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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

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SOLICITUD DE :

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☐

Capítulo I.

☒ X

Capítulo II.

②

SOLICITANTE

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IDENTIFICACION

C.C.

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Otro

☐

Cual

Número

③

REPRESENTANTE
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Número 79.782.747 Bta TP 74.295

④

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⑥ Título (54)

SALES DE CLORHIDRATO DE 5-[4-[2-(N-METIL-N-(2-PIRIDIL)AMINO)ETOXI]BENCIL]TIAZOLINA-2,4-

DIONA

⑦ Clasificación Internacional (51)

C07D 417/00 ; A61K 31/427

⑧

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SI

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Marzo 14, 2000

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⑨

Comprobante de pago No. 2,395

Fecha 11-01-02

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

27

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☐ Otros

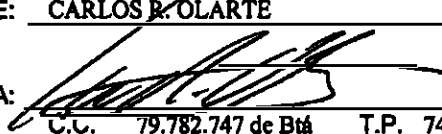
11

FIGURA CARATERISTICA

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

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C.C. 79.782.747 de Btá T.P. 74.295



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***** CONSIGNACION *****

OSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
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GE LUIS GOMEZ	RECIBO DE CAJA			5598	02/02/2001	356,640.00
GE LUIS GOMEZ	RECIBO DE CAJA			5599	02/02/2001	356,640.00
GE LUIS GOMEZ	RECIBO DE CAJA			5600	02/02/2001	356,640.00
GE LUIS GOMEZ	RECIBO DE CAJA			5601	02/02/2001	356,640.00
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GE LUIS GOMEZ	RECIBO DE CAJA			72670	20/11/2001	533,250.00

***** CONCEPTO *****

T. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	378,000.00
	TOTAL :	\$ 378,000.00

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(19) World Intellectual Property Organization
International Bureau



1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: HYDROCHLORIDE SALTS OF 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE

(57) Abstract: A substantially non-hydrated and non-hygroscopic or slightly hygroscopic hydrochloride salts of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione; a pharmaceutical composition containing such a compound, a process of preparing such a compound and the use of such a compound in medicine.

WO 01/68646 A1

HYDROCHLORIDE SALTS OF 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

5 European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of example 30 of EP 0,306,228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter also referred to as "Compound I").

10 International Patent Application, Publication Number WO94/05659 discloses certain salts of the compounds of EP 0,306,228 and in particular the maleic acid salt.

It has now been discovered that Compound I forms a novel, non-solvated hydrochloride salt (hereinafter also referred to as the "Hydrochloride") that is particularly stable and hence is suitable for bulk preparation and handling. Surprisingly the
15 Hydrochloride is indicated to be non-hygroscopic and shows good aqueous solubility. Moreover, the Hydrochloride is stable in aqueous solution and does not dissociate therein. It can also be prepared by an efficient, economic and reproducible process particularly suited to large-scale preparation.

The novel Hydrochloride also has useful pharmaceutical properties and in
20 particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride characterised in that it:

- 25 (i) provides an infrared spectrum containing peaks at about 1745, 1516, 1257, 1056 and 803 cm^{-1} ;
(ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at about 10.1, 13.4, 17.2, 22.2 and 29.4 $^{\circ}2\theta$; and/or
(iii) provides a Raman spectrum containing peaks at about 1314, 1242, 1185, 918 and
30 404 cm^{-1} .

In one favoured aspect, the Hydrochloride provides an infrared spectrum substantially in accordance with Figure I.

In one favoured aspect, the Hydrochloride provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Figure II.

35 In a further aspect, the Hydrochloride provides a raman spectrum substantially in accordance with Figure III.

The present invention encompasses the Hydrochloride isolated in pure form or when admixed with other materials.

Thus in one aspect there is provided the Hydrochloride in isolated form.

In a further aspect there is provided the Hydrochloride in pure form.

In yet a further aspect there is provided the Hydrochloride in crystalline form.

As indicated above the Hydrochloride is non-hygroscopic. The invention further
5 includes substantially non-hydrated and non-hygroscopic (or slightly hygroscopic)
hydrochloride salts of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-
2,4-dione.

The invention also provides a process for preparing the Hydrochloride,
characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-
10 2,4-dione (Compound I) or a salt thereof, preferably dispersed or dissolved in a suitable
solvent, is reacted with a source of hydrogen chloride; and thereafter the Hydrochloride is
recovered.

Preferably, the reaction is carried out under anhydrous conditions, for example in
a dried nitrogen atmosphere.

15 A suitable solvent is an alkanol, for example propan-2-ol, or a hydrocarbon, such
as toluene, a ketone, such as acetone, an ester, such as ethyl acetate, an ether such as
tetrahydrofuran, a nitrile such as acetonitrile, or a halogenated hydrocarbon such as
dichloromethane.

Conveniently, the source of hydrogen chloride is a solution of hydrogen chloride
20 in an appropriate solvent, usually the reaction solvent, for example propan-2-ol.
Alternatively, the source of hydrogen chloride may be provided by concentrated
hydrochloric acid or aqueous dilutions of concentrated hydrochloric acid which are
suitably diluted so as to provide the required product, although concentrated hydrochloric
acid is preferred.

25 It is considered that the Hydrochloride can be produced in the above mentioned reactions
in the presence of small amounts of water but as stated the reaction is preferably carried
out under anhydrous conditions.

The reaction is usually carried out at ambient temperature or at an elevated
temperature, although any convenient temperature that provides the required product may
30 be employed. A preferred temperature is in the range of from 20-120°C, such as 30°C to
80°C, for example 70°C.

Recovery of the required compound generally comprises crystallisation from an
appropriate solvent, conveniently the reaction solvent, usually by cooling to a temperature
in the range of from 0°C to 40°C, for example 20°C.

35 In one preferred form the recovery comprises initial cooling to a first temperature,
such as 35°C to 70°C, preferably 50°C to 60°C, thereby allowing initiating crystallisation
and thereafter cooling to a second temperature, suitably in the range of 0°C to 40°C, to
complete crystallisation.

Crystallisation can also be initiated by seeding with crystals of the Hydrochloride but this is not essential.

Compound I is prepared according to known procedures, such as those disclosed in EP 0,306,228 and WO94/05659. The disclosures of EP 0,306,228 and WO94/05659 are incorporated herein by reference.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

When used herein the terms relating to hygroscopicity are used in accordance with known criteria as set out in J C Callahan et al., Drug Development and Industrial Pharmacy, 1982, 8(3), 355-69 which classifies hygroscopicity with respect to the % weight gain of a test compound under controlled conditions of temperature and humidity (25° C and 75% relative humidity) wherein the test compound has been allowed to attain an approximately constant weight: the following classification is used:

<u>% Weight Gain</u>	<u>Classification</u>
<2%	non-hygroscopic
2-10%	slightly hygroscopic
10-20%	moderately hygroscopic
>20%	very hygroscopic

For the avoidance of doubt when used herein the terms "non-hygroscopic", "slightly hygroscopic", "moderately hygroscopic" and "very hygroscopic" are to have the meanings defined by the above mentioned criteria.

Furthermore, the term "slightly hygroscopic" can particularly mean a compound showing a % weight gain under the above mentioned criteria of any one of 2-9%, 2-8%, 2-7%, 2-6%, 2-5%, 2-4% and 2-3%.

Diabetes mellitus preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly provides the Hydrochloride for use as an active therapeutic substance.

5 More particularly, the present invention provides the Hydrochloride for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

10 Hydrochloride may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation of the Hydrochloride is generally as disclosed for Compound I in the above mentioned publications.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Hydrochloride and a pharmaceutically acceptable carrier therefor.

The Hydrochloride is normally administered in unit dosage form.

15 The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

20 Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

25 Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

30 Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

35 Solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Hydrochloride to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In a further aspect the present invention provides the use of Hydrochloride for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

5 In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Hydrochloride may be taken in amounts so as to provide Compound I in suitable doses, such as those disclosed in EP 0,306,228 and WO94/05659.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

10 The following examples illustrate the invention but do not limit it in any way.

Example 1: Preparation of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride

5 A mixture of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (6.0 g) and propan-2-ol (120 ml) was stirred and heated to 50°C under a nitrogen atmosphere. A solution of hydrogen chloride in propan-2-ol (5-6 N, 5.0 ml) was added and the stirred mixture warmed to 70°C, at which point a clear solution was observed. After cooling to 45°C over a period of one hour the resulting cloudy solution was
10 warmed to 60°C and maintained at this temperature for a period of 1 hour. The resulting thick white suspension was cooled to 30°C and the solid product collected by filtration, washed with propan-2-ol (25 ml) and dried under vacuum, over phosphorus pentoxide for 16 hours to give the title compound as a white crystalline solid (5.7 g).

15 Melting point 168 –170°C

DSC: $T_{\text{onset}} = 166.6^{\circ}\text{C}$, $T_{\text{peak}} = 169.5^{\circ}\text{C}$

Elemental Analysis:

20 Found: C; 54.88 H; 5.16 N; 10.56
Theory: (C₁₈H₂₀N₃O₃SCl) C; 54.89 H; 5.12 N; 10.67

Ionic chlorine: Determined as 9.0% wt/wt (theory for C₁₈H₂₀N₃O₃SCl : 9.0% wt/wt).

25 Water content: Determined as 0.2% wt/wt using a Karl Fischer apparatus.

Example 2: Preparation of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride

30 A mixture of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (4.0 g) and propan-2-ol (100 ml) was stirred and heated to 70°C. Concentrated hydrochloric acid (1.1 ml) was added to the stirred reaction mixture which was observed
35 to give a clear solution after approximately 3 minutes. The stirred solution was cooled to 58°C and then maintained at a temperature between 58 – 60 °C for 1 hour. The resulting white suspension was cooled to 30°C and the solid product collected by filtration, washed with propan-2-ol (20 ml) and dried under vacuum over phosphorus pentoxide for 64
40 hours to give the title compound as a white crystalline solid (4.3 g).

Hygroscopicity of the Hydrochloride

A sample of the hydrochloride salt (279 mg), prepared according to Example 1, was exposed to a 75% relative humidity atmosphere at 21°C for a period of 43 days. The sample attained constant weight during this period. The percentage weight gain of the sample was observed to be 0.4%.

Conclusion

The hydrochloride salt is non-hygroscopic.

Aqueous Stability and Solubility of the Hydrochloride

50mg of the salt was placed in a 20mL volumetric flask, and water added in 2.5mL aliquots. The sample was ultrasonicated at 21°C to aid dissolution after each subsequent addition of water and then examined. When a clear solution was obtained, the approximate solubility mg/mL was calculated. The solution was then examined at hourly intervals for evidence of subsequent clouding or precipitation.

Water added total (mL)	Observation
2.5mL	Cloudy suspension
5.0mL	Predominantly clear, only partially cloudy
7.5mL	Clear solution obtained. Remained clear after standing at 21°C for a further 2 hours. Approx. solubility 7mg/mL

Conclusion

The white crystalline solid dissolved readily to give a clear solution with a good aqueous solubility. The solution subsequently remained clear with no evidence of precipitation or clouding of the solution. This data confirms a previous experiment on a different batch of the Hydrochloride that also evidenced good solubility and provided a clear solution with no evidence of precipitation or clouding of the solution

Characterising data recorded for the product of Example 1:**A Infrared**

The IR spectrum (Figure I) was recorded as a liquid paraffin mull using a Perkin-Elmer 1720x FTIR instrument at a resolution of 2 cm⁻¹. The spectrum obtained is shown in Figure I. Bands were observed at:

1745, 1696, 1641, 1609, 1544, 1516, 1331, 1313, 1289, 1257, 1243, 1230, 1203, 1185, 1157, 1073, 1056, 1032, 1015, 984, 918, 907, 873, 841, 811, 803, 772, 738, 714, 657, 618, 605, 560, 527 and 505 cm⁻¹.

B X-Ray Powder Diffraction (XRPD)

The XRPD pattern of the Hydrochloride (Figure II) was recorded using a using the following acquisition conditions: Tube anode: Cu, Generator tension: 40 kV, Generator

current: 40 mA, Start angle: 2.0 °2θ, End angle: 35.0 °2θ, Step size: 0.02 °2θ , Time per step: 10.0 seconds.

Characteristic XRPD angles and relative intensities are recorded in Table I.

5

Table I.

Diffraction Angle (°2θ)	Relative Intensity (%)
10.1	4.9
11.8	15.2
12.4	8.1
13.4	24.7
14.0	4.5
14.6	2.6
15.0	10
16.1	38.2
16.3	91.6
17.2	28
17.7	69
18.1	49.5
19.3	14.2
19.6	46.1
20.4	14.2
20.9	6.9
21.2	24.9
22.2	100
22.4	72.5
22.7	36.4
23.6	98.2
23.8	79.8
24.8	49.1
25.5	10.6
26.1	18.9
26.4	35.9
27.1	35.2
27.4	22.9
28.1	32.6
29.4	32.9
30.0	18.8
30.6	21.4

31.1	11.8
32.1	20
32.6	20.5
33.0	19.8
33.9	23.5
34.5	29.6

C Raman

The Raman spectrum (Figure III) was recorded with the sample in a glass vial in a Perkin-Elmer 2000R FT-Raman system, at 4 cm⁻¹ resolution. Excitation was from a Nd:YAG laser (1064 nm) with a power output of 400mW. Bands were observed at: 3100, 3068, 2927, 2893, 2863, 1746, 1706, 1611, 1587, 1545, 1446, 1382, 1360, 1314, 1287, 1242, 1212, 1185, 1156, 1096, 1073, 1032, 1017, 984, 918, 828, 772, 741, 715, 659, 636, 619, 606, 527, 506, 471, 440, 404, 333, 302, 262 cm⁻¹.

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Claims:

1. A substantially non-hydrated and non-hygroscopic or slightly hygroscopic hydrochloride salts of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione.

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2. A compound 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride characterised in that it:

(i) provides an infrared spectrum containing peaks at about 1745, 1516, 1257, 1056 and 803 cm^{-1} ;

10 (ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at about 10.1, 13.4, 17.2, 22.2 and 29.4 $^{\circ}2\theta$; and/or

(iii) provides a Raman spectrum containing peaks at about 1314, 1242, 1185, 918 and 404 cm^{-1} .

15 3. A compound according to claim 2, wherein the Hydrochloride provides an infrared spectrum substantially in accordance with Figure I.

4. A compound according to claim 2 or claim 3, wherein the Hydrochloride provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Figure II.

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5. A compound according to any one of claims 2 to 4, wherein the Hydrochloride provides a raman spectrum substantially in accordance with Figure III.

6. A process for preparing the Hydrochloride according to claim 1, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a salt thereof, preferably dispersed or dissolved in a suitable solvent, is reacted with a source of hydrogen chloride; and thereafter the Hydrochloride is recovered.

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7. A process according to claim 6, wherein the reaction is carried out under anhydrous conditions.

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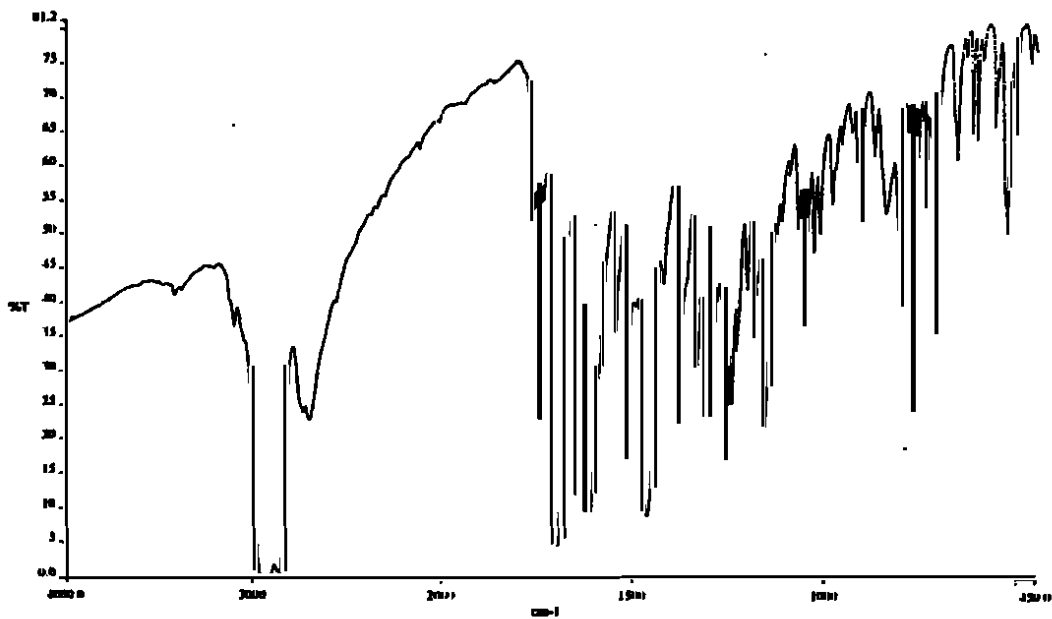
8. A compound according to any one of claims 1 to 5, for use as an active therapeutic substance.

9. A compound according to any one of claims 1 to 5, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

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10. A pharmaceutical composition comprising the Hydrochloride and a pharmaceutically acceptable carrier therefor.

Figure I IR Spectrum (liquid paraffin mull) of the Hydrochloride



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Figure II XRPD Pattern for the Hydrochloride

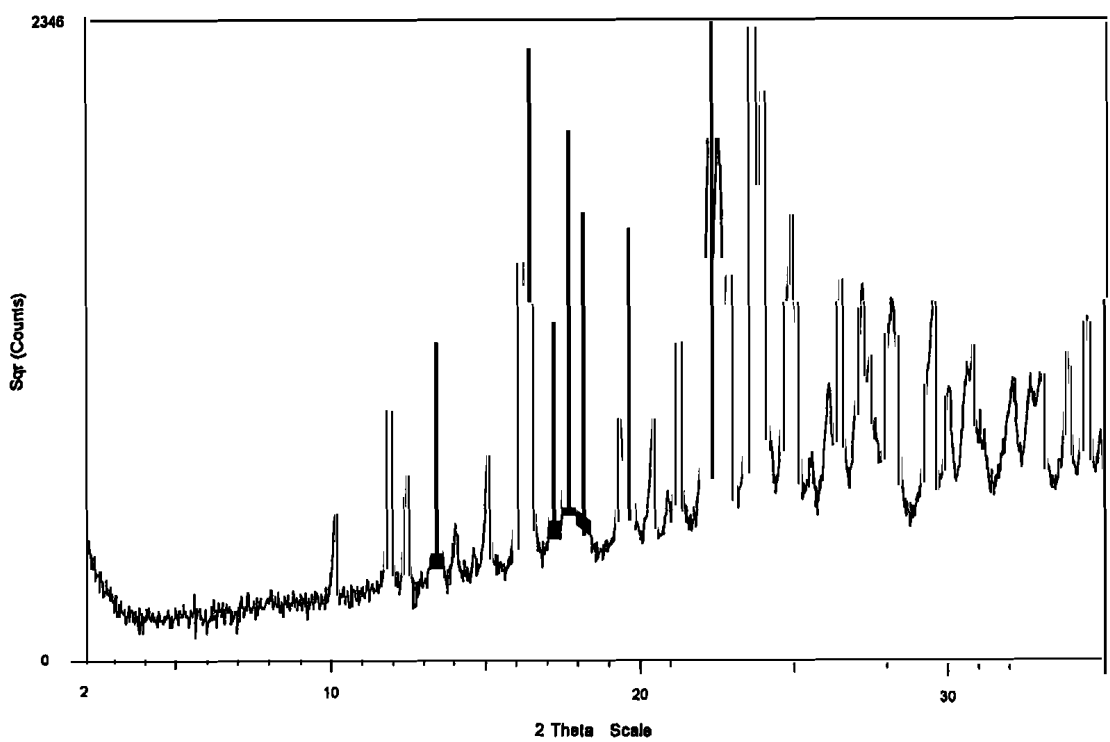
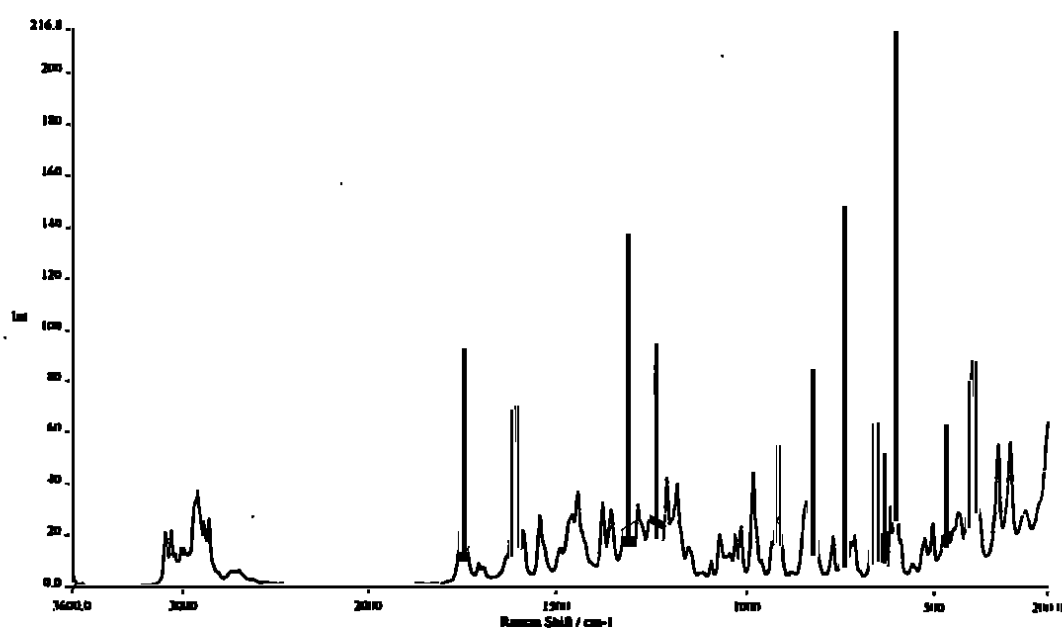


Figure III Raman Spectrum of the Hydrochloride

INTERNATIONAL SEARCH REPORT

tr. .ational Application No

PCT/GB 01/01131

14

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D417/12 A61K31/44 A61P3/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 05659 A (SMITHKLINE BEECHAM PLC ;POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 (1994-03-17) cited in the application page 1, line 20 - line 25 page 4, line 14 - line 16	1-10
X	EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 (1989-03-08) cited in the application example 30	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

5 June 2001

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INTERNATI NAL SEARCH REPORT

International Application No

PCT/GB 01/01131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9405659 A	17-03-1994	AP 513 A	30-07-1996
		AT 182147 T	15-07-1999
		AU 674880 B	16-01-1997
		AU 4973093 A	29-03-1994
		BR 1100916 A	04-07-2000
		CA 2143849 A	17-03-1994
		CN 1101911 A,B	26-04-1995
		CN 1183275 A,B	03-06-1998
		CN 1183413 A,B	03-06-1998
		CN 1183276 A	03-06-1998
		CZ 9500565 A	15-11-1995
		DE 69325658 D	19-08-1999
		DE 69325658 T	30-12-1999
		DK 658161 T	29-11-1999
		EP 0658161 A	21-06-1995
		EP 0960883 A	01-12-1999
		ES 2133410 T	16-09-1999
		FI 951004 A	03-03-1995
		FI 982413 A	06-11-1998
		GR 3030794 T	30-11-1999
		HK 1012363 A	05-05-2000
		HU 72639 A	28-05-1996
		IL 106904 A	30-09-1997
		JP 11147885 A	02-06-1999
		JP 2828777 B	25-11-1998
		JP 8501095 T	06-02-1996
		LU 90712 A	12-03-2001
		MX 9305397 A	31-01-1995
		NO 950852 A	03-03-1995
		NO 974646 A	03-03-1995
		NZ 255505 A	22-08-1997
		PL 307812 A	26-06-1995
		RU 2128179 C	27-03-1999
		SG 48302 A	17-04-1998
		SI 9300452 A	30-06-1994
		SK 27795 A	09-08-1995
		TW 385309 B	21-03-2000
		US 5741803 A	21-04-1998
		US 5910592 A	08-06-1999
		ZA 9306509 A	16-06-1994
EP 0306228 A	08-03-1989	AT 186724 T	15-12-1999
		AU 2173888 A	09-03-1989
		BR 1100841 A	20-06-2000
		CA 1328452 A	12-04-1994
		CA 1339902 A	09-06-1998
		CZ 9103916 A	17-03-1993
		DE 3856378 D	23-12-1999
		DE 3856378 T	11-05-2000
		DK 490288 A	05-03-1989
		DK 200001556 A	18-10-2000
		EP 0842925 A	20-05-1998
		ES 2137915 T	01-01-2000
		GR 3031873 T	29-02-2000
		JP 10194970 A	28-07-1998
		JP 10194971 A	28-07-1998
		JP 1131169 A	24-05-1989
		JP 2614497 B	28-05-1997

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0306228 A		JP 2817840 B	30-10-1998
		JP 9183771 A	15-07-1997
		JP 2837139 B	14-12-1998
		JP 9183726 A	15-07-1997
		JP 9183772 A	15-07-1997
		KR 164207 B	15-01-1999
		KR 164275 B	15-01-1999
		KR 169463 B	15-01-1999
		LU 90711 A	05-03-2001
		NZ 226027 A	26-03-1992
		PT 88410 A, B	31-07-1989
		SG 59988 A	22-02-1999
		US 5646169 A	08-07-1997
		US 5002953 A	26-03-1991
		US 5521201 A	28-05-1996
		US 5232925 A	03-08-1993
		US 5194443 A	16-03-1993
		US 5756525 A	26-05-1998
		US 5260445 A	09-11-1993
		ZA 8806536 A	26-07-1989

**SALES DE CLORHIDRATO DE 5-[4-[2-(N-METIL-N-(2-
PIRIDIL)AMINO)ETOXI]BENCIL]TIAZOLIDINA-2,4-DIONA**

MEMORIA DESCRIPTIVA

5

Esta invención describe un farmacéutico novedoso, un procedimiento para la preparación del farmacéutico y el uso del farmacéutico en la medicina.

La solicitud de patente europea, número de publicación
10 0,306,228 describe ciertos derivados de tiazolidinadiona que se describen por ,
tener una actividad hipoglicémica e hipolipidémica. El compuesto del ejemplo
30 de EP 0,306,228 es 5-[4-[2-(N-metil-N-(2-
piridil)amino)etoxi]bencil]tiazolidina-2,4-diona (de aquí en adelante referida
como "Compuesto I").

15 La solicitud de patente internacional, número de publicación
WO94/05659 describe ciertas sales de los compuestos de EP 0,306,228 y en
particular la sal del ácido maleico.

Se ha descubierto que el compuesto I forma una sal de
clorhidrato novedosa, no solvatada (de aquí en adelante referida como
20 "clorhidrato") que es particularmente estable y por tanto es adecuada para su
preparación y manejo a granel. De manera sorprendente el clorhidrato no es
higroscópico y muestra una buena solubilidad acuosa. Además, el clorhidrato
es estable en solución acuosa y no se disocia en ésta. También se puede

preparar a través de un procedimiento eficiente, económico y reproducible particularmente adecuado para una preparación a gran escala.

El clorhidrato novedoso también tiene propiedades farmacéuticas útiles y en particular es señalado por ser útil en el tratamiento y/o profilaxis de la diabetes mellitus, condiciones asociadas con la diabetes mellitus y ciertas complicaciones de ésta.

En consecuencia, la presente invención proporciona el clorhidrato de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidina-2,4-diona, caracterizado porque:

(i) proporciona un espectro infrarrojo que contiene picos en cerca de 1745, 1516, 1257, 1056 y 803 cm^{-1} ;

(ii) proporciona un diagrama de difracción de polvo de rayos de X (XRPD) que contiene picos en cerca de 10.1, 13.4, 17.2, 22.2 y 29.4°2 θ ; y/o

(iii) proporciona un espectro Raman que contiene picos en cerca de 1314, 1242, 1185, 918 y 404 cm^{-1} .

En un aspecto favorecido, el clorhidrato proporciona un espectro infrarrojo, substancialmente de acuerdo con la figura I.

En un aspecto favorecido, el clorhidrato proporciona un diagrama de difracción de polvo de rayos X (XRPD), sustancialmente de acuerdo con la figura II.

En un aspecto adicional, el clorhidrato proporciona un espectro raman substancialmente de acuerdo con la figura III.

La presente invención incluye el clorhidrato aislado en forma pura o cuando se mezcla con otros materiales.

De este modo en un aspecto se proporciona el clorhidrato en forma aislada.

5 En un aspecto adicional se proporciona el clorhidrato en forma pura.

Aún en un aspecto adicional se proporciona el clorhidrato en forma cristalina.

Como se indicó anteriormente el clorhidrato no es higroscópico.

10 La invención además incluye las sales de clorhidrato de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidina-2,4-diona, no hidratadas y no higroscópicas (o ligeramente higroscópicas).

La invención también proporciona un procedimiento para la preparación del clorhidrato, caracterizado porque 5-[4-[2-(N-metil-N-(2-
15 piridil)amino)etoxi]bencil]tiazolidina-2,4-diona (compuesto I) o una sal de esta, preferiblemente dispersada o disuelta en un solvente adecuado, reacciona con la fuente de cloruro de hidrógeno; y después se recupera el clorhidrato.

Preferiblemente, la reacción se realiza bajo condiciones anhidras, por ejemplo en una atmósfera de nitrógeno seco.

20 Un solvente adecuado es un alcohol, por ejemplo el propan-2-ol, o un hidrocarburo, tal como el tolueno, un cetona, tal como la acetona, un éster, tal como el acetato de etilo, un éter tal como el tetrahidrofurano, un

nitrito, tal como el acetonitrilo, o un hidrocarburo halogenado tal como el diclorometano.

De manera conveniente, la fuente de cloruro de hidrógeno es una solución de cloruro de hidrógeno en un solvente apropiado, usualmente el solvente de reacción, por ejemplo el propan-2-ol. De manera alterna, la fuente de cloruro de hidrógeno se puede proporcionar mediante el ácido clorhídrico concentrado o una dilución acuosa del ácido clorhídrico concentrado que es adecuadamente diluido para proporcionar el producto requerido, aunque se prefiere el ácido clorhídrico concentrado.

Se considera que el clorhidrato se puede producir en las reacciones mencionadas anteriormente en presencia de pequeñas cantidades de agua pero como se estableció, la reacción preferiblemente se realiza bajo condiciones anhidras.

La reacción de manera usual se lleva a cabo a temperatura ambiente o a una temperatura elevada, aunque cualquier temperatura conveniente que proporcione el producto requerido, se puede emplear. Una temperatura preferida se encuentra en la escala de 20-120°C, tal como de 30 a 80°C, por ejemplo a 70°C.

La recuperación del compuesto requerido en general comprende la cristalización de un solvente apropiado, convenientemente el solvente de reacción, usualmente a través del enfriamiento a una temperatura en la escala de 0 a 40°C, por ejemplo a 20°C.

En una forma preferida la recuperación comprende un enfriamiento inicial a una primera temperatura, tal como de 35 a 70°C, preferiblemente de 50 a 60°C, permitiendo de tal modo la iniciación de la cristalización y después el enfriamiento a una segunda temperatura, de manera adecuada en la escala de 0 a 40°C, para terminar la cristalización.

La cristalización también se puede iniciar al sembrar con cristales del clorhidrato, pero esto no es esencial.

El compuesto I se prepara de acuerdo a los procedimientos conocidos, tal como aquellos que se describen en EP 0,306,228 y WO94/05659. Las descripciones de EP 0,306,228 y WO94/05659 se incorporan aquí para referencia.

Cuando se usa aquí el término "profilaxis de condiciones asociadas con la diabetes mellitus" incluye el tratamiento de condiciones tales como la resistencia a la insulina, la tolerancia disminuida a la glucosa, hiperinsulinemia y diabetes gestacional.

Cuando son usados aquí los términos que se relacionan a la higroscopicidad, éstos se usan de acuerdo con criterios conocidos como se declara en J C Callahan et al., Drug Development and Industrial Pharmacy, 1982, 8(3), 355-69 que clasifica la higroscopicidad con respecto al porcentaje de peso ganado de un compuesto de prueba bajo condiciones controladas de temperatura y humedad (25°C y 75% de humedad relativa) en donde el compuesto de prueba se ha dejado que alcance un peso aproximadamente constante: se usa la siguiente clasificación:

% Peso ganado	Clasificación
< 2%	No higroscópico
2-10%	Ligeramente higroscópico
10-20%	Medianamente higroscópico
> 20%	Muy higroscópico

5 Para evitar la desconfianza cuando se usan aquí los términos "no higroscópico", "ligeramente higroscópico", "moderadamente higroscópico" y "muy higroscópico" estos tienen los significados definidos por los criterios anteriormente mencionados.

10 Además, el término "ligeramente higroscópico" particularmente puede significar un compuesto que muestra un % del peso ganado, bajo los criterios anteriormente mencionados de cualquiera del 2-9%, 2-8%, 2-7%, 2-6%, 2-5%, 2-4% y 2-3%.

 La diabetes mellitus preferiblemente significa diabetes mellitus del tipo II.

15 Las condiciones asociadas con la diabetes incluyen hiperglicemia y resistencia a la insulina y obesidad. Las condiciones asociadas adicionales con la diabetes incluyen la hipertensión, padecimientos cardiovasculares, especialmente la aterosclerosis, ciertos desórdenes alimenticios, en particular la regulación del apetito y el consumo de alimentos

20 en sujetos que padecen desórdenes asociados con una baja alimentación, tal como la anorexia nervosa, y desórdenes asociados con una sobrealimentación, tal como la obesidad y la anorexia bulimia. Las

condiciones asociadas adicionales con la diabetes incluyen el síndrome ovárico policístico y la resistencia a la insulina inducida por esteroides.

Las complicaciones de las condiciones asociadas con la diabetes mellitus incluidas aquí, incluyen padecimientos renales, especialmente
5 padecimientos renales asociados con el desarrollo de la diabetes del tipo II, que incluyen nefropatía diabética, glomerulonefritis, esclerosis glomerular, síndrome nefrótico, nefroesclerosis hipertensiva y padecimientos renales de etapa terminal.

Como se mencionó anteriormente, el compuesto de la invención
10 tiene propiedades terapéuticas útiles: la presente invención en consecuencia proporciona el clorhidrato para su uso como una sustancia terapéutica activa.

Más particularmente, la presente invención proporciona el clorhidrato para su uso en el tratamiento y/o profilaxis de la diabetes mellitus, condiciones asociadas con la diabetes mellitus y ciertas complicaciones de las
15 mismas.

El clorhidrato se puede administrar por sí mismo o, preferiblemente, como una composición farmacéutica que también comprende un portador farmacéuticamente aceptable. La formulación del clorhidrato en general se describe para el compuesto I en las publicaciones anteriormente
20 mencionadas.

En consecuencia, la presente invención también proporciona una composición farmacéutica que comprende el clorhidrato y un portador farmacéuticamente aceptable para el mismo.

El clorhidrato normalmente se administra en una forma de dosis unitaria.

El compuesto activo se puede administrar a través de cualquier vía adecuada, pero usualmente a través de vías orales o parentelas. Para cada uso, el compuesto normalmente se empleara en la forma de una composición farmacéutica asociada con un portador farmacéutico, diluyente y/o excipiente, aunque la forma exacta de la composición naturalmente dependerá del modo de administración.

Las composiciones son preparadas a través del mezclado y se adaptan adecuadamente para su administración oral, parenteral o local, y también pueden estar en la forma de tabletas, cápsulas, preparaciones líquidas orales, polvos, gránulos, grageas, pastillas, polvos reconstituibles, soluciones o suspensiones inyectables e infusibles, supositorios y dispositivos transdérmicos. Las composiciones que se pueden administrar de forma oral son las preferidas, en particular las composiciones orales conformadas, debido a que son más convenientes para un uso general.

Las tabletas y cápsulas para la administración oral, usualmente se presentan en dosis unitarias, y contienen excipientes convencionales tal como los agentes aglutinantes, rellenos, diluyentes, agentes formadores de tabletas, lubricantes, desintegrantes, colorantes, saborizantes, y agentes humectantes. Las tabletas pueden ser cubiertas de acuerdo a los métodos conocidos muy bien en la técnica.

Los rellenos adecuados para su uso, incluyen la celulosa, manitol, lactosa y otros agentes similares. Los desintegrantes adecuados incluyen el almidón la polivinilpirrolidona y derivados de almidón tal como el almidón glicolato de sodio. Los lubricantes adecuados incluyen, por ejemplo el

5 estearato de magnesio. Los agentes humectantes farmacéuticamente aceptables incluyen el lauril sulfato de sodio.

Las composiciones orales sólidas se pueden preparar a través de métodos convencionales de mezclado, llenado, formado de tabletas o lo similar. Las operaciones de mezclado repetidas se pueden usar para distribuir

10 el agente activo a través de aquellas composiciones que emplean grandes cantidades de rellenos. Tales operaciones son, por supuesto, convencionales en la técnica.

Las preparaciones líquidas orales, pueden estar en la forma de, por ejemplo, suspensiones acuosas o aceitosas, soluciones, emulsiones,

15 jarabes o elixirs, o pueden presentarse como un producto seco para la reconstitución con agua u otro vehículo adecuado antes de su uso. Tales preparaciones líquidas pueden contener aditivos convencionales, tal como agentes dispersantes, por ejemplo el sorbitol, jarabe, metilcelulosa, gelatina, hidroxietilcelulosa, carboximetilcelulosa, gel de estearato de aluminio o grasas

20 comestibles hidrogenadas, agentes emulsionantes, por ejemplo la lecitina, sorbitan monooleato, o la acacia; vehículos no acuosos (que pueden incluir aceites comestibles), por ejemplo, el aceite de almendra, aceite de coco fraccionado, ésteres aceitosos tal como los ésteres de glicerina, propilenglicol,

o alcohol etílico; conservadores, por ejemplo, el p-hidroxibenzoato de metilo o propilo o el ácido sórbico, y si se desea agentes saborizantes o colorantes convencionales.

Para la administración parenteral, las formas de dosis unitarias,
5 fluidas, se preparan conteniendo un compuesto de la presente invención y un vehículo estéril. El compuesto, dependiendo del vehículo y la concentración, puede ser suspendido o disuelto. Las soluciones parenterales normalmente se preparan al disolver el compuesto activo en un vehículo y esterilizando el filtro, antes del llenado en un frasco adecuado o ampollita y del sellado. De manera
10 conveniente, los adyuvantes tal como los anestésicos locales, conservadores y agentes reguladores también se disuelven en el vehículo. Para mejorar la estabilidad, la composición se puede congelar después del llenado en el frasco y la eliminación del agua bajo vacío.

Las suspensiones parenterales se preparan sustancialmente de
15 la misma manera excepto que el compuesto activo se suspende en el vehículo en vez de disolverse y esterilizarse a través de la exposición con óxido de etileno antes de suspenderse en el vehículo estéril. De manera conveniente, un agente tensioactivo o agente humectante esta incluido en la composición para facilitar la distribución uniforme del compuesto activo.

20 Como es común en la practica, las composiciones usualmente se acompañaran por instrucciones escritas o impresas para su uso en el tratamiento medico, involucrado.

Como se usa aquí el término "aceptable farmacéuticamente" comprende compuestos, composiciones e ingredientes para su uso humano y veterinario: por ejemplo el término "sal farmacéuticamente aceptable" comprende una sal de uso veterinario aceptable.

5 La presente invención además proporciona un método para el tratamiento y/o profilaxis de la diabetes mellitus, condiciones asociadas, con la diabetes mellitus y ciertas complicaciones de las mismas, en un mamífero humano o no humano que comprende la administración de una cantidad efectiva, no tóxica, de clorhidrato a un mamífero humano o no humano en
10 necesidad de la misma.

De manera conveniente, el ingrediente activo se puede administrar como una composición farmacéutica anteriormente definida, y ésta, forma un aspecto particular de la presente invención.

En un aspecto adicional de la presente invención, se proporciona
15 el uso del clorhidrato para la elaboración de un medicamento para el tratamiento y/o profilaxis de la diabetes mellitus, condiciones asociadas con la diabetes mellitus y ciertas complicaciones de las mismas.

En el tratamiento y/o profilaxis de la diabetes mellitus, condiciones asociadas con la diabetes mellitus y ciertas complicaciones de las
20 mismas, el clorhidrato se puede tomar en cantidades para proporcionar el compuesto I, en dosis adecuadas, tal como aquellas que se describen en EP 0,306,228 y WO94/05659.

No se indican efectos adversos, toxicólogos en los tratamientos anteriormente mencionados para los compuestos de la invención.

Los siguientes ejemplos ilustran la invención, pero no la limitan de ninguna manera.

5

EJEMPLO 1

Preparación del clorhidrato de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidina-2,4-diona

10 Una mezcla de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidina-2,4-diona (6.0 g) y propan-2-ol (120 ml), se agita y calienta a 50°C bajo una atmósfera de nitrógeno. Se añade una solución de cloruro de hidrógeno en propan-2-ol (5-6 N, 5.0 ml) y la mezcla agitada se calienta a 70°C, punto en el cual se observa una solución

15 transparente. Después del enfriamiento a 45°C por un periodo de 1 hora la solución turbia resultante se calienta a 60°C y se mantiene a esta temperatura por un periodo de 1 hora. La suspensión blanca, espesa, resultante se enfría a 30°C y el producto sólido colectado a través de filtración, se lava con propan-2-ol (25 ml) y se seca bajo vacío, sobre pentóxido de fósforo durante 16 horas

20 para proporcionar el compuesto del título como un sólido cristalino, blanco (5.7 g).

Punto de fusión 168-170°C

DSC: $T_{\text{principio}}=166.6^{\circ}\text{C}$, $T_{\text{límite}}=169.5^{\circ}\text{C}$

Análisis elemental: encontrado C; 54.88 H; 5.16 N; 10.56

Teórico: (C₁₈H₂₀N₃O₃SCl) C; 54.89 H; 5.12 N; 10.67

Cloro iónico: determinado como 9.0% p/p (teórico para C₁₈H₂₀N₃O₃SCl: 9.0% p/p).

- 5 Contenido de agua: determinado como 0.2% p/p usando un aparato Karl Fischer.

EJEMPLO 2

Preparación del clorhidrato de 5-[4-[2-(N-metil-N-(2-

piridil)amino)etoxi]bencil]tiazolidina-2,4-diona

- 10 Una mezcla de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidina-2,4-diona (4.0 g) y propan-2-ol (100 ml) se agita y calienta a 70°C. Se añade ácido clorhídrico concentrado (1.1 ml), a la
- 15 mezcla de reacción agitada la cual se observa que proporciona una solución transparente después de aproximadamente 3 minutos. Se enfría la solución agitada a 58°C y entonces se mantiene a una temperatura de entre 58 a 60°C durante 1 hora. La suspensión blanca resultante se enfría a 30°C y el producto
- 20 sólido se colecta por filtración, se lava con propan-2ol (20 ml) y se seca bajo vacío sobre pentóxido de fósforo durante 64 horas para proporcionar el compuesto del título como un sólido cristalino, blanco (4.3 g).

Higroscopicidad del clorhidrato

Una muestra de la sal de clorhidrato (279 mg), preparada de acuerdo al ejemplo 1, se expuso a una atmósfera con 75% de humedad relativa a 21°C durante un periodo de 43 días. La muestra alcanzo un peso constante durante este periodo. El porcentaje del peso ganado de la muestra se observo que fue del 0.4%.

Conclusión

La sal de clorhidrato no es higroscópica.

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Estabilidad y solubilidad acuosa del clorhidrato

Se colocan 50 mg de la sal en un matraz volumétrico de 20 ml, y se añade agua en alícuotas de 2.5 ml. La muestra se somete a ultrasonido a 21°C para ayudar a la disolución después de cada adición subsecuente de agua y después se analiza. Cuando se obtiene una solución transparente, la solubilidad aproximada en mg/ml se calcula. Entonces se analiza la solución a intervalos por hora para evidencia de la subsecuente precipitación o turbidez.

20	Agua total añadida (ml)	Observación
	2.5 ml	Suspensión turbia
	5.0 ml	Predominantemente clara, solo parcialmente turbia
	7.5 ml	Solución clara obtenida. Permanece transparente después de encontrarse a 21°C por 2 horas adicionales. Solubilidad aprox. de 7 mg/ml

Conclusión

El sólido cristalino blanco se disuelve fácilmente para proporcionar una solución clara con una buena solubilidad acuosa. La solución subsecuentemente permanece transparente sin evidencia de precipitación o turbidez de la solución. Estos datos confirman un experimento previo en un lote diferente del clorhidrato que también evidencia una buena solubilidad y proporciona una solución transparente sin evidencia de precipitación o turbidez de la solución.

10 Datos de caracterización registrados para el producto del ejemplo 1:

A Infrarrojo

El espectro IR (figura 1) se registra como una suspensión de parafina líquida usando un instrumento Perkin-Elmer 170x FTIR a una resolución de 2 cm⁻¹. El espectro obtenido se muestra en el cuadro 1. Las bandas se observaron a:

1745, 1696, 1641, 1609, 1544, 1516, 1331, 1313, 1289, 1257, 1243, 1230, 1203, 1185, 1157, 1073, 1056, 1032, 1015, 984, 918, 907, 873, 841, 811, 803, 772, 738, 714, 657, 618, 605, 560, 527 y 505 cm⁻¹.

B Difracción de polvo de rayos X (XRPD)

El diagrama de XRPD del clorhidrato (figura 2) se registra usando las condiciones de adquisición siguientes: ánodo tubular: Cu, voltaje del generador: 40 kV, corriente del generador: 40 mA, ángulo de inicio: 2.0
5 °2 θ , ángulo final: 35.0 °2 θ , tamaño del intervalo: 0.02 °2 θ , tiempo por intervalo: 10 segundos.

Los ángulos de XRPD característicos y los intensidades relativos se registran en el cuadro 1.

CUADRO 1

Angulo de difracción (°2θ)	Intensidad relativa (%)
10.1	4.9
11.8	15.2
12.4	8.1
13.4	24.7
14.0	4.5
14.6	2.6
15.0	10
16.1	38.2
16.3	91.6
17.2	28
17.7	69
18.1	49.5
19.3	14.2
19.6	46.1
20.4	14.2
20.9	6.9
21.2	24.9
22.2	100
22.4	72.5
22.7	36.4
23.6	98.2
23.8	79.8
24.8	49.1
25.5	10.6
26.1	18.9
26.4	35.9
27.1	35.2
27.4	22.9
28.1	32.6
29.4	32.9
30.0	18.8
30.6	21.4
31.1	11.8
32.1	20
32.6	20.5
33.0	19.8
33.9	23.5
34.5	29.6

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C Raman

El espectro Raman (figura 3) se registra con la muestra en un frasco de vidrio en un sistema Perkin-Elmer 2000R FT-Raman, a una resolución de 4 cm^{-1} . La excitación es de un láser Nd: YAG (1064 nm) con una potencia de salida de 400 mW. Las bandas se observaron a: 3100, 3068, 2927, 2893, 2863, 1746, 1706, 1611, 1587, 1545, 1446, 1382, 1360, 1314, 1287, 1242, 1212, 1185, 1156, 1096, 1073, 1032, 1017, 984, 918, 828, 772, 741, 715, 659, 636, 619, 606, 527, 506, 471, 440, 404, 333, 302, 262 cm^{-1} .

NOVEDAD DE LA INVENCION

REIVINDICACIONES

5 1.- Sales[?] de clorhidrato, no hidratado y no higroscópico o
 ligeramente higroscópico de 5-[4-[2-(N-metil-N-
 (2piridil)amino)etoxi]bencil]tiazolidina-2,4-diona.

 2.- Un compuesto de clorhidrato de 5-[4-[2-(N-metil-N-
 (2piridil)amino)etoxi]bencil]tiazolidina-2,4-diona, caracterizado porque: (i)
10 proporciona un espectro infrarrojo que contiene picos en cerca de 1745, 1516,
 1257, 1056 y 803 cm^{-1} ; (ii) proporciona un diagrama de difracción de polvo de
 rayos X (XRPD) que contiene picos en cerca de 10.1, 13.4, 17.2, 22.2 y 29.4
 °2 θ ; y/o (iii) proporciona un espectro Raman que contiene picos en cerca de
 1314, 1242, 1185, 918 y 404 cm^{-1} .

15 3.- El compuesto de conformidad con la reivindicación 2,
 caracterizado además porque el clorhidrato proporciona un espectro infrarrojo
 substancialmente de acuerdo con la figura I.

 4.- El compuesto de conformidad con la reivindicación 2 o la
 reivindicación 3, caracterizado además porque el clorhidrato proporciona un
20 diafragma de difracción de polvo de rayos X (XRPD) substancialmente de
 acuerdo con la figura II.

5.- El compuesto de conformidad con cualquiera de las reivindicaciones 2 a 4, caracterizado además porque el clorhidrato proporciona un espectro raman substancialmente de acuerdo con la figura III.

6.- Un procedimiento para la preparación del clorhidrato de acuerdo a la reivindicación, caracterizado además porque la 5-[4-[2-(N-metil-N-(2piridil)amino)etoxi]bencil]tiazolidina-2,4-diona (compuesto I) o una sal de la misma, que preferiblemente se dispersa o disuelve en un solvente adecuado, reacciona con una fuente de cloruro de hidrógeno; y después se recupera el clorhidrato.

7.- El procedimiento de conformidad con la reivindicación 6, caracterizado además porque la reacción se realiza bajo condiciones anhidras.

8.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado además porque se usa como una substancia activa, terapéutica.

9.- Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5, para utilizarse en el tratamiento y/o profilaxis de la diabetes mellitus, condiciones asociadas con la diabetes mellitus y ciertas complicaciones de las mismas.

10.- Una composición farmacéutica que comprende el clorhidrato y un portador farmacéuticamente aceptable del mismo.

RESUMEN DE LA INVENCION

Sales de clorhidrato de 5-[4-[2-(N-metil-N-(2piridil)amino)etoxi]bencil]tiazolidina-2,4-diona; substancialmente no
5 hidratadas, y no higroscópicas o ligeramente higroscópicas; una composición farmacéutica que contiene tal compuesto, un procedimiento de preparación del compuesto y el uso de este compuesto en la medicina.

7A/mmr*mmf*igp*ecj*

P02/1351F

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference KR/P32542	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB01/01131	International filing date (day/month/year) 14/03/2001	Priority date (day/month/year) 14/03/2000
International Patent Classification (IPC) or national classification and IPC C07D417/12		
Applicant SMITHKLINE BEECHAM PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 28/09/2001	Date of completion of this report 27.03.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich	Authorized officer Fritz, M 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB01/01131

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*)

Description, pages:

1-13 as originally filed

Claims, No.:

1-10 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB01/01131

- ☐ the drawings, sheets:
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-10
	No:	Claims
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-10
Industrial applicability (IA)	Yes:	Claims 1-10
	No:	Claims

**2. Citations and explanations
see separate sheet**

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB01/01131

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: EP-A-0 306 228 (BEECHAM GROUP PLC) 8 March 1989 (1989-03-08) cited in the application

D2: WO 94 05659 A (SMITHKLINE BEECHAM PLC ;POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 (1994-03-17) cited in the application

The present application relates to a non-hydrated and non-hygroscopic hydrochloride salt of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (claims 1-5), a process for the preparation thereof (claims 6-7), the hydrochloride compound for use in therapy (claims 8-10) as well as pharmaceutical compositions thereof (claim 10).

The compound according to claim 1 of the present case is the hydrochloride salt of the title compound according to ex. 30 of D1. It is also comprised in the subject-matter of claim 11 according to D1, as this claim encompasses the specific compound as well as possible pharmaceutical acceptable salts thereof.

The hydrochloride salt according to claim 1 of the present application is also comprised in the subject-matter of claim 1 of D2, as the counter-ion M⁻ cited therein may be a chloride anion (cf. D2, p. 2, lines 12-14).

It is also emphasized in D2 that the ionic compounds (I) disclosed therein have significant formulation and bulk handling advantages.

The compound according to claim 1 of the present case is, however, not explicitly disclosed which renders the subject-matter thereof novel in the sense of Article 33(2) PCT.

The problem of the present application was to provide 5-[4-[2-(N-methyl-N-(2-pyridyl)-amino)ethoxy]benzyl]thiazolidine-2,4-dione in a form which makes it suitable for bulk preparation and handling.

This problem has been solved, as can be seen in the description.

As, however, the neutral compound itself is already known (D1) and D2 emphasizes

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB01/01131

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the advantages of its salts (which even includes the mentioning of the hydrochloride) the solution disclosed in the present case must be considered obvious for the skilled man.

Therefore an inventive step in the sense of Article 33(3) PCT cannot be acknowledged for the subject-matter of claims 1-10.

Furthermore the following objections are raised:

The terms "substantially" (claims 1,3-5), "slightly" (claim 1) and "about" (claim 2) are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

Claims 3-5 contain references to the description and/or the drawings. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference KR/P32542	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB01/01131	International filing date (day/month/year) 14/03/2001	Priority date (day/month/year) 14/03/2000
International Patent Classification (IPC) or national classification and IPC C07D417/12		
Applicant SMITHKLINE BEECHAM PLC et al.		

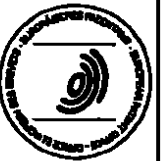
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- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
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- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 28/09/2001	Date of completion of this report 27.03.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fritz, M Telephone No. +49 89 2399 2792 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB01/01131

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

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Claims, No.:

1-10 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

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- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

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- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB01/01131

- ☐ the drawings, sheets:
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
- (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

**2. Citations and explanations
see separate sheet**

Re Item V

**Reasoned statement under Rule 68.2(a)(ii) with regard to novelty, inventive step
r industrial applicability; citations and explanations supporting such statement**

D1: EP-A-0 306 228 (BEECHAM GROUP PLC) 8 March 1989 (1989-03-08) cited in
the application

D2: WO 94 05659 A (SMITHKLINE BEECHAM PLC ;POOL COLIN RIPLEY (GB);
ROMAN ROBIN SHERWO) 17 March 1994 (1994-03-17) cited in the application

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The hydrochloride salt according to claim 1 of the present application is also comprised in the subject-matter of claim 1 of D2, as the counter-ion M⁺ cited therein may be a chloride anion (cf. D2, p. 2, lines 12-14).

It is also emphasized in D2 that the ionic compounds (I) disclosed therein have significant formulation and bulk handling advantages.

The compound according to claim 1 of the present case is, however, not explicitly disclosed which renders the subject-matter thereof novel in the sense of Article 33(2) PCT.

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This problem has been solved, as can be seen in the description.

As, however, the neutral compound itself is already known (D1) and D2 emphasizes

46

the advantages of its salts (which even includes the mentioning of the hydrochloride) the solution disclosed in the present case must be considered obvious for the skilled man.

Therefore an inventive step in the sense of Article 33(3) PCT cannot be acknowledged for the subject-matter of claims 1-10.

Furthermore the following objections are raised:

The terms "substantially" (claims 1,3-5), "slightly" (claim 1) and "about" (claim 2) are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

Claims 3-5 contain references to the description and/or the drawings. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

USUARIO RADICADOR

PATENTE DE INVENCION []

MODELO DE UTILIDAD [] []

- Indicación de que se solicita la concesión de una patente [] []
- Datos de identificación del solicitante o de la persona que presenta la solicitud [] []
- Descripción de la invención [] []
- Dibujos de ser estos pertinentes [] []
- Comprobante de Pago de las tasas establecidas [] []

COMPLETA []

INCOMPLETA [] []

DISEÑO INDUSTRIAL []

- Indicación de que se solicita el registro de Diseño Industrial. [] []
- Datos de identificación del solicitante o de la persona que presenta la solicitud. [] []
- Representación gráfica y foto gráfica del Diseño Industrial o muestra del material que incorpora el diseño. [] []
- Comprobante de pago de las tasas establecidas. [] []

COMPLETA []

INCOMPLETA [] []

ESQUEMA DE TRAZADO []

- Indicación de que se solicita el registro de un Esquema de trazado. [] []
- Datos de identificación del solicitante o de la persona que presenta la solicitud. [] []
- Representación gráfica del esquema de trazado [] []
- Comprobante de pago de las tasas establecidas. [] []

COMPLETA []

INCOMPLETA [] []

Firma Responsable

SUPERINDUSTRIA Y COMERCIO

Fe Radicación : 02042003 00000000 Folios: 46
Fecha (AMD): 2002-09-13 16:25:27
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Carrera 13 No. 27-00 Piso 2 mezzanina
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Fax: 350 52 20 e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

2020
Bogotá, D.C.,

Doctor:
CARLOS R. OLARTE
Apoderado
SMITHKLINE BEECHAM P.L.C.

Oficio N° **07044**

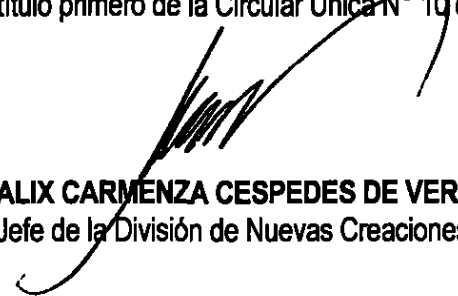
ASUNTO:	Radicación N°	02-82083
	Solicitud internacional	PCT/GB01/01131
	Fecha inicio fase nacional	14-10-2002
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).
- La solicitud no contiene el lugar de constitución de la sociedad solicitante (Art.27-c) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, **29 AGO. 2003**.

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