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Seæor

SUPERINTENDENTE DE INDUSTRIA V COMER(DIVISION DE NUEVAS CREACIONES
E. S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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No. 06-038134- -00005-0000
Fecha: 2009-11-24 16:53:20 Dep. 2020 DIR.NUEVASCR

TM. 11 PATENTEIYII Eve: 379 FASENACIONALII Act. 444 RESPUESTAREQUE Folios: 33

Re: P1.-WYETH.-Solicitud de Patente de Invenclón en Fase Nacional PCT łara "FORMULACIONES DE MULTIPARTICULADOS DE PANTOPRAZOL".-
Clase A61K 9/16.-ExDediente nimero 06-038.1.34.-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista del 6 de
Marzo de 2009, asI como a ml solicitud de plazo del 29 de Mayo del mismo aæo para dar respuesta al auto antes mencionado.

2. Con el fin de de responder a las objeciones expuestas por el seæor Examinadoren
el Concepto TØcnico No. 2832 en relación con la Claridad de las Reivindicaciones y el requlsito de Novedad, me permito dirigir su atención a las siguientes modificaciones al capItulo reivindlcatorio y a los siguientes argumentos tØcnlcos, por medio de las cuales no solo se superan dichas objeclones, sino que ademªs se demuestra en forma contundente la patentabilidad de la presente invención.

3. CLARIDAD DE LAS REIVINDICACIONES:

El seæor Examinador ha manifestado en su Concepto TØcnico que el capItulo reivindicatorio actualmente presentado no cumple con el requisito de Claridad exigido en el ArtIculo 30 de la Decision Andina 486, toda vez que:

(I) "El encabezado de la reivindicación 1 incluye tØrminos que evocan el resultado..., toda vez que con el diseæo del s/sternade entrega farmacØutico
se pretende disminuir la velocidad de jiberación del fÆrrnaco cuando se encuentra bajo las condiciones del pH gÆstrico y alcanzar una mayor aceleración cuando la forrnulación se encuentra sometida a pH neutro. Por lo anterior, se recornienda al seæor solicitante ellrninar del alcance de su invención las expresiones en cornento".

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Sobre este particular, me permito manifestar que el solicitante ha decidido eliminar la expresión "que tienen Iiberación reducida bajo condiciones gÆstricas y Iiberación rÆpida a pH neutro" del preÆmbulo de la reivindicación 1 actualmente presentada, acogiendo la sugerencia del senor Examinador y superando asI Ia observación expuesta al respecto en su Concepto TØcnico.

(ii) "Por otra parte, expresiones como revestimiento de sello inicial, no cuentan con el rigor tØcnico requerido para definir una primera capa de recubrirniento, por Jo que se recornienda definir las caracteristicas de los multiparticulados... Lo anterior, porque en virtud del contenido de las reivindicaclones pubJicadas en la so/icitud internacional W02005/032513 resulta evidente que la traducción del segundo cornponente de la formulación no es rigurosa, por /0 que se modifica eJ significado tØcnico de las caracterIsticas intrInsecas de la forrnu/ación".

En relación con las anteriores objeciones, el solicitante se permite hacer notar que la reivindicación 1 original no seæalaba el revestimiento de sello inicial y que el lenguaje presentado en la actual reivindicación 1 es consistente con la reivindicación 5 del documento sobre el cual se reivindica prioridad, la cual no definIa los componentes especIficos de este revestimiento inicial.

No obstante lo anterior, y nuevamente acogiendo las sugerencias realizadas por el senor Examinador, el solicitante ha modificado la reivindicación con el fin de seæalar ahora que el revestimiento se sello inicial estÆ comprendido especificamente por hidroximetilpropilcelulosa (hipromelosa), cuyo sustento se puede encontrar tanto en la reivindicación 22 actualmente presentada, como en diversos apartes a to largo de la memoria descriptiva, como por ejemplo en las pÆginas 6 y10 de la descripción.

De conformidad con esta modificación, se ha eliminado la reivindicación 22 del capItulo reivindicatorio actualmente presentado.

De igual forma, me permito dirigir la atención del senor Examinador al hecho de que el solicitante, acogiendo las recomendaciones realizadas en el Concepto TØcnico No. 2832 en relación con la claridad de las reivindicaciones, ha decidido modificar la reivindicación 1 adicionalmente con el fin de definir que el revestimiento entØrico que va sobre el revestimiento de sello inicial comprende un copolImero de Æcido metacrilicoy metacrilatos.

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El sustento para esta limitación se puede encontrar tanto en la reivindicaclón 17 actualmente presentada como en la pÆgina 11de la solicitud.

De conformidad con lo anterior, es claro que mediante las modificaciones seæaladasel solicitante ha dado plena respuesta a las observaciones que al respecto fueron planteadas por el seæorExaminador en su Concepto TØcnico
No. 2832, superando así tales objeciones y proporcionando mayor claridad sobre el objeto que se desea proteger.

(iii) "Con re/ac/on al contenido de la reivindicaciOn 31 es preciso seæalarque Un envase corresponde a una forma de presentaciOn comercial, por 10 que sus caracterIsticas esenciales no forman parte del concepto inventivo que agrupa
al particulado de pantoprazoL.., por /0 que esta forma de presentación
comercial debe ser eliminada del contenido de las reivindicaciones".

Frente a esta ültima objeción, me permito manifestar que el solicitante ha decidido eliminar la mencionada reivindicación 31, tal como fue solicitado por el seæor Examinador, superando asI dicha observación.

De conformidad con las modificaciones mencionadas, me permito seæalar que el capitulo reivindicatorio se encuentra conformado ahora por 37 reivindicaciones correspondlentes a las reivindicaciones 1 a 21, 23 a 30 y 32 a 39 actualmente presentadas, en las que se han realizado los debidos cambios en numeración y dependencia de acuerdo con las cancelaciones realizadas.

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Finalmente, me permito manifestar al seæor Examinador que las modificaciones realizadas no amplIan el alcance de protección iniclalmente solicitado, toda vez que las mismas corresponden a limitaciones significativas sobre las definiciones que conforman al objeto reclamado en la presente solicitud, realizadas precisamente con el fin de dar respuesta a las objeciones de claridad ya mencionadas.

Por todo lo anterior, resulta correcto afirmar que el capItulo relvindicatorio ahora presentado cumple a cabalidad con las disposiciones contenidas en el artIculo 30 de la Decision Andina 486, superando asI cualquier observación que tuviera como fundamento una falta al requisito de claridad aill
definido.

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Ahora bien, de conformidad con las objeciones expuestas en el Concepto TØcnico
No. 2832, el seæor Examinadorha considerado que el objeto de la presente invención carece de Novedad con base en las enseæanzasde los documentos WO 96/01624 (Dl) y US 6159499 (D2), toda vez que:

(I) "La publicación Dl revela una preparación farrnacØutica de un multiparticulado constituido por nÆcleos de un inhibidorde la ATPasa
presentes en la forma de partkulas, grØnulos o pellets. La sustancia activa
puede ser rnezclada con otros componente como aglutinantes, surfactantes,...

Los nOcleos presentan una capa de recubrimiento insoluble en agua que cornprende óxidos, celulosas, polIrneros orgÆnicos, ademÆs presentanuna de recubrimiento entØrico constituido por una capa inicial que separa la capa de recubrimiento insoluble de la capa de recubrimiento enter/co... Esta capa intermedia funciona como una barrera de difusión o buffer que actÆa de acuerdo con el pH de la zona donde se pretende la liberación del activo.

La capa final del recubrimiento entØrico corresponde a una solución o dispersion de un copolIrnero de Æcido metacrIllco,...

Los ntcleos pueden ser fabricados por extrusiOn / esferonizaciOn o compresiOn";

(ii) "La publicaciOn D2 revela una cornposición adaptada para administración oral que comprende: a) un nOcleo que contiene un bencirnidazol como ingrediente activo en la forma de una sal b) una capa interrnedia c) una capa
de recubrimiento entØrico.

Los ejemplos 6 a 8 seæalan preparacionesfarmacØuticas de pantoprazol para administraciOn oral";

(iii) "Al comparar elemento por elemento de las composiciones reivindicadas con los antecedentes tØcnicos relacionados en el estado del arte Ave posible establecer que cada uno de ellos de rnanera independiente anticipa las caracterIsticas de los microparticulados de pantoprazol que contienen nücleos esferoidales con una capa de recubrimiento y con cubierta enter/ca";

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(iv) "Por otra parte, el mØtodo para la fabricación de las composiciones seIalado
en la reivindicación 32 que comprende la aplicación de las tØcnicas de extrusion y esferonización tarnbiØn se encuentra anticipado en el docurnento

Dl".

Antes de presentar los argumentos tØcnicos que permiten demostrar la novedad y
el nivel inventivo tanto de los multiparticulados de pantoprazol, como del proceso para la obterición de dichos multiparticulados tal como han sido revelados en la presente solicitud, me permito dirigir la atención del seæor Examinador aalgunas consideraciones previas acerca del problema abordado por el solicitante y la solución dada al mismo.

En primer lugar, es bien sabido que las formulaciones orales comerciales actuales
de pantoprazol sódlco corresponden a tabletas revestidas unitarias individuales, que consisten de un nücleo, una capa intermedia y una capa exterior. Sin embargo, se reconocetamb.Øn pue el revestimiento actual tiene la tendencla de orovocar
una adhesividad Indeseable de la tableta all tracto gastrointestinal, dificultando
asI el proceso de traaado de dicha formulación en Daclentes con dificultades

para enaullir y en pacientes pediÆtricos,principalmente. J Prt,bltM c
De igual forma, se conocen varlos intentos no exitosos para desarrollar una formulación de multiparticulados de pantoprazol, que produjeron multiparticulados que
no eran bioequivalentes a las tabletas, encontrÆndose ónicamente un 70% de biodisponibilidad relativa. Otro intento usando diferentes tecnologIas, tales como revestimiento con semilla granulada y extrusión/esferoriización, dlo como resultado un producto que no proporciona la liberación apropiada en condiciones Æcidas. AdemÆs, estos intentos produjeron un producto que era inestable, tal como pudo observarse por la decoloración que se presentó cuando se almacenó a temperatura amblente.

Con el fin de satisfacer la necesidad de una formulación estable de multiparticulados de pantoprazol, el solicitante de la presenteinvenciónhadesarroIlad una for iKIcrn de multipart adcompuestos de un nücleo esferoideque comprende pantoprazol o un enantiómero del mismo, o una sal o hidrato del mismo, al menos un agente tensioactivo, al menos un desintegrante, y aproximadamente l% a aproximadamente 2% p/p de agua; un revestimiento entØrico en el nücleo que comprende un copolimero de addo metacrthcoy metacnlatosenellntervalode aproximadamente 15 a aproximadamente 45% p/p del nucleo esferoide, y un revestimiento de seHo inucual que
nuicleo y el revestimiento entØruco, en dondear

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un diÆmetro en el rango de 0.7 a 1.25 mm, y presentan las siguientes ventajas t’’ as:

) Vkeo

(i) La formulación de multiparticulados de pantoprazol de la invención es menos
propensa a adherirse a las paredes intestinales, tubos nasogÆstricos y

predecible del producto fârmaco al sitio de liberación de fÆrmaco;

(ii) TambiØn proporciona un inicio mÆs temprano de la acción para el alivio de
dolor gastróTntestinai y tiene una duradóndeasolda (liberacionextendida)que laformuiacióncomerciaientableta;

(iii) Esta formulación permite la dosificación a pacientes pediÆtricos y pacientes
quetenen dif’icultad para engullir alimentos sólidos; y

iv) Esta formulación tamblØn permite la administración del fÆrmaco mediante
tubos nasogÆstricosy de gastrostomia.

Adicionalmente, la invención proporciona un proceso que emplea u-n bajo esfuerzo cortante durante la granulación y una baja temperatura durante el secado para la preparación del multiparticulado con elfin de retener una cantidad de agua (humedad) especIfica, de forma tal que el proceso contribuye a la estabilidad del nücleo de los multiparticulados de la invención.

Finalmente, vale la pena mencionar que las formuladonesde multiparticulados de
la invención son, en forma ventajosa, estables bajo condiciones de almacenamiento a temperatura ambientºdurante al menos doce meses. En base al anÆlisls detendencias usando los datos a temperatura ambiente durante doce meses y los datos a 40°C/75% de humedad relativa (RH) durante 6 meses, disponibles a la fecha, los multiparticulados de Ia unvenondebentenerunavida enanaqueidurantemasde2anos.

En resumen, la formulación multiparticulada reivindicada proporciona una padentes que tnenthficuItades para tragarla
forrnulación -n tableta cornercial del producto Protonix. La formulación multiparticulada proporcionada es estable y bioequivalente a Ia tableta comercial, al mismo tiempo que proporciona un tiempo de retraso mÆs pequeæo parael comienzo de la acción y un intervalo rnâs prologando para la Iiberaclón comparada con1i table

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Para alcanzar tales beneficios, losmicroparticulados de pantoprazol del solicitante deben tener un rango de tamaæo especIfico y contener altas cantidades de tensioactivo en el nücleo. Ninguna de estas caracterIsticas ha sido enseæada o sugerida en los documentos citados como estado de la tecnica. En este sentido, el rango de 0,7 a 1,25 mm de diÆmetro no ha sido simplemente seleccionado de un rango mÆs amplio previamente descrito en el estado del arte previo. Los microparticulados del tamaæo reivindicado son crIticospara lograr la liberación eficiente
de los microparticuladosde la invención, por ejemplo, a travØs de un tubo nasogâstrico.

i9 rrwJo ihvj’Ie
El documento Dl se enfoca en una forma de dosJJción tableteada de unidades
mCiltiples, en cada uno de sus ejemplos de trab jo describe el recubrimiento a el

rociado del componente activo sobre una milla Adicionalmente, Dl enseæa la L r ilo compresión de sus "pellets" dentro de una tableta. Este no es un elemento de
la ilIivin uida en Ia esentesollcitud:1S1 no contiene enseæanzasde 230

pantoprazolsódico o un hidrato_del mismo, asI como tampoco hay enseiianza o ck.p.. Dj.
sugerencia alguna acerca del_sesquihidrato, pantoprazol.dIcico. Igualmente, en la FoliO
referenda citada se describe una amplia variedad de posibles_excipientespara la formulación en tableta allI revelada, pero no se proporciona alauna enseæanza () Q
acerca de aspectos crIticos a tener en cuenta Para la selección de tales OLAH
excipientes.

1’ho 2-86y23O-.
Por el contrario, tal como se ha mencionado en la pÆgina 7 de la memoria
descriptiva de la presente solicitud, los agentes tensioactivos "particularmente deseables son lauril-sulfato desodio, polisorbatos, inc/uyendo, por ejemplo, polisorbato
80, met as eestoscnrnponentec..j1pjcmente, elagente tensioactivo estÆ presente en el nócieo en una cantidad de aproximadamente 2 a aproximadamente 7% pIp, de manera deseable, aproximadamente 5% p/p del nócleo. En otra modalidad, ci agente tensloactivo se presenta en una relación de aproximadamente fÆrmaco:agentetensloactivo 5:3 (por ejemplo, sesquihidrato de pantoprazol sÆdico a lauril-sulfato de sod/a) a aproximadamente fÆrmaco:agente tensioactivo 10:1 (por ejemplo, sesquihidrato de pantoprazol sódico a polisorbato 80).
De manera ventajosa, se ha encontrado que los agentes tensloactivos en la formulación de muitiparticulados meloran la capacidad de humectaclón vde
esta manera. la veiocidªVºUprado dØ7t iachinyabsorción del iantonrazoI0
sódico de la formulación de multiarticulados de la invenclón" (resaltado fuera
de texto).

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De conformidad con lo anterior, es completamente claro que la--NQKedad de la formulación de multiparticulados de la presente solicitud no puede verse afectada por las enseæanzas generales de una referencia como Dl, que si bien seæalauna formUiädoue comprende un nücleo conformado por pellets, una capa de separación y un recubrimiento entØrico adecuada para ser comprimida en forma de tableta, de ninguna forma revela una formulación de micropa rticulados que estØ definida por Dresentar las sipuientes caracterIsticas tØcnicas simultÆneamente:

(i) Un nicleo esferoide que comprende pantoprazol o Un enantiómero del
mismo, o una sal o hidrato del mismo y un tensioactivo o una combinación
de tensioactivos presentes en una relación en peso de pantoprazol:tensioactivo(en una relacil6n en
peso de tensioactivo(SVªi6cleode2%a7%;

(ii) Un revestimiento de sello inicial sobre el nCicleo esferoide gue comrende hidroxipropilmetilcelulosa;

(iii) Un revestimiento entØrico pue comrende un copolimero de Æcido
metacrIlico y metacrilatos sobre el revestimiento de seflo inicial; y

(iv) Un diÆmetropara los multiparticulados revestidos en el ranao de 0.7

a 1.25 mm.

De conformidad con lo anterior, es completamente claro que no existe en el documento Dl ninguna anticipación claray directa de una formulacionde multiparticulados pue presente las cuatro caracterIsticas tØcnicas arriba meiicionadas,porlocualse puede afirmar sin dudaalgunaque el objeto de la presente invención si cumple con las disposiciones del Articulo 16 de la Decision Andina
486 frente a las enseæanzas dedicha referencia.

Por su parte, el documento D2 describe formulaciones q.tienennÆcIeos

C?) preparación de formulaciones que contienen un Æcido de bencimidazol lthbil por medio de Ia compresión del Ingrediente activo sobre un nücleo inerte para formar un

/ n6cleo que exento de compuestosreaosalca!inosyfæffit&.Et’eo" puede posteriormente ser recubuerto.

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Sobre este particular, me permito manifestar que en el caso de la referenda D2, dicho documento no solo no revela las caracterIsticas tØcnlcas ya seæaladasen el anÆlisis inmediatamente anterior para Dl, sino que ademÆs presenta una caracterIstica tØcnica fundamental para las composiciones allI enseæadasque no es considerada de ninguna forma por el solicitante de la presente invención, como lo es la presencia de un nücleo inerte indispensable para la cieneración
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del nücleo final gue Incorpore all aaente activo.

Por lo tanto, es posible afirmar que las enseæanzas de D2 tampoco pueden ser calificadas como suficientes para desvirtuar Ia Novedad de la formulación de multiparticulados de la presente invención, toda vez que existen claras diferencias tØcnicas entre ambas copostcIGnes_queJpldenelgrado de equivalencia necesario y requerido para obetardqijoconfirmandoasi que las formulaciones
multupartuctadasdela_rnvencuon en estudio efectwamentecumle con las
disposiciones del ArtIculo 16 de la Decision 486.

Ahora bien, en relación con las relvindicaciones de mØtodo, resulta importante
seæalar que el nCicleoesfØrico de la presente invenciOn se prepara mediante mezclado,
seguido por extrusion y esferonización, de forma t que l nücleo proporcionado por la C? invención contiene un componente activo especIfico uniformemente dispersado y un
tensioactivo en las proporciones particulares establecidas. El nücleo de la formulación reivindicada no contiene un princiDlo activo recubierto sobre un
material inerte. IV I/I 1 i i Ci (tL’C)f
- PoitOOty 102
En efecto, tal como se ha seæalado en las pØginas 14 a 16 de la memoria
descriptiva, los compuestos de pantoprazol no revestidos se preparan como sigue. Los

componentes secos, incluyendo al menosel compuesto de pantoprazol y el aglutinante, L.
se mezclan en seco en un mezclador adecuado baio condiciones de balo
esfuerzo cortante. Las condiclones adecuadas de bajo esfuerzo cortante se pueden
IogrÆr fÆcilmente usando por ejemplo un mezclador en un intervalo de
aproximadamente 25 rpm a 35 rpm, y de manera mÆs deseable, 32 rpm. Posteriormente, los componentes IIquidos, por ejemplo, el agente tensioactivo y el agua’se mezclan para dar un producto granulado por mezclado bajo condiclones de bajo esfuerzo cortante tales como las mencionadas anteriormente. La granulaciOn -- entonces se extruye y esferoniza usando un dispositivo adecuado y los esferoides resultantesse secan, se tarnJiy opcionaFmentese---mezcJnateseI

almacenamiento.

Ahora bien, los Inventores han encontrado que seproporciona una ventaja significativa a la estabilidad del compuesto cuando los multiparticulados de Ia

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invención se secan a baja temperatura. De manera deseable, los nCicleos esferoides de los multiparticulados de pantoprazol de la invención se secan a un por ciento (%) de pØrdida en el secado (LOD) de 3.4% a 4.3%. Como se usa en la presente, secado a baja temperatura se refiere a una temperatura que no exceae aproximadamente 40°C durante un periodo de 10 a 12 horas. Cuando las condiciones de secado exceden esta temperatura V Deriodo de tiemDo. se observan impurezas pue contribuven a la inestabilidad. En una modalidad, el secado del nÆcleo se realiza en el intervalo de 35°C a 40°C, o aproximadamente 37°C a 39°C durante aproximadamente 8 a 72 horas. En otra modalidad, el nücleo se seca a aproximadamente 40°C durante 10 a 12 horas. De manera adecuada, cuando las capas de revestimiento se aplican como se describe, la temperatura de secado para las varias capas de revestimiento tambiØn estÆen ese intervalo.

Opcionalmente, se puede aplicar un revestimiento de sello inicial de un poilmero hidrofIlico a los multiparticulados, no revestidos. Por ejemplo, un revestimiento de sello inicial compuesto de hidroxipropUmetilcelj a._agua_purIf1cada se puede aplicar en un revestidor de lecho fluido, por ejemplo, por rociado.

De igual forma, el revestimiento entØrico se puede aplicar directamente al ntcleo esferoide no revestido, es decir, el multiparticulado no revestido, o se puede aplicar sobre un revestimiento de sello inicial. El revestimiento entØrico como se describe anteriormente, se aptica tIpicamente en un revestidor Wurster de lecho fluido.

Tal como se establece en la descripción, se ha considerado que los pasos de

[r-e

ezclado en condiciones de bajo esfuerzo cortante y secado a baja temperatura para la

En este sentido, es completamente claro que no existe sugerencia alguna en
los documentos citados acerca del mØtodo reMiiicijiiiiiimeiie, porque no hay mención o reconocimiento acerca del significado e importancia

Ode

la retención de la cantidad de agua seæaladaen el nücleo, asI como tampoco acerca del mezclado de los componentes del nucleo en condiciones de bajo

baja. Estas son caracterIsticas de las reivindicaciones de mØtodo y no Dueden
ser icinoradas.

De conformidad con lo anterior, es completamente claro que el mØtodo para producir una formulación de multiparticulados de pantoprazol tal como el descrito en la presente invención es novedoso frente a las enseæanzasde los documentos citados, no solo porque conduce a la obtención de un producto que en sí mismo no ha sido

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anticipado por el estado de la tØcnica, sino porque adicionalmente comprende una serie de condiciones de operación que estÆn Intimamente relacionadas con las ventajosas propledades de estabilidad que presenta la formulación multi particulada obtenida a travØs del mismo.

Por consiguiente, se ha demostrado tambiØn en forma contundente que el proceso reclamado en las reivindicaciones 30 a 37 es novedoso frente a las enseiianzas generales de los documentos Dl y D2 citados como estado de la tØcnica mÆs cercano, cumpliendo asi con las exigencias del ArtIculo 16 de la decision Andina 486.

Finalmente, y con el objetivo de corroborar las ventajas tØcnicas proporcionadas
por la presente solicitud, adjunto me permito presentar una copia de la literatura del producto que acompaæa en los Estados Unidos al producto multiparticulado objeto dela presente invención.

Las formulaciones multiparticuladas que caen dentro del alcance de las reivindicaclones han recibido aprobación de comercialización para su uso en los Estados Unidos, y Si bien el componente activo de la tableta y de los multiparticulados es

idØntico, las formulaclones de la tableta y del multiparticulado son claramente distintas JJ -- De hecho, Ia Administracion de Alimentos y Medicamentos de los Estados Unidos (FDA
por su sigla en inglØs), trata los multiparticulados como una nueva formulación, razón por la cual se condujeron estudios clInicos adicionales en soporte de la aprobación de comercialización.

En este sentido, el solicitante ha sido capaz de lograr un multiparticulado
que es estable y bioequivalente a Ia tableta actualmente comercializada, siendo este un resultado que no ha sido fÆcil deconseguir y en el que otros han fallado en sus intentos para lograrlo.

De manera particular, me permito dirigir la atención del seæor Examinador al primer, cuarto y quinto pØrrafos de la pÆgina 2 del documento anexo, en donde se seæalala comparabilidad y bioequivalencia del producto basado en los microparticulados de la invención con la formulación en tabTºtÆ æTiiàlmente conocida, as[como tambien- -

al segundo parrafo de la pagina 5 de dicho documento, bajo el encabezado de ---------= - -- -- "FarmacodinÆmica",en donde se confirma la equlvalencla de ambas forrnulaciones.

De conformidad con la informaclón anteriormente seæalada y proporcionada, me permito dirigir la atención del seæor Examinador al hecho de que el objeto de la presente invención representa un verdadero avance en el campo de la formulación del pantoprazol, toda vez que por primera vez se cuenta en el estado de la tØcnica con una

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JOSE LLOREDA CAMACHO & CO.
CaIle 72 No. 5-83 Piso 5, Bogota, D.C. Tel: 6069700 Fax 6069701

formulación de multiparticulados de pantoprazol que es estable al almacenamiento y
que resulta adecuada para pacientes con dificultades para tragar y/o pediÆtricos, quees comparable y bioequlvalente a la formulación en tableta comercialmente conocida, dando asI solución efectiva a una necesidad tØcnica largamente sentida en el campo en el que se desarrolla la solicitud, lo cual confirma las caracterIsticas de patentabilidad que poseen tanto el producto como el proceso reivindicados.

5. CONCLUSION

En resumen, teniendo en cuenta las modificaciones realizadas en el capItulo reivindicatorio como respuesta a las observaciones expuestas por el seæorExaminador en su Concepto TØcnico No. 2832, resulta completamente claro que se han superado las objeciones relacionadas con la claridad del capItulo reivindicatorio de la solicitud de patente en cuestión.

De manera anÆloga, mediante los argumentos tØcnicos presentados, se ha demostrado que las nuevas reivindicaciones, tal como han sido modificadas y presentadas junto con este memorial, tambiØn cumplen con el requisito de novedad, toda vez que tanto la composición reclamada, como el proceso para su obtención, presentan caracterIsticas tØcnicas particulares que no han sido reveladas o enseæadas con anterioridad por los documentos citados.

De igual forma, el solicitante ha proporcionado evidencia experimental que corrobora los avances tØcnicos que en forma sorprendente se logran gracias al objeto de la solicitud en estudio, reiterando asI la patentabilidad del mismo.

Por lo tanto, se ha demostrado en forma contundente que el objeto de la presente solicitud cumple a cabalidad con los requerimientos de los ArtIculos 14, 16 y 30 de la Decision Andina 486 de 2000, seæalados por el seæor Examinador en su Concepto TØcnico No. 2832, por 10 cual es merecedor de (a protección por patente solicitada.

6. Anexo al presente memorial me permito presentar:

(a) Copia del nuevo capItulo reivindicatorio compuesto por 37 reivindicaciones,
que reemplaza al capItulo originalmente presentado y en el cual se han
realizado las modificaciones anteriormente mencionadas; y

(b) Copia de la de la literatura del producto que acompaæa al producto
multiparticulado objeto de Ia presente invención.

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7. En vista de 10 anterior, atentamente me permito solicitar a ese Despacho, proceder a estudlar nuevamente la solicitud a la luz de las modificaciones realizadas y de los argumentos aquI expuestos y con base en ellos conceder el privllegio de patente
solicitado.

SeæorSuperintendente,

CIA LLOREDA RICAURTE

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T.P. 53.215

NOTARA41 DEL CUL0D BOGOTA DC -
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El Notarlo 41 del c o d £tæ,da fe d3 qtte owqared6

Ideriffficeda (d) cm: VIA profeeloneldeabogadoNo. alrwmdel Consejo Superior d3 Is Judlcatura, quien autenfica la firma puesta por ella (el) mismo en este escrito.
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REIVINDICACIONES

Multiparticulados de pantoprazol, en donde cada uno de los multiparticulados comprende:
a) un nücleo esferoide que comprende pantoprazol o un enantiómero del mismo, o una sal o hidrato del mismo y un tensloactivo o una combinación de tensioactivos presentes en una relación en peso de pantoprazol:tensioactivo(s) de 10:1 a 5:3 y/o en una relación en peso de tensioactivo(s) a nCicleo de 2% a 7%;
b) un revestimiento de sello inicial sobre el ncicleo esferoide que comprende hidroxipropil met! lcelulosa;y
C) un revestimiento entØrico el cual comprende un copoilmero de Æcido metacrIlico y metacrilatos sobre el revestimiento de sello
inicial,
en donde los multiparticulados revestidos tiene un diâmetro en el rango de 0.7 a 1.25 mm

(I) Multiparticulados de pantoprazol de conformidad con la reivindicacjón 1, en donde dicho nücleo esferoide comprende un compuesto de pantoprazol presente en una cantidad de aproximadamente 40 mg de pantoprazol por 100 mg de multiparticulado no revestido, en donde la cantidad de pantoprazol
es medida en la forma de base libre.

(3) Multiparticulados de pantoprazol de conformidad con la reivindicación 1, en donde el pantoprazol o un enantiómero del mismo, o una sal o un hidrato del mismo es pantoprazol sódico.

Multiparticulados de pantoprazol de conformidad con cualquiera de
las reivindicaciones 1 a 3 en donde el tensioactivo comprende lauriI-sulfatodesodjoo un polisorbato o una combinación de los mismos.

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S. Multiparticulados de pantoprazol de conformidad con la
reivindicación 4 en donde el tensioactivo es polisorbato 80.

6. Multiparticulados de pantoprazol de conformidad con cualquiera de
las reivindicaciones 1 a 5 en donde el nücleocomprende ademÆs
un desintegrante que comprende del 20% al 70% en peso del
n CicI eo.

7. Multiparticulados de pantoprazol de conformidad con la
reivindicación 6, en donde dicho de nte.grç_se selecciona del grupo que consiste de celdsa microcristalina, crospDvid.oa.y mezcla de las,plmas.

8. Multiparticulados de pantoprazol de conformidad con cualquiera de
las reivindicaciones 1 a 7 en donde el nócleo comprende ademÆs
un aglutinante.

9. Multiparticulados de pantoprazol de conformidad con la
reivindicación 8 en donde dicho aglutinante estÆ presente en una cantidad de 50:1 a 40:1 en peso de pantoprazol a aglutinante.

10. Multiparticulados de pantoprazol de conformidad con la reivindicacjón 8 o la reivindicación 9, en donde dicho agJijtjnante
es hidroxipropiimethceMosa.

11. Multiparticulados de pantoprazol de conformidad con cualquiera de
las reivindicaciones 1 a 10 en donde los multiparticulados tienen
un diªmetro

12. Multiparticulados de pantoprazol de conformidad con cualquiera de
las reivindicaciones 1 a 11 en donde el nücleo comprende ademªs unstadnLdepH.

13. Multiparticulados de pantoprazol de conformidad con la reivindicación 12 en donde dicho ajustador dptLcrnprende
carbonato de sodio.

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14. Multiparticulados de pantoprazol de conformidad con la reivindicación 13 en donde el carbonato de sodio estÆ presenteen
una cantidad de 3% a 7% en peso del multiparticulado.

15. Multiparticulados de pantoprazol de conformidad con cualquiera de
las reivindicaciones 1 a 14 en donde dicho nücleo comprende
ademâs de l% a 24gua.

16. Multiparticulados de pantoprazol de conformidad con cualquiera de
las reivindicaciones 1 a 15 en donde dicho_pantoprazol_estÆ presente como pantoprazol sódico sesguihidratado.
-Th

17. Multiparticulados de pantoprazol de conformidad con cualquiera de
las reivindicaciones 1 a 16, en donde dicho revestimiento entØrico comprende un copolImero de ªcido metacrIlico y rnetasrilatos en
un intervalo de 15% a 45% en peso del nicleo.

18. Multiparticulados de pantoprazol de conformidad con cualquiera de
las reivindicaciones 1 a 17, que comprende ademªs un revestimiento de sello final sobre el revestimiento entØrico.

19. Multiparticulados de pantoprazol de conformidad con la reivindicación 18, en donde el revestimiento se sello final comprende 0.1 a 10% en peso de los multiparticulados.

20. Multiparticulados de pantoprazol de conformidad con la reivindicación 18 a la reivindicación 19 en donde el nevesfirmento
de sello final comprende hidroxipropilmetilcelulosa(hipromelosa).

21. Multiparticulados de pantoprazol de conformidad con cualquiera de
las reivindicaciones 1 a 20 en donde dicho revestimiento de sello inicial estÆ en el intervalo_de 2 a 4% en peso del peso del njcleo
sin revestimiento.

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22. Multiparticulados de pantoprazol de conformidad con cualquiera de las reivindicaciones 1 a 21 en donde el pantoprazol o un enantiómero del mismo o una sal o hidrato del mismo, estÆ presente en el intervalo de 5 a 50% en peso del nücleo esferoide.

23. Multiparticulados de pantoprazol de conformidad con la reivindicación 22, en donde el nicleo comprende celulosa. microcristalina en una cantidad de 25 a 30% en peso del nücleo

esferoide.

24. Multiparticulados de pantoprazol de conformidad con las reivindicaciones 22 6 23, en donde el nücleocotpende crospovidona en una cantidad de 14 a 16% en peso del nicIeo
esferoide.

25. MultiparUciadosde pantoprazol de conformidad con cualquiera de las reivindicaciones 1 a 24, en donde el nicleo esferoide consiste esencialmente de:

Pantoprazol sódico sesquihidratado 45% (p/p)
Celulosa microcristalina 27% (p/p)
Polisorbato 80 5% (pip)
Crospovidona 15% (p/p)

Hipromelosa 2208 1% (p/p); y (RPM C) Carbonato de sodio 7% (pip)
26. Multiparticulados de pantoprazol de conformidad con la reivindicación 25, en donde el revestimiento entØrico comprende 27.5 a 48% en peso del multiparticulado.

27. Multiparticulados de pantoprazol de conformidad con las reivindicaciones 25 6 26, en donde el revestimiento entØrico comprende aproximadamente 30% en peso de revestimiento de
un copolImero de Æcido metacrIlico y metacrilatos, aproximadamente 15% en peso de talco, aproximadamente 3%
de citrato de trietilo y un ajustador de pH; estando dichas cantidades en peso del multiparticulado.

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(J28 Una formulación de pantoprazol para suministrarla a pacientes
pediÆtricos, que comprende una suspension que comprende los multiparticulados de pantoprazol de conformidad con cualquiera
de las reivindicaciones 1 a 27 y un liquido de suspension fisiológicamente compatible.

29. Una cªpsula que comprende los multiparticulados de pantoprazol
de conformidad con cualquiera de las reivindicaclones 1 a 27.

(330 Un mØtodo para producir una formulación de multiparticulados de
pantoprazol, que comprende los pasos de:
a) producir un nicleo esferoide que comprende un compuesto de
flpantoprazol un tensioactivo o una combinaciOn de
tensloactivos presentes en una relación en peso de pantoprazol
a tensioactivo de 10:1 a 5:3 y/o de 2% a 7% en peso de
tensioactivo a nÆcleo,mediante extrusiOn esferonizaciOn;
b) aplicar un revestimiento de sello inicial que comprende hidroxipropilmetilcelulosa al nücleo esferoide;
C) aplicar un revestimiento entØrico que comprende un
copolImero de Æcido metacrIlico metacrilatos sobre el
revestimiento de sello inicial;
d) opcionalmente aplicar un revestimiento de sello final al nücleo esferoide con revestimiento entØrico.
En donde dichos multiparticulados tienen un diÆmetro en el intervalo de 0.7 a 1.25 mm.

31. El mØtodo de conformidad con la reivindicación 30, en donde el
nücleo esferoide se prepara mediante la mezcla de los ingredientes en un mezclador de bajo esfuerzo cortante en condiciones de bajo esfuerzo cortante en un intervalo de 25 rpm a
35 rpm.

32. El mØtodo de conformidad con la reivindicación 31, en donde las
condiciones de bajo esfuerzo cortante son 32 rpm.

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PROTONIXfi
(pantoprazole sodium)
Delayed-Release Tablets

PROTONIXfi
(pantoprazole sodium)
For Delayed-Release Oral Suspension

Ri only

DESCRIPTION

The active ingredient in PROTONIXfi (pantoprazole sodium) Delayed-Release Tablets and PROTONIXfi (pantoprazole sodium) For Delayed-Release Oral Suspension is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]- 1H-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is C16H14F2N3NaO4S x 1.5 H20, with a molecular weight of432.4. The structural formula is:

l.5 H20

Na

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

The stability ofthe compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

PROTONIX (pantoprazole sodium) is supplied as a delayed-release tablet for oral administration, available in 2 strengths (40 mg and 20 mg); and as delayed-release granules for oral administration, available in the 40 mg strength.

Each PROTONIX (pantoprazole sodium) Delayed-Release tablet contains 45.1 mg or 22.6 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg or 20 mg pantoprazole, respectively) with the following inactive ingredients: calcium stearate, crospovidone, hypromellose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. Pantoprazole Sodium Delayed-Release tablets (40 mg and 20 mg) complies with USP dissolution test 2.

PROTONIX (pantoprazole sodium) For Delayed-Release Oral Suspension contains the active ingredient pantoprazole sodium sesquihydrate, in the form of enteric-coated granules in unit dose packets. Each unit dose packet contains enteric-coated granules containing 45.1 mg pantoprazole sodium sesquihydrate (equivalent to 40 mg of pantoprazole) with the following inactive ingredients: crospovidone, hypromellose, methacrylic acid copolymer, microcrystalline cellulose, polysorbate 80, povidone, sodium carbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate, and yellow ferric oxide.

CLINICAL PHARMACOLOGY
Phannacokinetics

PROTONIX Delayed-Release Tablets are prepared as enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (Cm)
and area under the serum concentration time curve (AUC) increase in a manner proportional to
oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its
Th pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism) with normal liver function receiving an
oral dose ofthe enteric-coated 40 mg pantoprazole tablet, the peak concentration (C) is
2.5.tg/mL, the time to reach the peak concentration (tm) is 2.5 h and the total area under the
plasma concentration versus time curve (AUC) is 4.8 ighr/mL. When pantoprazole is given with food, its is highly variable and may increase significantly. Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6-14.0 L/h and its apparent volume of distribution is 11.0-23.6 L.

PROTONIXfi (pantoprazole sodium) For Delayed-Release Oral Suspension has been shown to be comparable to PROTONIXfi (pantoprazole sodium) Delayed-Release Tablets in suppressing pentagastrin-stimulated maximum acid output (MAO) in patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE) (see Clinical Pharmacology, Pharmacodynamics).

PROTONIX For Delayed-Release Oral Suspension is bioequivalent when administered orally in applesauce or apple juice, or mixed in apple juice and administered through a nasogastric tube. The plasma pharmacokinetic parameters from a crossover study in healthy subjects are summarized in the table below. In this study, a single oral 40 mg dose of Protonix For Delayed-Release Oral Suspension was administered to healthy subjects (N = 22) as granules sprinkled over a teaspoonful of applesauce, as granules mixed with apple juice and, mixed with apple juice followed by administration through a nasogastric tube.

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Pharmacokinetics parameters (mean::h SD) ofPantoprazole with Administration of Protonix For Delayed-Release Oral Suspension Sprinkled on Applesauce, Mixed with Apple Juice, Mixed with Apple Juice and Administered through a Nasogastric Tube

Pharmacokinetic Granules in Granules in Granules in
Parameters applesauce apple juice nasogastric tube

AUC(ig.hr/mL) 4.01– 1.53 3.99– 1.49 4.06– 1.73

(.tg/mL) 1.97 – 0.69 1.91 – 0.45 2.2 – 0.70

2.0 2.5 2.0

’Median values are reported for

’Th Absorption
The absorption ofpantoprazole is rapid, with a of 2.5 pg/mL that occurs approximately
2.5 hours after administration of a single or multiple oral 40 mg doses ofPROTONIXfi (pantoprazole sodium) Delayed-Release Tablets. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids.

Administration of PROTONIXfi (pantoprazole sodium) Delayed-Release Tablets with food may delay its absorption up to 2 hours or longer; however, the and the extent of pantoprazole absorption (AUC) are not altered. Thus, PROTONIXfi (pantoprazole sodium) Delayed-release Tablets may be taken without regard to timing ofmeals.

PROTONIXfi (pantoprazole sodium) For Delayed-Release Oral Suspension should be taken approximately 30 minutes before a meal.

Distribution

The apparent volume of distribution ofpantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent ofthe route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any ofthe pantoprazole metabolites have significant pharmacologic activity. CYP2C 19 displays a known genetic polymorphism due to its deficiency in some sub-populations (eg, 3% ofCaucasians and African-Americans and 17%-23% ofAsians). Although these sub-populations ofslow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (:!g 23%) with once daily dosing.

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Elimination

After a single oral or intravenous dose of ’4C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% ofthe dose was excreted in the urine with
18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Special Populations
Geriatric

Only slight to moderate increases in pantoprazole AUC and C (26%) were found in elderly volunteers (64 to 76 years of age) after repeated oral administration, compared with younger subjects. No dosage adjustment is recommended based on age.

Pediatric

The pharmacokinetics of pantoprazole have not been investigated in patients < 18 years of age.

Gender

There is a modest increase in pantoprazole AUC and C in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is needed based on gender (see PRECAUTIONS, Use in Women).

Renal Impairment
In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic Impairment
In patients with mild to severe hepatic impairment, maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage frequency adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once daily multiple-dose administration. No dosage adjustment is needed in patients with mild to severe hepatic impairment. Doses higher than 40 mg/day have not been studied in hepatically-impaired patients.

Drug-Drug Interactions
Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6, and 2C9. In in vivo drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer]), nifedipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac, naproxen and piroxicam (CYP2C9 substrates), and theophylline (a CYP I A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2136, 2C9, and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. In vivo studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, naproxen, piroxicam, and oral contraceptives [levonorgestrel/ethinyl

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estradiol]) metabolized by CYPs 2C19, 3A4, 2C9, 2D6, and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment ofsuch drugs is not necessary when they are coadministered with pantoprazole. In other in vivo studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole. Although no significant drug-drug interactions have been observed in clinical studies, the potential for significant drug-drug interactions with more than once daily dosing with high doses of pantoprazole has not been studied in poor metabolizers or individuals who are hepatically impaired.

Pharmacodynamics
PROTONTXfi (pantoprazole sodium) For Delayed-Release Oral Suspension has been shown to be comparable to PROTONIXfi (pantoprazole sodium) Delayed-Release Tablets in suppressing pentagastrin-stimulated MAO in patients (n = 49) with GERD and a history ofEE. In this multicenter pharmacodynamic crossover study a 40 mg oral dose ofProtonix For Delayed-Release Oral Suspension administered in a teaspoonful of applesauce was compared with a 40 mg oral dose of Protonix Delayed-Release Tablets after administration of each formulation once daily for 7 days. Both medications were administered thirty minutes before breakfast. Pentagastrin-stimulated (MAO) was assessed from hour 23 to 24 at steady state.

Mechanism ofAction

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H,K)-ATPase enzyme system at the secretory surface ofthe gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective ofthe stimulus. The binding to the (H,K’)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested.

Antisecretory Activity
Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20-80 mg) or a single dose ofintravenous (20-120 mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once a day dosing for
7 days the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half ofthe subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence ofrebound hypersecretion.

In a series of dose-response studies pantoprazole, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent oftime gastric pH was> 3 and > 4. Treatment with 40 mg of pantoprazole produced optimal increases in gastric pH which were significantly greater than the 20-mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole on median pH from one double-blind crossover study are shown below.

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Effect of Single Daily Doses of Oral Pantoprazole on Intragastric pH

Time Placebo

Median pH on day 7

20 mg 40 mg 80 mg

8 a.m. 8 a.m.

(24 hours) 1.3 2.9* 3.8*# 3.9*#

8 a.m. 10 p.m.
(Daytime) 1.6 3.2* 4.4*# 4.8*#

10 p.m. 8 a.m.
(Nighttime) 1.2 2.1* 30* 2.6*

* Significantly different from placebo
Significantly different from 20 mg

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies ofthe acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of PROTONIX for up to 8 weeks. At 4 weeks oftreatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the
10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8 week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups. Median serum gastrin levels remained within normal limits during maintenance therapy with PROTONIX Delayed-Release Tablets.

In long-term international studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months oftreatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following healing of gastric or duodenal ulcers with pantoprazole treatment, elevated gastrin levels return to normal by at least 3 months.

Enlerochromaffin-Like (ECL) Cell Effects
In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving

40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after 4 years.
In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation ofserum gastrin concentrations. The high density ofECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by proton pump inhibitors. However, there were no observed elevations

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in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility).

Other Effects
No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels ofthe following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and growth hormone.

In a 1 -year study of GERD patients treated with pantoprazole 40 mg or 20 mg, there were no changes from baseline in overall levels ofT3, T4, and TSH.

Clinical Studies
PROTONIX Delayed-Release Tablets were used in the following clinical trials:

Erosive Esophagitis (EE) Associated with Gastroesophageal Reflux Disease (GERD)
A U.S. multicenter double-blind, placebo-controlled study of PROTONIX 10 mg, 20 mg, or 40 mg once daily was conducted in 603 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above (Hetzel-Dent scale). In this study, approximately 25% of enrolled patients had severe EE of grade 3 and 10% had grade 4. The percentages of patients healed (per protocol, n = 541) in this study were as follows:

Erosive Esophagitis Healing Rates (per protocol)

PROTONIX Placebo

lOmgQD 20mgQD 40mgQD
Week (n = 153) (n = 158) (n = 162) (n = 68)

4 45.6%k 58.4% 75.00/.* 14.3%
8 66.0% 83.5 %# 92.6%* 39.7%

+ (p < 0.001) PROTONIX versus placebo. * (p <0.05) versus 10 mg, or 20 mg PROTONIX
# (p < 0.05) versus 10 mg PROTONIX

In this study, all PROTONIX treatment groups had significantly greater healing rates than the placebo group. This was true regardless ofH. pylori status for the 40-mg and 20-mg PROTONIX treatment groups. The 40-mg dose of PROTONIX resulted in healing rates significantly greater than those found with either the 20- or 10-mg dose.

A significantly greater proportion of patients taking PROTONIX 40 mg experienced complete relief of daytime and nighttime heartburn and the absence ofregurgitation starting from the first

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day oftreatment compared with placebo. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking placebo.

PROTONIX 40 mg and 20 mg once daily were also compared with nizatidine 150 mg twice daily in a U.S. multicenter, double-blind study of 243 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above. The percentages of patients healed (per protocol, n = 212) were as follows:

Erosive Esophagitis Healing Rates (per protocol)

PROTONIX Nizatidine

20mgQD 40mgQD l5OmgBID
Week (n = 72) (n = 70) (n = 70)

4 61.4% 64.0% 22.2%
8 79.2% 82.9% 41.4%

+ (p < 0.001) PROTONIX versus nizatidine.

Once daily treatment with PROTONIX 40 mg or 20 mg resulted in significantly superior rates of healing at both 4 and 8 weeks compared with twice daily treatment with 150 mg of nizatidine. For the 40 mg treatment group, significantly greater healing rates compared to nizatidine were achieved regardless ofthe H pylori status.

A significantly greater proportion ofthe patients in the PROTONIX treatment groups experienced complete relief of nighttime heartburn and regurgitation starting on the first day and of daytime heartburn on the second day compared with those taking nizatidine 150 mg twice daily. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking nizatidine.

Long-Term Maintenance of Healing of Erosive Esophagitis
Two independent, multicenter, randomized, double-blind, comparator-controlled trials of identical design were conducted in GERD patients with endoscopically-confirmed healed erosive esophagitis to demonstrate efficacy of PROTONIX in long-term maintenance of healing. The two U.S. studies enrolled 386 and 404 patients, respectively, to receive either 10 mg, 20 mg, or 40 mg of PROTONIX Delayed-Release Tablets once daily or 150 mg ofranitidine twice daily. As demonstrated in the table below, PROTONIX 40 mg and 20 mg were significantly superior to ranitidine at every time point with respect to the maintenance of healing. In addition, PROTONIX 40 mg was superior to all other treatments studied.

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Long-Term Maintenance of Healing ofErosive Gastroesophageal Reflux Disease (GERD Maintenance): Percentage ofPatients Who Remained Healed

PROTONIX PROTONIX Ranitidine
20mgQD 40mgQD l5OmgBID

Study n75 n=74 n75
Month 1 91* 99* 68
Month 3 82* 93 *# 54
Month 6 76* 90*# 44
Month 12 70* 86*# 35

Study n74 n=88 n=84
Month 1 89* 92*# 62
Month 3 78* 91 *# 47
Month 6 72* 88*# 39
Month 12 72* 83* 37

* (p <0.05 vs ranitidine)
# (p < 0.05 vs PROTONIX 20 mg)
Note: PROTONIX 10 mg was superior (p < 0.05) to ranitidine in study 2 but not study I.

PROTONIX 40 mg was superior to ranitidine in reducing the number of daytime and nighttime heartburn episodes from the first through the twelfth month oftreatment. PROTONIX 20 mg, administered once daily, was also effective in reducing episodes of daytime and nighttime heartburn in one trial.

Number of Episodes ofHeartburn (mean – SD)

PROTONIX Ranitidine

40mgQD l5OmgBID

Month I Daytime 5.1 1.6* 18.3 1.6
Nighttime 3.9–1.1* 11.9– 1.1

Month 12 Daytime 2.9– 1.5* 17.5– 1.5
Nighttime 2.5– 1.2* 13.8– 1.3

* (p < 0.001 vs ranitidine, combined data from the 2 U.S. studies)

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
In a multicenter, open-label trial of 35 patients with pathological hypersecretory conditions, such as Zollinger-Ellison syndrome with or without multiple endocrine neoplasia-type I, PROTONIX successfully controlled gastric acid secretion. Doses ranging from 80 mg daily to 240 mg daily maintained gastric acid output below 10 mEq/h in patients without prior acid-reducing surgery and below 5 mEq/h in patients with prior acid-reducing surgery.

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Doses were initially titrated to the individual patient needs, and adjusted in some patients based on the clinical response with time (see DOSAGE AND ADMINISTRATION). PROTONIX was well tolerated at these dose levels for prolonged periods (greater than 2 years in some patients).

INDICATIONS AND USAGE

PROTONIXfi Delayed-Release Tablets and PROTONIXfi For Delayed-Release Oral Suspension are indicated for:

Short-Term Treatment ofErosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)
PROTONIXfi is indicated for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those patients who have not healed after 8 weeks oftreatment, an additional 8-week course of PROTONIX may be considered.

Maintenance ofHealing of Erosive Esophagitis
PROTONIX is indicated for maintenance ofhealing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with gastroesophageal reflux disease (GERD). Controlled studies did not extend beyond 12 months.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome PROTONIX is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

CONTRAINDICATIONS

PROTONIX is contraindicated in patients with known hypersensitivity to any component ofthe formulation.

PRECAUTIONS
General
Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy:

Owing to the chronic nature of erosive esophagitis, there may be a potential for prolonged administration of pantoprazole. In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance ofthese findings to tumor development in humans is unknown.

Generally, daily treatment with any acid-suppressing medications over a long period oftime (eg, longer than 3 years) may lead to malabsorption of cyanocobalamin (Vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This possibility should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with pantoprazole, particularly in patients who were H. pylori positive.

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Information for Patients
Patients should be cautioned that PROTONIXfi Delayed-Release Tablets SHOULD NOT BE SPLIT, CRUSHED, OR CHEWED. PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of PROTONIXfi Delayed-Release Tablets.

Patients should be cautioned that PROTONIXfi For Delayed-Release Oral Suspension SHOULD NOT BE CRUSHED OR CHEWED. PROTONIX For Delayed-Release Oral Suspension should be taken approximately 30 minutes before a meal.

PROTONIX For Delayed-Release Oral Suspension should only be administered in apple juice or applesauce, not in water or other liquids, or foods.

(See the Dosage and Administration Section, Administration Options subsection)

Drug Interactions
Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and to a minor extent the CYP3A4 isozymes, and subsequently undergoes Phase II conjugation (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

Based on studies evaluating possible interactions of pantoprazole with other drugs, no dosage adjustment is needed with concomitant use ofthe following: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam (and its active metabolite, desmethyldiazepam), diclofenac, naproxen, piroxicam, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin (see below), midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when coadministered with pantoprazole, adjustment ofthe dosage ofpantoprazole or ofsuch drugs may not be necessary. There was also no interaction with concomitantly administered antacids. There have been postmarketing reports ofincreased INR and prothrombin time in patients receiving proton pump inhibitors, including pantoprazole, and warfarin concomitantly. Increases in 1NR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in TNR and prothrombin time.

Concomitant use of atazanavir and proton pump inhibitors is not recommended. Coadministration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant oftheir bioavailability (eg, ketoconazole, ampicillin esters, and iron salts).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell

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tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma ofthe duodenum at
50 mg/kg/day, and benign polyps and adenocarcinomas ofthe gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day
produced increased incidences offollicular cell adenomas and carcinomas for both male and
female rats.

Sporadic occurrences ofhepatocellular adenomas and a hepatocellular carcinoma were observed
in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of
fl 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffm-
like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose
selection for this study may not have been adequate to comprehensively evaluate the
carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of
5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced
gastric fundic ECL cell hyperplasia.

A 26-week p53 +/- transgenic mouse carcinogenicity study was not positive.

Pantoprazole was positive in the in vitro human lymphocyte chromosomal aberration assays, in
one oftwo mouse micronucleus tests for clastogenic effects, and in the in vitro Chinese hamster
ovarian cell/I-IGPRT forward mutation assay for mutagenic effects. Equivocal results were

observed in the in vivo rat liver DNA covalent binding assay. Pantoprazole was negative in the , in vitro Ames mutation assay, the in vitro unscheduled DNA synthesis (UDS) assay with rat
hepatocytes, the in vitro AS52/GPT mammalian cell-forward gene mutation assay, the in vitro
thymidine kinase mutation test with mouse lymphoma L5 1 78Y cells, and the in vivo rat bone
marrow cell chromosomal aberration assay.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human
dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended
human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

Pregnancy
Teratogenic Effects
Pregnancy Category B
Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to

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40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Pantoprazole and its metabolites are excreted in the milk ofrats. Pantoprazole excretion in human milk has been detected in a study of a single nursing mother after a single 40 mg oral dose. The clinical relevance ofthis finding is not known. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumongenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit ofthe drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Use in Women

Erosive esophagitis healing rates in the 221 women treated with PROTONIX Delayed-Release Tablets in U.S. clinical trials were similar to those found in men. In the 122 women treated long-term with PROTONIX 40 mg or 20 mg, healing was maintained at a rate similar to that in men. The incidence rates of adverse events were also similar for men and women.

Use in Elderly
In short-term U.S. clinical trials, erosive esophagitis healing rates in the 107 elderly patients (? 65 years old) treated with PROTONIX were similar to those found in patients under the age of
65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

Laboratory Tests
There have been reports offalse-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving most proton pump inhibitors, including pantoprazole. An alternative
fl confirmatory method should be considered to verify positive results.

ADVERSE REACTIONS

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration oftreatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

The adverse reaction profile for PROTONTXfi (pantoprazole sodium) For Delayed-Release Oral Suspension is similar to the established safety profile of PROTONTXfi (pantoprazole sodium) Delayed-Release Tablets.

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following

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adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more in the individual studies ofGERD patients on therapy with PROTONIX.

Most Frequent Adverse Events Reported as Drug Related in Short-term Domestic Trials

Incidence

Study 300-US Study 301 -US

PROTONIX Placebo PROTONIX Nizatidine
Study Event (n521) (n=82) (n161) (n82)

Headache 6 6 9 13 Diarrhea 4 1 6 6 Flatulence 2 2 4 0
Abdominal pain 1 2 4 4
Rash <1 0 2 0
Eructation 1 1 0 0 Insomnia <1 2 1 1 Hyperglycemia 1 0 <1 0

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In international short-term, double-blind or open-label clinical trials involving 20 mg to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Adverse Events in GERD Patients In Short-term International Trials

Incidence

Pantoprazole Ranitidine Omeprazole Farnotidine
Total 300 mg 20 mg 40 mg
Study Event (N 2805) (N 594) (N 474) (N 239)

Headache 2 3 2 1 Diarrhea 2 2 2 <1
Abdominal Pain 1 1 <1 <1

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 12 months, the following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more ofGERD patients on long-term therapy.

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Most Frequent Adverse Events Reported as Drug Related in Long-term Domestic Trials

Study Event

PROTONIX

(n=536)

% Incidence

Ranitidine

(n= 185)

Headache 5 2
Abdominal pain 3 1
Liver function tests abnormal 2 <1
Nausea 2 2

Vomiting 2 2

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short- and long-term domestic and international trials, the following treatment-emergent events, regardless of causality, occurred at a rate of?: 1% in pantoprazole-treated patients: anxiety, arthralgia, asthenia, back pain, bronchitis, chest pain, constipation, cough increased, dizziness, dyspepsia, dyspnea, flu syndrome, gastroenteritis, gastrointestinal disorder, hyperlipemia, hypertonia, infection, liver function tests abnormal, migraine, nausea, neck pain, pain, pharyngitis, rectal disorder, rhinitis, SGPT increased, sinusitis, upper respiratory tract infection, urinary frequency, urinary tract infection, and vomiting.

Additional treatment-emergent adverse experiences occurring in < 1% of pantoprazole-treated patients from these trials are listed below by body system. In most instances the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction, photosensitivity reaction.

CARDIOVASCULAR SYSTEM: abnormal electrocardiogram, angina pectoris, arrhythmia, atrial fibrillation/flutter, cardiovascular disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial infarction, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

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FIEPATO-BILIARY SYSTEM: biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

I-IEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, neuropathy, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pruritus, skin disorder, skin ulcer, sweating, urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

In an open-label US clinical trial conducted in 35 patients with pathological hypersecretory conditions treated with PROTONIX for up to 27 months, the adverse events reported were consistent with the safety profile ofthe drug in other populations.

Postmarketing Reports
There have been spontaneous reports of adverse events with the postmarketing use of pantoprazole. These reports include the following:

BODY AS A WHOLE: anaphylaxis (including anaphylactic shock), angioedema (Quincke’s edema).

DIGESTIVE SYSTEM: increased salivation, nausea, pancreatitis.

HEMIC AND LYMPHATIC SYSTEM: pancytopenia.

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H1EPATO-BILIARY SYSTEM: hepatocellular damage leading to jaundice and hepatic failure.

MUSCULOSKELETAL SYSTEM: elevated CPK (creatine phosphokinase), rhabdomyolysis.

NERVOUS SYSTEM: confusion, hypokinesia, speech disorder, vertigo.

SKIN AND APPENDAGES: severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal).

SPECIAL SENSES: anterior ischemic optic neuropathy, blurred vision, tinnitus.

UROGENITAL SYSTEM: interstitial nephritis.

Laboratory Values
In two U.S. controlled, short-term trials in patients with erosive esophagitis associated with GERD, 0.4% ofthe patients on PROTONIX 40 mg experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. In two U.S. controlled, long-term trials in patients with erosive esophagitis associated with GERD, none of 178 patients (0%) on PROTONIX 40 mg and two of 181 patients (1.1%) on PROTONIX 20 mg experienced significant transaminase elevations at 12 months (or earlier if a patient discontinued prematurely). Significant elevations of SGOT or SGPT were defined as values at least three times the upper limit of normal that were non-sporadic and had no clear alternative explanation. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Experience in patients taking very high doses of pantoprazole is limited. There have been spontaneous reports of overdosage with pantoprazole, including a suicide in which pantoprazole 560 mg and undetermined amounts of chloroquine and zopiclone were also ingested. There have also been spontaneous reports of patients taking similar amounts ofpantoprazole (400 mg
and 600 mg) with no adverse effects.

Pantoprazole is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

DOSAGE AND ADMINISTRATION

Treatment of Erosive Esophagitis
The recommended adult oral dose is 40 mg given once daily for up to 8 weeks. For those patients who have not healed after 8 weeks oftreatment, an additional 8-week course of PROTONIX may be considered (see INDICATIONS AND USAGE).

Maintenance ofHealing ofErosive Esophagitis
The recommended adult oral dose is PROTONIX 40 mg, taken daily (see CLINICAL PHARMACOLOGY, Clinical Studies).

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Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
The dosage of PROTONIX in patients with pathological hypersecretoty conditions varies with the individual patient. The recommended adult starting dose is 40 mg twice daily. Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered. Some patients have been treated continuously with PROTONIX for more than 2 years.

No dosage adjustment is necessary in patients with renal impairment, hepatic impairment, or for elderly patients. Doses higher than 40 mg/day have not been studied in hepatically-impaired patients. No dosage adjustment is necessary in patients undergoing hemodialysis.

PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach. If patients are unable to swallow a 40 mg tablet, two 20 mg tablets may be taken. Concomitant administration of antacids does not affect the absorption of PROTONIX Delayed-Release Tablets.

PROTONIX For Delayed-Release Oral Suspension should be administered in applesauce
or apple juice approximately 30 minutes prior to a meal. See Administration Options subsection below. Patients should be cautioned that PROTONIX Delayed-Release
Tablets and PROTONIX For Delayed-Release Oral Suspension should not be split,
chewed or crushed.

PROTONIX For Delayed-Release Oral Suspension should only be administered in apple juice or applesauce, not in water or other liquids, or foods.

Administration Options
PROTONIXFor Delayed-Release Oral Suspension - Oral Administration in Applesauce:
Open packet.

Sprinkle intact granules on one teaspoonful of applesauce.

Swallow within 10 minutes ofpreparation.

___ PROTONIXFor Delayed-Release Oral Suspension - OralAdministration in Apple Juice: Open packet.

Empty intact granules into a small cup containing 5 mL of apple juice (approximately one
teaspoonful).

Stir for 5 seconds and swallow immediately.

To ensure complete delivery ofthe dose, rinse the container once or twice with apple
juice to remove any remaining granules and swallow immediately.

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PROTONIXFor Delayed-Release Oral Suspension - Nasogostric Tube Administration For patients who have a nasogastric tube in place, PROTONIX For Delayed-Release Oral Suspension can be administered as follows:
Separate the plunger from the barrel of a 2 ounce (60 mL) catheter tip syringe.
Connect the catheter tip ofthe syringe to a 16 French (or larger) nasogastric tube.
Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending ofthe tubing in order to provide smooth flow of contents under
gravity.
Empty the contents ofthe packet into the barrel ofthe syringe.
Add 10 mL of apple juice and gently tap and/or shake the barrel ofthe syringe to help
fl empty the syringe.
Add an additional 10 mL of apple juice and gently tap and/or shake the barrel ofthe
syringe to help rinse the syringe and nasogastric tube. Repeat with at least 2 additional 10
mL aliquots of apple juice. No granules should remain in the syringe.
. Make sure the nasogastric tube is not clogged to ensure that patients receive the full dose.

HOW SUPPLIED

PROTONIXfi (pantoprazole sodium) Delayed-Release Tablets are supplied as 40 mg yellow oval biconvex delayed-release tablets imprinted with PROTONIX (brown ink) on one side.
They are available as follows:
NDC 0008-0841-81 bottles of 90

NDC 0008-0841-99 carton of 10 Redipakfi blister strips of 10 tablets each
PROTONIXfi (pantoprazole sodium) Delayed-Release Tablets are supplied as 20 mg yellow oval biconvex delayed-release tablets imprinted with P20 (brown ink) on one side.
They are available as follows:
NDC 0008-0843-81 bottles of 90

PROTONIXfi (pantoprazole sodium) For Delayed-Release Oral Suspension contains pale yellowish to dark brownish pantoprazole sodium enteric coated granules in a 40 mg unit dose packet.
They are available as follows:
NDC 0008-0844-02 unit dose carton of 30

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8. A tableted dosage form according to claim 1, wherein the individually enteric coating layered units are further covered with an over-coating layer comprising pharmaceutically acceptable exapients.

5 9. A tableted dosage form according to claim 1, wherein the dosage form is
divisible.

10. A tableted dosage form according to claim 1, wherein the dosage form is dispersible to a suspension of individually enteric coating layered units in an
10 aqueous liquid.

11. A tableted dosage form according to claim 1, wherein an optionally applied separating layer comprises pharmaceutically acceptable exdpients which are
soluble, or insoluble but disintegrating in water, and optionally alkaline
15 compounds.

12. A tableted dosage form according to claim 1, wherein the core material is a
seed layered with the active substance.

20 13. A tableted dosage form according to claim 12, wherein the seeds have a size of
0.1 -2 mm.

14. A processfor the manufacture of a pharmaceutical multiple unit tableted
dosage form comprising tablet exdpients and individually enteric coating layered
25 units of a core material containing active substance as defined in claim I
optionally mixed with alkaline compounds, wherein the core material is
optionally covered with one or more separating layer(s) and further covered with
one or more enteric coating layer(s), whereafter the individually enteric coating layered units are compressed into a tablet and whereby the enteric coating layer
30 has mechanical properties such that the compression of the individual units mixed
with the tablet excipients into the multiple unit tableted dosage form does not

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Enteric coating layer

Pellets covered with separating layer 7 200 g
Methacrylic acid copolymer 7 100 g
Tnethyl citrate 30 g

5 Mono- and dliglycerides7 5 g
Polysorbate 80 0.5 g

Purified water 309g PeiIQi;c

Tablets

10 Enteric coating layered pellets 200 g
Microcrystalline cellulose 299 g
Sodium stearyl fwnarate 1.2 g

Sodium lauryl sulfate is dissolved in purified water to form the granulation liquid.
15 Pantoprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-
mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.

The wet mass is forced through an extruder equipped with screens, aperture size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core
20 material is dried in a fluid bed dryer and classified. The prepared core material is covered
with separating layer in a fluid bed apparatus with a hydroxypropyl methyl-cellulose/water solution.

The enteric coating layer is applied to the pellets covered with separating layer
25 frgouspersionof methacrylic acid copolymer plasticized with
triethyl citrate to which a mono- and dig cerides/polvsorbatedspersjon has
been added. The pellets are dried in a fluid bed apparatus.

Enteric coating layered pellets, microcrystalline cellulose and sodium stearyl
30 fumarate are mixed and compressed into tablets with a tablet weight
corresponding to 20 mg active substance, using a single punch tableting machine equipped with 10 mm round punches.

ORAL-ADMINISTRATION FORMS OF A MEDICAMENT CONTAINING
PANTOPRAZOL

PRIOR ART

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European Patent Application EP-A-244 380 describes
oral presentation forms for acid-unstable active compounds
from the class of H/K-ATPase inhibitors having a pyridylrnethylsulphinyl-1B-benzimidazole structure, which
have a core, an intermediate layer, and an outer layer which
is resistant to gastric juice. European Patent Application EP-A-247 983 describes and claims the formulations dis-closed in EP-A-244 380 in connection with the 114/K-ATPase inhibitor omeprazole.

outer layer which is resistant to gastric juice, and which is characterized in that the core contains, in a dition to toazole or in addition to a pantoprazole salt,polyvinyjpy-rolitlone and/or hyd? roj!ylIIetvllulose as the binder, and1fdi?ttthfiIt1a. itional1y as an inert filler. For abasic reaction f the pellet core i6let coreifthe desired increase in pH has not already been achieved b using the active compo - ganic ase is

admixed to this. Exajies%rhicIch may be mentioned here are the pharmacologically tolerated alkali metal, alkaline earth

metal or earth metal

In addition to the filler and binder, other auxiliaries, in

In the case of the presentation forms claimed in European particular lubricants and release agents, Patent Applications EP-A-244 380 and EP-A-247 983, sta- disintegrating agents, are also employed

bilization of the acid-unstable active compounds is
achieved, in particular, by adding bases to the core and thus
increasing the pH; to achieve an adequate storage stability,
however, certain conditions must be maintained both during
preparation and during storage, and these can be reconciled

with an optimum pharmaceutical formulation and problem- free stock-holding only with difficulty. EP-A-247 983 thus appropriately states: "it is essential for long-term stability during storage that the water content of the presentation form containing the active compound omeprazole (tablets, capsules and pellets with a coating which is resistant to
gastric juice) is kept low and is preferably not more that 1.5 wt. %. Final packswith pellets which have a coating which is resistant to gastric juice and are contained in hard gelatine capsules accordingly are preferably to be provided with drying agents which reduce the water content of the gelatine shells to the extent that the water content in the pellets does not exceed 1.5 wt. V.

The water content, which is to be kept low during

preparation of pellet cores for stability reasons, thus means that the mass to be extruded for preparation ofthe pellet core is no longer sufficiently plastic for the extrudate subse-

quently to be rounded off into spherical particles. Rather, cylindrical bodies are formed, which, during the subsequent coating step, receive thinner lacquer coatings on the ends
and therefore do not have the required resistance to gastric

juice at these points, and moreover do not protect the core reliably from the coating which is resistant to gastric juice by a sub-coating, which is essential for the stability.
The stability problems described also arise if attempts are made to formulate the H*/KfATPase inhibitor pantoprazole
(prop. INN for the compound 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsuiphinyl]-1Hbenzimjdazole)

as described in European Patent Applications EP-A-244 380 ___________ and EP-A.247 983.
DESCRIPTION OF THE INVENTION

It has now been found, surprisingly, that if certain fillers

and binders often used as tablet auxiliaries, such as are mentioned for the preparation of the pellet and tablet cores in European Patent Applications EP-A-244 380 and EP-A-
247 983, are dispensed with, the stability problems described do not occur. These fillers and binders are, in
particular, lactose, microcrystalline cellulose and hydrox- ypropylcellulose.

The invention thus relates to a TedicaTent in pellet or tab e orm which contains the active c un pant rathlTs ió1ilknmistered oratty, is resistant to
g tric uice and s ía basic pe e core or et core, onepLQfnj,watc-solubleintnan

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of the tablet cores. -

as well as tablet- in the preparation

lubricants and release agents which may be men salts o(igiieanyIacicistcch as 20 e.g. calcium stearate.

Possible tablet-disintegrating agents are, in particular,

chemically inert agents. (Transversely) crosslinked polyvi- nylpyrroidone (e.g. Crospovidone) may be mentioned as a
25 preferred tablet-disintegrating agent.
In respect of the water-soluble intermediate layer(s) to be applied to the pellet core or tablet core, reference may be made to those water-soluble layers such as are usually used before application of layers wjucj2 are rcsislIaLm-gasuic

juice, or such as are described e.g. in DE-OS 39 01 151. 30 Examples which may be mentioned of film polymers which can be used for the intermediate layer are propyl-

methylcdllulose and/or volvvinvlvvrrolidone. to which olas-

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auuiuvesauuauxivanese.g. ouners, Oases or pigments) can

The iif knows, on the basis of his

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avoid organic solvents and since the core according to the invention does
4. to water known from the prior art).
The active compound pantoprazole is known from Euro-

pean Patent 166 287. Examples of salts of pantoprazole which may be mentioned are the salts mentioned in Euro-
pean Patent 166 287. The sodium salt is a preferred salt.

The use of mannitol as the sole filler for tablets requires a suiç inerjhich mustimp.arisitadequaiehardxiess.to

the core. Theiyvinylpyne dasabinder for

preparation of the core is, in particular, a product of higher moleciLla ght about 300,000 to 400,000)TPVP 90 (molecular weight about 360,000) may be mentioned as a preferred polyvinylpyrrolidone.
Compared with the presentation forms known from the prior art for other HIK’-ATPase inhibitors having the pyridylmethylsulphinyl1Hbepzijniclazo1e structure, the oral resentation form according to the invention is distinguished, in particular, in that a water content in the tablet core in excess of 1.5 wt. % does not lead to discol-oration (decomposition) of the active compound. Stable tablets are thus obtained even with a relatively high residual moisture content (of e.g. 5 to 8 wt. %) in the granules.

Pellets can be obtained by application of a re axt..___ isolation to sucrose starte e s an suuent applica-

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tion of a 30% solution of the active compound in isopro-
panol with hydroxymethyipropylcellulose as the binder.

The isolation layer can also be applied, analogously to
tablets, using corresponding ready-made dispersions (e.g. opadry). The coating with a layer which is resistant to gastric juice is carried out by a procedure analogous to that for tablets.

The following formulation examples illustrate the inven-tion in more detail, without limiting it.

EXAMPLES

1. Tablets

I. Tablet core

a) Pantoprazoic-Na scaqulhydrate 45.1 mg
b) Sodium carbonate 10.0 mg
c) Maanitol 42.7 mg
d Crospovidonc 50.0 mg
e) PVP 90 (povidone) 4.0 mg
I) Calcium stearEe 3.2 mg

155.0 mg

a) is mixed with some of b), c) and d). The remainders of b) and c) are added to a clear aqueous solution of e) and the pH is brought to >10 with b). Granules are obtained with this solution in a fluidized bed. The remainder of d), and f) are added to the dry granules and the granules are pressed on a suitable tablet-making machine.

II. Preliminary isolation (intermediate layer)

g) HPMC 2910.3 cps 15.83 mg
h) PVP 25 0.32 mg
1) Titanium dioxide 0.28 mg

f) LB tine oxide yellow 100 E 172 0.025 ins
kJ Propylene glycol 3.54 mg

20.00 mg
Total weight per preisolated core 175.00 mg

g) is dissolved in water and h) is added and also dissolved (A). i) and J) are suspended in water using a suitable stirrer (B). A and B are combined. After addition of k), the suspension is sieved immediately before further processing, during which the tablet cores obtained under I. are coated with an adequate layer thickness of the suspension in a suitable apparatus.

Ill. Coating with a layer which is resistant to gastric juice

I) Eudragit fi L 30 D 13.64 mg
m) Triethyl citrate 1.36 mg

15.00 mg Total -eight per film-coated tablet 190.00 mg
resistant to gastric juice

1) is diluted with water and m) is added. The dispersion is sieved before processing.

ill, is sprayed, in suitable apparatuses, onto the preisolated cores obtained under II.

2. Pellets
riier pellets

a) Sucrose pellets (0.7-0.85 mm) 950.08
b) Hydroxypropylnrethylceltuloae 50.0 g

a) is sprayed with an aqueous solution ofb) in a fluidized bed (Wurster process).
0 H. Active pellets

c) Pantoprazole-Na seaquihydratc 403.0 g
d) tlydroxypropylmethylcellulose 40-3g

15 c) and d) are dissolved in succession in 30% isopropanol,
and the solution is sprayed, in a fluidized bed (Wurster process), onto 900 g ofihe starter pellets obtained under I. HI. Preliminary isolation (intermediate layer)

The coating operation is carried out by a procedure 20 analogous to that described for the tablets, in a coating pan or in a fluidized bed.

IV Coating with a layer which is resistant to gastric juice The coating operation is carried out by a procedure analogous to that described for the tablets, in a coating pan 25 or in a fluidized bed.

Capsules of suitable size (e.g. 1) are then filled with the pellets.
We claim:
1. An orally administerable medicament in pellet or tablet
30 form which is resistant to gastric juice, and in which each pellet or tablet consists of

a core in which active compound or its physiologically- tolerated salt is in admixture with binder, filler and,
optionally, a member selected from the group consist-
35 ing of another tablet auxiliary and a basic physiologically-tolerated inorganic compound,

an inert water-soluble intermediate layer surrounding the core and
an outer layer which is resistant to gastric juice,
o wherein the active compound is pantoprazole, the binder is polyvinylpyrrolidone and/or hydroxypropylmethyl-cellulose and, optionally, the filler is mannitol.
2. Medicament according to claim 1 in tablet form, wherein polyvinylpyrrolidone and/or hydroxypropylmethyl-
s cellulose is the binder and mannitol is the filler.
3. Medicament according to claim 1 in pellet form, wherein polyvinylpyrrolidone and/or hydroxypropylmethyl-cellulose is the binder.

4. Medicament according to claim 1, wherein
so pantoprazole-sodium is the physiologically tolerated active compound salt.
5. Medicament according to claim 1, wherein pharmaco-logically tolerated alkali metal, alkaline earth metal or earth metal salt of a weak acid or pharmacologically tolerated 55 hydroxide or oxide of an alkaline earth or earth metal is the basic, physiologically tolerated inorganic compound.
6. Medicaments according to claim 1, wherein sodium carbonate. is the basic, physiologically tolerated inorganic compound.

60 7. A core of an orally-administrable medicament in pellet or tablet form wherein pantoprazole or a physiologically- tolerated salt thereof, as an essential active component, is in

admixture with binder, filler and, optionally, a member selected from the group consisting of another tablet auxiliary
65 and a basic physiologically-tolerated inorganic compound;
the binder being polyvinylpyrrolidone and/or hydrox-ypropylmethylcellulose.

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ORAL PHARMACEUTICAL COMPOSITION WITH DELAYED RELEASE OF ACTIVE INGREDIENT FOR PANTOPRAZOLE

RELATED APPLICATION

This application is related to Applicants’ concurrently-filed application Set. No. 08/498,391.

FIELD OF THE INVENTION

The present invention relates to oral pharmaceutical com-positions in pellet or tablet form for combined use of pantoprazole with an antimicrobially-active ingredient for the treatment of disorders caused by Helicobacter.

BACKGROUND

Pyridin-2-ylmethylsulflnyl-1H-benzimidazoles, as disclosed, for example, in EP-A 0005129, EP-A 0166287 and EP-A 0268956 are becoming increasingly important, because of their H’/K’ ATPase-inhibiting action, for the therapy of diseases which originate from increased gastric acid secretion. Examples of active ingredients which are already commercially available from this group are ome-prazole (INN), lansoprazole (INN) and pantoprazole (INN). These active ingredients are also called irreversible proton pump inhibitors.
Control of the microbe, Helicobacter pylon, which is thought to be responsible for certain gastric disorders, by combined use of an antirnicrobially-active ingredient which is active against Helicobacter pylori and of an agent which reduces gastric acid has been regarded as the method of choice for some time.

EP-A 0519365 proposes (for the active ingredient

pantoprazole) a formulation based on the principle of an alkaline core coated with a water-soluble intermediate layer

and with an enteric layer, where improved stability is achieved by using polyvinylpyrrolidone and/or hydroxypro-pylmethylcellulose as binder for the alkaline core.
EP-A 0342522 discloses a formulation for acid-sensitive benzimidazolcs, in which an intermediate layer is located between the alkaline core and the enteric coating and is composed of a film-forming material which has only low solubility in water, such as ethylcellulose and polyvinyl acetate, and of a fine-particle inorganic or organic material which is suspended therein and has low solubility in water, such as magnesium oxide, silicon oxide or sucrose fatty acid
esters.

JP-A 59020219 discloses an enteric composition for acid- labile active ingredients which comprises (under the enteric
coating) an intermediate layer of a film-forming material, such as hydroxypropylmethylcellulose, hydroxypropyleel-

lulose and hydroxypropylmethylcellulose phthalate with a content of higher fatty acids.
DE-A 3233764 proposes for enteric compositions an intermediate layer which is formed from a water-soluble cellulose ether and a water-soluble mono- or polybasic organic acid, such as citric acid, tartaric acid, and the like. Combined use of irreversible proton pump inhibitors with antimicrobially-active ingredients does indeed show a good effect against Helicobacter in vitro. However, the clinical effect achieved with this combined use is disappointing. Of practical inconvenience is the great delay in the onset of action.

SUMMARY OF THE INVENTION

The action of an antimicrobia]ly-active ingredient on Helicobacter surprisingly is enhanced by administering pan-

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toprazole in slow-release dosage form (extended release form). It must be regarded as particularly surprising that, in addition, administration of the slow-release pantoprazole results in the onset of action taking place significantly faster 5 than on administration in a form without retarding such release. The duration of treatment until Helicobacter is eradicated is shortened, saving considerable amounts of antibiotic and acid inhibitor.

The invention thus relates to oral pharmaceutical compo-
10 sitions in pellet or tablet form for combined use of panto-prazole with an antimicrobially-active ingredient for treat-ment of disorders caused by Helicobacter, wherein pantoprazole is present at least partly in slow-release form.

15 DETAILS

In connection with the present invention, pantoprazole is
the compound, 5-difluoromethoxy-2-[(3,4-dimethoxy.2-pyridinyl)methylsulfinyl]-lH-benzimidazole, its salts and solvates (e.g. hydrates), in particular the sodium salt with 20 one and a half molecules of water of crystallization (pantoprazole Nax15 H20).
Examples of suitable antimicrobially-active ingredients (active against Helicobacter and, in particular, against Heli-

cobacter pylon) are enumerated in European Patent Appli- 25 cation EP-A 0282131. These active ingredients include, for
example, bismuth salts (such as bismuth subcitrate or bis-

muth subsalicylate), sulfonamides, nitrofurans (such as nitrofurazone, nitro furantoin or furazolidonc), metronidazole, tinidazole, nimorazole or antibiotics. 3° Examples of antibiotics which may be mentioned in this
connection are, arranged according to particular classes of active ingredient: aminoglycosides, such as gentamicin, neomycin, kanamycin, amikacin or streptomycin;

is macrolides, such as erythromycin, azithromycin,

clarithromycin, clindamycin or rifampicin; penicillins, such as penicillin G, penicillin V, ampicillin, mezlocillin or amoxicillin; polypeptides, such as bacitracin or polymyxin;

tetracylines, such as tetracyline, chlorotetracycline,

oxytetracydline, minocydline or doxycycline; carbapenems, 40 such as imipenem, loracarbef, meropenem or panipenem;

cephalosporins, such as cefalexin, cefoxitin, cefuroxime

axetil, cefotaxime, cefpodoxim proxetil, cefaclor, cefadroxil or cephalothin; gyrase inhibitors, such as ciprofioxacin,
45 norfioxacin, ofloxacin or pefioxacin, or other different antibiotics, such as chloramphenicol.
Particularly worthy of mention in this connection is also
the conjoint administration of pantoprazole with a plurality of antimicrobially-active ingredients, for example with a 50 combination of bismuth salt and/or tetracycline with

metronidazole, or with the combination of anioxicilhin or clarithromycin with metronidazole.
Antimicrobially-active ingredients which may be empha-sized are erythromycin, azithromycin, clanithromycin, 55 clindamycin, rifampicin, ampicillin, mezlocillin, amoxicilhin, tetracycline, minocycline, doxycycline, imipenem, meropenem, cefalexin, cefuroxime axetil, cefpo-doxime proxetil, cefaclor, cefadroxil, ciprofioxacin, norfioxacin, ofioxacin and pefioxacin.

60 Clarithromycin and amoxicillin may be mentioned as antimicrobially-active ingredients which should be particu-
larly emphasized.
Combined administration means, for the purpose of the present invention, fixed and, in particular, free 65 combinations, i.e. either slow-release pantoprazole and the

antimicnobially-active ingredient are present together in one dosage unit, or slow-release pantoprazole and

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antiniicrobially-active ingredient, which are present in sepa-
rate dosage units, are administered in direct succession or at
a relatively large time interval; a relatively large time interval means a time span up to a maximum of 24 hours.
For use as separate dosage units, these are preferably made s available together in one pack. For example, the two dosage units are packed together in blister packs which are designed with regard to the relative arrangement of the two dosage units with respect to one another, the inscription and/or coloring in a manner known per se so that the times for 10 taking the individual components (dosage regimen) of the two dosage units are evident to a patient.
A dosage unit means, in particular, a medicinal dosage form in which slowing of pantoprazole release is achieved with as few problems as possible. This includes, in 15 particular, tablets, coated tablets or pellets, and microtablets in capsules, with the dosage form advantageously being designed so that the two active-ingredient components (pantoprazole on the one hand and antimicrobially-active ingredient on the other hand) are released, or made available 20 effectively for the body, in such as way that an optimal active ingredient profile, and thus action profile, is achieved.
It is possible to use (for retarding release) various types and degrees of retardation so that a pantoprazole plasma level, which persists as long as possible and is sufficient for 25 raising pH, is ensured.
The pharmaceutical formulation of the antimicrobially-active ingredient is carried out as is familiar per se to the

skilled worker for the individual active ingredient. 30 Rapid release of part of the pantoprazole and extending release of another part can be achieved, for example, also by layered tablets or multilayer tablets, in which case part of the pantoprazole is present in an outer coating in a form without retarding its release; this is followed by another coating 35 containing the antimicrobially-active ingredient and then the core with the pantoprazole, whose release is extended in a suitable manner.
The details of how to achieve slowing of or extending release are familiar to the skilled worker on the basis of his expert knowledge. The skilled worker is likewise familiar with suitable ancillary substances and vehicles for the required dosage forms (pharmaceutical formulations). Besides solvents, tablet auxiliary substances and other active ingredient excipients it is possible to use, for example, 45 tablet-coating compositions, plasticizers, antioxidants, preservatives, dyes, etc. Where incompatibilities between the active ingredients or between the active ingredients and ancillary substances are expected, suitable separating layers are provided where appropriate (for example in layered or multi-layer tablets).
The dosage of the active ingredients depends greatly on the nature of the antimicrobially-active ingredients used. A typical dosage for pantoprazole can be regarded as being a daily dose of from about 0.01 to about 20, preferably from s 0.05 to 5, in particular from 0.1 to 1.5, mg/kg of body weight, where appropriate in the form of a plurality ofsingle doses. Penicillins, such as amoxicillin, are administered in a daily dose of from about 5 to 40, preferably from 10 to 20, mg/kg of body weight. 6(Because of a great tendency to decompose in a neutral and, in particular, acidic environment, which also results in highly colored decomposition products, for oral compositions, it is necessary on the one hand to keep pantoprazole in an alkaline environment and, on the other 6 hand, to protect it from exposure to acids. It is generally known to coat tablets or pellets which contain an acid-labile

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active ingredient with an enteric coating which, after pas-sage through the stomach, rapidly dissolves in the alkaline medium in the intestine. In the case of pantoprazole, which in very acid-labile, it is necessary to process it in the tablet core or in pellets in the form of its alkaline salts, for example as sodium salts, or together with alkaline substances. Since the substances suitable for enteric coatings contain free carboxyl groups, a problem arises when the enteric coating is partly or even completely dissolved from the inside because of the alkaline medium in the interior, and the free carboxyl groups promote decomposition ofthe active ingre-dients. it is therefore necessary to provide a sealing inter-mediate layer (subcoating) between the enteric coating and the alkaline tablet core. EP-A 0244380 proposes to coat cores which contain the active ingredient together with alkaline compounds or as alkaline salt with at least one layer, which is soluble in water or rapidly disintegrates in water, of nonacidic, inert pharmaceutically-acceptable substance before the enteric layer is applied.
The intermediate layer or intermediate layers act as p11-buffering zones in which hydrogen ions, which diffuse in from the outside, are able to react with the hydroxyl ions which diffuse out of the alkaline core. In order to increase the buffer capacity of the intermediate layer, it is proposed to incorporate buffer substance into the intermediate layer (s). It is possible in practice by this method to obtain rather stable compositions. However, relatively thick intermediate layers are required to prevent the unsightly discoloration which occurs even on only slight decomposition. In addition, considerable effort must be made to avoid traces of moisture during manufacture.
It is a further aim within the scope of the present invention to provide an oral pharmaceutical composition with delayed and controlled release of active ingredients in pellet or tablet form for pantoprazole, which is distinguished by great resistance to decomposition and discoloration of the active ingredient caused by moisture and other effects.
This aim is particularly advantageously achieved by pro-viding at least one release-slowing intermediate layer of water-insoluble film former, which at the same time repre-sents a barrier for mutual interactions between the active ingredient with an alkaline reaction and the enteric coating with an acidic reaction.

In this connection, film formers are regarded as insoluble in water when they cannot be dissolved in water without further additions (organic solvents, detergents, alkalizing substances, etc.).
The invention therefore also relates to an oral pharma-ceutical composition in pellet or tablet form for acid-labile irreversible proton pump inhibitors comprising an alkaline pellet or tablet core, at least one release -slowing, release-controlling intermediate layer and an outer enteric layer which is soluble in the small intestine, wherein the inter-mediate layer for the pharmaceutical composition is formed from a water-insoluble film former, the film former being applied from anhydrous solution or aqueous dispersion. The slowing of release can be achieved, for example, by a semipermeable membrane, as disclosed in numerous pat-ents (e.g. EP B 0185331).
The details of how to achieve stowing of release are familiar to the skilled worker on the basis of his expert knowledge. The skilled worker is likewise familiar with suitable ancillary substances and vehicles for the required dosage forms (pharmaceutical formulations). Besides solvents, tablet ancillary substances and other active ingre-dient excipients it is possible to use, for example, tablet-

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coating compositions, plasticizers, antioxidants, preservatives, dyes, etc. Where incompatibilities between
the active ingredients or between the active ingredients and ancillary substances are expected, suitable separating layers
are provided where appropriate.
The oral pharmaceutical compositions according to the invention are distinguished from the prior art by controlled release of active ingredients and increased stability. It is particularly advantageous to keep the intermediate layer (which controls the release of active ingredients) very thin (between 20 and 80, preferably between 40 and 60,,u which leads to a considerable saving of material and shorter processing times. The insolubility of the intermediate layer in water means that the application of the enteric layer in the

form of aqueous suspensions is not critical because there can be no dissolution ofthe intermediate layer. Furthermore, oral
pharmaceutical compositions with a considerably smoother surface are obtained, which not only leads to a better visual appearance but also technically simplifies an imprinting process for tablets.
For a basic reaction of the pellet or tablet core it is mixed (where required increase in pH is not achieved simply by using an active-ingredient salt) with an inorganic base. Mention may be made in this connection of, for example, the

pharmacologically-suitable alkali-metal, alkaline-earth- metal or earth-metal salts of weak acids and the
pharmacologically-suitable hydroxides and oxides of alkaline-earth and earth metals. Sodium carbonate may be mentioned as a base to be emphasized by way of example. Besides filler and binder, other ancillary substances, in particular lubricants and nonstick agents, and tablet

disintegrants, are used in the manufacture of the tablet cores. A suitable binder is, in particular, polyvinylpyrrolidone in
various degrees of polymerization. Examples of lubricants and nonstick agents which may be mentioned are higher fatty acids and their alkali-metal and alkaline-earth-metal salts, such as calcium stearate. Suitable tablet disintegrants are, in particular, chemically inert agents. Tablet disinte-grants which may be mentioned as preferred are crosslinked polyvinylpyrrolidone, crosslinked sodium carboxymethyl-celluloses and sodium starch glycolate.
Examples of film-forming polymers which can be used in the water-insoluble release-slowing intermediate layer(s) (to be applied to the pellet or tablet core) include ethylcellulose, polyvinyl acetate, Eudragitfi RS, Eudragitfi RI, etc. (Each of Eudragitfi RS and Eudragitfi RL is an ammonio meth-acrylate copolymer.) The release rate can be controlled not only by incorporating therein suitable water-soluble pore formers, such as PEG, lactose, mannitol, sorbitol, HPMC, etc., but also by the thickness of the coating layer applied.

The solvents or dispersants used for the release- controlling polymer dispersion are non-aqueous organic
solvents, such as alcohols, ketones or halogenated hydro-carbons or mixtures of such solvents.

It is possible in a similar way to use osmotic systems with semipermeable membranes of cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, as described in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,036,227, U.S. Pat. No. 4,093,708, U.S. Pat. No. 4,096,238, U.S. Pat. No. 4,135,514 and U.S. Pat. No.

4,142,526, to control the release of active ingredients. These can be coated with aqueous dispersions of enteric lacquers
without changing release rate.
Examples ofsuitable polymers for the enteric coating are methacrylic acid/methyl methacrylate copolymer or meth-acrylic acid/ethyl methacrylate copolymer (Eudragitfi L) or

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cellulose derivatives, such as carboxymethylethylcellulose (CMEC, Duodcel), cellulose acetate phthalate (CAP), cel-lulose acetate trimellitate (CAT), hydroxypropylmethylcel-lulose phthalate (HP50, HPSS), hydroxypropylmethylcellu-S lose acetate succinate (HPMCAS) or polyvinyl acetate phthalate, to which it is also possible to add, if desired, plasticizer (such as propylene glycol) and/or other additives and ancillary substances (e.g. buffers, bases, such as, preferably, aluminum hydroxide, or pigments).
10 The layers are applied in conventional ways using equip-ment customary for these purposes.

EXAMPLES

The following formulation examples explain the inven-tion in detail without restricting it.

Example 1

20 Tablets

I. Production of uncoated core

a) Pantoprale Na x 1.5 H20 45.1 mg

25 b) Sodium carbonate 10.0 mg c) Mannitol 20.0 mg d) EPMC291O3Cps 25.0 mg e) flPMC 2910 15 cps 4.0 mg f) Calcium stearatc 2.1 mg

30 106.2 mg

a) is mixed with one part of b), c) and d). The remainder

of b) and c) is added to the clear aqueous solution of e), and the pH is adjusted to> 10 with b). This solution is 35 used for fluidized bed granulation. The remainder of d)
and t) is added to the dried granules, and the granules are compressed in a suitable tabletting machine.

H. Release-slowing layer 40

g) Elhylcellulose 9.85 mg h) Lactose micronized 2.37 erg Propylene glycol 0.98 mg

45 j) Ammonia 25% 0.80 erg
14.00 mg

g) is dissolved in 165 ml of isopropanol to prepare
50 solution (A). A fine suspension of h) in 165 ml of

isopropanol is prepared using a rotor-stator agitator, and subsequently i) and j) are stirred in using a suitable
agitator to prepare suspension The solution (A) and the suspension (B) are combined.

55 The tablet cores obtained from I are coated to an adequate layer thickness with the suspension obtained above in suit-able apparatus.

Ill. Enteric coating

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I) Eudragit fi L 13.64 erg in) Triethyl citrate 1.36 mg

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15.00 mg

1) is diluted with 140 ml of water, and m) is added. The resulting dispersion is screened before processing. The

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dispersion from ff1 is sprayed onto the presealed cores obtained from II in suitable equipment.

Example 2

Tablets

I. Production of the uncoated core

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-continued

8) Propylene glycol 201.5 g
h) NaOH 1.0 g

I), g), h), e) are successively dissolved in 4 liters of
purified water and sprayed onto 900 g of the pellets
obtained in i in a fluidized bed (Wurster method).

Production of the cores took place as in Example I point 10 III. Presealcd pellets

A release-slowing layer is applied in analogy to the

H. Release-slowing layer procedure described for tablets in a pan or fluidized bed.

IV. Enteric-coated pellets 8) Polyvinyl acetate 9.15 mg 15
h) Lactose micronized 2.27 mg The coating is applied in analogy to the procedure i) Propylene glycol 0.91 mg
j) Ammonia 25% 0.80 nag described for the tablets in a pan or fluidized bed.
The pellets are subsequently packed into capsules of
23.13 nag suitable size (e.g. size 1).
20

Example 4
g) is dissolved in 150 ml of a 1:1 acetone/chloroform
mixture to prepare a solution (A).
A fine dispersion of h) in 150 ml of a 1:1 acetone/
choroform mixture is prepared using a rotor-stator agitator, I. Active Pellets

and subsequently i) and j) are stirred in using a suitable 25
agitator to prepare a suspension (B). Solution (A) and
suspension (B) are combined. c) Pantopramle Na x 1.5 1120 403.0

[he tablet cores obtained in I are coated to a sufficient d) N carbonate 87.3 g e) Microcryst.11inc cellulose 117.0 8 layer thickness with the suspension obtained above in suit- 30 (Avicel PHIOI)

able apparatus. Ni carbozymethylcellulosc 18.0 g

Ill. Enteric coating c)-.t) are premixed dry and subsequently moistened to a
paste-like consistency with a solution of Na carbonate
I) Eudragit fi L 13.46 mg 35 and Na carboxymethylcellulose in water in a conven-
m) Thethyl citrate 1.36 nag tional kneader or high-speed mixer. The resulting com-

15.00 nag position is then extruded and shaped into pellets by the
Total weight per enteric film-coated 183.50 nag exi7idrmethod familiar to the skilled wok
tablet ThriThined pellets are dried in suitable equipment
40 (drying oven, fluidized bed, etc.).

1) is diluted with 135 ml of water, and m) is added. The M. Release-slowing layer
dispersion is screened before processing.

The dispersion from Ill is sprayed onto the presealed The release-slowing layer is applied in analogy to the
cores obtained in II in suitable equipment. procedure described for tablets in a pan or fluidized bed.

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IV. Enteric-coated pellets Example -3-,Thecoating is applied in analogy to the procedure / described for tablets in a pan or fluidized bed.

50 subsequently packed into capsules of

suitable size (?.g. s 1. Starter Pellets ’lvtion and its advantages are readily understood
a) Sucrose pellets (0.7-0.85 mm) 950.0 a from the foregoing dŁscription. As is apparent, vÆiioii
b Hydioxypropylmcthylcdllulose 40.0 8 changes can be made in the products and methods without
2910 (’)
c) Propylene glycol 9.9 g

55 departing from the spirit and scope of the invention or
J) NaOH 0.1 sacrificing its material advantages. The products and pro-
cesses hereinbefore described are merely illustrative of a
preferred embodiments of the invention.

a) is sprayed with an aqueous solution of b), c) and d) in what is claimed is: a fluidized bed (Wurster method). 60 1. An oral pharmaceutical composition comprising

pantoprazole, which is wholly or partly in slow-release
11. Active pellets form, in a multilayer tablet together with an antimicrobially-
active ingredient for treating a disorder caused by

c) Pantoprazole Nix 1.5 H 403.0 g Heicobacter, the multilayer tablet having a) an alkaline core
ri flydroxypropylmethylcellulose 403.0 g

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65 with all or part of the pantoprazole and b) at least one
2910 (UsP) intermediate layer which controls release of said pantopra-
zole.

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2. An oral pharmaceutical pantoprazole composition in combination with an antimicrobially-active ingredient for treating a disorder caused by Helicobacter, wherein at least
part ofthe pantoprazole is in slow-release form, wherein the slow-release form of pantoprazole has an alkaline pellet or tablet core, at least one intermediate layer controlling release of active ingredient, and an outer coterie layer which is soluble in the small intestine.

3. An oral pharmaceutical composition as claimed in claim 2, wherein at least one intermediate layer is formed from a water-insoluble, release-slowing film former.
4. An oral pharmaceutical composition as claimed in claim 3, wherein the film former has been applied from a solution or dispersion.
5. An oral pharmaceutical composition as claimed in claim 3, wherein the intermediate layer contains, as water-insoluble, release-slowing film former, water-insoluble cel-lulose ether and/or polyvinyl acetate.
6. An oral pharmaceutical composition as claimed in claim 2, wherein the outer enteric layer comprises a cellulose-based coating.
7. An oral pharmaceutical composition as claimed in claim 6, wherein the cellulose-based coating is a member selected from the group consisting of a carboxymethylethylcdllulose, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxy-propylmethylcellulose phthalate and hydroxypropylmethyl-
cellulose acetate succinate.

S. An oral pharmaceutical composition as claimed in claim 2, wherein a member selected from the group con-sisting of a pore former, plasticizer, buffer, base and pigment is additionally present in the intermediate layer.
9. A pharmaceutical as claimed in claim 2, wherein the antimicrobially-active ingredient is a member selected from the group consisting of bismuth subcitrate, bismuth subsalicylate, mtrofurazone, nitrofurantoin, furazolidone, metronidazole, tinidazole, nimorazole, gentamicin, neomycin, kanamycin, amikacin, streptomycin, erythromycin, azithromycin, clarithromycin, clindamycin, rifampicin, penicillin G, penicillin V, ampicillin, mezlocilhin, amoxicillin, bacitracin, polymyxin, tetracyline,

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chlorotetracycline, oxytetracycline, minocycline, doxycycline, imipenem, loracarbef, meropenem, panipenem, cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil, 5 cephalothin, ciprofloxacin, norfloxacin, ofloxacin, pefloxa-cin and chioramphenicol.
10. A process for producing an oral pharmaceutical com-position in pellet or tablet form for pantoprazole, as active

ingredient, or for combined use thereof with an 10 antimicrobially-active ingredient for treating a disorder
caused by Heicobacter, which comprises a) incorporating the active ingredient as an alkaline salt and/or with addition of an alkaline substance in a pellet or tablet core, b) applying 15 thereto at least one release-slowing intermediate layer com-prising a water-insoluble, release-slowing film former and c) subsequently applying an outer enteric layer which is soluble in the small intestine.

U. A process as claimed in claim 10, wherein the water-
20 insoluble, release-slowing film former for the intermediate layer is applied dissolved or dispersed in a non-aqueous organic solvent or other solvent mixture.
12. An oral pharmaceutical composition as claimed in claim 3, wherein the intermediate layer contains, as water-25 insoluble, release-slowing film former, ethyl cellulose, an ammonio methacrylate copolymer or polyvinyl alcohol.
13. An oral pharmaceutical composition as claimed in claim 12, wherein the outer enteric layer, which is soluble in the small intestine, comprises methacrylic acid/methyl 30 methacrylate copolymer or methacrylic acid/ethyl methacry-late copolymer.
14. A method for treating a disorder caused by Heico-bacter with pantoprazole, the improvement which comprises orally administering the pantoprazole in a composition of 3-1 claim 2.
15. In a method for treating a disorder caused by Heli-cobacter with pantoprazole, the improvement which com-prises orally administering the pantoprazole in a composi-tion of claim 1.

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desintegrante, un subrevestimiento que estÆ comprendidode hipromelosa y agua, un revestimiento entØrico en el subrevestimiento, y un revestimiento de sello final sobre el revestimiento entØrico que se compone de hipromelosa y agua.

Las formulaciones de multiples particulas muestran un efecto sobre los hÆbitos alimenticios reduciendo la variabilidad durante el vaciado gÆstrico, por lo que proporcionan efectos similares entre diferentes individuos que se sometan at tratamiento.

Reivindicaciones I a 27: Multiparticulados de pantoprazol en donde cada uno comprende:

a) Un nUcleo esferoide que comprende pantoprazol o un enantiOmero del mismo,
o una sal o hidrato y un tensioactivo o una combinaciOn de tensioactivos presentes en una relaciOn en peso de pantoprazol: tensioactivo(s) de 10:1 a
5:3.

b) Un revestimiento de sello inicial sobre el nücleo esferoide que comprende hidroxipropilmetilcelulosa y
c) Un revestimiento entØrico el cual comprende un copolimero de Æcido metacrIlico y metacrilatos sobre el revestimiento de sello inicial,

En donde los multiparticulados revestidos tienen un diÆmetro en elrango de 0.7 a
1.25mm.

En la clÆusula 25 se presenta de manera particular la composiciOn de los multiparticulados de pantoprazol:

Pantoprazol sôdico sesquihidratado 45% (pIp)
Celulosa microcristalina 27% (pIp)
Polisorbato 80 5% (p/p)
Crospovidona 15% (PIP)
Hipromelosa 1% (p/p); y
Carbonato de sodio 7% (pIp)

ReivindicaciOn 28: Formulaciôn de pantoprazol para suministrarla a pacientes pediÆtricosque comprende una suspension de los multiparticulados de pantoprazol.

Reivindicaciôn 29: CÆpsula que comprende los multiparticulados de pantoprazol.

Reivindicaciones 30 a 37: Se reivindica un mØtodo para producir una formulaciOn de multiparticulados de pantoprazol que comprende los pasos de:

a) Producir un nücleo esferoide que comprende un compuesto de pantoprazol y un tensioactivo o una combinaciôn de tensioactivos presentes en una relaciôn
en peso de pantoprazol a tensioactivo de 10:1 a 5:3 yio de 2% a 7% en peso
de tensioactivo a nücleo, mediante extrusiOn y esferonizaciOn.
b) Aplicar un revestimiento de sello inicial al nUcleo esferoide.
c) Aplicar un revestimiento entØrico sobre el revestimiento de sello inicial, y
d) Opcionalmente, aplicar un revestimiento de sello final al nücleo esferoide con revestimiento entØrico.

En donde los multiparticulados revestidos tienen un diÆmetro en el de 0.7 a 1.25mm.

Una vez catalogada la invenciôn Østa se clasificô en la secciôn: A 61
de la ClasificaciOn Internacional de Patentes.

3. Determinación del Estado de la TØcnica

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El Estado de la TØcnica se determinô con base en la fecha de presentaciOn de la solicitud de prioridad: Octubre 01 de 2003 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Fecha de Documento TItulo Publicación
"Multiple unit pharmaceutical
Dl W096/01624 preparation containing proton pump 25/01/1996
inhibitor"
"Composition containing and acid labile
D2 US6159499 benzimidazole an process for its 12/12/2000
preparation"

D3 US5997903 "Oral-administration forms of a 07/12/1999 medicament_containing_pantoprazol"
"Oral pharmaceutical composition with
D4 US5945124 delayed release active ingredient for 31/08/1999
pantoprazole"

Anterioridad Dl en los folios 222 a 231 y 280 a 284. Anterioridad D2 en los folios 232 a 239 y Anterioridad D3 en los folios: 291 a 294. Anterioridad 04 en los folios 295 a 300.

4. AnÆlisisde patentabilidad (artIculo 14 D. 486)

La reivindicación I consiste en multiparticulados de pantoprazol en donde cada uno comprende:

a) Un nUcleo esferoide que comprende pantoprazol o Un enantiOmero del mismo,
a una sal o hidrato y un tensioactivo o una combinaciôn de tensioactivos presentes en una relaciôn en peso de pantoprazol: tensioactivo(s) de 10:1 a
5:3.

b) Un revestimiento de sello inicial sobre el nücleo esferoide que comprende hidroxipropilmetilcelulosa y
c) Un revestimiento entØrico el cual comprende un copollmero de Æcido metacrIlico y metacrilatos sobre el revestimiento de sello inicial,

En donde los multiparticulados revestidos tienen un diÆmetroen el rango de 0.7 a 1.25mm.

En la clÆusula 25 se presenta de manera particular la composiciOn de los multiparticulados de pantoprazol:

Pantoprazol sOdico sesquihidratado 45% (p/p)
Celulosa microcristalina 27% (p/p)
Polisorbato 80 5% (p/p)
Crospovidona 15% (p/p)
Hipromelosa 1% (p/p); y

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Carbonato de sodio 7% (pIp)

- El estado del arte previo a la invenciôn presenta los siguientes documentos:

La publicaciOn Dl revela una preparacion farmacØutica de un multiparticulado constituido por nUcleos de un inhibidor de la ATPasa presentes en la forma de particulas, grÆnulos opellets. El principio activo puede ser pantoprazol, tal y como se establece en el folio

La sustancia activa puede ser mezclada con otros componentes como aglutinantes, surfactantes, agentes de relleno, desintegrantes, aditivos alcalinos, entre otros. Ej: HPMC, HPC, CMCNa, PVP, laurilsulfato de sodio. Los nücleos presentan una capa de recubrimiento insoluble en agua que comprende óxidos, celulosas polimeros orgÆnicos,ademÆs presentan una capade recubrimiento entØnco constituido por una capa inicial que separa la capa de recubrimiento insoluble de la capa de recubrimiento ent(?rico y que puede contener azücar, polietilenglicol, PVP, polivinil-alcohol, polivinilacetato, HPC, metil-celulosa, etil-celulosa, HPMC, CMCNa. Esta capa intermedia funciona coma una barrera de difusiOn o buffer que actUa de acuerdo con el pH de la zona donde se pretende la liberación del activo.

La capa final del recubrimiento entØrico corresponde a una soluciôn o dispersion de un copoilmero de ÆcidometacrIlico, acetato ftalato de celulosa, HPMC ftalato, HPMC acetato-succinato, Polivinilacetato-ftalato, trimelitato acetato celulôsico, CMEC y gomas laca Shellac. Y los nücleos pueden ser fabricados por extrusiOn I esferonizaciôn o compresion.

La publicaciOn D2 revela una composiciOn adaptada para administración oral que comprende:

a) Un nUcleo que contiene un bencimidazol como ingrediente activo en la forma de una sal
b) Una capa intermedia
c) Una capa de recubrimiento entØrico

Los ejemplos ejemplos 6 a 8 seæalanpreparaciones farmacØuticas de pantoprazol para administración oral que contienen los siguientes elementos caracteristicos:

CornposiciOn del Nücleo

Pantoprazol 40,00mg
HPMC 20,00mg
Lactosa 120,00mg
Polisorbato 80 1,00mg
Estearil-furnarato de sodio 1,00mg
Crospovidona 20,00mg
Agua 250,00mg

Composiciôn de la capa intermedia

Talco 2,5mg
DiOxido titanic 1,0mg
HPMC 5,0mg
Agua 35,0mg

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ComposiciOn de la Cubierta entØrica

Copoilmero de ÆcidometacrIlico 10,0mg
Trietil-acetato 1,5mg
Talco 2,0mg
Agua 40,0mg

La anterioridad D3 hace referenda a formas de administraciOn oral que contienen pantoprazol que presentan un nücleo, una capa intermedia y una pelicula de recubrimiento resistente a los jugos gastricos. En especial, la publicaciOn hace referencia a los Microgranulados activos de pantoprazol que presentan los siguientes elementos caracteristicos:

I. Microgranulado inicial

a) Microgranulado de sucrosa 950,Og
b) Hidroxipropilmetilcelulosa 50,09

a) es sometido a aspersion con una soluciôn acuosa de b) en un lecho fluidizado. (Proceso Wurster)

II. Microgranulado activo

c) Pantoprazol sódico sesquihidratado 403.Og
d) Hidroxipropilmetilcelulosa 40,3g

C) y d) se disuelven de forma consecutiva en una soluciOn de isopropanol 30%. La

soluciOn es sometida a aspersion en un lecho fluidizado (Proceso Wurster) en 900g de los Microgranulados obtenidos inicialmente en (I).
Ill. Peilcula de recubrimiento preliminar

La operaciOn de recubrimiento es Ilevada a cabo por un procedimiento anÆlogoat utilizado para el caso de las tabletas, mediante la aplicaciOn de una pelIcula compuesta por:

g) HPMC 2910, 3cps 15,83mg
h) PVP 25 0,32mg
i) DiOxido de titanio 0,28mg
j) Oxido de hierro amarillo 100 E172 0,025mg
k) Propilenglicol 3,54mg

IV. Recubrimiento con pelicula resistente a los jugos gÆstricos

La operaciOn de recubrimiento es Ilevada a cabo por un procedimiento anÆlogo al utilizado para el caso de las tabletas, mediante la aplicaciOn de una pelIcula compuesta por:

I) Eudragit fi L30D 13,54mg m) Trietil citrato 1,36mg

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La anterioridad D4 revela una composiciOn farmacØutica oral que permite la liberaciôn modificada del principio activo pantoprazol. Las formulaciones divulgadas se presentan en la forma de tabletas o Microgranulados.

El ejemplo 3 de D4 divulga Microgranulados obtenidos por la tØcnica de lecho fluidizado que presenta los siguientes elementos caracterIsticos:

I. Microgranulado inicial

a) GrÆnulosde sucrosa [0,7-0,85mm] 950,09
b) Hidroxipropilmetilcelulosa 2910 (USP) 40,Og
C) Propilenglicol 9,9g
d) NaOH 0,1g

II. Microgranulado con agente activo

e) Pantoprazol Na x 1,51-1 403,Og
f) Hidroxipropilmetilcelulosa 2910 (USP) 403,Og
g) Propilenglicol 9,9g
h)NaOH 0,1g

Ill. Microgranulado precubierto

I) Polivinil-acetato 9,15mg
j) Lactosa micronizada 2,27mg
k) Propilenglicol 0,91mg
I) Amoniaco 25% 0,80mg

Ill. Microgranulado con recubrimiento entØrico

m) Eudragit fi L 1346mg
n) Trietil citrato 1,36mg

El ejemplo 4 de D4 divulga la composicion cuali-cuantitativa de una clase de Microgranulado en el que se incorpora una primera capa de recubrimiento y sobre ella el recubrimiento entØrico. Este Microgranulado se obtiene por la tØcnica de premezclado y extrusión/esferonizaciôn, tal y como a continuaciôn se establece:

Microgranulados

I. Microgranulado activo

a) Pantoprazol Na x 1.5 H20 403,Og
b) Carbonato Na 87,3g
C) Celulosa microcristalina (Avicel PHI01) 117,09
d) Carboximetilcelulosa Na 18,Og

c -f) son sometidos a premezcla en estado seco y luego se forma un aglomerado de consistencia pastosa con la adiciôn de carbonato sOdico y carboximetilcelulosa sOdica en agua. La composicion resultante es luego sometida a proceso de extrusion y esferonizaciOn con elfin de formar el Microgranulado. Los grÆnulosobtenidos se someten a proceso de secado en un equipo de lecho fluidizado o una cÆmarade secado.

Ill. Recubrimiento primario

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La peilcula de recubrimiento primarlo que modifica la liberaciOn del agente activo presenta los siguientes componentes:

e) Polivinil acetato 9,15mg
f) Lactosa micronizada 2,27mg
g) Propilenglicol 0,91mg
h) Amoniaco 25% 0,80mg

III. Microgranulado con recubrimiento entØrico

i) Eudragit fi L 13,46mg
j) Trietil citrato 1,36mg

Tabla 1. Comparacion entre los elementos tØcnicos reivindicados y los antecedentes
Dl, D2, D3yD4.

Materia Reivindicada Antecedente Dl Antecedente D2 Antecedente D3 Antecedente D4 (W096101 624) (US6I 59499) (US5997903) (LJS59451 24)

(Ver ejemplo 2 folio 286)

(Ver ejemptos 6-8 columna

12 folio 234) (Ver columna 4 llneas 1 a (Ver ejemplo 4 columna 8 del Mulparticulados de
pantoprazol que comprende. Microgranulado de Composiciones de 25 folio 293)

Micropranulado de

folio 299)
pantoprazol microtabtetas Microgranulado de de
pantoprazol pantoprazol pantoprazol

a) Nücleo esferoide que a) Composiciôn de los a) Composición de los a) Composicion de los a) Microgranulado acvo comprende nUcleos: ncleos: nUcleos
i) Pantoprazol o un i)Pantoprazol i) Pantoprazol I) Pantoprazol sódico I) Pantoprazol sÆdicox
enanômero, sal o hidrato del Nidroxipropil celulosa HPMC Sucrosa I.5HO
mismo Manitot Lactosa sesquihidratado Celulosa microcristalina
Celulosa microcristalina Crospovidona Hidroxipropilmetilcelulosa Carbonato de sodio
Agua punficada Polisorbato 80 Carboximetilcelulosa sOdica
Agua
ii) un tensioactivo o ii) Lauril-sulfato de sodio ii) Lauril-sulfato de sodio
combinación de tensioactivos. Estearil-fumarato de
sodio
F-0 itoprazol: tensloactivos
10:1 a 5:3 relación en peso
de tensioactivos a nUcleo de
2%a7%.

b) Revestimiento de sello b) Composicion de la b) Composiciôn de la b) Recubrimiento b) Recubrimiento prnario inicial sobre el nücleo pelicula de cubrimiento: pelicula intermedia preliminar esferoide que comprende HPMC HPMC HPMC Polivinil acetato

HPMC Agua puhficada Talco PVP 25 Lactosa micronizada
Dióxido de htanio Diôxido de titanio Propilenglicol
Agua Oxido de hierro amallo Amoniaco 25%

Propilenglicol c) Revestimiento entØrico que c) Cornposiciôn del C) Composición de la c) Recubrimiento entØrico C) Recubrimiento entØrico comprende recubrimiento entØrico cubierta entØrica: resistente a jugos Eudraciit L

copolimero de Æcido Copotirnero de Æcido CopotImero de âcido gastricos Trietil citrato
metacrilico metacrilatos metacrllico metacrllico Eudrapit L
sobre el revestirniento de sello Trietil-citrato Trietil citrato Trietil citrato
inicial Mono diglicØridos Talco
Polisorbato 80 Agua
Agua purificada

DiÆmetro [0,7 1,25mmj DiÆmetroMicrogranulado DiÆmetroMicrogranulado DiÆmetroMicrogranulado 0,5mm [0,7 0,85mm] [0,7 0,85mm]

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AnÆlisis de Diferencias TØcnicas:

La diferencia entre la invenciôn definida en la reivindicación I y el documento Dl consiste en el tamano o diÆmetro del Microgranuladotoda vez que Øste oscila entre [0,7 y 1,25mm], mientras que en el qaso del Microgranulado revelado en Dl su tamaæo apenasalcanza los 0,5mm de diÆmetro(Ver folio 287 lmneas 18 y 19). Y el mØtodo utilizado para fabricar el microgranulado es extrusiôn/esferonizaciôn.

Frente a las enseæanzas del documentoD2 la diferencia estriba en que la invención presenta un Microgranulado, mientras que en D2 se divulgan microtabletas sin especificar el tamano que alcanzan. Y el mØtodo utilizado para obtener las microtabletas es la granulacion por lecho fluidizado (Ver folio 293 columna 4 lIneas 8 a 18).

Con respecto al documento D3 la diferencia estriba en la composicion de los nücleos que en el caso de la materia reclamada incorpora un agente tensioactivo, mientras que en el caso de D3 no incluye ningün agente tensioactivo. Y el mØtodo utilizado para fabricar el microgranulado es la granulaciOn por lecho fluidizado.

Y frente al documento D4 la diferencia estriba en que la composición de los nücleos reivindicados presenta dentro de sus ingredientes un agente de tension superficial, mientras que los divulgados en D4 no incorporan esta clase de excipiente. Y por otra parte, los nUcleos reivindicados presentan un recubrimiento primario con HPMC, mientras que en D4 si bien se divulga un recubrimiento primario, Øste no estÆ compuesto por HPMC. Y el mØtodo utilizado para fabricar el microgranulado segün D4 es extrusiôn/esferonizaciôn (ver folio 299 lIneas 36 a 38)

Del problema tØcnico objetivo y del efecto inesperado:

El problema tØcnico objetivo que pretende resolver esta invención estriba en la necesidad de disenar una formulaciôn estable de pantoprazol, bioequivalente y con menor propensión a adherirse a las paredes intestinales, tubos nasdgÆstricosy gastronOmicos y material de bolsa, debido a que los revestimientos convencionales presentan la tendencia a provocar la adhesividad de la tableta al tracto gastrointestinal, dificultando el proceso de tragado de la formulaciôn en pacientes con dificultades para engullir y en pacientes pediÆtricos.

Para solucionar este problema, el seæorsolicitante presenta una formulaciOn que permite la liberaciôn prolongada del activo y que presenta variabilidad reducida en tØrminos de sus parÆmetrosfarmacocinØticos.

Sin embargo, la forma de presentaciôn de Microgranulados de pantoprazol en la forma de nUcleos estratificados ha sido divulgada por el estado del arte con anticipaciôn a la fecha de prioridad reivindicada. De hecho, en los antecedentes Dl, o bien D2 se presentan nücleos para microgranulados fabricados a partir de la combinaciôn de pantoprazol y agentes de tensiOn superficial, tal es el caso de lauril sulfato de sodio o su combinaciOn con estearil-fumarato de sodio. Los mencionados nUcleos incluyen un recubrimiento primario o inicial fabricado a partir del polimero HPMC y presentan una segunda capa de recubrimiento fabncada a partir de copollmeros de âcido metacrIlico, denominada de recubrimiento entØnco porque protegen la formulaciôn del efecto corrosivo causado por los jugos gastricos.

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Por otra parte, en los antecedentes D3, o bien D4, se divulgan nücleos de pantoprazol que permiten la liberaciôn modificada del agente activo y que ademÆs incluyen excipientes tipo: celulosa microcristalina, sucrosa o carbonato de sodio dentro del nücleo y cuya función desintegrante aseguran la Iiberaciôn del agente activo. Asimismo, divulgan microgranulados protegidos por una primera capa de recubrimiento fabricada a partir de HPMC y una segunda, con función de recubrimiento entØrico y fabricada a partir de Æcido metacrulico. Los granulos divulgados en estos antecedentes presentan un tamaæocomprendido entre [0,7 y 0,85mm], es decir, en el mismo rango senalado por el seæor solicitantepara el caso de los microgranulos reivindicados.

En consecuencia, una persona del oficio, normalmente versada en ciencias farmacØuticas y con la intención de diseæar formulaciones tipo microgranuladosde pantoprazol y con un perfil bioequivalente y marcada estabilidad se encontraba en capacidad de derivar los elementos caracterIsticos de las composiciones con fundamento en las ensenanzas que divulgan los antecedentes [Dl y D3] o bien, [D2 y D4].

Finalmente esta Superintendencia se permite seæalarque la reivindicación I cumple el requisito de novedad (art. 16 D. 486), pero carece de nivel inventivo y por consiguiente no cumple las disposiciones normativas del art. 18 D. 486.

Por otra parte, el mØtodo para la fabricaciOn de las composiciones seæaladoen la clÆusula 30 que comprende la aplicacion de las tØcnicas de extrusion y esferonizaciOn se encuentra anticipado por los documentos Dl, o bien D4, por lo que esta Superintendencia concluye que la secuencia lOgica de etapas descrita en el mØtodo tambiØn carece de altura inventiva.

5. Conclusion:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados asI:

N° Documento N° Reivindicaciones

Afectadas Requisito que Afecta
Dl W096/01624 I a 37 Nivel Inventivo
D2 US61 59499 1 a 29 Nivel Inventivo
D3 US5997903 1 a 29 Nivel Inventivo
D4 US5945124 I a 37 Nivel Inventivo

6. Respuesta a los argumentos del seæorsolicitante:

Mediante memorial de fecha 24/11/2009 el seæorsolicitante argumenta Ia siguiente:

1. Frente a las enseæanzas deDl: "Dl se enfoca en una forma de dosificaciOn tableteada de unidades mfltiples yen cada uno de sus ejempios de trabajo describe el recubrimiento o el rociado del componente activo sobre una semi/la. Adicionalmente, Dl ensefia la compresión de sus pellets dentro de una tab/eta"

Al respecto es pertinente senalar que Dl revela formas de dosificaciOn tipo microgranulados para administraciOn en formas de presentación tipo tabletas. Sin

embargo, la composiciOn del granulado y su tamaæoes cercana a las caracterusticas del microgranulado reclamado, tal y como se comprueba a partir de la comparaciOn tØcnica que se presenta en la Tabla 1, en particular, cuando se analizan los componentes que divulga el ejemplo 2 del citado antecedente.