LLOREDA & CIA.-S. A.
ABOGADOS

SUPERINTENDE,"ICIA [’I- INDUSTRIA Y COMERCIO

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Fecha: 2007-06 -ve
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Act 4-14

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Re: P1.-GLAX0 GROUP LIMITED.-Sol icitud de Patente de Invenclo’n en Fase
Naclonal PCT para "DERIVADOS DE FENETANOLAMINA PARA EL TRATAMIENTO DE ENFERMEDADES RESPIRATORIAS".-Clase C07C 311/29.-Exl2ediente n6mero 03-068.568-

1. Me refiero al auto dictado por ese Despacho notificado por fijacio’n en lista de 30
de Marzo de 2007.

2. Modificaciones

Con el fin de dar respuesta a las objeclones hechas por el Sefior Examinador en su Concepto Tdcnico No. 510, atentamente, me permito manifestar a ese Despacho que es

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deseo del solicitante modificar el capitulo relvindicatorio de la presente solicitud con el fin de su.perar las objeciones hechas en dicho Concepto T6cnico, quedando el capi ulo relvindicatorio compuesto por 16 reivindicaciones, tal como se muestra a continuaci6n:

La Reivindicaci6n original 7 ha sido cancelada.
La Relvindicad6n original 8 pasa a ser la nueva reivindicacl6n 7, con las modificaciones en las dependencias correspondlentes.
Las Reivindicaciones originales 9 y 10 pasan a ser las nuevas relvindicaciones 8
y 9, las cuales han sido modificadas en su contenido al reemplazar la frase "uno
o m6s de otros ingredientes terapduticos" por la frase "uno o mAs agentes terapduticos seleccionados de agentes; antlinflamatorios, agentes anticolinergicos, otros antagonlstas del P2-adrenoreceptor, agentes antlinfectivos o anti hIstaminas". Esta modificacl6n se encuentra plenamente sustentada en el capitulo descriptivo, en particular, en la p6gina 29 lineas 8 a 16.

Las Relvindicaciones originales 11 y 12 pasan a ser las nuevas reivindicaciones 10 y 11, con las modificaciones en las dependenclas correspondlentes.
La Reivindicaci6n original 13 ha sido cancelada.

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La Relvindicac16n original 14 pasa a ser las nueva relvindicaci6n 12, con las modificaciones en las dependencias correspondientes.
La Reivindicaci6n orlainal 15 ha sido cancelada.

Se presentan los novedosos intermedlarlos de referencla (11), (111) y (IV) en las nuevas reivindicaclones 13, 14, 15 y 16 respectivamente, definidos a travds de
su estructura quimica seg6n se detalla en el capitulo descriptivo, en particular,
en la pdglna 45, Ifneas 10 a 24 (reivindicaci6n 13); en la p6gina 47 lineas 18 a
p6gina 48 l(nea 3 (reivindicaciones 14 y 15); y en la p6gina 48 linea 23 a
p6gina 49 linea 7 (reivindicaci6n 16).

Sobre e’ste particular, atentamente me permito manifestar que las anterlores modificaciones no amplian de manera alguna el alcance de la presente solicitud en concordancia con lo establecido en el art1culo 34 de la Decisl6n 486, de 2000, toda vez que lo que pretenden es definir las enseflanzas de la presente Invenclo’n y proteger objetos especificos que se encuentran Incluldos dentro de dichas enseflanzas.

3. Obleciones a las reivindicaciones orlainales 9 a 12 (nuevas reivindicaciones
8 a 111

Atendiendo a las objeciones realizadas por el seflor Examinador sobre la
patentabilidad de las relvindicaciones originales 9 a 12, basado en los artkulos 28 y 30 de la Decisi6n 486, atentamente me permito manlfestar ante ese Despacho que el solicitante ha decidido modificar dichas reivindlcaclones para establecer de una forma mAs clara y precisa el alcance de la expreslo’n "uno o mas de otros ingredientes terapduticos" en menc16n, al ser esta reemplazada por la frase "uno o m6s agentes terapduticos seleccionados de agentes antlinflamatorlos, agentes anticolinergicos, otros antagonistas del 02-adrenoreceptor, agentes antlinfectivos o antihistaminas" seg6n se establec!6 anteriormente. De esta forma, ha sido superada la objec!6n hecha por el seflor Examinador.

4. Objeclones a las reivindicaciones orlainales 7 v 13

Frente a las objeciones realizadas por el seflor Examinador basadas en el articulo 20
de la Decls16n 486, sobre la no patentabillidad de la reivindicaci6n original 7 por hacer referencla a un m6todo de tratamilento, el sollicitante ha decidido cancellar esta reivindicac!6n en el capitulo reivindicatorlo modificado. Asimismo, frente a las objeciones realizadas por el seflor Examinador basadas en los articulos 14, 19 y 21 de la Declsi6n 486, sobre la no patentabillidad de la reivindicaci6n original 13 por reivindicar un Uso de un compuesto, el solicitante ha decidido cancelar dicha reivindicaci6n en el capitulo relvindicatorio modificado descrito anterlormente. De esta

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forma, se han superado las objeclones; respecto a las excepciones de patentabilidad y usos hechas en el Concepto Tdcnico No. S10.

S. Obieci6n a la rellyindicacl6n original 15

El sefior Examinador ha objetado la patentabilidad de la relvindicaclo’n original 15 basado en los articulos 28 y 30 de la decisl6n 486, argumentando que "Los compuestos (II), (III), (IV) no est6n definidos en el capitulo relvindicatorlo mediante su nombre, ni estructura quimica. Adem6s, son materia que no aparece en la descripci6n". Sobre este particular, me permito sefialar ante ese Despacho, que el solicitante ha decidido cancelar [as reivindicaci6n original 15 y presentar nuevas relvindicaciones; 13 a 16 donde se han protegido los compuestos indexados como (11), (111) y (IV). Asl se logran presentar estos compuestos de manera explicita y a travds de sus formulas estructurales, los cuales efectivamente han sido revelados en el capitulo descriptivo, en particular se puede mencionar que:

El compuesto (11) es revelado en la pa’gina 45, lineas 10 a 24.
El compuesto (III) es revelado en la p6g!na 47 lifnea 18 a pa’gina 48 linea 3.
El compuesto (IV) es revelado en la pa’gina 48 linea 23 a p6gina 49 linea 7.

Asi, se confirma que estos novedosos compuestos; intermediarlos aparecen en la descripci6n y se supera la objec16n realizada por el sefior Examinador.

6. Problema Mcnico v solucl6n DrOlRuesta Dor la Rresente invenc16n

Antes de entrar a demostrar con argumentos t6cnicos que la presente Invenclo’n si cumple con los requisitos de patentabilidad consagrados en las disposiclones Andinas, a continuaci6n me permito definir en forma m6s clara el problema tdcnico planteado en la presente solicitud y la solucl6n dada por el sollcitante, con el fin de facilitar su comprensl6n.

a. Problema Ucnlico Planteado:

Tal y como claramente se establece en la descripci6n de la presente solicitud,
clertos compuestos de fenetanolamina se conocen en el arte previo, porque
estan caracterizados por tener una accl6n estimulante selectiva en los P2-adrenoreceptores y por lo tanto tienen utilidad en el tratarniento del asma bronquial y des6rdenes relaclonados. No obstante muchos de estos compuestos tienen una duracio’n ma’xima de acci6n de 12 horas, por lo tanto en ocasiones se requiere una dosificacio’n de dos veces al dia. Existe as[un problema t6cnico, a saber, la necesidad c1linica de compuestos que 3

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tengan accl6n estimulante potente y sellectiva al D2-adrenoreceptor,, con un perfill de accl6n ventajoso.

b. Solucl6n propuesta:

El solicitante logra solucionar el problema tdcnico anterior al proporcionar compuestos de formula (1)

 0(CH2)0

con los sustituyentes definidos como se Indica en la reivindicaci6n 1 y con realizaciones preferidas seg6n se sefiala en relvindicaciones dependientes. Asimismo, revela composiciones de estos compuestos que tambidn soluclonan
el problema tdcnlco. Finalmente, ofrece un proceso para la obtenclo’n de estos compuestos, enseflando los novedosos intermediarios de formulas (11), (111) y
(IV) obtenidos en el proceso.

7. Unidad de Invencli6n de las relivindicaclones originales 9 a 12 (nuevas reivindicaciones 8 a 111

Una vez establecido el problema tdcnico asi como la solucl6n lograda por el solicitante, me permlto dirigir [a atenc!6n de ese Despacho a la objeci6n realizada por el seflor Examinador en su Concepto Tdcnico No. 510, sobre la falta de unidad de Invencio’n de las reivindicaciones originales 9 a 12 (nuevas reivindicaciones 8 a 11).

La objec16n en menc16n afirma que "Las reivindicaciones 9-12 que se refieren a
una combinaci6n farmacdutica que contiene un compuesto de las reivindicaciones 1-5 y otros Ingredientes terapduticos (reivindicaciones) no mantienen el principio de unidad de invenci6n. Porque los diversos compuestos activos tienen estructuras quirnicas diferentes a la del compuesto objeto de la solicitud, y no hay un concepto Inventivo unico que los relaclone". Al respecto, me permito manifestar ante ese Despacho, que tal y como claramente lo ha establecido el solicitante dentro de su invenci6n, las combinaciones de las reivindicaciones originales 9-12 (nuevas reivIndicaciones 8 a 11) representan un aspecto, particular de la invencl6n segdn se detalla en las reivindicaciones 1 a S. En efecto, la caracteristica t&cnica especial de las relvindicaciones 1 a 5 son los cornpuestos de f6rmula (I), puesto que corno se

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reivindicaciones originales 9 -12 (nuevas reivindicaciones 8-11), es que toclas ellas hacen referencia a los compuestos cle formula estructural (1), blen sea por su menc16n directa o de una seleccl6n de estos compuestos (reivindicaclones 1 a 5), o porque las combinaclones que revelan presenta como componente esenclal los compuestos de formula (I).

Por otra parte, el nivel inventivo de las combinaciones de la reivindicac!6n 12 frente a las ensehanzas del clocumento D1 ha sido clemostrado, basado en que:

Las combinaciones de la reivindicac!6n 12 resuelven un problema tdcnico diferente al planteado en el clocumento 131: Las combinaclones revelaclas en
esta solicitud son 6tiles en la profilaxis y el tratamlento de enfermedades respiratorias surninistraclas mediante inhalaci6n; mientras aquellas revelaclas en el clocumento D1 son 6tiles como agentes anti-inflamatorlos por aplicaclo’n t6pica.
Las combinaclones de la relvindicacl6n 12 tienen nivel Inventivo por presentar
como componentes esenciales los noveclosos; e Inventivos compuestos de formula (I). Dichas combinaclones vencen el prejuiclo tdcnico seg6n el cual los compuestos derivados de la fenetanolamina tenlan una duracl6n m6x!ma de
acclo’n de 12 horas.

Los anterlores argumentos: son contundentes a la hora de clemostrar como el clocumento citado por el seflor Examinador no resulta relevante para desvirtuar la falta de un 6nico concepto inventivo entre las reivindicaciones, y asimismo son relevantes para desvirtuar la objeci6n por la falta de nivel Inventivo que supuestamente posee la presente sollcitud. Por lo tanto, debe reconocerse sin lugar a duclas tanto la unidad de invenc16n como el nivel Inventivo de las relvindicaciones objetaclas.

10. Anexos me permito presentar:

(a) Reclbo n6mero 07-43.372, expedido por la Superintendencia de Inclustria y Comerclo, que acredita el pago de las modificaclones mencionaclas; y

(b) Copia del nuevo capitulo reivindicatorio, que reemplaza al anteriormente presentado, sobre el cual se han realizado las modificaciones expuestas anteriormente.

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e I.

11. En vista de todo lo anterior, ruego a ustedproceder a estudlar nuevarnente la
solicitud a la luz de las argumentaclones presentadas y de las modlflcaciones reallzadas y conceder el privilegio de patente solicitado.

Sellor Superintendente,

ALI iA LLOREDA FUCAURTE
T.P..53.215

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3-(3-([7-(((2R)-2-Hidroxi-2-[4-hidroxi-

3(hidroximentil)fenil]etillamino)heptil]oxi)propil)bencensulfonamida;

3-(3-f (7-(((2S)-2-Hidroxi-2-[4-hidroxi-

3(hidroxi mentil)fen 1 I]eti Ila mino)heptiI]oxi)prop! 1) bencensulfonamida;

3-(3-? (7-(((2RS)-2-Hidroxi-2-[4-hldroxl-

3(hidroximentil)fenil]etil)amino)heptil]oxi)propil)bencensulfonamida;

y sales, solvatos y derivados fisiol6glcamente aceptables de los mismos.

6. El compuesto de conformidad con cualesquiera de las reivindicaciones
1 a al 5, en donde el compuesto estA en forma de una sal formada con un Scido farmacduticamente aceptable seleccionado de cInAmico, cinSmico substituldo, trifenilackico, s6ifamico, sulfanflico, naftalenacrilico, benzoico, 4- metoxibenzoico, 2- 6 4-hidroxibenzoico, 4-clorobenzoico y 4- fenllbenzolco.

7. Un compuesto de formula (1), (Ia) 6 (Ib)de conformidad con
cualesquiera de las reivindIcaciones; 1 a la 5, o una sal, solvato o derivado fisiol6gicamente funclonal del mismo, farmaduticamente aceptable para su uso en terapla m6dica.

8. Una formulacl6n farmacdutica que comprende un compuesto de
f6rmula (1), (Ia) 6 (1b)de conformidad con cualesquiera de las relvindicaclones 1 a la 5, o una sal, solvato o derivado fisiol6gicamente funclonal del mlsmo, farmac6uticamente aceptable y un portador o exipiente farmacduticamente aceptable u opcionalmente uno o mAs agentes terap6uticos selecclonados de agentes anti I nfla matorlos, agentes anticollnergicos, otros antagonistas del P2-adrenoreceptor, agentes antlinfectivos o antihistaminas.

d?b

ICA?

175

9. Una combinac16n que comprende un compuesto, de f6rmula
(1), (Ia) 6 (Ib)de conformidad con cualesquiera de las reivindicaciones 1 a la 5, o una sal, solvato o derivado fisiol6gicamente funclonal del mismo, farmacduticamente aceptable y uno o mAs agentes terapduticos seleccionados de agentes antlinflamatorlos, agentes anticolinergicos, otros antagonIstas del 02-adrenoreceptor, agentes andinfectivos o antihistaminas.

10. Una comblnac!6n de conformidad con la reivindicac!6n 9 en donde el
otro ingredlente terapdutico es un inhibidor de PDE4 o anticolln6rgico o corticosteroide.

11. Una combinaci6n que comprende un compuesto de f6rmula f6rmula
(1), (Ia) 6 (Ib)de conformidad con cualesquiera de las reivindicaclones; I a la 5, o una sal farmaduticamente aceptable, solvato o derivado fisiol6gicamente funclonal del mismo, y ester S-fluorometil del Scido 6a,9a-dlfluoro-17a-[(2-furanlicarbonll)oxi]-llo -hidroxi-16a -metil-3-oxo-androsta-1,4-dien-17p-carboti6ico.

12. Un proceso para la preparacl6n de un compuesto de f6rmula (I), (1a) 6
(Ib)de conformidad con cualesquiera de las reivIndicaciones; 1 a la 5, o una sal farmacduticamente aceptable, solvato o derivado fisiol6gicamente funclonal del mismo, que comprende

a) La desproteccl6n de un Intermediario protector, por ejemplo de la
formula (11):

WOCH,, R2

WOO KCH.NR’OCFeFt1(CH,),;O(CH..). -b-IH

o una sal o solvato del mismo, en donde RI, Fk?, R3, Fe, R5, m, y n son

como se definen por el compuesto de la f6rmula (1), (1a), (1b), W, R9,

(12) UK Patent Application (19)GB (11) 2 140 800 A

(21) Application No $410124

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855 658 659 65X 602 866 068 075 682 697 699
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UIS 1318 C2C

(56) Documents cited
001529972 OB 1200886

(68) Reid of search
C2C

(54)’Phenothanolamine derivatives

(57) Phenothanolamine derivatives are disclosed of formula

HOCH R1

H CHCH2NH (CH2)mO(CH2)nAr

R2

wherein m is 2 to 8; n Is I to provided that m + n is 4 to 12; by an Ar is phenyl or phenyl substituted by one or two halogen atoms, alkVI or alkoxy groups or

alkylenedioxy group;
R1 and R2 are hydrogen or alkyl provided that the sum total of carbon atoms in R’ and R2 is not
more than 4;

and the physiologically acceptable salts and solvates thereof.
nter alia, in The compounds have a selective stimulant action at pradrenoreceptors and may be used I the treatment of diseases associated with reversible airways obstructions such as asthma and chronic bronchitis. The compounds may be formulated in conventional manner as pharmaceutical compositions with physiologically acceptable carriers or excipients.
The compounds may be prepared, for example by alkylation of an amino:

RGOOCH2

R5 CHCH2NR3k

L -

where R3, Re and Re is hydrogen or a protecting group. followed by removal of any protecting group. Formulae in the printed specification were reproduced from drvMngs submitted the date of filing, In accordance with Rule 20(14) of the Patents Rules 1982.

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SPECIFICATION

Phanothanolamine derivatives

5 This Invention relates to phenethanolamine compounds having a stimulant action at 6
adrenoreoeptors, to processes for their preparation, to pharmaceutical compositions containing
them and to their use in medicine.
Certain phenethanolamine compounds are known to possess either stimulant or blocking
actions at P-adrenoreceptors. For example, British Patent Specification No. 1200886 describes
10 a group of such phenethanolamines of general structure: 10

15 HO

X,

OH

?NRA

Is
R1

where, inter alia, X, is hydroxyalkyl, R, and R2 is each a hydrogen atom, and R. is straight or
branched C,-, alkyl, aralkyl or aryloxyalkyl. One compound from within this particular group has
20 been developed for clinical use. This Is salbutemoll C(al-tort-butylaminomethy)-4-hydroxV-m- 20
xylene-a%e-diol; X, - CH20H, R, H, R2 H; R3 - t-butyl, above] which at the present
time is widely prescribed for the treatment of conditions such as bronchial asthma and chronic bronchitis. The success of salbutamol devolves from its profile of action, In particular Its
potency, coupled with a selective stimulant action at P2-adrenoreceptors.
25 All A-Inimulants currently used in clinical practice suffer from the disadvantage that they have 25 a relatively short duration of action when administered by inhalation. A 02-stimulant with a
relatively long duration of action would therefore offer a significant advance in the treatment of bronchial asthma and related disorders.
In a search for new #-stimulants with advantageous properties, we have now found a novel
30 group of phenethanolemine derivatives, which differ structurally from the group of compounds 30
described in British Patent Specification No. 1200886, and which in our tests have shown a
potent selective stimulant action at,81-adrenoreceptors, and, In addition, have an advantageous
profile of action.
Thus, the present invention provides compounds of the general formula (1)
35 35

HOCH2 R1

0 [(CH2)M-0(CH2)6Ar 40 qCH2NHC
2

40

RI

wherein
45 m is an integer from 2 to 8 and 45
n is an Integer from 1 to 7 with the proviso that the sum total of m + n Is 4 to 12;
Ar represents a phenyl group optionally substituted by one or two substituents selected from
halogen atoms, C1-3 alkyl or C,-3 alkoxy groups, or by an alkylenedioxy group of formula
O(CH2) 0- where p is 1 or 2; and RI and R2 each represents a hydrogen atom or a C1-3 alkyl
50 group wil the proviso that the sum total of carbon atoms in RI and R2 is not more than 4; 50
and physiologically acceptable salts and solvates (e.g. hydrates) thereof.
It will be appreciated that the compounds of general formula (1) possess one or two
asymmetric carbon atoms, namely the carbon atom of the

55 CH 65
I
OH

group and, when RI and R2 are different groups, the carbon atom to which these groups are
60 attached. 60
The compounds according to the invention thus include all enantlomers, diastereolsomers and
mixtures thereof, including racernates. Compounds in which the carbon atom in the

2 GB 2 140 BOOA 2

 CH

I
0H
5 5

group is in the R configuration are preferred.
In the general formula (1), the chain (CH2). may be, for example, (CH2)3, (CH2)4,
 (CH2)5, (CH2)6 or (CH2),, and the chain (CH2),, may be, for example, (CH2)2-1

 (CH2)3, (CH24-1 (CH2)5 or (CH2)6-- 10 Preferably the sum total of the number of carbon atoms in the chains (CH2), and (CH2), is 10

6 to 12 inclusive and may be, for example, 7, 8, 9 or 10. Compounds wherein the sum total of
m + n is 7, 8 or 9 are particularly preferred.
Preferred compounds of general formula (1) are those wherein m is 3 and n Is 6, or m is 4
andnis 3, 4or5, ormis5and n 1s2, 3, 4or5, orm is6 and n is2or3.

15 RI and R2, for example, may each be methyl, ethyl, propyl, or isopropyl groups except that if 15
one of R1 and R2 is a propyl or Isopropyl group, the other Is a hydrogen atom or a methyl
group. Thus, for example, R’ may be a hydrogen atom or a methyl, ethyl or propyl group. R2,
for example, may be a hydrogen atom or a methyl group.
RI and R2 are each preferably a hydrogen atom or a methyl group.
20 A preferred group of compounds is that wherein RI and R2 are both hydrogen atoms. In 20
another preferred group of compounds RI is a hydrogen atom and R2 IS a CI -3 alkyl group,
2 particularly a methyl group. In yet another preferred group of compounds R, and R are both
methyl groups.

26 R’ 25
1
The chain C(CH2).O(CH2). in general formula (1)
I
R2

30 30
may be, for example (CH2)40(CH2)4, (CHA60(CH2)2

CH3

35

1
 (CH2)60(CH2)3, (CH2)5UkL1n2)4-1 t;H(CH2)40(CH2)3, 35

CH3 CH3 CH3

I 1 1 CH(CH2)40(CH2)4-1 -Ur’P-r’2)5,VV-r’2)31 1.Hj%.H2)50(CH2)4-1

40 40
CH3 R1

I I
 C(CH2),O(CH2)1, or -ZHkCH2)6Qj%,H2)2-1 where R1 is
1
46 CH3 46

mothyl, ethyl or propyl.
Examples of the optional substiduents which may be present on the phony[group represented
by Ar include bromine, iodine or, in particular, chlorine or fluorine atoms, or methyl, ethyl,
60 methoxy or ethoxV groups. In general, Ar Is preferably an unsubstituted phanyl group. 50
According to another preference, Ar is a phonyl group substituted by one substituent,
particularly a fluorine or chlorine atom or a methoxy or methyl group.
Suitable physiologically acceptable salts of the compounds of general formula (1) include acid
addkiion salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides,
56 sulphates, phosphates, maleates, tartrates, citrates, benzoates, 4-mothoxybenzoates, 2- or 4- 56
hydrokyberizoates, 4-chlorobenzoates, p-toluenesulphonates, methanesulphonates, ascorbates, salicylates, acetates, fumerates, succinates, lactates, glutarates, gluconates, tricarballylates, hydroxynaphthalenecarboxylates e.g. 1 -hydroxy- or 3-hydroxy-2-naphthanionecarboxylates, or
oleates. The compounds may also form salts with suitable bases. Examples of such salts are
60 alkali metal (e.g. sodium and potassium), and alkaline earth metal (e.g. calcium and magnesium) 60 salts.
The compounds according to the invention have a selective stimulant action at #2-adrenore-
captors, which furthermore is of a particularly advantageous profile. The stimulant action was demonstrated In the guinea-pig, where compounds were shown to cause relaxation of PGF2ci-
66 contracted isolated trachea. In another test, compounds of the invention were shown to afford 66

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@ Pharmaceutical compositions comprising effective amounts of salmeterol (and/or a physiologically accept-able salt thereol) and fluticasone proplonate as a combined preparation for simultaneous, sequential or separate administration by Inhalation In the treatment of respiratory disorders.

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MEOICAMENTS

This invention relates to improvements In the treatment of asthma and other respiratory disorders. More particularly, It relates to the use of a bronchodilator drug In combination with a steroidal anti-Inflarnmatory drug for the treatment of respiratory disorders such as asthma, and to pharmaceutical compositions containing the two active Ingredients.
6 Asthma Is a condition characterlsed by variable, reversible obstruction of the airways which Is caused by a complex inflammatory process within the lungs. In most cases, this process is Initiated and maintained by the Inhalation of antigens by sensitive atopIc Individuals (extrinsic asthma). However, In some patients It is caused by other mechanisms which at present are poorly understood but do not Involve an allergic process (Intrinsic asthma). The disease has therefore two components, spasm of the bronchial (or
io breathing) tubes and inflammation or swellIng of the breathing tubes.
Salbutamol, the first highly selective 02-adrenoceptor stimulant has been used successfully and effectively by inhalation for the Immediate relief of spasm In asthma. However, when given by Inhalation, salbutamol has usually a four to six hour duration of action, which Is too short either to control nocturnal asthma or for convenient maintenance of the disease In some patients.
is Antloinflarnmatory corticosterolds such as, for example, beclomethasone d1proplonats have also been administered by Inhalation in the treatment of asthma, although unlike salbutarnol the therapeutic benefits resulting from reduced Inflammation may not be Immediately apparent
It has been recognised that asthma may be treated by using both a bronchodilator for Immediate relief
and a prophylactic anti-Inflammatory corticosterold to treat the underlying inflammation. Such combination
2o therapy directed at the two main underlying events In the lung O.e. relief of spasm In the breathing tubes
and treatment of inflammation In the breathing tubes) using a combination of salbutamal and be-clomethasone diproplonate has previously been proposed (Vendde, Glaxo Group trade mark). but suffers a number of disadvantages in view of the above-mentioned short duration of action exhibited by salbutamol. Thus the need for a 4-hourly dosing regimen may discourage effective patent compliance and also renders
26 the product less than satisfactory In the treatment of nocturnall asthma since the bronchodilator may not
remain effective for the duration of ft night, leading to Impaired sloop for asthmatics troubled by nocturnal cough, breathlessness and wheeze.
The present Invention is based on the concept of a novel combination therapy which has markedly greater efficiency and duration of bronchodilator action then previously known combinations and which
3o permits the establishment of a twice daily (bis In them - b1d) dosing regimen with consequent substantial
benefits in, for example, the treatment of astFms5RcuIarIY nocturnal asthma.
Thus we have found that if the 02-adrenoreceptor stimulant brochodilator salmeteroll and/or a phys-iologically acceptable salt thereof Is combined with the anti-inflammatory corticosterold fluticasone pro-pionate In a form suitable for administration by Inhalation, the resulting compositions may be administered
35 on a b1d. basis to provide highly effective treatment and/or prophylactic therapy for asthmatics. In
particular such administration has been shown to lead to significant Improvement In daytime lung function, requirement for additional symptomatic bronchodilator and almost complete abolition of nocturnal asthma while giving rise to minimal systemic side effects.
Salmeteroll is one of a range of bronchodilators having extended duration of action which Is described In
4o British Patent Specification No. 2140800, and Is systematically named 4-hydmxy-a’-U[S-(4-phenylbutoxy)-
hoxyllamino]methyl]-1,3-benzonedimethanol. Fluticasone proplonats Is one of a range of topical ana-inflammatory cordoostarolds with minimal liability to undesired systemic side effects which is described in British Patent Specification No. 2088877, and Is systematically named 8-fluoromethyl 8&.9a-difluoro-11 I p-hydroxy-16a-methyl-17a-proplonytoxy-3-oxoandrosta-1,4-diene-170-carbothioate. We have found these two
45 compounds to be particularly compatible and complementary in their activity and thus highly effective In the
treatment of asthma and other respiratory disorders.
Thus according to one aspect of the invention there are provided pharmaceutical compositions comprising effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and fluticasone proplonate as a combined preparation for simultaneous, sequential or separate administration by Inhalation
5o in the treatment of respiratory disorders.
The Invention additionally relates to the use of salmeterol (and/or a physiologically acceptable salt thereoO and fluticasone proplonate In the manufacture of pharmaceutical compositions as combined preparations for simultaneous, sequential or separate administration of salmeterol and fludcasone proplonate by inhalation in the treatment of respiratory disorders.
According to a further feature of the Invention there Is provided a method of treating respiratory

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disorders which comprises the simultaneous, sequential or separate administration by Inhalation of effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and fluticasone proplonate.
Suitable physiologically acceptable salts of salmeterol Include acid addition sab derived from Inorganic
and organic acids, such as the hydrochloride, hydrobromide, sulphate, phosphate, maleate, tartrate, citrate,
6 benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate. methanesulphonate, ascorbate, salicylate, acetate, fumarate, succinate, lactate, glutarate, gluconate, tricar-ballylate, hydroxynaphthalenecarboxylate e.g. 1-hydroxy- or 3-hydroxy-2-naphthalenewrboxylets, or oleate. Salmeterol is preferably used In the form of Re 1-hydroxy-2-naphthalene carboxylate salt (hydroxynaphthoate).
to For administration by Inhalation. the compositions according to the Invention are conveniently delivered by conventional means. e.g. In the form of a metered dose Inhaler prepared In a conventional manner or In combination with a spacer device such as the Volumadc (Glaxo Group trade mark) device. In the case of a metered dose inhaler, a metering valve Is provided to deliver a metered amount of the composition. Spray compositions may for example be formulated as aqueous solutions or suspensions and may be admin-
16 Istered by a nebullser. Aerosol spray formulations, for example In which the active Ingredients are
suspended, optlonally together with one or more stabillsers, In a propellent, e.g. a halogenated hydrocarbon such as ttichlorofluoromethans, dichlorodffluoramethane, LUIchlorotetrafluoroethane, trich-lorotrifluoroathane, monochloropentafluoroethane, chloroform or methylene chloride, may also be employed. The two drugs may be administered separately In similar ways.
20 Aftematively, for administration by Inhalation or insufflation, the compositions according to the invention may take the form of a dry powder composition, for example a powder mix of the active ingredients and a suitable carrier such as lactose. The powder compositions may be presented in unit dosage form In, for example, capsules, cartridges or blister packs from which the powder may be administered with the aid of an Inhaler such as the Rotahaler Inhaler (Glaxo Group trade mark) or In the case of blister packs by means
25 of the Dlskhaler Inhaler (GIaxo Group trade mark).
The ratio of salmeterol to fluticasone proplonate in the compositions according to the Invention Is preferably within the range 4.1 to 1:20. The two drugs may be administered separately In the same ratio. Each metered dose or actuation of the inhaler will generally contain from 25 tLg to 100 tLg of salmeterol and from 25 ag to 500 iAg of fluticasone proplonate. As hereinbefore indicated, it Is intended that the
3o pharmaceutical compositions will be administered twice daily.
A suitable daily dose of salmeterol for Inhalation Is In the range 50 ag to 200 &Lg.
A suitable daily dose of flutIcasone proplonate for Inhalation Is In the range 50 jLg to 2000 tLg depending on the severity of the disease.
The precise dose employed will of course depend on the method of administration, the age, weight and
35 condition of the patent and will be determined by the clinician depending on the severity and the type of
asthma.

In order that the Invention may be more fully understood, the following examples are given by way of illustration only.

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EXAMPLE I - Metered Dose Inhaler

Active Ingredient Target per Per Inhaler
AERdon % w1w

Salmeterol 25.0 iig
(as hydroxynaphthoate) 0.0448
Fluticasone propionate 25.0 ag 0.0309
Stabiliser 5.0 ag 0,0076
Tdchlorofluoromethane 23.70 mg 27.8759
Dichlorodffluorom0ans 61.25 mg 72.0588

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