Dt)^{1/2}}{\pi L^2}$$

This equation is accurate to within 1% for $M_t/M_\infty < 0.6$.

The diffusion coefficients for buprenorphine were $6.6 \pm 0.72 \times 10^{-5}$ and $2.2 \pm 0.14 \times 10^{-6} \text{ cm}^2/\text{h}$ for the 90:10 and 80:20 hydrogels, respectively.

Flux from systems in vitro

Steady-state flux across dog buccal mucosa from a solution of buprenorphine (10 mg/ml in $10 \text{ mM KH}_2\text{PO}_4$, pH 4) was $87.1 \pm 30.3 \text{ } \mu\text{g}/\text{cm}^2/\text{h}$ with a time lag of $1.3 \pm 0.33 \text{ h}$, $n=7$ (Fig. 4). The permeability coefficient was $2.42 \pm 0.84 \times 10^{-6} \text{ cm/s}$. The steady-state flux from the same solution loaded onto a non-woven chamber was $78.7 \pm 26.4 \text{ } \mu\text{g}/\text{cm}^2/\text{h}$ with a time

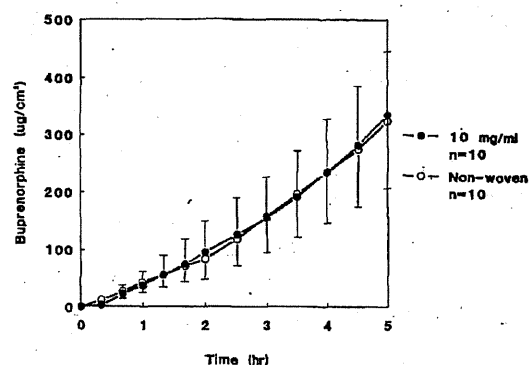


Fig. 4. Cumulative flux of buprenorphine across dog buccal mucosa from a solution of 10 mg/ml ($n=10$) and from $220 \text{ } \mu\text{l}$ of a 10 mg/ml solution loaded on to a non-woven system ($n=10$).

lag of 0.95 ± 0.24 h, $n=11$ (Fig. 4). There was no significant difference between the flux from solution or from the non-woven device, suggesting that the use of non-woven systems in vivo would be equivalent to the application of a solution to the buccal mucosa without the associated problems of leakage and clamping of the device in place. Although there was a fairly large variation in the fluxes among animals, the flux across tissue from a single animal was much more reproducible. Paired experiments were performed using solutions, 90:10 and 80:20 hydrogel discs on buccal mucosa from 4 dogs in vitro in Ussing chambers (Fig. 5). The steady-state fluxes were 65.0 ± 19.0 , 20.8 ± 3.1 and 10.4 ± 2.4 $\mu\text{g}/\text{cm}^2/\text{h}$ with time lags of 1.8 ± 0.15 , 1.4 ± 0.21 and 2.1 ± 0.12 h, respectively.

Buprenorphine pharmacokinetics in the dog

Representative plasma levels of buprenorphine following an intravenous bolus of 0.3 mg of buprenorphine hydrochloride are shown in Fig. 6. The pharmacokinetic parameters determined for each dog are shown in Table 1. The experimental data were fitted to a biexponential rate equation to give the following mean parameter values:

$$C(t) = 79.2e^{(-5.89)t} + 7.5e^{(-0.33)t}$$

where $C(t)$ is the plasma concentration in ng/

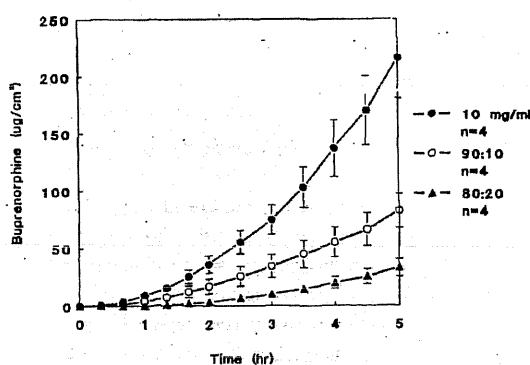


Fig. 5. Cumulative flux of buprenorphine across dog buccal mucosa from solution (10 mg/ml), 90:10 and 80:20 hydrogel discs, $n=4$.

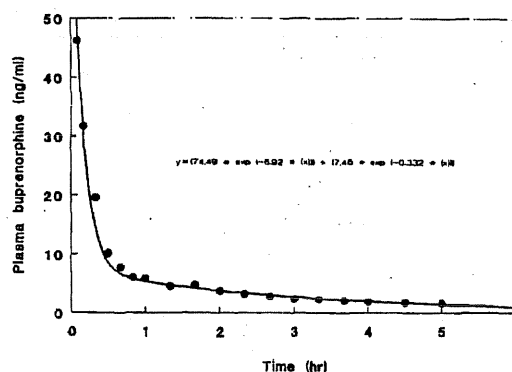


Fig. 6. Representative plasma profile of buprenorphine following administration of a 0.3 mg intravenous bolus. The data points were fitted to the curve shown by the dotted line using the equation in the figure.

ml at time t (h) after dosing. The mean clearance value was 144 ± 10 ml/min and the total volume of distribution was 26.3 ± 2.3 l ($n=6$). These values are similar to those reported in the literature [19].

Buccal absorption in vivo

Plasma buprenorphine levels following buccal application of one and three 1 cm^2 non-woven devices are shown in Fig. 7. Steady-state levels (C_{ss}) were calculated from the linear portions of the cumulative area under the plasma concentration time curves (AUC) versus time plots and the time lag to steady-state was the intercept on the abscissa (Fig. 8). The steady-state plasma levels were 8.2 ± 1.1 ($n=6$), 1.6 ± 0.06 ($n=3$) and 1.5 ng/ml ($n=2$) during the application of three 1 cm^2 discs, four 0.5 cm^2 discs and one 1 cm^2 disc, respectively. Steady-state flux (J_{ss}) was calculated from the following equation

$$J_{ss} = \frac{C_{ss} \times \text{Clearance}}{A}$$

where A = area in cm^2

The steady-state fluxes were 22.0 ± 3.4 $\mu\text{g}/\text{cm}^2/\text{h}$ ($n=6$) from three 1 cm^2 devices, 7.0 ± 0.3 from four 0.5 cm^2 discs and 12.7 $\mu\text{g}/\text{cm}^2/\text{h}$ from a single 1 cm^2 device. The steady-state flux of buprenorphine from the smaller (0.5 cm^2) devices

TABLE I

Pharmacokinetic parameters for an intravenous bolus of buprenorphine hydrochloride (300 µg)

Parameter	Dog No.						Mean ± SEM
	616567	991911	99267	996971	581216	487945	
Weight (kg)	9.5	10.5	10.2	10.2	10.2	11.8	10.4 ± 0.3
Sex	F	F	F	F	M	F	
A (ng/ml)	74.5	156.3	64.8	66.4	59.3	53.7	79.2 ± 15.7
α (h ⁻¹)	6.9	8.1	4.1	5.6	4.9	5.8	5.9 ± 0.6
B (ng/ml)	7.5	9.5	8.9	6.2	6.8	6.2	7.5 ± 0.6
β (h ⁻¹)	0.33	0.37	0.33	0.37	0.31	0.29	0.33 ± 0.01
Clearance ¹ (ml/min)	151	110	116	173	148	163	144 ± 10
V _d ² (l)	27.5	18.0	21.1	28.4	28.5	34.0	26.3 ± 2.3

$$^1\text{Clearance} = \frac{\text{Dose}}{\text{Area under curve}}$$

$$^2V_d = \frac{\text{Clearance}}{\text{Terminal half life}}$$

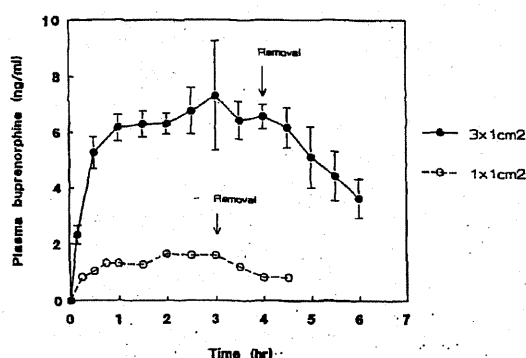


Fig. 7. Plasma levels of buprenorphine obtained after application of one or three 1 cm² non-woven buccal devices. The single device was applied for 3 h and the three devices for 4 h.

was significantly lower than that from three 1 cm² devices ($p < 0.01$), when expressed on the basis of area.

Using the 80:20 hydrogels, steady-state plasma levels of 3.7 ± 0.6 ng/ml ($n=3$) and 1.6 ± 0.4 ng/ml ($n=3$) were achieved following application of one 3.75 cm² and three 1 cm² discs, respectively (Fig. 9). The time-lags to steady-state were 0.9 ± 0.4 and 0.7 ± 0.1 h, respectively. The steady-state fluxes were 8.6 ± 0.9 and 4.8 ± 0.7 µg/cm²/h from one 3.75 cm² and three 1 cm² discs, respectively. The flux from three 1 cm² hydrogel

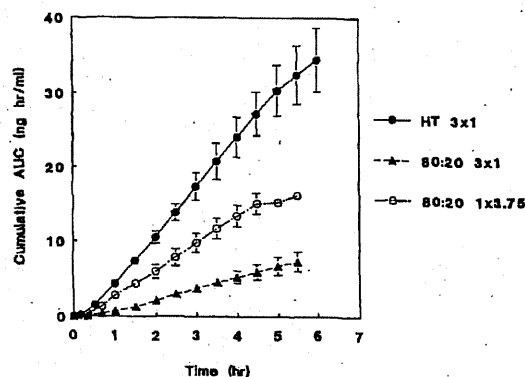


Fig. 8. Cumulative AUC versus time curves following the application of non-woven and hydrogel systems to canine buccal mucosa.

discs was significantly lower than that from three 1 cm² non-woven discs ($p < 0.01$) and the time lag to steady-state was significantly longer (0.7 vs. 0.3 h, $p < 0.01$). Using the higher water content hydrogels of various sizes (0.5 to 3.75 cm²) steady-state plasma levels were not achieved and considerable variation was seen. The flux data are summarized in Table 2.

Discussion

The solubility of buprenorphine hydrochloride was highly pH dependent, with an exponen-

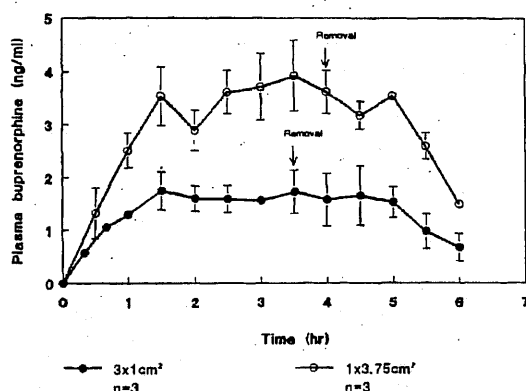


Fig. 9. Plasma levels of buprenorphine following the buccal application of 80:20 hydrogel discs. The time of application for the 3.75 cm² disc was 4 hours and for the three 1 cm² discs, 3.5 hours.

TABLE 2

In vivo fluxes of buprenorphine from prototype systems in the dog

System*	Flux ($\mu\text{g}/\text{cm}^2/\text{hr}$)	Steady-state plasma concentration (ng/ml)	n
Non-woven			
3x1 cm ²	22.0 $\pm$ 3.4	8.2 $\pm$ 1.1	6
4x0.5 cm ²	7.0 $\pm$ 0.3	1.6 $\pm$ 0.06	3
1x1 cm ²	12.7	1.5	2
80:20 hydrogels			
1x3.75 cm ²	8.6 $\pm$ 0.9	3.7 $\pm$ 0.6	3
3x1 cm ²	4.8 $\pm$ 0.7	1.6 $\pm$ 0.4	3

*Number of systems $\times$ area of system.

Results are the mean $\pm$ 1 SEM.

tial increase in solubility as the pH decreased. Its behavior in solution was similar to that reported for fentanyl and sufentanil, which are also weakly basic narcotic analgesics [20]. The presence of salts at a physiological concentration decreased the solubility from 17.3 mg/ml in phosphate buffer to 4.2 mg/ml.

The permeation of buprenorphine through rabbit buccal mucosa in vitro was linearly related to the donor concentration over the range 0.04 to 4.3 mg/ml, which is supportive of passive diffusion as the mechanism of transport. The permeability of canine buccal mucosa was about seven-fold greater than that of the rabbit, with

permeability coefficients of 14.4 and 2.7×10^{-7} cm/s, respectively. The relative permeability was similar to that reported for CGS 16617, a highly hydrophilic angiotensin converting enzyme inhibitor [8]. The addition of sodium azide, an uncoupler of oxidative phosphorylation, resulted in significantly increased flux of buprenorphine across rabbit buccal mucosa. Azide abolishes the spontaneous transepithelial potential difference and the barrier properties of buccal mucosa from a variety of species [8]. The flux of buprenorphine was the same from a 10 mg/ml donor in free solution or loaded onto a non-woven chamber in vivo would be equivalent to the application of a drug solution to the mucosa. The use of cups containing solutions has been associated with leakage and the problems of clamping a cup securely in position without it moving or compromising the blood supply to the area.

The application of non-woven systems to the buccal mucosa for 3 to 4 h resulted in steady-state plasma levels which were maintained until the removal of the systems. The slower decline in plasma levels compared to the rapid fall after an intravenous dose suggests the presence of a depot in the buccal mucosa. The lower flux from smaller systems even when corrected for area may reflect an edge effect which may be due to poor contact with the tissue. The 80:20 hydrogel systems also produced steady-state plasma levels with a similar slow decline after system removal (Fig. 9), but the flux was significantly lower than that obtained during the application of non-woven systems of the same size. The higher water content hydrogels gave rise to much more erratic plasma levels and steady-state was not achieved.

Conclusions

Steady-state plasma levels of buprenorphine were obtained in the dog using two different prototype systems, one non-woven and the other a hydrogel. The lag times were less than 1 h in both cases which would therefore provide rapid delivery of this analgesic. Good analgesic effect was obtained in man with sublingual buprenorphine

following a similar delay in absorption [7]. The dog has been reported to be a good model for man [9,10] and extrapolation of these results to man suggests that the buccal route of delivery of buprenorphine would be feasible and would offer an excellent treatment modality for pain relief.

References

- 1 R.C. Heel, R.N. Brodgen, T.M. Speight and G.S. Avery, Buprenorphine: a new strong analgesic, *Curr. Ther.* 5 (1979) 29-33.
- 2 P.J.Q. Watson, H.J. McQuay, R.E.S. Bullingham, M.C. Allen and R.A. Moore, Single-dose comparison of buprenorphine 0.3 and 0.6 mg i.v. given after operation: clinical effects and plasma concentrations, *Br. J. Anaesth.* 54 (1982) 37-43.
- 3 H. Adriaenssens, B. Mattelaer and H. Vanmeenen, A long-term open, clinical and pharmacokinetic assessment of sublingual buprenorphine in patients suffering from chronic pain, *Acta Anaesthesiol. Belg.* 1 (1985) 33-40.
- 4 D. Brewster, M.J. Humphrey and M.A. McLeavy, Biliary excretion, metabolism and enterohepatic circulation of buprenorphine, *Xenobiotica* 11 (1981) 189-196.
- 5 M.J. Rance and J.S. Shillingford, The metabolism of phenolic opiates by rat intestine, *Xenobiotica* 7 (1977) 529-36.
- 6 P.C. Rutter, F. Murphy and H.A.F. Dudley, Morphine: controlled trial of different methods of administration for postoperative pain relief, *Br. Med. J.* 1 (1980) 12-13.
- 7 R.E.S. Bullingham, H.J. McQuay, D. Dwyer, M.C. Allen and R.A. Moore, Sublingual buprenorphine used post-operatively: clinical observations and preliminary pharmacokinetic analysis, *Br. J. Clin. Pharm.* 12 (1981) 117-122.
- 8 E. Quadros, J. Cassidy, K. Gniecko and S. LeRoy, Buccal and colonic absorption of CGS 16617, a novel ACE inhibitor, *J. Controlled Release* 19 (1991) 77-86.
- 9 C.D. Ebert, V.A. John, P.T. Beall and K.A. Rosenzweig, Transbuccal absorption of diclofenac sodium in a dog model, *Controlled-Release Technology* (1987), W.R. Good and P. Lee, Eds: American Chemical Society, pp. 310-321.
- 10 J. Cassidy, B. Berner, K. Chan, V. John, S. Toon, B. Holt and M. Rowland, Buccal delivery of diclofenac sodium in man using a prototype hydrogel delivery device, *Proc. Int. Symp. Controlled Release Bioact. Mat.* 16 (1989) 91-92.
- 11 E. Quadros and J. Cassidy, Buccal flux of buprenorphine in vitro, *Pharm. Res.* 8 (1991) S-156.
- 12 J. Cassidy and E. Quadros, Sustained buccal delivery of buprenorphine in the dog in vivo, *Pharm. Res.* 8 (1991) S-155.
- 13 S. Reiser and P.A. Christiansen, The properties of Na⁺-dependent and Na⁺-independent lysine uptake by isolated intestinal epithelial cells, *Biochim. Biophys. Acta* 307 (1973) 212-222.
- 14 U. S. Pharmacopeia (1985) pp. 1419-1420.
- 15 Geigy Scientific Tables, Vol. 3 (1984) C. Lentner, Ed. Ciba-Geigy, Limited, Basle, pp. 58-60.
- 16 H.A. Krebs and K. Henseleit, Untersuchungen über die Harnstoffbildung im Tierkörper, *Hoppe-Seyler's Z. Physiol. Chem.* 210 (1932) 33-66.
- 17 W.R. Good and K.F. Mueller, A new family of monolithic hydrogels for controlled release application, *Controlled Release of Bioactive Materials*, Academic Press, New York, 1980, pp. 155-175.
- 18 J. Crank, The mathematics of diffusion, 2nd ed., Clarendon Press, Oxford, 1975.
- 19 E.R. Garrett and V.R. Chandran, Pharmacokinetics of morphine and its surrogates X: analyses and pharmacokinetics of buprenorphine in dogs, *Biopharm. Drug Disp.* 11 (1990) 311-350.
- 20 S.D. Roy and G.L. Flynn, Solubility behavior of narcotic analgesics in aqueous media: solubilities and dissociation constants of morphine, fentanyl and sufentanil, *Pharm. Res.* 6 (1989) 147-151.

REIVINDICACIONES

1. Una composición farmacéutica que comprende micropartículas de buprenorfina, o una sal farmacéuticamente aceptable de la misma, en una
5 cantidad en la composición comprendida entre 0.1 mg y 50 mg, partículas que comprenden ácido cítrico, naloxona, o una sal farmacéuticamente aceptable de la misma, en una cantidad en la composición comprendida entre 0.125 mg y 12.5 mg, y un disgregante seleccionado de croscarmelosa sódica, glicolato de almidón sódico, polivinilpirrolidona reticulada o una mezcla de los mismos,
10 donde la proporción de la dosis de buprenorfina:naloxona es de aproximadamente 4:1 (calculada como bases libres) y donde las micropartículas de buprenorfina y las partículas que comprenden ácido cítrico están en contacto íntimo entre sí.
- 15 2. Una composición de acuerdo con la reivindicación 1, en la que las micropartículas de buprenorfina tienen un diámetro medio en base al peso inferior a 15 μm .
- 20 3. Una composición de acuerdo con una cualquiera de las reivindicaciones precedentes, que se presenta como una mezcla interactiva que comprende micropartículas de buprenorfina o una sal farmacéuticamente aceptable de la misma presentada sobre las superficies de partículas vehículo.
- 25 4. Una composición de acuerdo con la reivindicación 3, en la que las partículas vehículo son de un tamaño que está entre 100 y 800 μm .

5. Una composición de acuerdo con la reivindicación 3 o la reivindicación 4, en la que las partículas vehículo son hidrosolubles.

5 6. Una composición de acuerdo con una cualquiera de las reivindicaciones 3 a 5, en la que las partículas vehículo comprenden manitol.

7. Una composición de acuerdo con una cualquiera de las reivindicaciones 3 a 6, en la que las partículas de ácido cítrico, se presentan y
10 actúan como partículas vehículo.

8. Una composición de acuerdo con una cualquiera de las reivindicaciones precedentes, que está en forma de un comprimido adecuado para administración sublingual.
15

9. Un procedimiento para la preparación de una composición como se ha definido en una cualquiera de las reivindicaciones 3 a 8, que comprende mezclar en seco las partículas vehículo con buprenorfina o una sal de la misma.
20

10. Un procedimiento para la preparación de un comprimido sublingual como se ha definido en la reivindicación 8, que comprende comprimir o compactar directamente una composición como se ha definido en una cualquiera de las reivindicaciones 1 a 7.
25