

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
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DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 10
ACT: 476 TRASTITULARSOLI	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
LUZ CLEMENCIA DE PÁEZ

Asunto: Radicación: 14-27709- -8
 Trámite: 11
 Evento: 378
 Actuación: 476
 Oficio: 3280
 Folios: 10

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/EP2011/063829				
Fecha de Presentación Internacional	11/08/2011				

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Radicado No. 14-027709-00000-0000	10/Febrero/2014
Reivindicaciones:	Radicado No. 14-027709-00000-0000	10/Febrero/2014
	Radicado No. 14-027709-00004-0000	16/Julio/2014
	Radicado No. 14-027709-00007-0000	12/Noviembre/2014
Oposiciones:	Radicado No. 14-027709-00005-0000	Lafrancol 06/Agosto/2014
Respuesta del solicitante:	Radicado No. 14-027709-00007-0000	12/Noviembre/2014

2. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del capítulo primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las

cubiertas por la tasa pagada. En el presente caso se tiene en cuenta la totalidad del capítulo reivindicatorio.

Título de la solicitud: "Composición farmacéutica que comprende un medicamento que contiene por lo menos una función toxicófora y N-acetil-L-cisteína".

El problema planteado en esta solicitud consiste en la necesidad de proporcionar una composición farmacéutica útil para prevenir y/o reducir la ocurrencia de reacciones idiosincráticas adversas de los medicamentos, causadas por un medicamento que contiene por lo menos una función toxicófora y la cual comprenda el medicamento que contiene por lo menos una función toxicófora.

Para resolver este problema técnico la solicitud en estudio proporciona una composición farmacéutica que comprende al menos un medicamento que contiene al menos una función toxicófora, N-acetil-L-cisteína (NAC), al menos un agente antioxidante y al menos un excipiente fisiológicamente aceptable, en donde dicho medicamento que contiene al menos una función toxicófora es nimesulida.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K 31/18, A61K 31/196, A61K 31/198, A61P 43/00.

3. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es concisa porque reclama una composición farmacéutica sin establecer las proporciones de los componentes en la misma. Se recuerda al solicitante que una composición se debe caracterizar por sus componentes y las proporciones de éstos. Adicionalmente, la reivindicación 1 no es clara porque se refiere a un componente de la composición por su función y no por su nombre químico, cuando establece que la composición farmacéutica comprende al menos un agente antioxidante, lo que genera una gran cantidad de posibles composiciones no soportadas en la descripción. Se sugiere establecer las posibilidades de agente antioxidante de acuerdo a lo efectivamente soportado en la descripción.

La reivindicación 9 no es clara, y se refiere a un resultado a alcanzar cuando señala que la N-acetil-L-cisteína (NAC) tiene una biodisponibilidad más rápida que aquella de al menos un medicamento, no define al producto porque la invención no queda definida por el resultado a alcanzar, puesto que la reivindicación incluiría no sólo la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Se sugiere reemplazarlo por las características esenciales, estructurales o funcionales, que contribuyen a la obtención de ese efecto. Adicionalmente, se sugiere cambiar la referencia de medicamento por nimesulida, con el fin de que no se presente ninguna confusión a la hora de determinar el alcance del capítulo reivindicatorio.

La reivindicación 10 no es concisa porque no establece claramente cuales son los componentes de la composición y la proporción de éstos. Se recuerda al solicitante que una composición se debe caracterizar por sus componentes y las proporciones de éstos. La reivindicación 10 se refiere a un componente de la composición por su función y no por su nombre químico, cuando establece que la composición farmacéutica comprende al menos un agente antioxidante, lo que genera una gran cantidad de posibles composiciones no soportadas en la descripción. Se sugiere

establecer las posibilidades de agente antioxidante de acuerdo a lo efectivamente soportado en la descripción.

4. Análisis de la Oposición

Argumentaciones de Lafrancol

1. Afirma el oponente que las composiciones y formulaciones farmacéuticas que comprenden por lo menos un medicamento que contiene por lo menos una función toxicófora, N-acetil-L-cisteína (NAC), por lo menos un agente antioxidante y por lo menos un excipiente farmacéuticamente aceptable, útiles en la prevención y/o reducción de la ocurrencia de reacciones adversas de los medicamentos (IADRs), son prácticas y eventos totalmente conocidos en la industria farmacéutica y que no existe ninguna novedad sobre estos preceptos y mucho menos nivel inventivo. Y agrega que las composiciones y formulaciones farmacéuticas que involucran moléculas como las propuestas en la presente solicitud, no presentan ninguna clase de novedad, ni de nivel inventivo, luego sería inadecuado conceder un beneficio patentario para las mismas.
2. Señala el oponente que no puede la solicitante pretender accede a un beneficio patentario sobre composiciones y formulaciones farmacéuticas que comprenden moléculas que se encuentran descubiertas y plenamente identificadas en el sector químico-farmacéutico, así como la atorvastatina, para lo cual hace referencia a la monografía de atorvastatina presente en el libro “The Merck Index”, en la cual se referencia los documentos de patente EP4049281 y US5273995.
3. El oponente menciona que la solicitud reclama materia no patentable como métodos de tratamiento.
4. El oponente menciona que un efecto sinérgico nuevo no se considera inventivo como tal, dado que puede ser obvio para una persona versada en la materia y para esto hace referencia a un fragmento del libro Pautas para el examen de patentes farmacéuticas, CEIDIE, Pag. 8. Además agrega que las combinaciones deben considerarse excluidas de beneficios de patente.
5. Finalmente, el oponente señala que la solicitud en curso carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención, particularmente en materia de novedad y/o nivel inventivo si se tiene en cuenta la materia revelada en los documentos: WO9847534; EP1574221; Drug Induced liver injury: a clinical update; Anticonvulsant hypersensitivity síndrome: is there a role for immunomodulation?; N-acetylcysteine attenuates NSAID-induced rat renal failure by restoring intrarenal prostaglandin synthesis; intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure.

Respuestas del Solicitante

El solicitante señala que en el nuevo pliego reivindicatorio fueron eliminadas las reivindicaciones 12 a 14 que hacían referencia a métodos de tratamiento o usos.

El solicitante menciona que el oponente se limita a reproducir una copia de los documentos citados en el informe de búsqueda internacional puesto que los documentos citados corresponden a los analizados por la Oficina Europea de Patentes, en los que algunos de los documentos fueron citados como referencia y no para sustentar una objeción por incumplimiento de alguno de los requisitos de patentabilidad.

Con respecto a que las mezclas o combinaciones de compuestos conocidos no son patentables el solicitante establece que el Tribunal de Justicia de la Comunidad Andina, por vía de interpretación prejudicial ha desvirtuado la afirmación del oponente y señala

que en ciertos casos la combinación o mezcla de compuestos conocidos puede llegar a ser patentable.

El solicitante argumenta que el capítulo reivindicatorio fue modificado para especificar que la nimesulida es el medicamento que comprende una función toxicófora.

Y establece que las referencias citadas por la sociedad opositora, así como la mayor parte de las objeciones realizadas serían irrelevantes porque ninguno de los documentos citados se refiere específicamente a la nimesulida, a la combinación específica de nimesulida con N-acetil-L-cisteína, así como la prevención y/o reducción de IADRs con dicha combinación junto a un antioxidante.

El solicitante argumenta que el documento D1 se refiere a NAC como estabilizador de una serie de NSAIDs entre los que la nimesulida no se encuentra incluida. Respecto al documento D2 señala que éste se refiere al uso de NAC en la estabilización de formulaciones inyectables de diclofenaco, y que éste no referencia la nimesulida como tampoco la prevención y/o reducción de IADRs.

En cuanto al documento D3 establece que éste se refiere a una investigación epidemiológica en la ocurrencia de IADRs en diferentes poblaciones, y menciona que la referencia contiene solo especulaciones y conclusiones preliminares, y que la NAC está reportada incorrectamente como un antídoto para pacientes con insuficiencia hepática aguda. Además, agrega que la nimesulida no se menciona en ninguna parte del documento.

El solicitante argumenta respecto al documento D4 que este se refiere al uso combinado de NAC e inmunoglobulina para prevenir la lesión hepática debida al tratamiento con fenitoína y que las dosis de NAC administradas son mucho más altas que las que se administrarían en las formulaciones de la presente solicitud. El solicitante señala que el último párrafo del documento D4 establece que los autores no pueden estar seguros de que una de las terapias individualmente pueda ser eficaz, y que el documento D4 en ningún momento se refiere a la nimesulida.

Frente al documento D5 el solicitante indica que éste enseña la administración parenteral de NAC en combinación con NSAID, en partículas diclofenaco, en un modelo de NSAID inducido por insuficiencia renal, y señala que el documento esencialmente se refiere a la toxicidad general del diclofenaco mediada por la síntesis de PGE2 la cual según éste es bastante diferente de la reacción adversa idiosincrática de la solicitud.

Finalmente, el solicitante expresa que el documento D6 revela la administración intravenosa de altas dosis de NAC a pacientes con insuficiencia hepática aguda e indica que el documento esencialmente se refiere a la posibilidad de una supervivencia prolongada de los pacientes libre de transplantes con insuficiencia hepática aguda y no menciona la nimesulida.

Respuesta del Examinador Técnico

Este despacho encuentra que el oponente se limita a nombrar los documentos citados en la búsqueda internacional, sin establecer como dichos documentos afectan los requisitos de patentabilidad de las composiciones reclamadas. Sin embargo, este despacho procede a analizar dichos documentos:

- WO9847534: Se refiere a composiciones estabilizadas que comprenden una combinación de un AINES, NAC y una combinación de antioxidantes. La anterioridad divulga un medicamento estabilizado con una cantidad de compuestos cisteinil o dicisteinil, particularmente N-acetilcisteina en combinación con un agente analgésico no-esteroideo para suprimir el daño de un órgano,

especialmente el hígado y el daño inflamatorio, conteniendo una mezcla estabilizadora comprendiendo al menos tres ingredientes de la serie que comprende: a) ácido ascórbico (vitamina C), b) uno o más tocoferoles (vitamina E), c) uno o más carotenoides y/o vitamina A y d) uno o más flavonoides naturales o sintéticos, bioflavonoides, flavonoles, o catequinas (Reiv. 1).

A pesar que el documento WO9847534 no menciona específicamente la nimesulida, si menciona varios AINES de estructura diferente, por lo cual se considera que el documento puede ser tenido en cuenta durante el análisis de patentabilidad (se usará su equivalente en inglés US2003119909).

- EP1574221: Se refiere a composición inyectable estable que comprende diclofenaco, una ciclodextrina, y un antioxidante seleccionado de monotioglicerol o una combinación de EDTA y N-acetilcisteína. El documento no será tenido en cuenta durante el examen de patentabilidad puesto que está enfocado a mejorar la estabilidad de las composiciones inyectables de diclofenaco y no a prevenir los efectos adversos idiosincráticos del mismo. Adicionalmente, la NAC en la anterioridad se usa como un antioxidante en combinación con EDTA y es opcional.
- Drug Induced liver injury: a clinical update: El documento enseña que el uso de N-acetilcisteína es beneficioso para pacientes con daño hepático agudo idiosincrático causado por medicamentos entre los que menciona AINES, antibióticos, entre otros medicamentos de diversos tipos (todo el documento; Pág. 6, tercer párr.; conclusión). Será tenido en cuenta durante el examen de patentabilidad ya que sugiere los efectos benéficos de la NAC para contrarrestar los efectos adversos de los AINES y otro tipo variado de medicamentos.
- Anticonvulsant hypersensitivity síndrome: is there a role for immunomodulation?: No sera tenido en cuenta durante el examen de patentabilidad debido a que se refiere al uso combinado de NAC e inmunoglobulina intravenosa en el tratamiento de un síndrome de hipersensibilidad a algunos anticonvulsivantes y no hace referencia a AINES, ni a nimesulida.
- N-acetylcysteine attenuates NSAID-induced rat renal failure by restoring intrarenal prostaglandin synthesis: No sera tenido en cuenta en el análisis de patentabilidad porque se refiere a que la NAC atenúa el deterioro renal causado por AINES, principalmente diclofenaco. El documento no hace ninguna referencia al uso de NAC para prevenir las reacciones hepáticas adversas de los AINES y no menciona la nimesulida.
- Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophan acute liver failure: NO sera tenido en cuenta durante el examen de patentabilidad porque a pesar que menciona los beneficios de la NAC en pacientes con DILI (Drug Induced Liver Injury), no especifica los medicamentos causantes de DILI.

Los documentos WO9847534 y Drug Induced liver injury: a clinical update presentados en la Oposición desvirtúan el Nivel Inventivo del objeto de esta solicitud; por lo cual se considerarán dentro del Examen de Patentabilidad.

5. Determinación del estado de la técnica

El estado de la técnica se determinó con base en la fecha de presentación internacional: Agosto 11 de 2011 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	US2003119909	Stabilized medicament containing cysteinyl derivatives	26/Junio/2003
D2	Curr Opin	Drug-induced liver injury: a clinical	Mayo/2010

Ítem	Documento	Título	Fecha de Publicación
	Gastroenterol. 2010 May ; 26(3): 222–226.	update	

D1 [http://worldwide.espacenet.com/publicationDetails/biblio?CC=US&NR=2003119909A1&KC=A1&FT=D&ND=3&date=20030626&DB=worldwide.e](http://worldwide.espacenet.com/publicationDetails/biblio?CC=US&NR=2003119909A1&KC=A1&FT=D&ND=3&date=20030626&DB=worldwide.espacenet.com&locale=en_EP)
[spacenet.com&locale=en_EP](http://worldwide.espacenet.com/publicationDetails/biblio?CC=US&NR=2003119909A1&KC=A1&FT=D&ND=3&date=20030626&DB=worldwide.espacenet.com&locale=en_EP)

divulga un medicamento estabilizado con una cantidad de compuestos cisteinil o dicisteinil, particularmente N-acetilcisteina en combinación con un agente analgésico no-esteroideo para suprimir el daño de un órgano, especialmente el hígado y el daño inflamatorio, conteniendo una mezcla estabilizadora comprendiendo al menos tres ingredientes de la serie que comprende: a) ácido ascórbico (vitamina C), b) uno o más tocoferoles (vitamina E), c) uno o más carotenoides y/o vitamina A y d) uno o más flavonoides naturales o sintéticos, bioflavonoides, flavonoles, o catequinas (Reiv. 1).

D2 enseña que el uso de N-acetilcisteina es beneficioso para pacientes con daño hepático agudo idiosincrático causado por medicamentos entre los que menciona AINES, antibióticos, entre otros medicamentos de diversos tipos (todo el documento; Pág. 6, tercer párr.; conclusión).

6. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en una composición farmacéutica que comprende al menos un medicamento que contiene al menos una función toxicófora, N-acetil-L-cisteina (NAC), al menos un agente antioxidante y al menos un excipiente fisiológicamente aceptable, en donde dicho medicamento que contiene al menos una función toxicófora es nimesulida.

Comparación de las características técnicas **esenciales**, con las del estado de la técnica:

Características esenciales	D1	D2
Composición farmacéutica que comprende:	Composición farmacéutica que comprende:	Establece que la N-acetilcisteina es beneficiosa para pacientes con daño hepático agudo idiosincrático causado por medicamentos entre los que menciona AINES, antibióticos, entre otros (todo el documento; Pág. 6, tercer párr.; conclusion).
al menos un medicamento que contiene al menos una función toxicófora, en donde dicho medicamento que contiene al menos una función toxicófora es nimesulida.	Un NSAID (Reiv. 1)	
N-acetil-L-cisteina (NAC)	Un compuesto cisteinil o dicisteinil, particularmente N-acetilcisteina (Reiv. 1)	
al menos un agente antioxidante, y	Al menos tres componentes de la serie ácido ascórbico (vitamina C), uno o más tocoferoles (vitamina E), uno o más carotenoides y/o vitamina A y uno o más flavonoides naturales o sintéticos, bioflavonoides, flavonoles, o catequinas (Reiv. 1)	
al menos un excipiente fisiológicamente aceptable	Así como aditivos farmacéuticamente aceptables y/o agentes portadores para administración per oral, tópica, parenteral o rectal si se requiere (Reiv. 1; Párrs.	

Características esenciales	D1	D2
	[0023], [0055], [0056]).	

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque:

El documento D1 divulga un medicamento estabilizado con una cantidad de compuestos cisteinil o dicisteinil, particularmente N-acetilcisteína en combinación con un agente analgésico no-esteroideo para suprimir el daño de un órgano, especialmente el hígado y el daño inflamatorio, conteniendo una mezcla estabilizadora comprendiendo al menos tres ingredientes de la serie que comprende: a) ácido ascórbico (vitamina C), b) uno o más tocoferoles (vitamina E), c) uno o más carotenoides y/o vitamina A y d) uno o más flavonoides naturales o sintéticos, bioflavonoides, flavonoles, o catequinas (Reiv. 1).

La diferencia entre la invención, definida en la reivindicación 1 y la composición farmacéutica divulgada en el documento D1 consiste en que el documento D1 no establece que el AINES pueda ser específicamente nimesulida.

El efecto que logra el incluir esta característica es que previene específicamente de las reacciones hepáticas idiosincráticas que puede causar la nimesulida.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “cómo modificar la composición divulgada en el documento D1 para obtener una composición que comprenda nimesulida y que prevenga específicamente las reacciones hepáticas idiosincráticas que puede causar dicho fármaco”.

Sin embargo, el documento D1 sugiere el uso de diverso tipo de AINES, de diferentes estructuras (Reiv. 2).

Por otro lado, el documento D2 enseña que el uso de N-acetilcisteína es beneficioso para pacientes con daño hepático agudo idiosincrático causado por medicamentos entre los que menciona AINES, antibióticos, entre otros medicamentos de diversos tipos (todo el documento; Pág. 6, tercer párr.; conclusión), y es del conocimiento común de la persona versada en la materia que la nimesulida es un AINES que produce hepatotoxicidad idiosincrática, al igual que otros AINES¹.

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría la nimesulida dentro de las formulaciones divulgadas en el documento D1, porque el documento D1 divulga que se puede usar un AINES como agente activo en combinación con N-acetilcisteína y menciona diferentes tipos de AINES, y el documento D2 enseña que el uso de N-acetilcisteína como benéfico en el tratamiento de persona con daño hepático agudo idiosincrático causado por medicamentos como los AINES, por lo cual tendría una expectativa razonable de obtener con la nimesulida el mismo efecto que se obtiene con los demás AINES divulgados en el documento D1 porque es de su conocimiento común que la nimesulida causa hepatotoxicidad idiosincrática al igual que otros AINES². Por lo cual el objeto de la reivindicación 1 se considera obvio.

Conclusión:

La reivindicación 1 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18), de la misma forma que sus reivindicaciones dependientes 2 – 9.

1 Drug Saf. 2002;25(9):633-48. Mechanisms of NSAID-induced hepatotoxicity: focus on nimesulide.

2 Drug Saf. 2002;25(9):633-48. Mechanisms of NSAID-induced hepatotoxicity: focus on nimesulide.

La reivindicación 10 consiste en un comprimido multicapa que comprende al menos una capa que contiene:

- N-acetil-L-cisteína,
- al menos un antioxidante, y
- opcionalmente al menos un excipiente fisiológicamente aceptable;

Y al menos una segunda capa que contiene:

- nimesulida; y
- al menos un excipiente fisiológicamente aceptable.

Comparación de las características técnicas **esenciales**, con las del estado de la técnica:

Características esenciales	D1	D2
un comprimido multicapa que comprende al menos una capa que contiene:	Composición farmacéutica que puede ser una tableta multicapa que comprende (Párr. [0054]):	Establece que la N-acetilcisteína es beneficiosa para pacientes con daño hepático agudo idiosincrático causado por medicamentos entre los que menciona AINES, antibióticos, entre otros (todo el documento; Pág. 6, tercer párr.; conclusion).
-N-acetil-L-cisteína, - al menos un antioxidante, y - opcionalmente al menos un excipiente fisiológicamente aceptable;	Un compuesto cisteinil o dicisteinil, particularmente N-acetilcisteína (Reiv. 1), Al menos tres componentes de la serie ácido ascórbico (vitamina C), uno o más tocoferoles (vitamina E), uno o más carotenoides y/o vitamina A y uno o más flavonoides naturales o sintéticos, bioflavonoides, flavonoles, o catequinas (Reiv. 1). Así como aditivos farmacéuticamente aceptables y/o agentes portadores para administración per oral, tópica, parenteral o rectal si se requiere (Reiv. 1; Párrs. [0023], [0055], [0056]).	
Y al menos una segunda capa que contiene: -nimesulida; y - al menos un excipiente fisiológicamente aceptable.	Un NSAID (Reiv. 1) Así como aditivos farmacéuticamente aceptables y/o agentes portadores para administración per oral, tópica, parenteral o rectal si se requiere (Reiv. 1; Párrs. [0023], [0055], [0056]).	

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 2 porque:

El documento D1 divulga un medicamento, que puede ser una tableta multicapa multicapa, estabilizado con una cantidad de compuestos cisteinil o dicisteinil, particularmente N-acetilcisteína en combinación con un agente analgésico no-esteroideo para suprimir el daño de un órgano, especialmente el hígado y el daño inflamatorio, conteniendo una mezcla estabilizadora comprendiendo al menos tres ingredientes de la serie que comprende: a) ácido ascórbico (vitamina C), b) uno o más tocoferoles (vitamina E), c) uno o más carotenoides y/o vitamina A y d) uno o más flavonoides naturales o sintéticos, bioflavonoides, flavonoles, o catequinas (Reiv. 1; Párr. [0054]).

La diferencia entre la invención, definida en la reivindicación 10 y la composición

farmacéutica divulgada en el documento D1 consiste en que el documento D1 no establece que el AINES pueda ser específicamente nimesulida.

El efecto que logra el incluir esta característica es que previene específicamente de las reacciones hepáticas idiosincráticas que puede causar la nimesulida.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “cómo modificar la composición divulgada en el documento D1 para obtener una composición que comprenda nimesulida y que prevenga específicamente las reacciones hepáticas idiosincráticas que puede causar dicho fármaco”.

Sin embargo, el documento D1 sugiere el uso de diverso tipo de AINES, de diferentes estructuras (Reiv. 2).

Por otro lado, el documento D2 enseña que el uso de N-acetilcisteína es beneficioso para pacientes con daño hepático agudo idiosincrático causado por medicamentos entre los que menciona AINES, antibióticos, entre otros medicamentos de diversos tipos (todo el documento; Pág. 6, tercer párr.; conclusión), y es del conocimiento común de la persona versada en la materia que la nimesulida es un AINES que produce hepatotoxicidad idiosincrática, al igual que otros AINES³.

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría la nimesulida dentro de las formulaciones divulgadas en el documento D1, porque el documento D1 divulga que se puede usar un AINES como agente activo en combinación con N-acetilcisteína y menciona diferentes tipos de AINES, y el documento D2 enseña que el uso de N-acetilcisteína como benéfico en el tratamiento de persona con daño hepático agudo idiosincrático causado por medicamentos como los AINES, por lo cual tendría una expectativa razonable de obtener con la nimesulida el mismo efecto que se obtiene con los demás AINES divulgados en el documento D1 porque es de su conocimiento común que la nimesulida causa hepatotoxicidad idiosincrática al igual que otros AINES⁴. Por lo cual el objeto de la reivindicación 10 se considera obvio.

Conclusión:

La reivindicación 10 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18), del mismo modo que su reivindicación dependiente 11.

7. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US2003119909	1 – 11	Nivel Inventivo
D2	Curr Opin Gastroenterol. 2010 May ; 26(3): 222–226.	1 – 11	Nivel Inventivo

³ Drug Saf. 2002;25(9):633-48. Mechanisms of NSAID-induced hepatotoxicity: focus on nimesulide.

⁴ Drug Saf. 2002;25(9):633-48. Mechanisms of NSAID-induced hepatotoxicity: focus on nimesulide.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

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Drug-induced liver injury: a clinical update

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Abstract

Purpose of review—To gather new and important data published on idiosyncratic drug-induced liver injury (DILI) over the past 2 years in the peer-reviewed literature. Clinical studies focusing on mechanisms of injury, clinical evaluation and prognosis will be reviewed.

Recent findings—The most common drugs leading to DILI in the United States are antibiotics, central nervous system agents, herbal/dietary supplements and immunomodulatory agents. Hepatocellular type of DILI is more common in younger patients, whereas cholestatic pattern increases with older age. Certain human leukocyte antigen genotype increases the likelihood of flucloxacillin-induced liver injury. Idiosyncratic DILI was shown to have an important dose-dependency and drugs with extensive hepatic metabolism are associated with higher frequency of DILI. Chronic DILI may occur, but development of clinically important liver injury after severe DILI is rare. *N*-acetylcysteine seems to be beneficial for patients with acute liver failure caused by medications or herbal agents.

Keywords

diagnosis; drug-induced liver injury; hepatotoxicity; natural history

Introduction

Drug-related hepatotoxicity is a serious health problem, with broad implications for patients, healthcare providers, the pharmaceutical industry and governmental regulatory agencies. Drug-induced liver injury (DILI), whether dose-related as with acetaminophen or idiosyncratic, is the most common cause of acute liver failure in the United States [1]. In addition, DILI is the most common cause of aborted development or withdrawal of otherwise promising drugs [2].

The risk factors, pathogenesis and outcomes of idiosyncratic DILI are poorly understood. The study of DILI is confounded by the heterogeneity of its clinical presentation and course of injury, ranging from asymptomatic transient elevations in liver enzymes to liver failure and in rare cases chronic liver disease; the delay in establishing its diagnosis as it requires exclusion of other causes of liver injury; the lack of standardized criteria or specific ‘gold standard’ diagnostic tests for DILI; and underreporting of cases of DILI or their final outcomes. This paper reviews recent publications on this topic over the past 2 years.

Epidemiology

The epidemiology of DILI is influenced by geographic and cultural factors, as well as by variable study designs and definitions. In western countries, acetaminophen is the leading cause of DILI and it is well known to be dose-related or intrinsic in nature. Idiosyncratic DILI, however, is a rare and unpredictable event and may not be identified in preclinical or clinical testing. DILI in the case of any single drug is thought to occur approximately in one per 10 000–100 000 treated patients. The variable incidence of DILI in a number of large retrospective studies underscores the challenges in diagnosing DILI and the need for prospective data.

The Drug Induced Liver Injury Network (DILIN), a federally funded consortium of several centers in the United States, recently reported the preliminary results of its prospective study [3^{**}]. It consisted of 300 patients with suspected DILI enrolled prospectively over a 3-year period between 2004 and 2007. This study excluded patients with acetaminophen-related hepatotoxicity and patients with preexisting autoimmune liver diseases such as primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). Patient ages were 2–18 years in 7% of cases, 18–65 in 75% and more than 65 in 18%, whereas 60% were females. Similar to prior registry reports, a single drug was most commonly implicated, accounting for 73% of DILI cases. However, multiple drugs were implicated in 18% of cases and herbal or dietary supplements in 9% of cases, which were higher than the rates reported by the prospective Spanish registry study [4]. This may be potentially related to greater polypharmacy and the use of herbal or dietary supplements in the US population. More than 100 different compounds were implicated in this DILIN prospective study, but antimicrobials (45.5%) and central nervous system agents (15%) were the two most common classes of agents implicated. Less common classes included immunomodulatory agents (5.5%), analgesics (5%), antihypertensive agents (5%), antineoplastic agents (4%) and lipid-lowering agents (3.4%). The most common single causative agents were amoxicillin–clavulanate in 23 cases, and trimethoprim–sulfamethaxazole, nitrofurantoin and isoniazid in 13 cases each.

The use of herbal or dietary supplements, when implicated in DILI, was intended for muscle building or weight loss in 60% of those cases [3^{**}]. The importance of these supplements as a cause of DILI is further underscored by a retrospective Japanese study, in which 10% of 879 cases of single agent DILI from 1997 to 2006 were attributed to dietary supplements and 7% to Chinese herbal drugs [5]. These rates were significantly higher than those reported in a 1998–1999 study of 0.7 and 4.7%, respectively [6]. Symptomatic DILI was more common with Chinese herbals, which may account for increased reporting of those cases, whereas DILI related to dietary supplements was less frequently symptomatic and may be the result of increased use of these products by the Japanese population. Taken together, these data may reflect evolving cultural trends and impact of obesity within the sphere of geographic variability influencing the incidence and etiology of DILI.

Risk factors

Susceptibility to DILI is thought to be influenced by certain patient characteristics, predominantly age and sex, though there have been insufficient data to define increased risk in any given patient subpopulation. In addition to any effect of age on physiologic reserves, the influence of age may be multifactorial as it relates to the number and type of medications and underlying comorbidities. In a recent Japanese study of 396 hospitalized patients with acute hepatitis (142 for DILI), age at least 65 was associated with a higher proportion of patients with DILI (62 vs. 26%, $P < 0.001$) [7]. Age at least 75 was associated with more frequent use of concomitant drugs and a cholestatic injury pattern.

Women are thought to have greater susceptibility to DILI in several previous studies. Fulminant liver failure and liver transplantation due to DILI were more common in women in a recent analysis of the Spanish registry data [8*]. This finding was not corroborated by the DILIN study, which revealed no difference in the proportion of female sex in those with severe (59%) or mild-to-moderate (57%) DILI [3**]. However, the data from both studies appear to suggest an association of age and female sex with the pattern of liver injury. In the DILIN prospective study, compared to mixed and cholestatic pattern of DILI, hepatocellular DILI had lower mean age (mean age 44 years in the hepatocellular group vs. 54 years in two other groups, $P < 0.0001$) and higher proportion of female sex (65% in the hepatocellular group vs. 57 and 50% in other two groups, $P = 0.09$) [3**]. In the Spanish registry, hepatocellular DILI was more common in women under the age of 60 years (1.2-fold increase over men), whereas cholestatic pattern was more common in men over the age of 60 [8*].

Novel findings from the DILIN study indicate that diabetes mellitus and alcohol use were significantly associated with DILI severity [3**]. In a multivariate analysis that included these factors, age, sex, race, duration of drug exposure and pattern of liver injury, the only significant predictors of DILI severity were diabetes mellitus (odds ratio 2.6) and alcohol use in the preceding 12 months (odds ratio 0.33). A protective effect of alcohol was surprising as alcohol use increased the probability score of DILI by a causality algorithm used by this and other recent studies. However, data are relatively scanty to support the inclusion of alcohol consumption as a risk factor in the Roussel Clef Causality Assessment Model (RUCAM) causality instrument [9*].

There has been a recent surge of genetic studies in the field of DILI. The association between *N*-acetyltransferase 2 (NAT-2) genotype and an increased risk for isoniazid hepatotoxicity was noted in a reproducible fashion [10]. A UK genome-wide association study of 51 cases of flucloxacillin-related DILI and 282 matched controls identified human leukocyte antigen (HLA)-B*5701 genotype as a major determinant of flucloxacillin DILI (odds ratio 80.6, $P = 9 \times 10^{-19}$) [11**]. Interestingly this genotype is more common in northern Europe than Asia or Africa (www.allelefrequencies.net/); therefore, race or ethnicity may increase susceptibility to DILI with certain agents, although current data do not allow meaningful epidemiologic analysis.

Causality assessment

In the absence of a 'gold standard' diagnostic test for DILI, causality is established based on the clinical history, chronology of exposure and injury, exclusion of competing etiologies and subjective assessment based on clinical experience and published data wherever available. Causality assessment algorithms have been developed by hepatotoxicity experts to measure the strength of association between suspected DILI and an implicated agent [12]. Validation of such instruments is critical to standardizing their clinical and research application in DILI. The reliability of RUCAM, an instrument used by both the DILIN and the Spanish registry studies, was tested by researchers from DILIN in cases of well defined DILI [13*]. Clinical summaries of 40 selected cases of clinically well defined DILI were reviewed by the enrolling site primary investigator and two external investigators on two occasions at least 5 months apart. Cases were independently scored using RUCAM on both occasions, and the scores were compared for interobserver and test-retest reliability. Enrolling investigator mean RUCAM scores (7.2 ± 0.5) were higher than external investigator scores (6.4 ± 0.5 , $P = 0.007$). Overall interobserver reliability was 0.45 and test-retest reliability was 0.54, whereas test-retest reliability in enrolling site investigators only improved to 0.65. Although these results raise concerns about the validity of this algorithm, analyzing scores by five categories of highly probable (>8), probable (6–8),

possible (3–5), unlikely (1–2) and excluded (≤ 0), improved reliability marginally. At present, there are no superior algorithms, and current studies combine these instruments with opinions of expert panels by design [3^{••},8^{*}]. Modification of existing algorithms or development of novel instruments is needed to establish causality more robustly.

The exclusion of competing etiologies of liver disease is integral to the evaluation of suspected DILI. Interestingly, a small number of patients in the DILIN study were diagnosed with hepatitis C infection, detectable only by RNA in some cases, with no obvious risk factors, emphasizing the need for hepatitis C RNA testing in the course of evaluation [3^{••}].

Drug properties as risk factors for drug-induced liver injury

In general, idiosyncratic DILI is considered to be unpredictable as well as dose-independent [14]. However, it has been suggested that there is dose-dependency for some drugs [15]. It was suggested by Uetrecht [16] that most drugs associated with severe liver injury were prescribed at a daily dose greater than 50 mg, suggesting some dose-dependency at least for severe cases of DILI. This hypothesis that idiosyncratic DILI may have a component of dose-dependency was tested in a recent study [17^{••}]. By using two pharmaceutical databases, the relationship between daily doses of commonly prescribed medications in the United States and reported frequency of their hepatic adverse events was examined. Furthermore, serious DILI cases, that is, DILI with concomitant jaundice reported to Swedish authorities, were examined for any signals supporting the relationship between daily dose and the idiosyncratic DILI, based on patients' data reported in a previous study [18]. Drugs were categorized into the following groups: 10 mg/day or less, 11–49 mg/day and at least 50 mg/day. Among US prescription medications, a statistically significant relationship was observed between daily dose of oral medicines and reports of liver failure, liver transplantation and death caused by DILI but not of alanine aminotransferase (ALT) more than three times upper limit of normal (ULN) or jaundice. Of approximately 600 Swedish cases, only 9% belonged to the 10 mg/day or less group, 14% to the 11–49 mg/day group and almost 80% to the at least 50 mg/day group. Authors reanalyzed the previously reported cases of acute liver failure caused by DILI requiring liver transplantation in the United States [19] and found that 90% of cases belonged to the at least 50 mg/day group. Thus, this study consisting of different datasets supports a relationship between the daily dose of an oral medication and its propensity to cause serious liver injury. The results of this study were recently confirmed by data from the Spanish registry of hepatotoxicity [8^{*}]. Among approximately 600 cases, 77% were receiving daily doses of at least 50 mg/day, which was exactly the same percentage that was found in the Swedish dataset in the study by Lammert *et al.* [17^{••}]. It is unknown whether the classes of agents overrepresented in these two series [e.g., antibacterials and nonsteroidal antiinflammatory drugs (NSAIDs)] are more hepatotoxic because their usual daily dose was at least 50 mg/day or whether the association between daily dose and DILI is driven by the enrichment of these classes of agents in the at least 50 mg/day group.

Regardless, this purported relationship between daily dose and idiosyncratic DILI supports the reactive metabolite theory for the pathogenesis of idiosyncratic DILI. Further support for that hypothesis came from another recently published group by the Indiana group [20^{••}]. This study examined the relationship between hepatic metabolism of oral medications and idiosyncratic DILI. By using two pharmaceutical databases, the metabolism characteristics of approximately 200 most prescribed drugs in the United States were analyzed. Compounds with more than 50% hepatic metabolism were characterized as those with significant hepatic metabolism. Compared with compounds with lesser hepatic metabolism, compounds belonging to the significant metabolism group had significantly higher frequency of ALT more than three times ULN, liver failure and fatal DILI but not of jaundice or liver

transplantation. Twelve compounds with no hepatic metabolism had no reports of liver failure, liver transplantation or fatal DILI. Compared with drugs without biliary excretion, compounds with biliary excretion had significantly higher frequency of jaundice. Furthermore, an additive effect of daily dose and hepatic metabolism was observed. Thus, compounds with more than 50% hepatic metabolism and also given at a dose of more than 50 mg/day had the highest risk of hepatotoxicity compared with other groups. Although this study is a database study, with retrospective collection data with several limitations, its results are of importance. Supporting data for the reactive metabolite have been limited and if reproduced by others might facilitate the development of safer medications.

More recently, Suzuki *et al.* [21] found that certain coadministered medications may adversely influence the outcome of acetaminophen-associated liver injury. Data from more than 6000 cases with acetaminophen-induced liver injury and fatal vs. nonfatal cases were compared with a particular focus on concomitant use of nine drug classes using multiple regression analyses. Among female patients, concomitant use of statins, fibrates or NSAIDs was associated with decreased likelihood of fatality, whereas concomitant alcohol use increased the risk of fatality. In men, concomitant use of statins was associated with decreased likelihood, whereas use of sympathetic stimulants or alcohol was associated with increased likelihood. Thus, this study supports the notion observed in numerous experimental studies that net tissue damage is determined by the balance between injury and repair.

Clinical course and natural history

In the vast majority of DILI patients who survive the initial liver injury, biochemical and histological recovery is complete, but a small proportion of patients may develop chronic liver disease (chronic DILI). In the first study investigating the natural history of DILI, a high proportion of patients with persistent abnormalities were found, but these patients were identified through a histological database, indicating a selection bias [22]. A prospective follow-up of DILI patients registered in the Spanish hepatotoxicity registry revealed a 5.7% incidence of chronic DILI [23]. Recently, 6 months after enrollment in the prospective DILIN study, 14% of patients had persistent laboratory abnormalities [3**].

However, whether these patients or other patients reported to have chronic DILI will experience liver-related morbidity or mortality is not clear. A recent follow-up study of DILI patients from Sweden with a mean follow-up of 10 years revealed that development of a clinically important liver disease after severe DILI (all had jaundice initially) was very rare [24*]. A total of 23 of 685 DILI patients who had survived acute DILI were hospitalized for liver disease during the study period and five had liver-related mortality [24*]. Among these patients, five out of eight did not have an identifiable cause of cirrhosis, in which DILI might have played a role for this development. A significantly longer duration of drug treatment before the diagnosis of DILI was significantly more common in patients who experienced liver-related morbidity and mortality than in those who did not.

All available data indicate that continuing medication after DILI onset is ominous. Thus, prompt recognition of DILI and cessation of therapy is not only important to decrease the risk for acute liver injury but may also avoid chronic consequences of DILI.

Brinker *et al.* [25*] reported the clinical characteristics of patients with suspected telithromycin-induced hepatotoxicity. Out of 42 patients retrieved, five had a severe outcome such as death or liver transplantation. Typical clinical features were very short latency (median 10 days) and abrupt onset of fever, abdominal pain, jaundice and sometimes ascites even in cases that resolved. The range of onset or signs of the liver injury was 2–43 days. Interestingly, among seven patients with latency of 3 days or less ($n = 4$ at 2 days; $n =$

3 at 3 days), only one patient reported previous exposure to telithromycin. Unusually short latency period after initiation of treatment with this drug, as brief as 1–2 days, makes this series very intriguing. Idiosyncratic DILI develops rarely so rapidly. However, other drugs with this ‘signature’ of remarkable short latency include fluoroquinolones that may also have 1–2 days of latency period [26].

The management of suspected idiosyncratic DILI includes exclusion of competing etiology, prompt cessation of the suspected agent(s) and appropriate supportive care. In rare instances of fulminant liver failure or severe cholestatic injury caused by DILI, orthotopic liver transplantation can be life-saving. The US Acute Liver Failure Study Group recently reported the result of their experience with intravenous *N*-acetylcysteine (NAC) to treat acute liver failure caused by causes other than acetaminophen. In this prospective, double-blind trial, patients with acute liver failure (nonacetaminophen) were randomized to receive NAC or placebo infusion for 72 h [27^{**}]. Acute liver failure caused by DILI ($n = 45$) represented the single largest group among 173 patients who were randomized. Although the overall survival at 3 weeks was not significantly different between the groups, the transplant-free survival was significantly better among those patients randomized to NAC (40 vs. 27%, $P = 0.043$). The benefits of NAC were primarily seen in patients with early course of the disease with coma grade I–II (52 vs. 30% transplant-free survival) but not in those with advanced coma grade (III–IV) at randomization. When the overall and transplant-free survival of the four largest etiologic groups was considered, patients with DILI and hepatitis B virus (HBV) showed improved outcome in comparison with the AIH and indeterminate groups. In the DILI patients, transplant-free survival was 58% for those receiving NAC compared with 27% for those receiving placebo. Therefore, this study suggests that therapy with intravenous NAC should be considered in patients with acute liver failure due to idiosyncratic DILI.

Conclusion

Though rare, DILI must be considered in all patients with abnormal liver functions. Recent data highlight antibiotics, central nervous system agents, herbal/dietary supplements and immunomodulatory agents as the most common causes of DILI in the United States. Hepatocellular injury patterns are more common in younger patients and cholestatic patterns in older patients. An association between certain HLA genotypes and risk of flucloxacillin-related DILI has been established. The limitations of current instruments to measure causality in DILI may be minimized by the use of expert panel opinions, while efforts are underway to establish reliable biomarkers of DILI. Idiosyncratic DILI was shown to be dependent on both the daily dose and the extent of the hepatic metabolism of drug. Although chronic DILI may occur, the development of clinically important liver disease after severe DILI is rare. NAC seems to be beneficial for patients with acute liver failure caused by medications or herbal agents.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 290–291).

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INFORME DE BÚSQUEDA DE PATENTES PARA EL No de Radicación: 14-27709						
CRITERIOS PARA LA BÚSQUEDA (anexar pantallazo o reporte en PDF, junto con los booleanos utilizados)						
Palabras clave utilizadas		NAC; N-acetil-cysteine; N-acetylcysteine; nimesulide and acetylcysteine; nimesulide antidote; nimesulide poisoning treatment				
CLASIFICACIONES INTERNACIONALES UTILIZADAS PARA LA BÚSQUEDA		A61K31/4738, C07D491/22				
BASES DE DATOS CONSULTADAS.						
ESPACENET		Patbase				
uspto		Patentfamily (SIP)				
COLOMBIANA		Google				
Patent scope						
INFORMES DE EXÁMENES REALIZADOS EN OTRAS OFICINAS (documentos patentes, literatura no patente etc...)						
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					SI	NO
EUROPEA	11-02-2014	WO9847534	1 – 11	Nivel Inventivo	x	
		Curr Opin Gastroenterol. 2010 May ; 26(3): 222–226.	1 – 11	Nivel inventivo	x	
DOCUMENTOS ADICIONALES ENCONTRADOS POR EL EXAMINADOR DE ACUERDO A LOS CRITERIOS DE BÚSQUEDA.						
US20030119909						
Drug Saf. 2002;25(9):633-48. Mechanisms of NSAID-induced hepatotoxicity: focus on nimesulide.						
Observaciones						
Fecha del reporte de búsqueda:						

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Rank	CC	DocNo	Title	Filed	Applicant	Inventor
1	US	2010226943	SURFACE TOPOGRAPHIES FOR NON-TOXIC BIOADHESION CONTROL ...nimesulide, nimetazepam, nimidane, nimodipine, nimorazol.....acetylcysteine, acetyldigitoxin, acetylleucine, acetyltributy...	2009-08-31	univ florida	long christopher james
2	US	8758816	Compositions Comprising Azelastine and Methods of Use Thereof ...nimesulide. 26. The composition of matter of clai.....acetylcysteine and domase alpha. 28. The composition o.....nimesulide. 61. The unit dosage form of claim 4.....acetylcysteine and domase alpha. 63. The unit dosage for.....nimesulide. 94. The method of claim 81, wherei...	2009-09-29	fuge dennis	fuge dennis
3	US	2010087455	SUBSTITUTED XANTHINE COMPOUNDS ...nimesulide, oxyphenbutazone, parecoxib, phenylbutazon.....acetylcysteine, bromhexine, carbocisteine, eprazinone, mesn...	2009-10-06	auspex pharmaceuticals inc	gant thomas g
4	US	2010016262	Compositions and methods for reducing hepatotoxicity associated with drug administration and treating non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and associated cirrhosis ...nimesulide, nefazodone, ximelagatran, citalopram (Celex.....acetylcysteine, amantadine, lamictal, acamprosate, memantin.....nimesulide, nefazodone, ximelagatran, citalopram (Celex.....acetylcysteine, amantadine, lamictal, acamprosate, memantin...	2009-06-30	univ yale	mehal wajahat
5	US	2009292021	ANTICONVULSIVE PHARMACEUTICAL COMPOSITIONS ...nimesulide. 21. The pharmaceutical composition accordin.....acetylcysteine, alpha-lipoic acid, Resveratrol, ramelteon, agomelati...	2007-07-31	inst nat sante rech med	simonutti manuel
6	WO	9531194	COMPOSITIONS FOR TREATMENT OF CHRONIC INFLAMMATORY DISEASES ...nimesulide; oxamethacin; oxaprozin; suxibuzone; piroprof.....acetylcysteine; dexamethasone; indomethacin; prednisolone, a.....nimesulide; oxamethacin; piroprofen; pnenazone; sulinda.....acetylcysteine; dexamethasone, as well as pharmaceutically acceptabl.....nimesulide; oxamethacin; piroprofen; proquazone; sulinda...	1995-05-11	shapiro howard k	shapiro howard k
7	WO	9966919	PHARMACEUTICAL COMPOSITION CONTAINING A SALT OF ACETAMINOPHEN AND AT LEAST ONE OTHER ACTIVE INGREDIENT	1999-06-09	mcneil ppc inc	ohannesian lena a

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1) Family number: 23695873 (US2005090553A) Similar Translate Full-text Status Citations

Title: [EN] Compositions and method for treatment of chronic inflammatory diseases

Abstract: Source: US2005090553A [EN] This invention defines novel compositions that can be used for clinical treatment of a class of chronic inflammatory diseases. Increased generation of carbonyl substances, namely aldehydes and ketones, occurs at sites of chronic inflammation and is common to the etiologies of all of the clinical disorders addressed herein. Such carbonyl substances are cytotoxic and additionally serve to perpetuate and disseminate the inflammatory process. This invention defines use of compositions, the orally administered required primary agents of which are primary amine derivatives of benzoic acid capable of covalently reacting with the carbonyl substances. p-Aminobenzoic acid (or PABA) is an example of the required primary agent of the present invention. PABA has a small molecular weight, is water soluble, has a primary amine group which reacts with carbonyl-containing substances and is tolerated by the body in relatively high dosages for extended periods. The method of the present invention includes administration of a composition comprising: (1) an orally consumed therapeutically effective amount of at least one required primary agent; (2) at least one required previously known medicament co-agent recognized as effective to treat a chronic inflammatory disease addressed herein administered to the mammalian subject via the oral route, other systemic routes of administration or via the topical route; and (3) optionally one or more additional orally consumed co-agent selected from the group consisting of antioxidants, vitamins, metabolites at risk of depletion, sulfhydryl co-agents, co-agents which may facilitate glutathione activity and nonabsorbable primary amine polymeric co-agents, so as to produce an additive or synergistic physiological effect of an anti-inflammatory nature.

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International (IPC): A01N37/10 A01N37/12 A01N37/44 A61K31/00 A61K31/13 A61K31/19 A61K31/195 A61K31/196 A61K31/74 A61K31/785 A61K45/06 A61K45/08 A61K9/48 A61P29/00 C07C229/00
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1	WO	9531194	COMPOSITIONS FOR TREATMENT OF CHRONIC INFLAMMATORY DISEASES ...nimesulid.....acety.....cystein.....nimesulid.....acety...	1995-05-11	shapiro howard k	shapiro howard k
2	CA	2190107	COMPOSITIONS FOR TREATMENT OF CHRONIC INFLAMMATORY DISEASES	1995-05-11	shapiro howard k	shapiro, howard k.
3	AU	698881	Compositions for treatment of chronic inflammatory diseases ...nimesulid.....acety.....cystein.....nimesulid.....acety...	1995-05-11	shapiro howard k	howard k. shapiro
4	WO	9904758	A PROCESS FOR THE PREPARATION OF A GRANULATE SUITABLE TO THE PREPARATION OF RAPIDLY DISINTEGRABLE MOUTH-SOLUBLE TABLETS ...Acety.....Nimesulid.....cystein.....Nimesulid.....Acety...	1998-07-20	bonadeo danielle	pagano, alberto
5	EP	1001748	A PROCESS FOR THE PREPARATION OF A GRANULATE SUITABLE TO THE PREPARATION OF RAPIDLY DISINTEGRABLE MOUTH-SOLUBLE TABLETS ...Acety.....Nimesulid.....cystein.....Nimesulid.....Acety...	1998-07-20	alpex pharma sa	pagano alberto
6	US	6149938	Process for the preparation of a granulate suitable to the preparation of rapidly disintegrable mouth-soluble tablets and compositions obtained thereby ...Acety.....Nimesulid.....cystein.....Nimesulid.....Acety...	1998-07-23	elan pharma int ltd	pagano alberto
7	US	2006128676	Compositions of nicotinic agonists and therapeutic agents and methods for treating or preventing diseases or pain ...acety.....nimesulid.....cystein.....Nimesulid.....acety...	2005-07-13	pharmacofore inc	shafer steven l
8	WO	2004098538	NITROSATED AND NITROSYLATED COMPOUNDS, COMPOSITIONS AND METHODS OF USE ...nimesulid.....acety.....cystein.....cystein.....Cystein...	2004-03-15	stevenson cheri a	stevenson cheri a

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Drug-induced liver disease
S Chitturi, GC Farrell - Current treatment options in gastroenterology, 2000 - Springer
... Nimesulide Arthritis ALF [11 ... N-acetylcysteine Standard dosage Intravenous: N-acetylcysteine (Parvolex; David Bull Laboratories, Victoria, Australia) 150 mL/kg in 200 mL 5% dextrose solution over 15 minutes, followed by 50 ... Contraindications Known sensitivity to acetylcysteine. ... Citado por 62 Artículos relacionados Las 5 versiones Citar Guardar

Drug-induced hepatotoxicity
DN Juurlink - N Engl J Med, 2003 - Mass Medical Soc
... 2. Prescott LF, Illingworth RN, Critchley JA, Stewart MJ, Adam RD, Proudfoot AT. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. ... 3. Andrade RJ, Lucena MJ, Fernández MC, González M. Fatal hep- atitis associated with nimesulide. ... Citado por 28 Artículos relacionados Las 6 versiones Citar Guardar

[crtas] Severe hemolytic anemia and fatal hepatic failure associated with nimesulide
AP Betrosian, K Flevari, I Andrianakis... - Digestive and Liver ..., 2009 - WB Saunders
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[HTML] Transplantation for acute liver failure in patients exposed to NSAIDs or Paracetamol (Acetaminophen)
SE Gulmez, D Larrey, GP Pageaux, S Lignot... - Drug safety, 2013 - Springer
... CrossRef, Traversa G, Bianchi C, Da Cas R, Abraha I, Menniti-Ippolito F, Venegoni M. Cohort study of hepatotoxicity associated with nimesulide and other non ... Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. ... Citado por 26 Artículos relacionados Las 13 versiones Citar Guardar

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Antidotal Efficacy of a New Combination in Treatment of Subacute T-2 Toxin Poisoning in Rats
VM Jacevic, AS Bocarov-Stancic, RD Resanovic... - 2007 - iaea.org
... properties (significant persistence in the environment, cheap manufacture, difficult detection and absence of a specific **antidote**) that make it ... In our previous experiments, nonsteroidal anti-inflammatory drug (NSAID) **nimesulide** (NIM), as a selective COX-2 inhibitor, and ... **antidotes** ...
Las 2 versiones Citar Guardar Más

Acute organophosphate poisonings: therapeutic dilemmas and new potential therapeutic agents
S Vucinic, D Jovanovic, Z Vucinic, V Todorovic, Z Segrt - 2007 - iaea.org
... **antidotes**. T2 was given in a dose of 0.15 mg/kg sc (0.1 LD50), 5 times per week, 4 weeks to adult Wistar rats. ... These results imply that combined treatment with **nimesulide** and zeolite absorbent affords a significant protection against subacute T-2 toxin poisoning in rats. ...
Citado por 3 Artículos relacionados Las 2 versiones Citar Guardar Más

Bosnia and Herzegovina and Croatia: the medicalisation of the experience of war
M Bergovec, I Vasilj - The Lancet, 1999 - thelancet.com
... worlds. Mental-health models have never really acknowledged the role of social engagement (including work) as an **antidote** to mental ill-health. ... Wien Med Wochenschr 1992; 142: 430-33. **Nimesulide** and COX - 2 inhibito rs S ...
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IPNRI Radiological Dispersal Polonium-210 and Lessons for Public Health
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... study of fetal side effects during and after the short-term maternal administration of indomethacin, sulindac, and **nimesulide** for the **treatment** of preterm labor
RJ Sawdy, S Lye, NM Fisk, PR Bennett - American journal of obstetrics and ... 2003 - Elsevier
... effects after long-term maternal **nimesulide** **ingestion** and the established renal toxic effects of indomethacin **ingestion**. 12 and 20 After our initial case report of no major renal effects after long-term **nimesulide** **treatment**, we have reported a series of 44 similarly **treated** cases. ...
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Neonatal end-stage renal failure associated with maternal **ingestion** of cyclo-oxygenase-type-1 selective inhibitor **nimesulide** as tocolytic
L Peruzzi, B Gianoglio, MG Porcellini, R Coppo - The Lancet, 1999 - Elsevier
... case of neonatal irreversible end-stage renal failure after maternal **ingestion** of **nimesulide** ... 32nd week she had sudden onset of oligohydramnios persisting after discontinuation of **nimesulide**. ... for the persistence of oligoanuria and to start automated peritoneal dialysis **treatment**. ...
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Nimesulide in the **treatment** of patients intolerant of aspirin and other NSAIDs
GE Senna, G Passalacqua, G Andri, AR Dama... - Drug Safety, 1996 - Springer
... Bronchospasm generally develops 30 to 45 minutes after **ingestion** and may be accompanied by systemic adverse effects, ie ... **Nimesulide** in Patients Intolerant of NSAIDs ... card/allergist's evaluation) than terfenadine alone, over a 1-month **treatment** period.[72] On the other hand ...
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Antipyretic and anti-inflammatory efficacy of **nimesulide** vs paracetamol in the symptomatic **treatment** of acute respiratory infections in children

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