

Señor Jefe

DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Santa Fe de Bogotá, D.C.

SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

02-01-08 -
Re.: Expediente No. 00 - 28.927

Solicitud de Patente

SMITHKLINE BEECHAM PLC

Debidamente traducida adjunto acompaño las copias oficiales de las solicitudes de patente básicas Británicas No.9909471.6 y No.99121195.6 las cuales le solicito agregar a este expediente para los efectos legales respectivos.

De Usted atentamente,

GERMAN CASTILLO GRAU

T.P.#2.978 del C.S.J.



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INVESTOR IN PEOPLE

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The Patent Office
Concept House
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NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed *AmBrewer*

Dated 26 April 2000

Patents Form 1/77

9. Enter number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description 5

Claim(s)

Abstract

Drawings 3

10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 1/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11.

We request the grant of a patent on the basis of this application

Signature K Rutter Date 23-Apr-99

K Rutter

12. Name and daytime telephone number of person to contact in the United Kingdom

K Rutter 01279 644396

Warning

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Notes

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NOVEL PHARMACEUTICAL

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

International Patent Application, Publication Number WO94/05659 discloses
certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic
activity including 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-
2,4-dione, maleic acid salt (hereinafter also referred to as "Compound (I)").

10 It has now been discovered that Compound (I) exists in a novel polymorphic
form which is particularly suitable for bulk preparation and handling. The novel form
can be prepared by an efficient, economic and reproducible process particularly suited
to large scale preparation.

The novel polymorphic form ('the Polymorph') also has useful pharmaceutical
15 properties and in 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 a polymorphic form of 5-[4-[2-
(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt
20 characterised in that it provides:

- (i) an infrared spectrum substantially in accordance with Figure I;
- (ii) a Raman spectrum substantially in accordance with Figure II; and /or
- (iii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with
Figure III.

25 The present invention encompasses the Polymorph isolated in pure form or
when admixed with other materials, for example the known forms of Compound I or
any other material.

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

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

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

The invention also provides a process for preparing the Polymorph,
characterised in that a solution of Compound (I) in denatured ethanol is seeded with
the Polymorph then cooled to 20-25°C to provide the Polymorph. The Polymorph is
then recovered from the denatured ethanol.

35 The solution of Compound (I) in the denatured ethanol is conveniently
prepared by dissolving Compound (I) in the required amount of denatured ethanol at
an elevated temperature, for example 60°C.

Conveniently the Polymorph is recovered from the denatured ethanol by filtration and subsequent drying.

Compound (I) is prepared according to known procedures, such as those disclosed in WO94/05659. The disclosures of WO94/05659 are incorporated herein
5 by reference.

When used herein "denatured ethanol" means ethanol containing small amounts of methanol for example ethanol containing 4%v/v of methanol.

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

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
15 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.

20 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.

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

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

The Polymorph may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation of the Polymorph and dosages thereof are generally as disclosed for Compound (I) in International Patent Application, Publication Number WO94/05659.

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

The Polymorph is normally administered in unit dosage form.

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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.

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.

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.

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

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.

In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

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 the Polymorph 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 the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Polymorph may be taken in doses, such as those described above.

Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

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

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

The following example illustrates the invention but do not limit it in any way.

Characterising data

Infrared

The infrared absorption spectrum of a mineral oil dispersion of the Polymorph was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm^{-1} resolution. Data were digitised at 1 cm^{-1} intervals. The spectrum obtained is shown in Figure I.

Raman

The Raman spectrum of the Polymorph was recorded through a glass vial using a Perkin Elmer 2000R spectrometer at 4 cm^{-1} resolution and is shown in Figure II. Excitation was achieved using a Nd:YAG laser (1064 nm) with a power output of 500 mW.

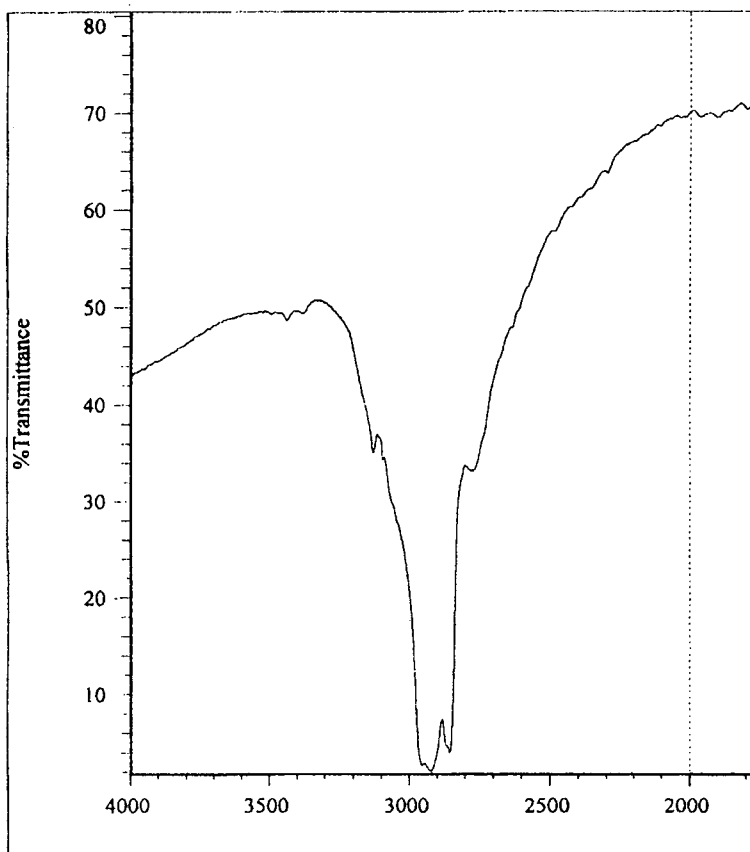
X-Ray Powder Diffraction (XRPD)

The XRPD pattern of the Polymorph is shown in Figure III and a summary of the XRPD angles and calculated lattice spacings characteristic of the Polymorph is given in Table I.

A Bruker AXS D8 Advance X-ray powder diffractometer (Cu X-ray source) was used to generate the pattern using the following acquisition conditions:

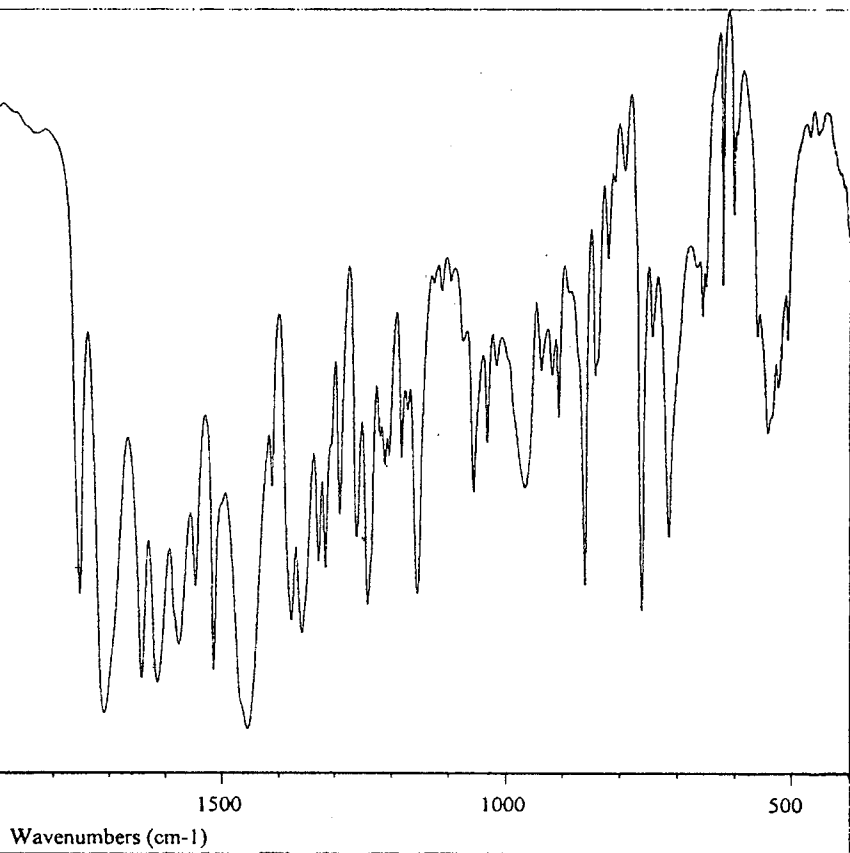
Tube anode:	Cu
Generator tension:	40 kV
Generator current:	40 mA
Start angle:	$2.0^\circ 2\theta$
End angle:	$35.0^\circ 2\theta$
Step size:	$0.02^\circ 2\theta$
Time per step:	2.5s

- 9 -



P32293

Figure I: Infrared Spectrum of the Polymorph.



P32293

Figure II: Raman Spectrum of the Polymorph

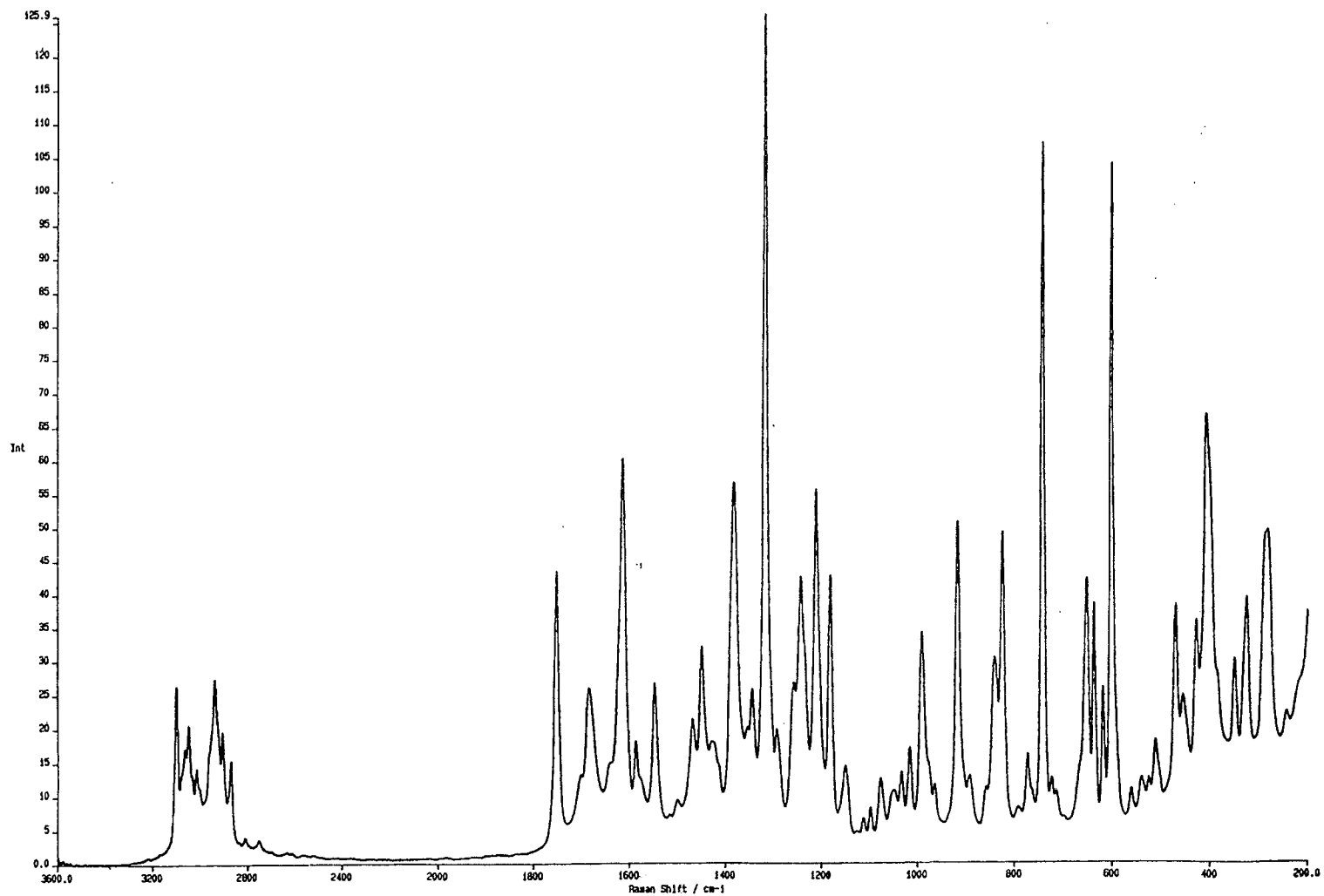
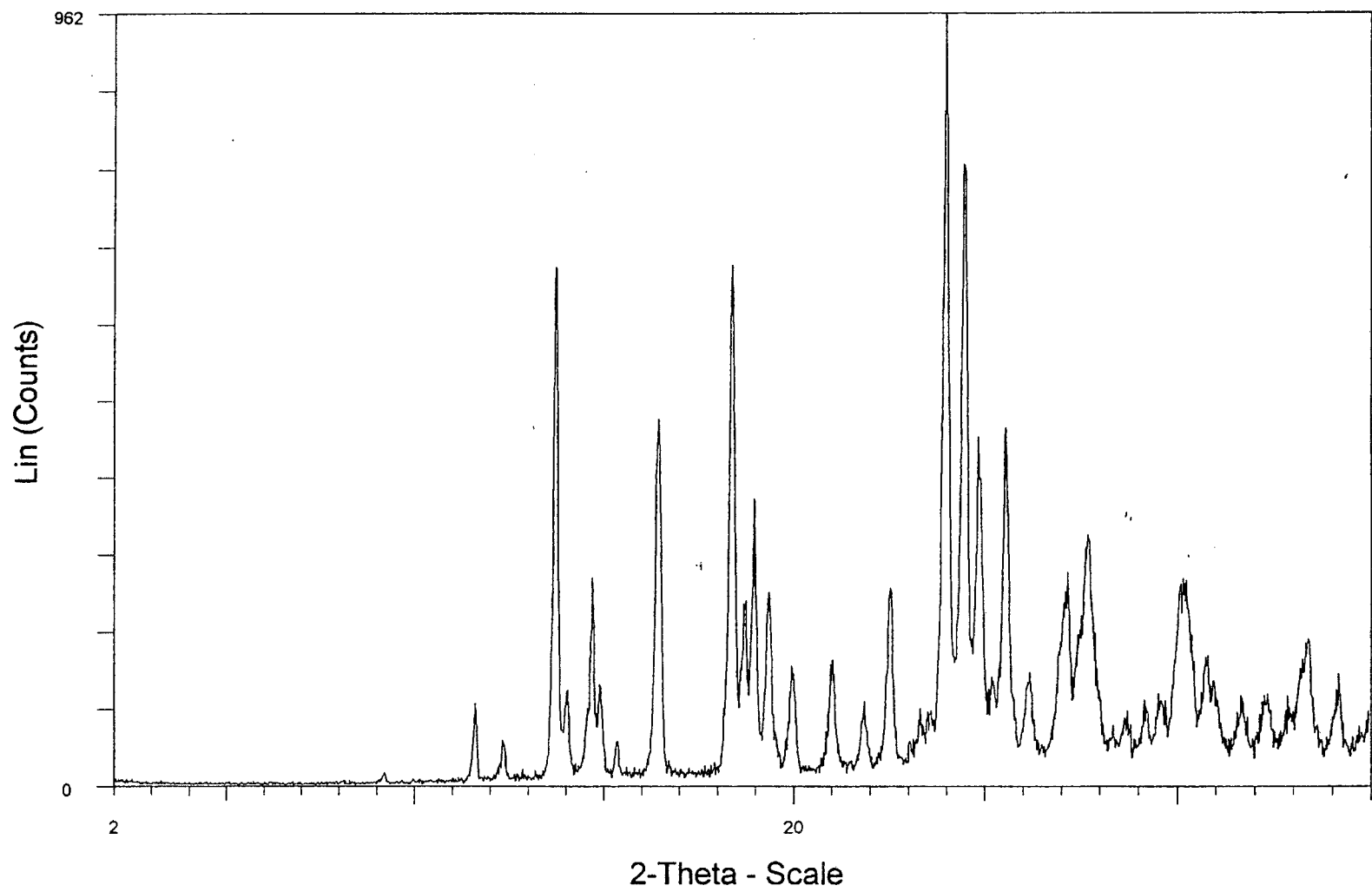


Figure III: X-Ray Powder Diffraction Pattern of the Polymorph



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LEGALIZACIONES

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NP10 8QQ

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras "sociedad anónima" o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue registrada.

De acuerdo con las reglas, las palabras "sociedad anónima" (o en inglés *public limited company*) pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) ANDREW BREWER

FECHA: 26 de abril de 2000

(SELLO DE LACRE)

OFICINA DE PATENTES**SOLICITUD DE PATENTE**

1. Su referencia: **KR/JW/P32293**

2. Solicitud No. **9909471.6** 23 de abril de 1999

3. Nombre completo y código postal de cada solicitante:

Dirección: SMITHKLINE BEECHAM plc.
New Horizons Court,
Brentford, Mddlesex TW8 9EP

No. APD 7605058001

Si el solicitante es una entidad, indique el pais/estado de constitución:

REINO UNIDO

4. TITULO DEL INVENTO:

COMPUESTOS NOVEDOSOS

5. NOMBRE DE SU AGENTE:

Nombre del Agente: **CORPORATE INTELLECTUAL PROPERTY**

Dirección para notificaciones: **SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP**

NO. ADP Patentes 5800974004

6. N/A

7. N/A

8. SI



9. Número de hojas radicadas (En inglés). Descripción: 5 Reivindicaciones:

Resumen : - Dibujos: - 3

10. Solicitud de examen preliminar y búsqueda:

11. Solicitamos se nos adjudique una patente con base en esta solicitud.

K. RUTTER

23 de abril de 1999

12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el

Reino Unido (FIRMA) K. RUTTER

01279 644396

PRODUCTO FARMACÉUTICO NOVEDOSO

Esta invención se refiere a un producto farmacéutico novedoso, a un proceso para la preparación del fármaco y al uso del fármaco en medicina.

La Solicitud de Patente Internacional No. WO94/05659 revela ciertos derivados de tiazolidinediona que tienen actividad hipoglicémica e hipolipidémica incluyendo 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidine-2,4-diona, sal de ácido maléico (referido en adelante como "Compuesto I")

Se ha descubierto que el Compuesto I existe forma polimorfa novedosa, particularmente útil para preparación y manejo en volúmenes. La forma novedosa puede ser preparada mediante un proceso eficiente, económico y reproducible indicado para preparación a grande escala.

La forma polimorfa novedosa (el "Polimorfo") también tiene propiedades farmacéuticas útiles, y en particular es indicado para ser útil en el tratamiento y/o profilaxis de diabetes mellitus, condiciones asociadas con diabetes mellitus y ciertas complicaciones de la misma.

Por lo tanto, la presente invención provee una forma polimorfa de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]tiazolidina-2,4-diona, sal de ácido maléico, caracterizado en que:

- i) provee un espectro infrarrojo sustancialmente de acuerdo con la Figura I;
- ii) provee un espectro Raman, sustancialmente de acuerdo con la Figura II; y/o

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- iii) provee un patrón de difracción de polvo de rayos X (XRPD), sustancialmente de acuerdo con la Figura III.

En un aspecto, la invención provee un proceso para convertir el Polimorfo en el Compuesto (I), en donde una solución del Polimorfo en un solvente adecuado, tal como acetona o etanol, es germinado con el Compuesto (I). En términos generales, la solución del Polimorfo se obtiene disolviendo el Polimorfo a una temperatura elevada en el solvente, tal como acetona o etanol.

El Compuesto I se prepara según procedimientos conocidos, tales como los revelados en la WO94/05659 cuyo contenido se incorpora en este contexto por referencia.

El término "etanol desnaturalizado" significa etanol que contiene pequeñas cantidades de metano, por ejemplo metanol con 4% volumen por volumen de metanol.

Diabetes mellitus significa preferiblemente diabetes mellitus Tipo II.

Condiciones asociadas con diabetes incluyen hiperglicemia y resistencia a la insulina y obesidad. Otras condiciones asociadas con diabetes incluyen hipertensión, enfermedad cardiovascular, especialmente aterosclerosis, ciertos trastornos de alimentación, en particular la regulación de apetito e ingestión de alimentos en sujetos que sufren de trastornos asociados con mala alimentación, tales como anorexia nerviosa y trastornos asociados con sobrealimentación, tales como obesidad y anorexia bulimia. Otras condiciones asociadas con diabetes incluyen síndrome de ovario policístico y resistencia a la insulina inducida por esteroides.

Las complicaciones de las condiciones asociadas con diabetes melitus que se incorporan en este contexto, incluyen enfermedades renales, especialmente enfermedad renal asociada con el desarrollo de diabetes Tipo II, incluyendo

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nefropatía diabética, glomerulonefritis, esclerosis glomerular, síndrome nefrótico, nefrosclerosis hipertensa y enfermedad renal de etapa final.

La presente invención además provee un método para el tratamiento y/o profilaxis de diabetes mellitus, condiciones asociadas con diabetes mellitus y ciertas complicaciones de la misma, en un mamífero humano o no humano, que consiste en administrar a un ser humano o a un mamífero, una cantidad efectiva, no tóxica del Polimorfo.

Para los tratamientos de la invención no se indican efectos toxicológicos



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49
1/77Z6MAY99 E449914-5 D02029
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Request for grant of a patent

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The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

KR/JW/P32311

2. Patent :

(The Patent Office will ...)

9912195.6

25 MAY 1999

3. Full name, address and postcode of the or of each applicant (*underline all surnames*)

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP,
Great Britain

Patents ADP number (*if you know it*)

If the applicant is a corporate body, give the country/state of its incorporation

5800974002

4. Title of the invention

Novel Pharmaceutical

5. Name of your agent (*if you have one*)

CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number (*if you know it*)

5800974004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (*if you know it*) the or each application number

Country Priority application number Date of filing
(if you know it) (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer yes if:*

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is named as an applicant, or
- c) any named applicant is a corporate body

See note (d)

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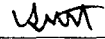
Request for preliminary examination
and search (*Patents Form 9/77*)

Request for substantive examination
(*Patents Form 10/77*)

Any other documents
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Signature   Date 25-May-99
K Rutter

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20 Accordingly, the present invention provides a polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt characterised in that it provides:

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

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The invention also provides a process for preparing the Polymorph, characterised in that a solution of Compound (I) in denatured ethanol is seeded with the Polymorph then cooled to 20-25°C to provide the Polymorph. The Polymorph is then recovered from the denatured ethanol.

35 The solution of Compound (I) in the denatured ethanol is conveniently prepared by dissolving Compound (I) in the required amount of denatured ethanol at an elevated temperature, for example 60°C.

Conveniently the Polymorph is recovered from the denatured ethanol by filtration and subsequent drying.

In a further aspect, the invention provides a process for converting Polymorph to Compound (I), wherein a solution of Polymorph in a suitable solvent, such as acetone or ethanol, is seeded with Compound (I). Generally, the solution of Polymorph is obtained by dissolving Polymorph at an elevated temperature in the solvent, such as acetone or ethanol.

Compound (I) is prepared according to known procedures, such as those disclosed in WO94/05659. The disclosures of WO94/05659 are incorporated herein by reference.

When used herein "denatured ethanol" means ethanol containing small amounts of methanol for example ethanol containing 4%v/v of methanol.

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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 the Polymorph for use as an active therapeutic substance.

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

The Polymorph may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation

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of the Polymorph and dosages thereof are generally as disclosed for Compound (I) in International Patent Application, Publication Number WO94/05659.

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

The Polymorph is normally administered in unit dosage form.

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.

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.

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.

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.

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.

5 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.

10 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
15 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.

In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

20 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.

25 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 the Polymorph to a human or non-human mammal in need thereof.

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

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Polymorph may be taken
35 in doses, such as those described above.

Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

In a further aspect the present invention provides the use of the Polymorph 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 No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following example illustrates the invention but do not limit it in any way.

Example 1: Conversion of Polymorph to Compound (I)

Polymorph (10.0 g) was added to denatured ethanol (90 ml) under nitrogen. The resulting mixture was stirred and heated to 68°C, and held at this temperature for 30 min. The solution was hot filtered to a preheated vessel (56°C) and the filter washed with hot denatured ethanol (10ml). The temperature of the filtrate was adjusted to 60°C and then cooled with stirring. At 55°C the solution was seeded with Compound (I) (0.4 g) and cooling, with stirring, continued. The resulting slurry was stirred at ambient temperature for 1 h, and the solid isolated by filtration, washed with denatured ethanol and dried at 50°C *in vacuo* to give 8.4 g (84%) Compound (I).

Example 2: Conversion of Polymorph to Compound (I)

Polymorph (5.0 g) was added to acetone (170 ml) and the mixture was stirred and heated to reflux temperature. After complete dissolution, the solution was heated at reflux for 30min, then filtered. The filtered solution was concentrated by distillation at atmospheric pressure (120ml of distillate was collected). The remaining solution was stirred and cooled at about 1°C and at 50°C seeded with Compound (I) (0.2 g). Cooling was continued at 1°C, and when the slurry reached 20°C stirring was continued for 1 h. The solid was isolated by filtration, washed with acetone and dried *in vacuo* at 50°C to give 4.2 g (84%) of Compound (I).

Characterising data**Infrared**

The infrared absorption spectrum of a mineral oil dispersion of the Polymorph was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm⁻¹ resolution. Data were digitised at 1 cm⁻¹ intervals. The spectrum obtained is shown in Figure I.

Raman

The Raman spectrum of the Polymorph was recorded through a glass vial using a Perkin Elmer 2000R spectrometer at 4 cm⁻¹ resolution and is shown in Figure II. Excitation was achieved using a Nd:YAG laser (1064 nm) with a power output of 500 mW.

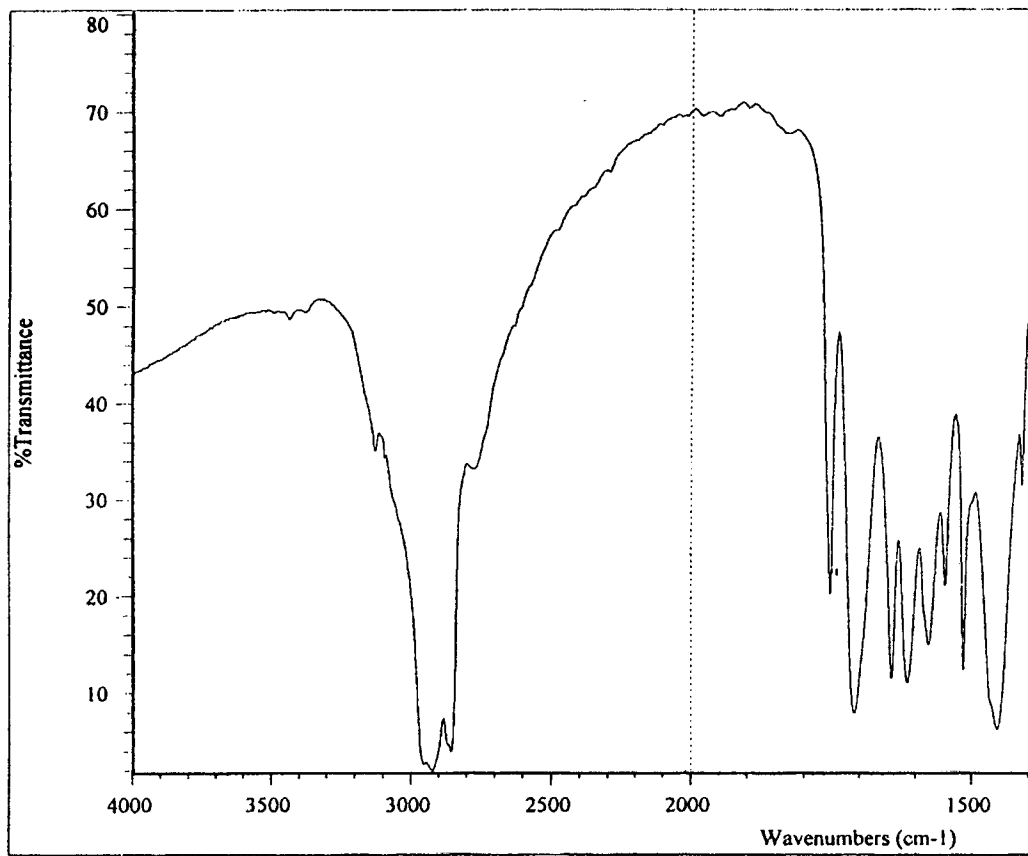
X-Ray Powder Diffraction (XRPD)

The XRPD pattern of the Polymorph is shown in Figure III and a summary of the XRPD angles and calculated lattice spacings characteristic of the Polymorph is given in Table I.

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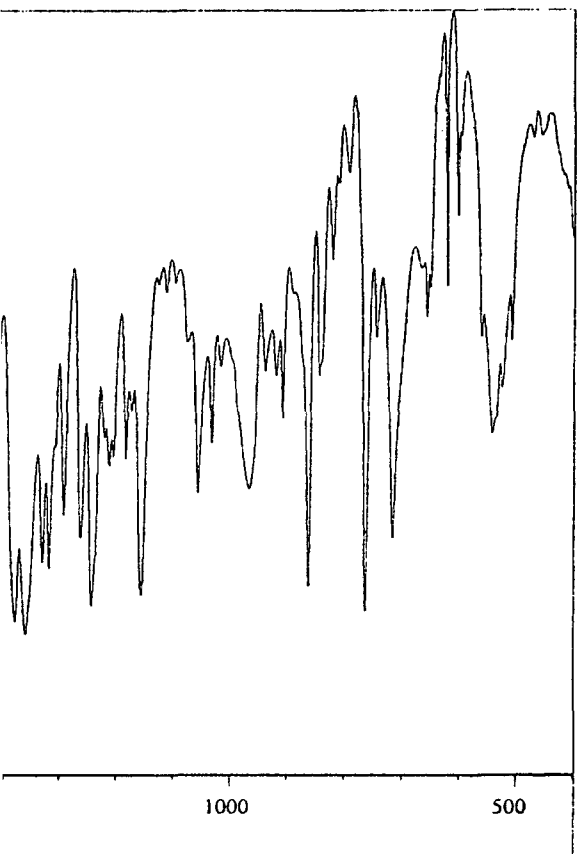
A Bruker AXS D8 Advance X-ray powder diffractometer (Cu X-ray source) was used to generate the pattern using the following acquisition conditions:

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:	2.5s



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Figure 1: Infrared Spectrum of the Polymorph.



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Figure II: Raman Spectrum of the Polymorph

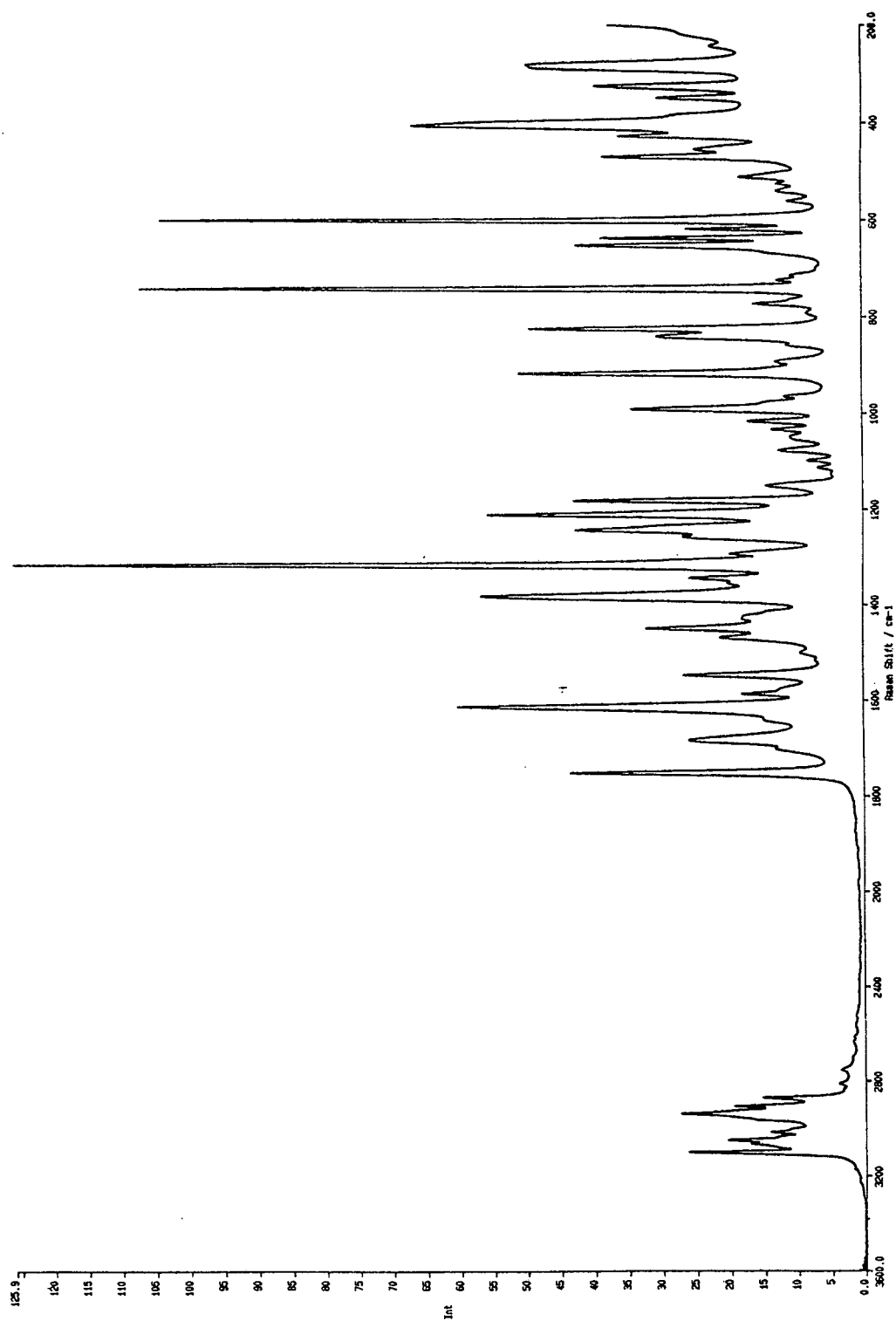
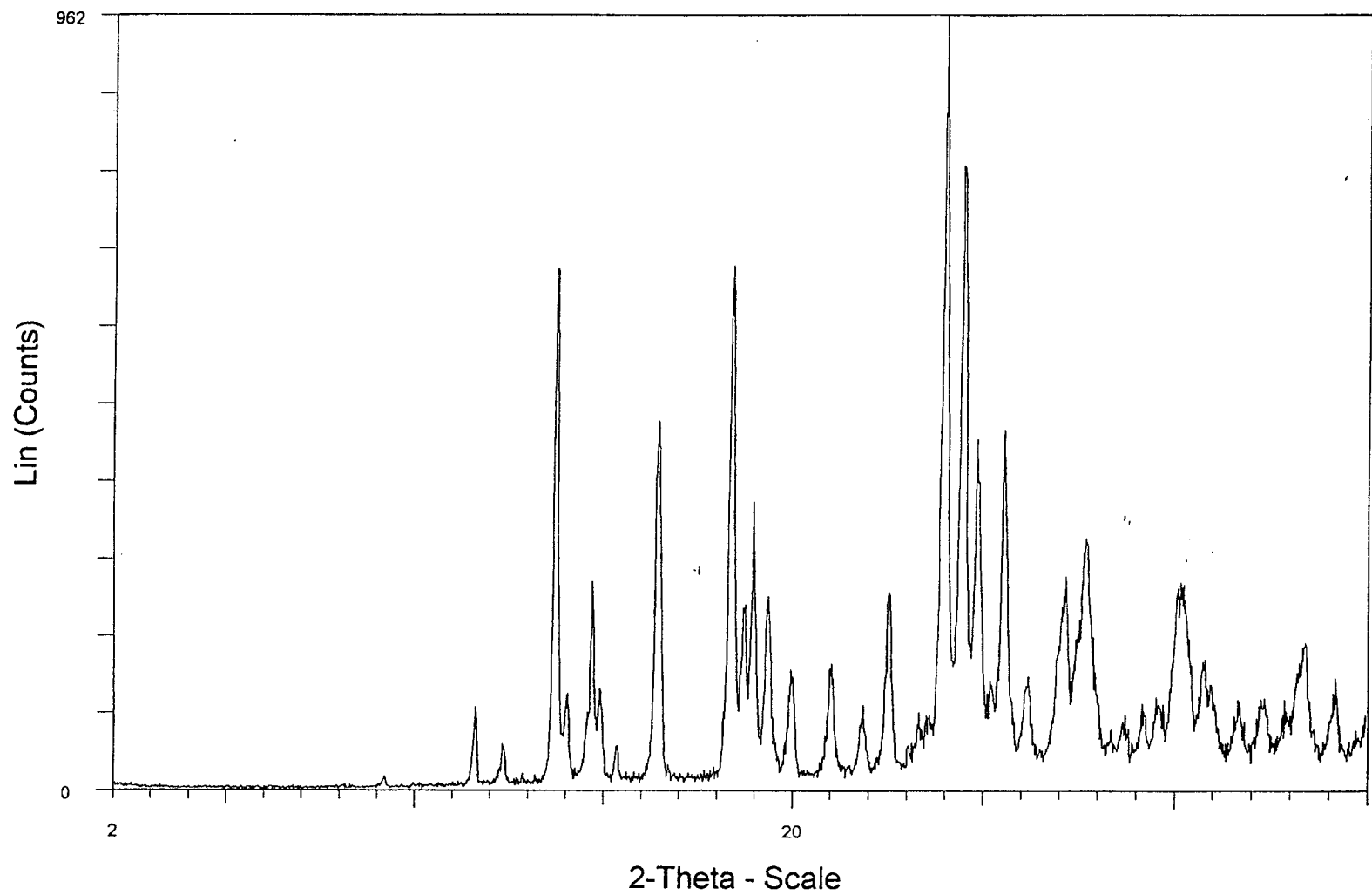


Figure III: X-Ray Powder Diffraction Pattern of the Polymorph



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SOLICITUD DE PATENTE

1. Su referencia: **KR/JW/P32311**

2. Solicitud No. **9912195.6** 25 de mayo de 1999

3. Nombre completo y código postal de cada solicitante:

Dirección: SMITHKLINE BEECHAM plc.
New Horizons Court,
Brentford, Mddlesex TW8 9EP

No. APD 5800974002

Si el solicitante es una entidad, indique el país/estado de constitución:

REINO UNIDO

4. TITULO DEL INVENTO:

FARMACÉUTICO NOVEDOSO

5. NOMBRE DE SU AGENTE:

Nombre del Agente: CORPORATE INTELLECTUAL PROPERTY

Dirección para notificaciones: SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

NO. ADP Patentes 5800974003

6. N/A

7. N/A

8. SI

9. Número de hojas radicadas (En inglés). Descripción: 10 Reivindicaciones:

Resumen : - Dibujos: -

10. Solicitud de examen preliminar y búsqueda:

11. Solicitamos se nos adjudique una patente con base en esta solicitud.

K. RUTTER

25 de mayo de 1999

12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el
Reino Unido (FIRMA) K. RUTTER 01279 644396

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N

LEGALIZACIONES

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NP10 8QQ

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras "sociedad anónima" o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras "sociedad anónima" (o en inglés *public limited company*) pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) ANDREW BREWER

FECHA: 26 de abril de 2000

(SELLO DE LACRE)

PRODUCTO FARMACÉUTICO NOVEDOSO

Esta invención se refiere a un producto farmacéutico novedoso, a un proceso para la preparación del fármaco y al uso del fármaco en medicina.

La Solicitud de Patente Internacional No. WO94/05659 revela ciertos derivados de tiazolidinediona que tienen actividad hipoglicémica e hipolipidémica incluyendo 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidine-2,4-diona, sal de ácido maléico (referido en adelante como "Compuesto I")

Se ha descubierto que el Compuesto I existe forma polimorfa novedosa, particularmente útil para preparación y manejo en volúmenes. La forma novedosa puede ser preparada mediante un proceso eficiente, económico y reproducible indicado para preparación a grande escala.

La forma polimorfa novedosa (el "Polimorfo") también tiene propiedades farmacéuticas útiles, y en particular es indicado para ser útil en el tratamiento y/o profilaxis de diabetes mellitus, condiciones asociadas con diabetes mellitus y ciertas complicaciones de la misma.

Por lo tanto, la presente invención provee una forma polimorfa de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]tiazolidina-2,4-diona, sal de ácido maléico, caracterizado en que:

- i) provee un espectro infrarrojo sustancialmente de acuerdo con la Figura I;
- ii) provee un espectro Raman, sustancialmente de acuerdo con la Figura II; y/o

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- iii) provee un patrón de difracción de polvo de rayos X (XRPD), sustancialmente de acuerdo con la Figura III.

En un aspecto, la invención provee un proceso para convertir el Polimorfo en en el Compuesto (I), en donde una solución del Polimorfo en un solvente adecuado, tal como acetona o etanol, es germinado con el Compuesto (I). En términos generales, la solución del Polimorfo se obtiene disolviendo el Polimorfo a una temperatura elevada en el solvente, tal como acetona o etanol.

El Compuesto I se prepara según procedimientos conocidos, tales como los revelados en la WO94/05659 cuyo contenido se incorpora en este contexto por referencia.

El término "etanol desnaturalizado" significa etanol que contiene pequeñas cantidades de metano, por ejemplo metanol con 4% volumen por volumen de metanol.

Diabetes mellitus significa preferiblemente diabetes mellitus Tipo II.

Condiciones asociadas con diabetes incluyen hiperglicemia y resistencia a la insulina y obesidad. Otras condiciones asociadas con diabetes incluyen hipertensión, enfermedad cardiovascular, especialmente aterosclerosis, ciertos trastornos de alimentación, en particular la regulación de apetito e ingestión de alimentos en sujetos que sufren de trastornos asociados con mala alimentación, tales como anorexia nerviosa y trastornos asociados con sobrealimentación, tales como obesidad y anorexia bulimia. Otras condiciones asociadas con diabetes incluyen síndrome de ovario policístico y resistencia a la insulina inducida por esteroides.

Las complicaciones de las condiciones asociadas con diabetes melitus que se incorporan en este contexto, incluyen enfermedades renales, especialmente enfermedad renal asociada con el desarrollo de diabetes Tipo II, incluyendo

nefropatía diabética, glomerulonefritis, esclerosis glomerular, síndrome nefrótico, nefrosclerosis hipertensiva y enfermedad renal de etapa final.

La presente invención además provee un método para el tratamiento y/o profilaxis de diabetes mellitus, condiciones asociadas con diabetes mellitus y ciertas complicaciones de la misma, en un mamífero humano o no humano, que consiste en administrar a un ser humano o a un mamífero, una cantidad efectiva, no tóxica del Polimorfo.

Para los tratamientos de la invención no se indican efectos toxicológicos