



OPOS

Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

04-61363

54. TÍTULO Composiciones farmacéuticas que comprenden metformina y glibenclámido para el tratamiento de la diabetes mellitus tipo II

51. CLASIFICACIÓN INTERNACIONAL A61K 9/20//A61K 31/132//A61K 31/13

71. SOLICITANTE Mencini International Operations Luxembourg SA

DOMICILIO 1, Avenue de la gare 1611 Luxembourg

74. APODERADO Dra. Doris Tlaca Gomez Diaz

22. BOGOTÁ, D. C., Junio 29 de 2004

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE :

☒

Patente de Invención

☐ Patente de Modelo de Utilidad

☐ Capítulo I.

☒

Capítulo II.

2
SOLICITANTE
(71)

Nombre: MENARINI INTERNATIONAL
OPERATIONS LUXEMBOURG S.A.
Dirección: 1, Avenue de la Gare 1611
LUXEMBOURG
Nacionalidad o Domicilio: LUXEMBURGO
Lugar de Constitución: LUXEMBURGO
Teléfono:

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ OTRO ☐

Cual:
Número:

3
REPRESENTANTE
APODERADO

Nombre: DORA MARIA GOMEZ DIAZ
Dirección: CARRERA 7 No. 32 - 85 OFICINA 501
Teléfono: 2859058 - 2452462
Fax: 2859919
E-mail: gerencia@gomezydiaz.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ OTRO ☐

Cual:
Número: 52.145.354 Bogotá
T.P.: 95.718 C.S. de la J.

4
INVENTOR (ES)
(72)

Nombre: Alessandro TOSETTI, Mauro GUIDUCCI, Giovanni VITI
Dirección: Vía F. Paoletti, 13, I-50012 Bagno A Ripoli-ITALIA, Vía Tullio Levi
Civita, 1, I-52100 Arezzo-ITALIA, Viale A. Guidoni, 179, I-50127 FIRENZE-
ITALIA (RESPECTIVAMENTE)
Nacionalidad o Domicilio: ITALIA

5 PCT (86)

Solicitud Internacional No. PCT/EP02/13497
Publicación Internacional No. WO 03/045355 A1

Fecha: 29 NOVIEMBRE 2002
Fecha: 5 JUNIO DE 2003

6 Título (54)

**COMPOSICIONES FARMACEUTICAS QUE COMPRENDEN
METFORMINA Y GLIBENCLAMIDA PARA EL TRATAMIENTO DE LA
DIABETES MELLITUS TIPO II**

7 Clasificación Internacional (51): A61 K 9/20 // A61K31/132 // A61K31/18.

8 Prioridad

SI ☒ NO ☐

(33) País de Origen

ITALIA

(32) Fecha

29/11/01

(31) Número de Solicitud

PT20014000230

9 Comprobante de pago No. 04-48,436 Y 04-48,435

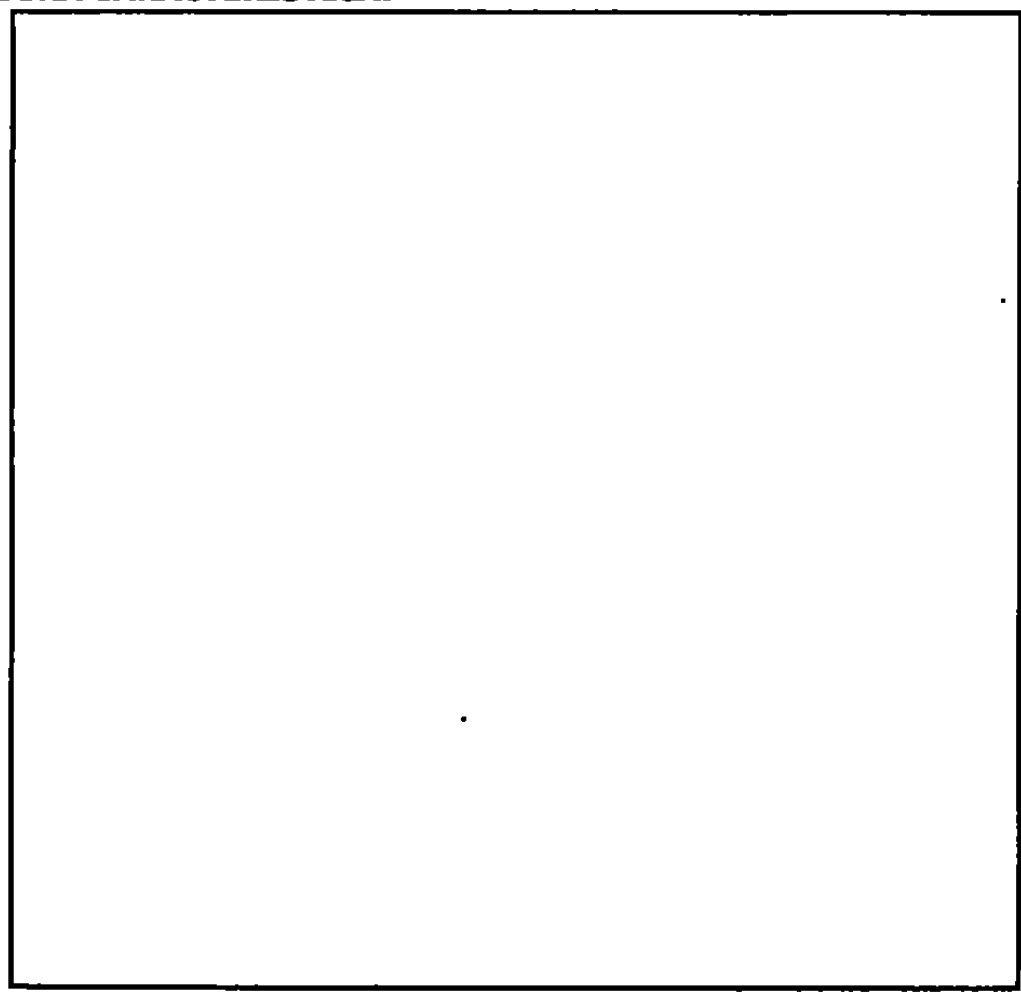
Fecha: JUNI 18/2004

2.

- ☒ Comprobante de pago de la tasa de presentación de la solicitud \$422.000.00
- ☒ Comprobante de pago por reivindicación de prioridad \$118.000.00
- ☐ 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 12x12
- ☐ 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

FIGURA CARACTERÍSTICA:

11



12

Solicito la concesión de la patente, NOMBRE: DORA MARIA GOMEZ DIAZ

FIRMA:

C.C.: 52.145.354 Bogotá T.P.: 95.718 C.S.J.

NIT : 900174029-2

SUPERINDUSTRIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 04 - 19,435
FECHA : JUNIO 18 DE 2004

Radicacion : 04061363 00000000 Folios: 156
Fecha (AMD): 2004-06-29 08:52:36
Tramite : 011 PCT-PATENT 379 FASE NUCT 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
DORA MARIA GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	27450144	18/06/2004	422,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
		TOTAL :	\$ 422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____ 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

NIT : 900176009-2

SUPERINDUSTRIA Y COMERCIO

Folios: 156

Radicacion : 04061363 00000000

Fecha (AMD): 2004-06-29 08:52:36

Tramite : 011 PCT-PATENT 379 FASE NACT 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 49,135
FECHA : JUNIO 19 DE 2004

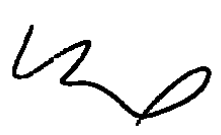
***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
ACRA : ARIA GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	27450143	18/06/2004	118,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	82 INVOCACION DE UNA PRIORIDAD EN NJ	118,000.00
		TOTAL :	\$ 118,000.00

SOM: CIENTO DIEZ Y OCHO MIL PESOS



RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 June 2003 (05.06.2003)

PCT

(10) International Publication Number
WO 03/045355 A1

(51) International Patent Classification⁷: A61K 9/20, 31/64

(21) International Application Number: PCT/EP02/13497

(22) International Filing Date:
29 November 2002 (29.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
FI2001A000230 29 November 2001 (29.11.2001) IT

(71) Applicant (for all designated States except US): MENAR-
INI INTERNATIONAL OPERATIONS LUXEM-
BOURG S.A. [LU/LU]; 1, avenue de la Gare, L-1611
Luxembourg (LU).

(72) Inventors; and

(75) Inventors/Applicants (for US only): TOSETTI, Alessan-
dro [IT/IT]; Via F. Paolotti, 13, I-50012 Bagno A Ripoli
(IT). GUIDUCCI, Mauro [IT/IT]; Via Tullio Levi Civita,
1, I-52100 Arezzo (IT). VITI, Giovanni [IT/IT]; Viale A.
Guldoni, 179, I-50127 Firenze (IT).

(74) Agent: GERLI, Paolo; c/o Notarbartolo & Gervasi, Corso
di Porta Vittoria, 9, I-20122 Milan (IT).

(81) Designated States (national): AE, AG, AL, AM, AT, AU;
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

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

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING METFORMINE AND GLIBENCLAMIDE FOR THE
TREATMENT OF TYPE-II DIABETES MELLITUS

(57) Abstract: Orally administrable pharmaceutical compositions in the form of tablets, comprising glibenclamide and metformin,
or pharmaceutically acceptable salts thereof, as active ingredients, maintained separate from one another within the same composi-
tion, are described for the treatment of type-II diabetes mellitus.

WO 03/045355 A1

**PHARMACEUTICAL COMPOSITIONS COMPRISING METFORMINE AND GLIBENCLAMIDE
FOR THE TREATMENT OF TYPE II DIABETES MELLITUS**

Field of the invention

The present invention relates to new pharmaceutical compositions comprising
5 glibenclamide and metformin, effective for the treatment of type-II diabetes
mellitus, wherein the two active ingredients are maintained separate from one
another although within the same composition.

State of the art

Non-insulin dependent type-II diabetes is a metabolic disorder characterised by
10 hyperglycaemia, linked to an insulin deficiency, a resistance of peripheral tissues
to insulin itself, an increase in the production of glucose by the liver, a reduced
glucose tolerance.

Two major categories of antidiabetic drugs exist: the sulphonylureas, amongst
which we note glibenclamide, chlorpropamide, glicazide, tolazamide, glipizide,
15 glipizide, tolbutamide and the biguanides, among which we note fenformin and
metformin. Whilst the sulphonylureas act through the stimulation of the production
of insulin by the pancreas, and a residual activity of this organ is necessary for this
category of drugs to be effective, the biguanides act through the increase of the
use of glucose, reducing the insulin-resistance and hepatic glucogenesis.

20 Therefore for this category of drug to have any effect, a residual insulin production
by the beta cells of the pancreas is necessary.

It is known that the initial treatment of type-II diabetes can be uniquely based on
the control of diet and physical exercise, but frequently these lifestyle changes are
insufficient for an optimal control of glycaemia such that the use of said oral
25 antidiabetic drugs become necessary.

The treatment of type-II diabetes mellitus by monotherapy with an oral antidiabetic
drug can be effective in the long term but, for a broad percentage of patients the
effectiveness is progressively reduced over the years.

Having been always more frequently demonstrated in type-II diabetes patients
30 there is an agreement between the insulin production deficiency and the peripheral
insulin resistance, so that the sulphonylureas and biguanides possess
complimentary modes of action, it is evident that the treatment consisting of the

association of the two said categories of drugs are today already consolidated. Furthermore, to improve the compliance of the patient, tablets containing the two drugs already in association have been produced.

The combined sulphonylureas and biguanides treatment assumes therefore an important role in the therapy of type-II diabetes, in that it allows an improved metabolic control in these patients in which biguanides or sulphonylureas alone have shown themselves ineffective with passing time.

Amongst the two categories of said drugs, the biguanides and sulphonylureas, those most used for the treatment of type-II diabetes are metformin and glibenclamide respectively.

The association of metformin and glibenclamide presents notable advantages with respect to the administration of the two active ingredients separately, since it significantly improves the 'compliance' and in addition, especially in older patients and/or in patients subjected to polytherapy with other drugs, it reduces the risk of errors in administration.

Today, five combinations which envisage the presence of a single tablet of glibenclamide and metformin in different dosages are present on the market, in particular:

- 1) glibenclamide at a dosage of 1.25 mg and metformin hydrochloride at a dosage of 250 mg (glibenclamide/metformin weight ratio of 1:200);
- 2) glibenclamide at a dosage of 2.5 mg and metformin hydrochloride at a dosage of 500 mg (glibenclamide/metformin weight ratio of 1:200);
- 3) glibenclamide at a dosage of 5 mg and metformin hydrochloride at a dosage of 1000 mg (glibenclamide/metformin weight ratio of 1:200);
- 4) glibenclamide at a dosage of 2.5 mg and metformin hydrochloride at a dosage of 400 mg (glibenclamide/metformin weight ratio of 1:160);
- 5) glibenclamide at a dosage of 5 mg and metformin hydrochloride at a dosage of 500 mg (glibenclamide/metformin weight ratio of 1:100).

From the most recent data in the literature it emerges that the maximum recommended daily dosage of glibenclamide for the most serious and poorly controlled patients is 20 mg, in one or more administration. Such a dosage, in order to obtain an optimal therapeutic effect, can be combined with a daily dosage

of metformin comprised of between 1000 and 2000 mg. The metformin is excreted unmodified in the urine; it is in fact not subjected to hepatic metabolism (in fact no metabolites are found in humans) nor to biliary excretion. In subjects with reduced renal function (based on creatinine clearance) the plasma half-life of metformin is prolonged and the renal clearance is diminished in proportion to the reduction of the clearance of creatinine.

In view of the different optimal dosages, it is evident that the ratio between metformin and glibenclamide in association with each other must be maintained in a ratio of around 100:1 or greater, we are therefore in general in the presence of a massive dosage of metformin associated with relatively modest dosages of glibenclamide.

Also the solubility in water is notably different between the two active ingredients and, whilst metformin is extremely soluble in water, glibenclamide is relatively poorly soluble.

The simplest way of association between the two active ingredients is that of mixing them closely together with appropriate excipients.

Vigneri et al. (Diabetes & Metabolism, 1991, 17, 232-234) have proposed an association of the two compounds in a daily dosage of 1500 mg of metformin and 15 mg of glibenclamide.

In WO9717975 the use of an association of the two ingredients in a ratio of 100:1 is claimed for the treatment of type-II diabetes mellitus in the case of failure due combinations having a higher ratio in metformin.

In WO0003742, the inventors of LIPHA SA have clearly demonstrated that simple mixing of metformin and glibenclamide in ratios of 100:1 with certain excipients, resulted in a heavy reduction in the bioavailability of the glibenclamide, visible through the area under the curve (AUC) with respect to that obtainable with a co-administration of the same active ingredients in the same dosages. The inventors have succeeded in avoiding this problem by micronising the glibenclamide prior to adding it to the mixture.

The technique of micronising is also followed by Bristol-Myers Squibb for the preparation of commercial associations with the trade name Glucovance® in which, using particles of glibenclamide with average dimensions still more reduced

than those described in WO0003742, they manage to achieve an AUC which is even superior, even if by little, to that of non-micronised glibenclamide, sold under the trade name Micronase, when given in co-administration with metformin (Summary of Product Characteristics of Glucovance® distributed by Bristol-Myers Squibb through their Internet site, as sales support, starting from 31/07/2000).

Since that the advantages of the administration in association of metformin and glibenclamide, or salts thereof, are now evident, the need to resolve the problem of reduced bioavailability of glibenclamide when this is mixed with metformin is very much felt.

Summary of the invention

The Applicant has now surprisingly found that preparing pharmaceutical compositions comprising metformin and glibenclamide, or salts thereof, as active ingredients so as that the two active ingredients are maintained separated from each other, there is not, as the consequence of the association of these active ingredients with high metformin/glibenclamide ratios, a heavy reduction in the bioavailability of the glibenclamide.

An effective way to maintain the two active ingredients separate has been found by the Applicant in the preparation of tablets, for example multi-layered tablets (two or more layers, in each of which is exclusively one of the two drugs) or metformin tablets uniformly coated with glibenclamide.

The advantageous characteristics of the formulations in the invention have in addition been further improved by the selection of appropriate pharmaceutically acceptable excipients.

Therefore the subject of the present invention are orally administrable pharmaceutical formulations in the form of tablets, comprising as active ingredients glibenclamide and metformin, or pharmaceutically acceptable salts thereof, characterised by the fact that said active ingredients are comprised in layers separated from each other.

The characteristics and the advantages of the pharmaceutical compositions according to the present invention will be illustrated in the detailed description that follows.

Detailed description of the invention

The simplest way for the preparation of an association of two drugs for which a different location or a different method of absorption is not envisaged is surely that of mixing them closely together, but in the case of glibenclamide with metformin, as said above, the absorption of glibenclamide is unexplainably hindered by the massive presence of metformin.

The evaluation of the absorption is always quite complex, but, in the first approximation, we can consider the percentage of dissociation of the tablet containing the active ingredient as an indication of the absorption that we might expect (*J. Pharm. Pharmacol.* 2000, 52, 831-838, *Drug Development and Industrial Pharmacy*, 1993, 19 (20), 2713-2741).

Micronisation of the glibenclamide, as one in the art might deduce from the solution proposed in the International Patent Application No. WO0003742 and from the solution described by Bristol Myers Squibb, does not seem to be generally satisfactory; in our case the micronisation of the glibenclamide according to the specifics adopted by us, even if different from the conditions used in the two methods mentioned above, has not been sufficient to make the tablets containing a mixture of glibenclamide and metformin dissolve in a comparable way to that of the tablets comprising glibenclamide and metformin separated from each other.

By maintaining the two active ingredients separate from each other, but in the same pharmaceutical formulation, it has been surprisingly possible to resolve the problem allowing the dissolution of the glibenclamide in a comparable or even higher way to that which would have been obtained by administering the two active ingredients in two completely separate formulations. The maintenance of the two active ingredients in a single formulation guarantees greater 'compliance' with the patient and at the same time can guarantee a therapeutic treatment comparable to that with the two active ingredients separated, without the risk of under dosing for glibenclamide (in the change from a therapy with two separate drugs to that with the two drugs mixed together).

To obtain formulations in which the two active ingredients are maintained separated from each other is technically a little more complex than simply mixing them, but the advantages that have surprisingly been found render the formulations of the invention of great interest.

Not all the formulations in which the two active ingredients are maintained separated constitute equally satisfactory solutions for the present invention. It would in fact be auspicious that the part containing glibenclamide dissolves quickly in the medium. One way to reach this speed of dissolution, is that of having a large erosion surface and to maintain this surface as large as possible with time until the complete dissolution is achieved.

There are two preferred pharmaceutical forms according to the present invention:

1) multilayered tablets, preferably selected from:

a) bi-layered tablets in which the glibenclamide is compressed into a relatively thin layer over a tablet of metformin, and

b) tri-layered tablets in which the glibenclamide is compressed into two layers positioned over and under a central layer of metformin,

2) coated tablets, preferably selected from:

a') tablets of metformin uniformly coated by a thin layer containing glibenclamide which is compressed all around it, and

b') tablets of metformin externally painted with a solution of glibenclamide which layers over it.

In the embodiment of the present pharmaceutical formulations glibenclamide in micronised form or otherwise, can be used indifferently.

We can better understand what above said by observing the exemplifying schematic diagram below.



A



B

A and B represent transverse sections of two cylindrical tablets: A represents a bi-layer in which the dark part is the layer containing glibenclamide, and B represents a tablet of just glibenclamide, but with the same total volume of the part containing glibenclamide as A.

The tablets schematised as B, currently on the market or commonly realisable by any person skilled in the art, containing from 1.25 to 5 mg of glibenclamide (for a

total weight, including excipients, of 100 - 150 mg with a maximum of 200 mg) present a surface exposed to erosion less than, or at the most comparable to, the surface offered by the layer of glibenclamide compressed over the support of metformin, as outlined in A. But what is more important is that the erosion surface of B reduces rapidly during dissolution; whilst in case A the reduction of the surface is negligible at the beginning of the process and is discernible only in the advanced stages of dissolution. As a consequence the dissolution kinetics of the glibenclamide in A will be much faster than in B and the differences in dissolution between the two tablets will increase with time, as the difference between the erodible surfaces of A and of B increases.

Also the other solutions described in points 1 and 2 show kinetic advantages analogous to these described for the bi-layered tablet in figure A.

For the above stated reasons it is particularly efficacious for the purposes of the invention, and it is therefore to be considered as a particularly preferred solution of the invention, the multi-layered tablet, more preferably the bi-layered or tri-layered tablet of type 1.

As previously mentioned, the bioavailability of the glibenclamide in association with metformin has a complex behaviour which can be also influenced by other factors in addition of the mixing with metformin: in fact, it is a further subject of the present invention also the selection of appropriate excipients and/or additives which serve to increase the dissolution of the portion containing glibenclamide and consequently its bioavailability.

Furthermore, the fundamental choice of keeping the two active ingredients separated, allows to dosage the excipients and/or the additives necessary to obtain the desired bioavailability of the glibenclamide, only into the layer comprising the glibenclamide, thereby reducing their use to that which is strictly necessary, and avoiding potential problems with the metformin.

The tablets realisable according to the present invention are suitable for amounts of glibenclamide ranging between 1 and 20 mg for each tablet, preferably between 2.5 and 5 mg; and for amounts of metformin ranging between 200 and 1000 mg for each tablet, and preferably between 500 and 850 mg.

The present formulations in tablet form can be prepared according to the

methodologies commonly used in pharmaceutical techniques. The bi-layered tablets of the invention, for example, can be prepared in the following manner: the compositions of the layer containing metformin and of the layer containing glibenclamide are prepared separately; the first can be obtained by mixing metformin powders previously sieved and appropriate pharmaceutically acceptable excipients, then granulating such a mixture together with one or more dispersing agents, drying the so obtained granulate, which is then calibrated and added with one or more lubricating agents. The composition of the glibenclamide layer can be instead prepared by directly mixing such active ingredient with appropriate pharmaceutically acceptable excipients and then sieving the mixed powders. Then using a press suitable for the production of bi-layered tablets, the compression of the above said compositions is achieved.

The coated tablets of the invention can be realised preparing a metformin nucleus by compression of the above said composition, then uniformly coating this nucleus with a thin layer containing glibenclamide by compression of the above said composition containing glibenclamide or by painting the nucleus with a solution of glibenclamide.

Preferred excipients for the portion containing glibenclamide in tablet form according to the invention are surfactants and hydrosoluble dispersing agents.

In the case of surfactants, an amount ranging between 0.1 and 10 mg can be used in the part of each tablet containing glibenclamide, preferably between 0.5 and 2 mg; the preferred surfactants according to the invention are selected from the alkaline or alkaline earth salts of lauryl sulphate and of Polysorbate 80. A particularly preferred surfactant is sodium lauryl sulphate.

In the case of the hydrosoluble dispersing agents, these can be used in quantities comprised of between 20 and 100 mg in the part of each tablet containing glibenclamide, preferably between 45 and 55 mg; the preferred hydrosoluble dispersing agents are selected from the group of the polyethylene glycols, among these particularly preferred is Macrogol 6000.

When a solid surfactant is used, such as a salt of lauryl sulphate, the moist surfactant can be possibly dispersed in the lubricating agent (for example Mg stearate) prior to using it in the granulation, in order to improve the wetting effect of

the surfactant itself.

When a hydrosoluble dispersing agent is used, it can optionally be preferable to melt the dispersing agent (for example Macrogol 6000), then disperse the glibenclamide in it, allow to solidify again, pulverise the so obtained solid, and use it for the later preparation of the granulate.

The following examples are reported for the purposes of non limiting illustration of the present invention.

EXAMPLE 1 (COMPARISON)

Preparation of 5 mg Glibenclamide tablets

Composition of each tablet in mg:

Glibenclamide	5
Pre-gelatinised corn starch	58.3
Hydrated colloidal silica	0.5
Lactose monohydrate	96.2
Na lauryl sulphate	1
Talc	0.5
Magnesium stearate	0.5

Preparation:

The mixture of the active ingredients and excipients is subjected to granulation and the resulting granulate is dried, then subjected to compression until obtaining tablets each containing 5 mg of glibenclamide and having the above reported composition.

EXAMPLE 2 (COMPARISON)

Preparation of 400 mg Metformin tablets

Composition of each tablet in mg:

Metformin HCl	400
Microcrystalline cellulose	65
Corn starch	60
Anhydrous colloidal silica	20
Gelatine	40
Glycerine	17.5
Talc	17.5

Magnesium stearate	7.5
Cellulose acetate phthalate	2

The mixture of the active ingredients and the excipients is subjected to granulation and the resulting granulate is dried, then subjected to compression so as to obtain tablets each containing 400 mg of metformin and having the above reported composition.

EXAMPLE 3 (COMPARISON)

Preparation of tablets containing the mixture of Glibenclamide + Metformin (5 + 400 mg)

Composition of each tablet in mg:

Metformin HCl	400
Glibenclamide	5
Microcrystalline cellulose	65
Corn starch	55
Pre-gelatinised corn starch	58.3
Anhydrous colloidal silica	20
Hydrated colloidal silica	0.5
Lactose monohydrate	96.2
Gelatine	40
Glycerine	17.5
Talc	18
Magnesium stearate	8
Cellulose acetate phthalate	2
Na lauryl sulphate	1
Diethylphthalate	0.5

The two active ingredients and the excipients have been granulated together. The granulate thus obtained is dried and, upon completion of drying, is calibrated. To the calibrated granulate is added the Mg stearate and is mixed. The mixture obtained is subjected to fine granulation so as to obtain tablets, each having the above reported compositions.

EXAMPLE 4 (COMPARISON)

Preparation of separated tablets of 5 mg of Glibenclamide and 400 mg of

Metformin:**Metformin tablet****Metformin HCl 500****Macrogol 4000 24.7****5 Anhyd. coll. silica-Aerosil® 200- 5****Polyvinylpyrrolidone K 25 20****Mg stearate 5.9****Glibenclamide tablet****Glibenclamide 5****10 Lactose mon.-granul. 128****Corn starch 40****Microgr. Cell.-Avicel® PH 102- 15****HPMC -5- 4.8****Na croscarmellose 13****15 Anhydr. coll. silica-Aerosil® 200- 0.7****Polysorbate 80 0.5****Mg stearate 1****Yellow Iron oxide 1****Red Iron oxide 1**

20 The separated tablets have been prepared as described above in Examples 1 and 2.

EXAMPLE 5 (COMPARISON)

Preparation of tablets containing the mixture Glibenclamide + Metformin (5 + 400 mg) (separate granulation)

25 Composition of each tablet in mg:

Metformin HCl 500**Macrogol 4000 24.7****Anhyd. coll. silica -Aerosil® 200- 5****Polyvinylpyrrolidone K 25 20**

30 Mg stearate 5.9

Glibenclamide 5**Lactose mon.-granul. 200-128**

	Cpm starch	40
	HPMC -5-	4.8
	Na croscarmellose	13
	Anhyd. coll. silica -Aerosil® 200-	0.7
5	Polysorbate 80	0.5
	Mg stearate	1
	Yellow Iron oxide	1
	Red Iron oxide	1

10 The two active ingredients have been granulated separately, each with their respective excipients (analogous to Example 4), but then have been mixed together and subjected to compression to form tablets each having the above reported composition.

EXAMPLE 6 (COMPARISON)

15 Preparation of tablets containing the mixture Glibenclamide + Metformin (5 + 500 mg)

Composition of each tablet in mg:

	Metformin HCl	500
	Macrogol 4000	24.7
	Polyvinylpyrrolidone K 25	20
20	Glibenclamide	5
	Lactose mon.-granul.	40
	Microgr. Cell.-Avicel® PH 102-	15
	HPMC -5-	4.8
	Na croscarmellose	13
25	Anhyd. coll. silica -Aerosil® 200-	5.7
	Polysorbate 80	0.5
	Mg stearate	6.9
	Yellow Iron oxide	1
	Red Iron oxide	1

30 The preparation is analogous to that reported above for Example 3.

EXAMPLE 7

Preparation of Glibenclamide + Metformin (5 + 500 mg) bi-layered tablets

Composition of the Metformin layer for each tablet, in mg:

Metformin HCl	500
Macrogol 4000	24.7
Polyvinylpyrrolidone	20
5 Anhydrous colloidal silica	5

Composition of the Glibenclamide layer for each tablet, in mg:

Glibenclamide	5
Lactose monohydrate	50.75
Na lauryl sulphate	0.75
10 Microcrystalline cellulose	100
Sodium croscarmellose	5.5
Anhydrous colloidal silica	0.5
Magnesium Stearate	3.4
Yellow Iron oxide colouring E 172	1
15 Red Iron oxide colouring E 172	1

Preparation:**Metformin layer**

- Granulating solution: dissolve the Macrogol 4000 under stirring.
- Granulation: sieve the metformin, Polyvinylpyrrolidone and anhydrous colloidal silica.
- Mix the sieved powders, then granulate using the previously prepared granulating solution. Dry the so obtained granulate and, once the drying procedure is completed, calibrate the same.
- Final mixture: add the Mg stearate to the calibrated granulate and mix.

Glibenclamide layer

- Mixture preparation: mix the anhydrous colloidal silica, glibenclamide, Na lauryl sulphate, Na croscarmellose, yellow iron oxide colouring, red iron oxide colouring and c.a. 20% of lactose monohydrate. Sieve the mixed powders, Microcrystalline Cellulose and the remaining lactose monohydrate. Mix, add the Mg stearate and mix again.

Bi-layered tablet

Using a press suitable for the production of bi-layered tablets, the two layers are

compressed.

The tablets thus realised have the following values in disgregation test:

glibenclamide layer: complete disgregation in less than one minute (30 seconds on average)

5 metformin layer: complete disgregation in 10 minutes on average.

EXAMPLE 8

Preparation of Glibenclamide + Metformin (5 + 500 mg) bilayered tablets

Composition of the Metformin layer for each tablet, in mg:

Metformin HCl 500

10 Macrogol 4000 24.7

Anhyd. coll. Silica-Aerosil® 200- 5

Polyvinylpyrrolidone K 25 20

Mg stearate 5.9

Composition of the Glibenclamide layer for each tablet, in mg:

15 Glibenclamide 5

Macrogol 6000 50

Lactose mon. S.D. 34

Microgr. Cell.-Avicel® PH 102- 70

Na croscarmellose 5

20 Coll. silica anhydr.-Aerosil® 200- 0.5

Mg stearate 0.5

The preparation is analogous to that reported above for Example 7.

EXAMPLE 9

Preparation of Glibenclamide + Metformin (5 + 500 mg) bilayered tablets

25 Composition of the Metformin layer for each tablet, in mg:

Metformin HCl 500

Macrogol 4000 24.7

Coll. silica anhydr.-Aerosil® 200- 5

Polyvinylpyrrolidone K 25 20

30 Mg stearate 5.9

Composition of the Glibenclamide layer for each tablet, in mg:

Glibenclamide 5

15

Micr. Cell.-Avicel® PH102- 100

Na croscarmellose 5.25

Anhydr. coll. silica -Aerosil® 200- 0.5

Na lauryl sulphate 0.5

5 Mg stearate 0.5

Yellow Iron oxide 1

Red iron oxide 0.75

The preparation is analogous to that reported above for Example 7.

EXAMPLE 10

10 Preparation of Glibenclamide + Metformin (5 + 400 mg) bilayered tablets

Composition of the Metformin layer for each tablet, in mg:

Metformin HCl 400

Microcrystalline cellulose 65

Corn starch 60

15 Anhydrous colloidal silica 20

Gelatine 40

Glycerine 17.5

Talc 17.5

Magnesium stearate 7.5

20 Cellulose acetate phthalate 2

Diethylphthalate 0.5

Composition of the Glibenclamide layer for each tablet, in mg:

Glibenclamide 5

Pre-gelatinised corn starch 58.3

25 Hydrated colloidal silica 0.5

Lactose monohydrate 96.2

Na lauryl sulphate 1

Talc 0.5

Magnesium stearate 0.5

30 The preparation is analogous to that reported above for Example 7.

EXAMPLE 11

Preparation of Glibenclamide + Metformin (5 + 500 mg) bi-layered tablets

Composition of the Metformin layer for each tablet, in mg:

Metformin HCl 500
Macrogol 4000 24.7
Anhydr. coll. silica -Aerosil® 200- 5
5 Polyvinylpyrrolidone K 25 20
Mg stearate 5.9

Composition of the Glibenclamide layer for each tablet, in mg:

Glibenclamide 5
Lactose mon.-granul. 128
10 Corn starch 40
Microgr. Cell.-Avicel® PH 102- 15
HPMC -5- 4.8
Na croscarmellose 13
Anhydr. coll. silica -Aerosil® 200- 0.7
15 Polysorbate 80 0.5
Mg stearate 1
Yellow Iron oxide 1
Red Iron oxide 1

The preparation is analogous to that reported above for Example 7.

20 EXAMPLE 12**Preparation of Glibenclamide + Metformin (2.5 + 500 mg) bi-layered tablets****Composition of the Metformin layer for each tablet, in mg**

Metformin HCl 500
Macrogol 4.000 24.7
25 Anhydrous colloidal silica 8.2
Polyvinylpyrrolidone 20
Magnesium Stearate 5.9

Composition of the Glibenclamide layer for each tablet, in mg:

Glibenclamide 2.5
30 Lactose monohydrate 89
Sodium lauryl sulphate 0.750
Microcrystalline cellulose 150

Sodium croscarmellose 5.500
Anhydrous colloidal silica 0.750
Magnesium Stearate 0.750
Yellow Iron oxide E 172 0.750

5 The preparation procedure is as described in Example 7.

The tablets can be coated with substances well known in the pharmaceutical field.

EXAMPLE 13

Preparation of Glibenclamide + Metformin (5 + 500 mg) bi-layered tablets

Composition of the Metformin layer for each tablet in mg

10 Metformin HCl 500
Macrogol 4.000 24.7
Anhydrous colloidal silica 8.2
Polyvinylpyrrolidone 20
Magnesium Stearate 5.9

15 Composition of the glibenclamide layer for each tablet in mg

Glibenclamide 5
Lactose monohydrate 86.75
Sodium lauryl sulphate 0.750
Microcrystalline cellulose 150
20 Sodium croscarmellose 5.500
Anhydrous colloidal silica 0.750
Magnesium Stearate 0.750
Yellow Iron oxide E 172 0.125
Red Iron oxide E 172 0.375

25 The preparation procedure is as described in Example 7.

The tablets can be coated with substances which are well known in the pharmaceutical field.

EXAMPLE 14

Preparation of Glibenclamide + Metformin (2.5 + 850 mg) bi-layered tablets

30 Composition of the Metformin layer for each tablet in mg

Metformin HCl 850
Macrogol 4.000 42

Anhydrous colloidal silica 14

Polyvinylpyrrolidone 34

Magnesium stearate 10

Composition of the glibenclamide layer for each tablet in mg

5 Glibenclamide 2.5

Lactose monohydrate 89

Sodium lauryl sulphate 0.750

Microcrystalline cellulose 150

Sodium croscarmellose 5.500

10 Anhydrous colloidal silica 0.750

Magnesium Stearate 0.750

Yellow iron oxide E 172 0.750

The method of preparation is as described in Example 7.

15 The tablets can be coated with substances which are well known in the field of pharmaceuticals.

EXAMPLE 15:

Preparation of Glibenclamide + Metformin (5 + 850 mg) bi-layered tablets

Composition of the Metformin layer for each tablet in mg

Metformin HCl 850

20 Macrogol 4.000 42

Anhydrous colloidal silica 14

Polyvinylpyrrolidone 34

Magnesium stearate 10

Composition of the glibenclamide layer for each tablet in mg

25 Glibenclamide 5

Lactose monohydrate 86.75

Sodium lauryl sulphate 0.750

Microcrystalline cellulose 150

Sodium croscarmellose 5.500

30 Anhydrous colloidal silica 0.750

Magnesium Stearate 0.750

Yellow iron oxide E 172 0.125

Red iron oxide E 172 0.375

The method of preparation is as described in Example 7.

The tablets can be coated with substances which are well known in the pharmaceutical field.

5 DISSOLUTION TEST

The studies on the glibenclamide bioavailability in the various formulations can be uselessly complex, for which for the study of the various formulations the dissolution test has been considered assuming as a first approximation that a greater dissolution in a given defined time corresponds to a greater bioavailability
10 (*J. Pharm. Pharmacol.*, 2000, 52, 831-838; *Drug Development and Industrial Pharmacy*, 1993, 19 (20), 2713-2741).

The tablet under test is added to an aqueous solution (900 ml) containing 0.05 M phosphate buffer at pH 7.4 at 37°C and dissolved using a paddle at 35 rpm. Unless otherwise specified, a sample of the solution is taken following 45 minutes
15 and the glibenclamide dosaged by HPLC (internal method). The dissolution test is repeated at least 6 times on tablets of the same batch and the mean value is considered.

Experiment 1) Dissolution of commercial compounds

a)

- 20 - Glibenclamide 5 mg 37%
(DAONIL®)
- Glibenclamide 5 mg + Metformin 500 mg 42%
(DAONIL® + GLUCOPHAGE®)
- Glibenclamide 5mg + Metformin 500 mg 39%
25 (EUGLUCON® + GLUCOPHAGE®)

As can be seen from the results reported above, the dissolution of commercial Glibenclamide tablets (Daonil® or Euglucon®) in the presence of a Metformin 500 mg commercial tablet (Glucophage®), does not seem to be different from the dissolution of Glibenclamide tablets alone.

30 b)

- Glibenclamide 5 mg 58%
(GLIBORAL®)

- Glibenclamide 5 mg + Metformin 500 mg 52%
(GLIBORAL® + SIOFOR®)
- Glib+Met (5+500 mg) mixture 26%
(GLIBOMET®)

5 The dissolution of commercial glibenclamide tablets (Gliboral®) alone or in the presence of a metformin 500 mg commercial tablet (Siofor®) is comparable, whilst the dissolution of glibenclamide in mixture with metformin in a single commercial tablet (Glibomet) is heavily reduced. The commercial products have been selected on the basis of their similarity in composition and the type of excipients used so as
10 to minimise their influence.

Experiment 2)

- Glib. 5 mg (Example 1) 88%
- Glib. 5 mg + Met. 400 mg (Examples 1 + 2) 92%
- Glib + Met 5 + 400 mg (Example 3) 15%
- 15 - Glib + Met 5 + 400 mg (Example 10) 89%

The tablets have the compositions described in the Examples specifically indicated. The excipients which constitute the glibenclamide tablet (Example 1) are qualitatively and quantitatively identical to these which constitute the glibenclamide layer in the bi-layered tablet (Example 10). Analogously, the excipients which
20 constitute the metformin tablet (Example 2) are qualitatively and quantitatively identical to these which constitute the metformin layer in the bi-layered tablet. The excipients in the glibenclamide/metformin mixture tablet (Example 3) are qual/quantitatively equal to the sum of the excipients of the metformin and glibenclamide tablets (Examples 1 and 2). In this manner it was attempted to
25 minimise the effect of the excipients themselves on the dissolution of one tablet or the other.

Glibenclamide, when mixed with metformin, has a notable reduction in the percentage dissolution with respect to when the two compounds are maintained in separate compositions (as already observed for the commercial tablets in
30 experiment 1b). Surprisingly the use of a bi-layered tablet eliminates the problem and the glibenclamide dissolves in comparable percentages with respect to the two separate products.

Experiment 3)**Composition 5' 15' 45%****-Glib 5 + Met 500 (Example 4)) 54% 65% 86%****-Glib + Met 5+500 (Example 5) 11% 44% 64%****5 -Glib + Met 5 + 500 (Example 6) 27% 53% 53%****-Glib + Met 5+500 (Example 11) 52% 86% 103%**

In experiment 3) the dissolution values are measured at three different times, i.e. at 5, 15 and 45 minutes. The formulations used in the present experiment, analogously to the preceding experiment 2, have excipient contents comparable so as to eliminate their effects within the specific group examined.

One can effectively note that the excipients can play an important role in dissolution by comparing the dissolution obtained with the mixture of Examples 5 and 6 in comparison with that of 3 or with the commercial examples. With the use of appropriate excipients it is possible to obtain also for mixtures of Glib + Met, dissolution values comparable to these of Glib + Met given separately up to final times of 45'. An analysis can attempt as a function of time, to show however that at short times (following 5') the dissolution of the mixtures is still much lower than these of the separate tablets (11% and 27% as opposed to 54%), but this appears evident also following 15' (44% and 53% as opposed to 65%). These data might not allow an equal bioavailability profile in vivo and therefore different behaviour and pharmacodynamics. One such importance derives also from the method of preparation of the mixtures, in fact at short times, the glibenclamide dissolves more rapidly when the granulation is performed on the already prepared mixture (Example 6) rather than when the two active ingredients are granulated separately and then mixed (Example 5).

However the superiority of the corresponding bi-layered tablets appears very clear (Example 11), the dissolution percentage of which is practically comparable at 5 minutes to that of the two separate tablets, and is always greater in all the other cases.

30 Experiment 4) Bi-layered tablets**- Example 7 66%****- Example 8 86%**

- Example 9 53%
- Example 10 89%
- Example 11 103%

The dissolution of the glibenclamide in the bi-layered tablets appears always very
5 good, always comparable or superior to these obtained with separate tablets.

CLAIMS.

1. Pharmaceutical formulations for the oral administration in tablet form, comprising glibenclamide and metformin, or pharmaceutically acceptable salts thereof, as active ingredients, characterised by the fact that said active ingredients are comprised in layers separated from each other.
2. The pharmaceutical formulations according to claim 1, wherein said tablets are selected from multi-layered tablets and coated tablets wherein the glibenclamide is always located in at least one external layer of the multi-layered tablets or on the coating of the coated tablets.
3. The pharmaceutical formulations according to claim 2, wherein said multi-layered tablets are selected from:
 - a) bi-layered tablets wherein the glibenclamide is compressed into a relatively thin layer over a tablet of metformin, and
 - b) tri-layered tablets wherein the glibenclamide is compressed into two layers placed one above and the other below a central layer of metformin.
4. The pharmaceutical formulations according to claim 3, wherein said multi-layered tablets are bi-layered tablets wherein the glibenclamide is compressed into a relatively thin layer over a metformin tablet.
5. The pharmaceutical formulations according to claim 2, wherein said coated tablets are selected from:
 - a') metformin tablets uniformly coated by a thin layer comprising glibenclamide which is compressed all around it; and
 - b') metformin tablets externally painted with a solution of glibenclamide which is layered onto it.
6. The pharmaceutical formulations according to claims from 1 to 5, wherein the amount of glibenclamide in each tablet ranges between 1 and 20 mg and the amount of metformin in each tablet ranges between 200 and 1000 mg.
7. The pharmaceutical formulations according to claim 6, wherein the amount of glibenclamide in each tablet ranges between 2.5 and 5 mg and the amount of metformin in each tablet ranges between 500 and 850 mg.
8. The pharmaceutical formulations according to the claims from 1 to 7, comprising in addition pharmaceutically acceptable excipients.

9. The pharmaceutical formulations according to claim 8, wherein the part of the formulation comprising glibenclamide comprises at least one surfactant or a hydrosoluble dispersing agent as excipients.

10. The pharmaceutical formulations according to claim 9, wherein the part of the formulation comprising glibenclamide comprises a surfactant at a concentration of from 0.1 to 10 mg as excipient.

11. The pharmaceutical formulations according to claim 10, wherein the concentration of said surfactant is comprised of between 0.5 to 2 mg.

12. The pharmaceutical formulations according to claim 9, wherein said surfactant is selected from the alkaline or alkaline earth salts of lauryl sulphate and Polysorbate 80.

13. The pharmaceutical formulations according to claim 12, wherein said surfactant is sodium lauryl sulphate.

14. The pharmaceutical formulations according to claim 9, wherein the part of the formulation comprising glibenclamide comprises a hydrosoluble dispersing agent at a concentration of between 20 to 100 mg as excipient.

15. The pharmaceutical formulations according to claim 14, wherein the concentration of said hydrosoluble dispersing agent is comprised of between 45 and 55 mg.

16. The pharmaceutical formulations according to claim 9, wherein said hydrosoluble dispersing agent is selected from the polyethylene glycols.

17. The pharmaceutical formulations according to claim 16, wherein said hydrosoluble dispersing agent is Macrogol 8000.

18. The pharmaceutical formulations according to claim 1, which are:

- Glib + Met (5+500mg)

Metformin layer : Metformin HCl, 500; Macrogol 4000, 24.7; Polyvinylpyrrolidone, 20; Anhydrous colloidal silica, 5;

Glibenclamide layer : Glibenclamide, 5; Lactose monohydrate, 50.75; Na lauryl sulphate, 0.75 ; Microcrystalline cellulose, 100; Sodium croscarmellose 5.5; Anhydrous colloidal silica 0.5; Magnesium Stearate 3.4; Yellow Iron oxide E 172, 1; Red Iron oxide E 172, 1;

- Glib + Met (5+500mg)

Metformin layer: Metformin HCl 500; Macrogol 4000, 24.7; Anhydr. coll. silica - Aerosil 200, 5; Polyvinylpyrrolidone K 25, 20; Mg stearate, 5.9

Glibenclamide layer: Glibenclamide, 5; Macrogol 6000, 50; Lactose mon. S.D., 34; Microgr. Cell.-Avicel PH 102, 70; Na croscarmellose, 5; Anhydr. coll. silica - Aerosil 200, 0.5; Mg stearate, 0.5

- Glib + Met (5+500 mg)

Metformin layer: Metformin HCl 500; Macrogol 4000 24.7; Anhydr. coll. silica - Aerosil 200, 5; Polyvinylpyrrolidone K 25, 20; Mg stearate 5

Glibenclamide layer: Glibenclamide 5; Microgr. Cell.-Avicel PH 102, 100; Na croscarmellose, 5.25; Anhydr. coll. silica - Aerosil 200, 0.5; Na lauryl sulphate 0.5; Mg stearate 0.5; Yellow Iron oxide, 1; Red Iron oxide 0.7

-Glib + Met (5+400mg)

Metformin layer: Metformin HCl, 400; Microcrystalline cellulose 65; Corn starch 60; Anhydrous colloidal silicate 20; Gelatine 40; Glycerine 17.5; Talc 17.5; Magnesium stearate 7.5; Cellulose acetate phthalate 2; Diethylphthalate 0.5;

Glibenclamide layer: Glibenclamide, 5; Pregelatinised corn starch 58.3; Hydrated colloidal silica 0.5; Lactose monohydrate 96.2; Na lauryl sulphate 1; Talc 0.5; Magnesium stearate 0.5;

- Glib + Met (5+500mg)

Metformin layer: Metformin HCl 500; Macrogol 4000, 24.7; anhydr. coll. silica - Aerosil 200, 5; Polyvinylpyrrolidone K 25, 20; Mg stearate, 5.9;

Glibenclamide layer: Glibenclamide 5; Lactose mon.-granul. 128; Corn starch 40; Microgr. Cell.-Avicel PH 102, 15; HPMC -5, 4.8; Na croscarmellose, 13; Anhydr. coll. silica -Aerosil 200, 0.7; Polysorbate 80, 0.5; Mg stearate 1; Yellow Iron oxide

1; Red Iron oxide 1;

-Glib+ Met (2.5 + 500 mg)

Metformin layer: Metformin HCl 500; Macrogol 4000, 24.7; Anhydrous colloidal silica 8.2; Polyvinylpyrrolidone 20; Magnesium Stearate 5.9;

Glibenclamide layer: Glibenclamide 2.5 ; Lactose monohydrate 89; Sodium lauryl sulphate 0.75; Microcrystalline cellulose 150; Sodium croscarmellose 5.5; Anhydrous colloidal silica 0.75; Magnesium Stearate 0.75; Yellow Iron oxide E 172 0.75;

- Glib+ Met (5 + 500 mg)

metformin layer : Metformin HCl 500; Macrogol 4.000, 24.7; Anhydrous colloidal silica 8.2; Polyvinylpyrrolidone 20; Magnesium Stearate 5.9;

glibenclamide layer: Glibenclamide 5; Lactose monohydrate 86.75; Sodium lauryl sulphate 0.750; Microcrystalline cellulose 150; Sodium croscarmellose 5.5; Anhydrous colloidal silica 0.75; Magnesium Stearate 0.75; Yellow iron oxide E 172, 0.125; Red iron oxide E 172, 0.375;

- Glib+ Met (2.5 + 850 mg)

metformin layer: Metformin HCl 850; Macrogol 4000, 42; Anhydrous colloidal silica 14; Polyvinylpyrrolidone 34; Magnesium stearate 10;

glibenclamide layer : Glibenclamide 2.5; Lactose monohydrate 89; Sodium lauryl sulphate 0.75; Microcrystalline cellulose 150; Sodium croscarmellose 5.5; Anhydrous colloidal silica 0.750; Magnesium Stearate 0.750; Yellow iron oxide E 172, 0.750

- Glib + Met (5 + 850 mg)

metformin layer : Metformin HCl 850; Macrogol 4000, 42; Anhydrous colloidal silica 14; Polyvinylpyrrolidone 34; Magnesium Stearate 10;

glibenclamide layer: Glibenclamide 5; lactose monohydrate, 86.75; Sodium lauryl sulphate 0.75; Microcrystalline cellulose 150; Sodium croscarmellose 5.5; Anhydrous colloidal silica 0.75; Magnesium Stearate 0.75; Yellow iron oxide E 172, 0.125; Red iron oxide E 172, 0.375;

19. Use of glibenclamide and metformin, or pharmaceutically acceptable salts thereof, for the preparation of pharmaceutical compositions as described in the claims from 1 to 18 for the treatment of type II diabetes mellitus.

INTERNATIONAL SEARCH REPORT

 Int. Application No.
 PCT/EP 02/13497

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/20 A61K31/64

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 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)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, 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.
Y	FR 2 244 481 A (HOECHST AG) 18 Apr11 1975 (1975-04-18) page 3, line 35 - line 41 page 2, line 24 - line 40 page 5 -page 9; examples	1-19
Y	WO 00 03742 A (BONHOMME YVES ;LIPHA (FR); NICHOLSON SARAH J (GB); CAVE GILLIAN (G) 27 January 2000 (2000-01-27) cited in the application the whole document	1-19
A	WO 97 17975 A (GENTILI IST SPA ;BARELLI GIULIO (IT); REGIS MASSIMO DE (IT)) 22 May 1997 (1997-05-22) cited in the application the whole document	1-19
	-/-	

☒ 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
- "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "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

"Z" document member of the same patent family

Date of the actual completion of the international search

23 Apr11 2003

Date of mailing of the international search report

06/05/2003

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentzen 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Boulois, D

INTERNATIONAL SEARCH REPORT

In International Application No.

PCT/EP 02/13497

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 82875 A (AEROPHARM TECHNOLOGY INC) 8 November 2001 (2001-11-08) page 3, line 10 - line 13	1-19
P,X	WO 02 055009 A (KHANNA SATISH C ;ZALA YASHORAJ RUPSIH (IN); DHARMADHIKARI NITIN B) 18 July 2002 (2002-07-18) page 23, line 21 - line 23 page 25, line 27 - line 28 page 27, line 13 - line 31	1,6-8,19

INTERNATIONAL SEARCH REPORT

Patent Application No

PCT/EP 02/13497

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
FR 2244481	A	18-04-1975	DE 2347531 A1	30-04-1975
			AU 7349374 A	25-03-1976
			BE 820222 A1	24-03-1975
			DK 496774 A	26-05-1975
			FI 274174 A	22-03-1975
			FR 2244481 A1	18-04-1975
			JP 50053521 A	12-05-1975
			NL 7412254 A	25-03-1975
			NO 743394 A	14-04-1975
			SE 7411852 A	24-03-1975
			ZA 7405981 A	29-10-1975
WO 0003742	A	27-01-2000	EP 0974356 A1	26-01-2000
			AU 753604 B2	24-10-2002
			AU 5417999 A	07-02-2000
			BR 9906600 A	18-07-2000
			CA 2303537 A1	27-01-2000
			CN 1275082 T	29-11-2000
			WO 0003742 A2	27-01-2000
			EP 1011684 A2	28-06-2000
			JP 2002520371 T	09-07-2002
			NZ 503248 A	27-09-2002
			US 6303146 B1	16-10-2001
WO 9717975	A	22-05-1997	IT MI952337 A1	14-05-1997
			AU 7566896 A	05-06-1997
			BR 9611448 A	23-03-1999
			CA 2237571 A1	22-05-1997
			DE 869796 T1	19-04-2001
			WO 9717975 A1	22-05-1997
			EP 0869796 A1	14-10-1998
			ES 2150889 T1	16-12-2000
			US 5922769 A	13-07-1999
			US RE37330 E1	14-08-2001
WO 0182875	A	08-11-2001	AU 2753501 A	12-11-2001
			WO 0182875 A2	08-11-2001
			US 6403121 B1	11-06-2002
			US 2001046515 A1	29-11-2001
WO 02055009	A	18-07-2002	WO 02055009 A1	18-07-2002
			WO 02080887 A2	17-10-2002

A1

DEMANDE
DE BREVET D'INVENTION

(21)

N° 74 32021

(54)

Composition thérapeutique pour le traitement du diabète par voie orale.

(51)

Classification internationale (Int. Cl.⁷). A 61 K 31/155, 31/18.

(22)

Date de dépôt 23 septembre 1974, à 15 h 38 mn.

(33) (32) (31)

Priorité revendiquée : *Demande de brevet déposée en République Fédérale d'Allemagne le 21 septembre 1973, n. P 23 47 531.2 au nom de Farbwerke Hoechst AG. Vormalis Meister Lucius et Brünig.*

(41)

Date de la mise à la disposition du
public de la demande B.O.P.I. — «Listes» n. 16 du 18-4-1975.

(71)

Déposant : Société dite : HOECHST AKTIENGESELLSCHAFT, résidant en République Fédérale d'Allemagne.

(72)

Invention de :

(73)

Titulaire : *Idem* (71)

(74)

Mandataire : Cabinet Lavoix, 2, place d'Estienne-d'Orves, 75441 Paris Cedex 09.

La présente invention concerne une composition thérapeutique pour le traitement du diabète par voie orale et son procédé de préparation.

Plus particulièrement, l'invention concerne une composition 5 thérapeutique constituée d'une association de N-4/2-(5-chloro-2-méthoxybenzamido)-éthyl-7-phényl-sulfonyl-N'-cyclohexylurée (dénommée Glibenclamide) et de chlorhydrate de 1-(2-phényléthyl)-biguanide (dénommé chlorhydrate de Phenformine) ou d'un autre sel pharmaceutiquement acceptable.

10 Le diabétique, qui ne nécessite pas de l'insuline, mais qui répond insuffisamment au seul régime, est traité additionnellement avec des médicaments administrés par voie orale. A cette fin, on utilise des sulfonyl-urées, dont le mécanisme d'action principal consiste dans la libération d'insuline endogène, ou des composi- 15 tions à base de bi-guanides qui abaissent le taux de sucre sanguin du diabétique essentiellement par une inhibition de la gluco-néogénèse, par une augmentation du métabolisme anaérobie du glucose et par une inhibition de la résorption intestinale de glucose.

La combinaison libre, à savoir l'administration séparée de 20 sulfonyl-urée et de préparations de bi-guanides a été éprouvée depuis des années dans la thérapie de diabétiques, qui ne répondent pas à une mono-thérapie avec des sulfonyl-urées. Dans un fort pourcentage de cas, le métabolisme de carbo-hydrates peut être re-compensé par une thérapie de combinaison. En raison de leur mécanisme 25 d'action différent, les substances béta-zytotropes et les bi-guanides se complètent en ce qui concerne l'effet anti-diabétique.

Par une thérapie avec les deux substances en combinaison libre, on obtient un effet additif sur l'abaissement de la glycémie. On a à plusieurs reprises signalé l'avantage d'une telle thérapie 30 combinée; elle a particulièrement bien éprouvée dans le cas de non réponse à une mono-thérapie avec des sulfonyl-urées. Ainsi, on a indiqué que le traitement combiné rendait possible chez 50 % de cas donnant une non-réponse, la poursuite pendant plus de deux ans d'un traitement avec des comprimés.

35 Bien qu'on ne s'attendait pas à des avantages essentiels d'une association par rapport à une combinaison libre, on a constaté, et cela était surprenant, que l'association selon l'invention de sel de Phenformine et de Glibenclamide non seulement présente les avantages de la combinaison libre, mais aussi que l'activité de l'association est supérieure à celle obtenue par une administration séparée des deux constituants. 40

D'une association ayant une telle activité synergétique, le Glibenclamide doit être libéré immédiatement dans l'estomac et le sel de phenformine doit être libéré de manière retardée. On obtient cela en combinant les deux substances actives en une dose unitaire, 5 dans laquelle le sel de phenformine est présent sous une forme à libération retardée et le Glibenclamide est présent sous une forme soluble dans le suc gastrique.

On préfère, en particulier, des comprimés à deux couches, des dragées ou des comprimés enrobés, chez les deux derniers les no-
10 yaux étant constitués par le sel de phenformine sous une forme à libération retardée, qui sont munis d'une couche de Glibenclamide ou que l'on enrobe avec le Glibenclamide.

Les compositions de l'invention sont préparées selon des méthodes connues.

15 De préférence, on enrobe le sel de phenformine dans une matrice de cire avec des véhicules usuels et des substances régulant la libération, par exemple le chlorure de sodium, le citrate de sodium, le phosphate de sodium ou de potassium, ou, en particulier, le lactose. Comme cires, conviennent des cires naturelles ou syn-
20 thétiques, par exemple la cire d'abeilles ou la cire d'ester de lignite. Parmi les véhicules utilisables, on mentionnera, par exemple le phosphate ou le sulfate de calcium ou l'oxyde d'aluminium ainsi que, en particulier, l'hydroxyde d'aluminium.

La proportion des constituants individuels Glibenclamide: sel
25 de Phenformine est, de préférence, de 1 à 10. On préfère des compositions qui contiennent de 2,5 à 5,0 mg de Glibenclamide et de 25 à 50 mg de chlorhydrate de Phenformine. Dans le cas d'une dose élevée de substance active, le comprimé à deux couches est particulièrement avantageux.

30 L'effet synergétique des deux substances actives dans la composition selon l'invention a été mis en évidence à l'aide des essais suivants :

Le comprimé à deux couches utilisé dans les essais contenait par unité 2,5 mg de Glibenclamide à libération immédiate et 25 mg
35 de chlorhydrate de Phenformine enrobé dans une couche à libération retardée (selon l'exemple 1).

Donc, on calcula d'abord quelle dose de Glibenclamide et d'une bi-guanide (100 mg de Buformine et 500 mg de metformine ont été prises égaux à 50 mg de Phenformine) correspond à une certaine
40 qualité de stabilisation avant le passage à l'association. Puis

on établit pour tous les patients les doses ayant la même qualité de stabilisation, on calcula la dose totale et on la divisa par le nombre respectif de cas.

L'essai clinique de la composition de l'invention conduisit 5 au résultat surprenant suivant: dans le cas de diabétiques, qui présentaient dans le cas de la thérapie préalable par une combinaison libre des qualités de stabilisation très bonnes ou bonnes, on pouvait réaliser une économie de doses.

Donc, avec l'administration des deux substances actives associées 10 sous une forme thérapeutique, une synergie pharmacologique se réalise.

L'avantage particulier de cette composition réside donc dans le fait, qu'on obtient l'effet thérapeutique désiré avec des doses 15 qui sont inférieures à celles requises dans un traitement avec les constituants individuels.

Le Tableau 1 montre la réduction nette des deux constituants (environ 1/3) chez les patients présentant une très bonne à bonne stabilisation.

TABLEAU 1

Comparaison des quantités de substance active dans le cas d'une combinaison libre et dans le cas d'une thérapie avec la composition selon l'invention à qualité de stabilisation égale (économie de dose)

Qualité de stabilisation	Nombre de patients	Combinaison libre (dose moyenne)		Composition de l'invention (dose moyenne)	
		Biguanide* mg	Glibenclamide mg	Phenformine mg	Glibenclamide mg
très bonne	23	89	10,6	64	6,4
bonne	24	85	12,5	84	8,4

* par rapport à : 50 mg de phenformine = 100 mg de Bufermine
= 500 mg de Metformine
(n = 129)

224481

Un autre avantage de l'association sur l'administration séparée des constituants individuels est que le nombre de diabétiques présentant une stabilisation modérée ou qui ne répondent pas au traitement a été réduit.

5 Aussi dans le cas de diabétiques, qui présentaient pendant la thérapie précédente une stabilisation meilleure que modérée, la condition du métabolisme s'améliorait après passage à la composition de l'invention. Quelques patients soumis à l'insuline pou-
vaient aussi passer à l'association de Glibenclamide et de Phen-
10 formine.

La composition est particulièrement avantageuse pour des pa-
tients âgés (souvent oublieux). Pour eux, l'association est parti-
culièrement avantageuse, car elle réduit le risque de l'oubli ou
d'une prise erronée de deux constituants prescrits séparément, c
15 qui doit être toujours pris en considération lors d'une médication
permanente. Des effets désavantageux de cette association n'ont
pas été observés.

En ce qui concerne la Phenformine, on sait qu'à partir d'une
certaine dose individuelle, elle peut provoquer des effets secon-
20 daires, surtout gastro-intestinaux, la forme d'application galéni-
que de l'invention a l'avantage particulier que la proportion de
chlorhydrate de Phenformine enrobée dans une matrice de cire est
libérée de manière retardée, de sorte que les incompatibilités
gastro-intestinales sont réduites au minimum. Contrairement à cela,
25 une libération rapide du Glibenclamide est désirée. Ces deux exi-
gences sont satisfaites par la préparation de l'invention.

Les exemples suivants, qui décrivent la composition selon l'
invention et sa préparation, illustrent l'invention.

Exemple 1 (comprimés à deux couches)

30 Composition :

<u>Couche de Glibenclamide</u>	<u>1 comprimé</u>	<u>100 000 comprimés</u>
1 - Glibenclamide	2,50 mg	0,250 kg
2 - lactose	39,50 mg	3,950 kg
3 - amidon de maïs	35,25 mg	3,525 kg
35 4 - talc	1,50 mg	0,150 kg
5 - acide silicique colloïdal (p.e. Aerosil 200)	1,00 mg	0,100 kg
6 - stéarate de magnésium	0,25 mg	0,025 kg
	<u>80,00 mg</u>	<u>8,000 kg</u>

Couche de phenformine à libération retardée

	<u>1 comprimé</u>	<u>100 000 comprimés</u>
7 -chlorhydrate de Phenformine	25,00 mg	2,500 kg
8 - colorant jaune 2 pour aliments		
5 (International : FD&C Yellow 5) comme laque à base d'alumine P. ex. Lebensmittelgelblack ZLT 2 de la Société Siegle)	0,50 mg	0,050 kg
9 - gel d'hydroxyde d'aluminium	40,00 mg	4,000 kg
10 10 - Cire d'ester de lignite (p.ex. Hoechstwachs E)	20,00 mg	2,000 kg
11 - lactose	16,25 mg	1,625 kg
12 - acide silicique colloïdal (p.ex. Aérosil 200)	2,25 mg	0,225 kg
15 13 - stéarate de magnésium	1,00 mg	0,100 kg
	<u>105,00 mg</u>	<u>10,500 kg</u>

Préparation de la couche de glibenclamide (100 000 comprimés)

On prépare un mélange homogène à partir des constituants 1 à 3, et on le malaxe pour obtenir une pâte à l'aide d'empois d'amidon de maïs (= 0,5 kg de l'amidon de maïs comme partie de 3), et on met le tout sous forme de granulés selon la manière habituelle.

Aux granulés séchés, on ajoute en mélangeant 0,275 kg d'amidon de maïs (comme partie de 3) et les composants 4, 5 et 6.

25 Préparation de la couche de phenformine à libération retardée (100 000 comprimés)

On mélange les constituants 7, 8, 9 et 11 jusqu'à l'obtention d'un mélange homogène et on imprègne avec une solution de la cire (10) sur un appareil de mélangeage ou de pétrissage.

30 Comme solvants pour la cire conviennent des hydrocarbures chlorés.

On sèche de la manière habituelle la masse uniformément mouillée, on granule et on mélange ensuite avec les constituants 12 et 13.

35 On comprime ensuite les granulés de Glibenclamide et les granules de phenformine à libération retardée en des comprimés à deux couches.

Exemple 2 (comprimés enrobés)

Composition :

<u>Couche d'enrobage de Glibenclamide</u>		<u>1 comprimé</u>	<u>100 000 comprimés</u>
1 - Glibenclamide		2,5 mg	0,25 kg
2 - lactose		136,0 mg	13,60 kg
3 - amidon de maïs		122,0 mg	12,20 kg
5 4 - talc		5,0 mg	0,50 kg
5 - acide silicique colloïdal (p.e. Aerosil 200)		3,5 mg	0,35 kg
6 - stéarate de magnésium		1,0 mg	0,10 kg
		270,0 mg	27,00 kg
<u>10 Noyau de Phenformine à libération retardée</u>			
7 - chlorhydrate de phenformine		25,0 mg	2,50 kg
8 - lactose		36,0 mg	3,60 kg
9 - gel d'hydroxyde d'aluminium		46,0 mg	4,60 kg
15 10 - cire d'ester de lignite (p.e. Hoechstwachs E)		20,0 mg	2,00 kg
11 - acide silicique colloïdal (p.ex. Aérosil 200)		2,0 mg	0,20 kg
12 - stéarate de magnésium		1,0 mg	0,10 kg
		130,0 mg	13,00 kg

20 Préparation des granulés de Glibenclamide

comme décrite à l'exemple 1.

Pour faire une pâte du mélange de 1 à 3, on utilise de l'empois d'amidon de maïs, préparée à partir de 4,7 kg d'amidon de maïs (partie de 3). La proportion d'amidon de maïs ajoutée aux

25 granulés séchés est de 1 kg (partie de 3).

Préparation des granulés de Phenformine à libération retardée

On imprègne le mélange des constituants 7, 8 et 9, comme décrit à l'exemple 1, avec la solution de la cire et on mélange les granulés secs préparés à partir de ce mélange avec les constituants

30 11 et 12.

On comprime les granulés de Glibenclamide et les granulés de Phenformine retard sur un Press-coater en comprimés enrobés. On comprime d'abord un noyau des granulés de Phenformine retard et on enrobe ce noyau avec les granulés de Glibenclamide.

35 Exemple 3 (comprimés à deux couches)

Composition :

<u>Couche de Glibenclamide</u>	<u>1 comprimé</u>	<u>100 000 comprimés</u>
1 - Glibenclamide	5,0 mg	0,50 kg
2 - lactose	79,0 mg	7,90 kg

	<u>1 comprimé</u>	<u>100 000 comprimés</u>
3 - amidon de maïs	70,5 mg	7,05 kg
4 - talc	3,0 mg	0,30 kg
5 5 - acide silicique colloïdal (p.ex. Aérosil 200)	2,0 mg	0,20 kg
6 - stéarate de magnésium	0,5 mg	0,05 kg
	<u>160,0 mg</u>	<u>16,00 kg</u>
<u>Couche de phenformine retard</u>		
7 - chlorhydrate de Phenformine	50,0 mg	5,00 kg
10 8 - jaune pour aliments 2 (FDA C Yellow 5) comme laque à base d'alumine (p.ex. Lebens- mittelgelblack ZTL 2, Société Siegle)	1,0 mg	0,10 kg
15 9 - gel d'hydroxyde d'aluminium	80,0 mg	8,00 kg
10 - cire d'esther de lignite (p.ex. Hoechstwachs E)	30,0 mg	3,00 kg
11 - lactose	42,5 mg	4,25 kg
12 - acide silicique colloïdal (p.ex. Aérosil 200)	4,5 mg	0,45 kg
20 13 - stéarate de magnésium	2,0 mg	0,20 kg
	<u>210,0 mg</u>	<u>21,00 kg</u>

Préparation de la couche de Glibenclamide (100 000 comprimés)

Selon l'exemple 1. On peut comprimer les granulés décrits à
25 l'exemple 1 avec un poids final double.

Préparation de la couche de Phenformine retard
(100 000 comprimés)

selon l'exemple 1. On comprime les granulés de Glibenclamide
et les granulés de Phenformine retard en comprimés à deux couches.

30 Exemple 4 (dragées)

On comprime des noyaux biconvexes de Phenformine retard ayant
la composition décrite à l'exemple 2 (1 noyau contenant 25 mg de
chlorhydrate de Phenformine:).

On enrobe de manière habituelle les noyaux de Phenformine re-
35 tard tout en incorporant dans la couche enrobante 2,5 mg de Gliben-
clamide.

A cet effet, on disperse le Glibenclamide dans la suspension
d'enrobage et on le distribue uniformément par pulvérisation sur
les noyaux.

Un autre procédé consiste à mouiller uniformément les noyaux de dragées avec une solution adhésive ayant la composition suivante :

	saccharose	1,000 kg
5	gélatine	0,050 kg
	sirop d'amidon	0,375 kg
	eau distillée	0,500 kg

On pulvérise le Glibenclamide en mélange avec des agents auxiliaires sur les noyaux mouillés uniformément avec la solution adhésive et on sèche par de l'air soufflé. On répète ce procédé jusqu'à ce que la quantité totale de substance active soit distribuée uniformément sur la surface des noyaux.

Composition du mélange de pulvérisation contenant le Glibenclamide

15	1 - Glibenclamide (contenant 12% d'addition)	2,8 mg	0,28 kg
	2 - sucre pulvérisé	22,7 mg	2,27 kg
	3 - amidon de maïs	3,0 mg	0,30 kg
	4 - talc	1,5 mg	0,15 kg
20		<u>30,0 mg</u>	<u>3,00 kg</u>

On enrobe ultérieurement de manière habituelle les noyaux des dragées recouvert de Glibenclamide.

Revendications

1 - Composition thérapeutique pour le traitement du diabète par voie orale, caractérisé en ce qu'elle contient une association de N-4-[2-(5-chloro-2-méthoxybenzamido)-éthyl]-phényl-sulfonyl-N'-cyclohexyl-urée et de chlorhydrate de 1-(2-phényl-éthyl)-biguanide ou d'un autre sel pharmaceutiquement acceptable.

2 - Composition selon la revendication 1, caractérisée en ce qu'elle contient, à côté de l'association de N-4-[2-(5-chloro-2-méthoxybenzamido)-éthyl]-phényl-sulfonyl-N'-cyclohexyl-urée et du sel de 1-(2-phényl-éthyl)-biguanide, encore d'autres substances actives, adjuvants ou véhicules.

3 - Composition selon la revendication 1 ou la revendication 2, caractérisée en ce que le rapport de dose entre le Glibenclamide et le sel de Phenformine est de 1:10.

4 - Composition selon l'une quelconque des revendications 1 à 3, caractérisée en ce qu'elle contient 2,5 à 5,0 mg de Glibenclamide et 25 à 50 mg de chlorhydrate de Phenformine par unité de dosage.

5 - Composition selon l'une quelconque des revendications 1 à 4, caractérisée en ce que le Glibenclamide est présent sous une forme soluble dans le suc gastrique et le chlorhydrate de Phenformine est présent sous une forme à libération retardée.

6 - Composition selon l'une quelconque des revendications 1 à 5, caractérisée en ce qu'elle est formée d'un comprimé à deux couches, d'une dragée ou d'un comprimé enrobé.

7 - Procédé de préparation d'une composition selon l'une quelconque des revendications 1 à 6, caractérisé en ce que le sel de Phenformine est enrobé dans une matrice de cire avec addition de véhicules et de substances régulant la libération et mis avec le Glibenclamide sous forme de doses unitaire.

8 - Procédé selon la revendication 7, caractérisé en ce qu'on prépare un comprimé à deux couches, une dragée ou un comprimé enrobé.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31 /64	A2	(11) International Publication Number: WO 00/03742 (43) International Publication Date: 27 January 2000 (27.01.00)
(21) International Application Number: PCT/EP99/05571 (22) International Filing Date: 12 July 1999 (12.07.99) (30) Priority Data: 98401781.4 15 July 1998 (15.07.98) EP (71) Applicant (for all designated States except US): LIPHA [FR/FR]; 34, rue Saint-Romain, F-69008 Lyon (FR). (72) Inventors; and (75) Inventors/Applicants (for US only): BONHOMME, Yves [FR/FR]; Le Bucley, 21, avenue de la Paix, F-69260 Charbonnières les Bains (FR). NICHOLSON, Geoffrey [GB/GB]; 48 Langdon Avenue, Aylesbury, Buckinghamshire HP21 9UT (GB). CAVE, Gillian [GB/GB]; 26 Hilbre Drive, Ellesmere Port CH65 9JQ (GB). NICHOLSON, Sarah, J. [GB/GB]; 4 Redstone Hill, Helsby, Cheshire WA6 9PE (GB). (74) Agent: OBOLENSKY, Michel; Cabinet Lavoix, 2, place d'Estienne d'Orves, F-75441 Paris Cedex 09 (FR).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: SOLID ORAL DOSAGE FORM COMPRISING A COMBINATION OF METFORMIN AND GLIBENCLAMIDE (57) Abstract The present invention relates to a solid oral dosage form comprising a combination of metformin and glibenclamide in which the size of glibenclamide is such that the glibenclamide bioavailability is comparable to the glibenclamide bioavailability obtained with a separate administration of metformin and glibenclamide.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

"Solid oral dosage form comprising a combination of metformin and glibenclamide".

The present invention relates to solid oral dosage forms for the treatment of non-insulin dependent diabetes.

Non-insulin dependent diabetes is a metabolic disorder characterized by hyperglycaemia, which occurs due to insulin deficiency, 5 insulin resistance and reduced glucose tolerance.

There are two main groups of oral antidiabetic drugs available: these are the sulphonylureas and the biguanidines. Sulphonylureas act by stimulating insulin release and are thus only effective with some residual pancreatic beta-cell activity, examples of sulphonylureas available are 10 glibenclamide, gliclazide, tolbutamide, glipizide, tolazamide, gliquidone and chlorpropamide. The biguanidines, such as metformin, act by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose, and as they require endogenous insulin they are only effective with some residual pancreatic islet cell activity.

15 The initial treatment of non-insulin dependent diabetes involves diet control and exercise. Only after this has been shown to be inadequate are oral antidiabetic drugs used, and then only to complement the effect of diet and not replace it. Monotherapy with an oral antidiabetic can be an effective treatment for many years. However the efficiency can decrease 20 with time. Due to sulphonylureas and biguanidines having complementary modes of action, combined therapy is now an established form of treatment for non-insulin dependent diabetes.

To improve patient compliance a combined tablet would be an advantage. The present invention relates to solid oral dosage forms 25 comprising a combination of metformin and glibenclamide (also named glyburide).

A combination of metformin with glibenclamide has been disclosed in WO 97/17975 for the treatment of type II diabetes with a defined ratio of the two active ingredients, which is a requirement in order to obtain an 30 optimum therapeutic effect. This prior art defines an optimum therapeutic ratio of metformin hydrochloride to glibenclamide of 100:1, for example 500mg of metformin hydrochloride with 5mg glibenclamide in a single

dosage unit. This ratio allows a range of daily doses, based on increasing the number of tablets taken per day, that avoid poor disease control through underdosing of either ingredient when there is a requirement for co-administration, and avoids hypoglycaemia by overdosing of either component when so co-administered. Assurance of performance in clinical use, which will derive from having a product exhibiting appropriate bioavailability of the glibenclamide component, is a key requirement for physicians wishing to treat patients with a combination formulation. Appropriate bioavailability implies that 5mg of glibenclamide formulated into a combination tablet with metformin is absorbed to an acceptably similar extent, and at a comparable rate, to glibenclamide dosed as a single entity formulation of the same strength when dosed concurrently with a single entity formulation of metformin.

This prior art does not teach how to formulate a combination product of metformin with glibenclamide so as to assure appropriate bioavailability of the glibenclamide component. There is no issue in this respect in the case of metformin hydrochloride on account of its high water solubility and therefore the bioavailability of metformin from combination formulations will not be discussed further. It is however a very important aspect to consider for glibenclamide as this is a poorly soluble drug substance (solubility is 0.1mg/ml in water at 25°C – practically insoluble as defined by the USP).

As such, its rate of solution after administration of a dosage form will influence the rate and extent of entry of the drug into the bloodstream (bioavailability). The control of the rate and extent of entry into the bloodstream is important for appropriate therapeutic effect.

Hence, the reference discloses a suitable ratio of the two active ingredients in a single dosage form, in order to model how the two individual ingredients might be desirably co-administered (based on how they would be dosed according to usual practice associated with currently available single entity formulations), it does not teach how to assure that such a combination formulation will perform in terms of bioavailability of

glibenclamide. This bioavailability should be as similar as possible to when the relevant doses of the two single entity formulations are co-administered.

In addition, when a combination tablet using standard galenic procedures is proceeded with standard generic glibenclamide in the combination tablet, a reduced bioavailability in comparison to the co-prescribed situation was apparent.

It has now been found using in-vitro and in-vivo testing that the reduced bioavailability is related to the particle size and the particle size distribution of the glibenclamide. It has been found that particles which are too small result in high glibenclamide blood levels with consequent risk of hypoglycaemia and particles which are too large cannot dissolve sufficiently rapidly to give comparable bioavailability with the co-prescribed situation. It is therefore necessary to have a closely defined particle size distribution of the glibenclamide in the combination form.

The selection of a specific size fraction of glibenclamide enables the production of a solid oral dosage form comprising a combination of metformin and glibenclamide, and in particular a tablet, exhibiting glibenclamide bioavailability comparable to the bioavailability obtained with the separated administration of metformin and glibenclamide, when judged by the area under the curve of the in-vivo analysis.

The present invention provides in particular a tablet comprising a combination of metformin and glibenclamide, exhibiting a comparable glibenclamide bioavailability to the co-administered tablets.

In a first embodiment, the solid oral form such as a tablet, according to the invention, contains a combination of glibenclamide and metformin in which the size of the glibenclamide is such that at most 10% of the particles are less than 2 μm and at most 10% of the particles are greater than 60 μm . Preferably, the size of the glibenclamide is such that at most 10% of the particles are less than 3 μm and at most 10% of the particles

are greater than 40 μm . This specific particle size range of glibenclamide may be obtained by sieving or air jet milling.

In a second embodiment, the solid oral dosage form comprises a combination of metformin and glibenclamide in which the size of
5 glibenclamide is such that at most 25 % of the particles are less than 11 μm and at most 25 % of the particles are greater than 46 μm .

Preferably, 50 % of particles are less than 23 μm .

Metformin may be used as a salt of metformin, such as hydrochloride, fumarate, hydrobromide, p-chlorophenoxy acetate or
10 embonate. The weight ratio of metformin salt to glibenclamide should preferably be between 50/1 to 250/1.

The preferred compositions for the oral dosage form is provided in the table below, with ranges on components being provided:

15

Product identity	Amount of ingredient, mg per tablet		
	500/5	500/2,5	250/1.25
Ingredient			
Metformin hydrochloride	500.0	500.0	250.0
Glibenclamide	5.00	2.50	1.25
Croscarmellose sodium	6.0 – 30.0	6.0 – 30.0	3.0 – 15.0
Microcrystalline cellulose	30.0 – 120.0	30.0 – 120.0	15.0 – 60.0
Polyvinyl pyrrolidone	6.0 – 36.0	6.0 – 36.0	3.0 – 18.0
Magnesium stearate	0.6 – 15.0	0.6 – 15.0	0.3 – 7.5
Film coat*	9.0 – 24.0	9.0 – 24.0	4.5 – 12.0

* a commercially-available film coat composition is used, such as Opadry (Colorcon, UK).

The especially preferred compositions are as follows:

Product identity	Amount of ingredient, mg per tablet		
	500/5	500/2,5	250/1.25
Ingredient			
Metformin hydrochloride	500.0	500.0	250.0
Glibenclamide	5.00	2.50	1.25
Croscarmellose sodium	14.0	14.0	7.0
Microcrystalline cellulose	54.0	56.5	28.25
Polyvinyl pyrrolidone	20.0	20.0	10.0
Magnesium stearate	1.2 – 12.0	1.2 – 12.0	0.6 – 6.0
Film coat*	9.0 – 24.0	9.0 – 24.0	4.5 – 12.0

* a commercially-available film coat composition is used, such as Opadry (Colorcon, UK).

The tablet according to the present invention may be obtained by a process comprising:

- forming granules by wet granulation of a mixture of metformin and glibenclamide;
- blending the granules with a tableting aid and diluent, and
- tableting the blend thus obtained into tablets.

Advantageously the mixture used for forming the granules comprises a granulating binder. This granulating binder is in particular a polyvinylpyrrolidone such as for example, a polyvinylpyrrolidone having a molecular weight of 45 000. The polyvinylpyrrolidone may be used in a proportion of 2 to 4% by weight with respect to the final tablet.

After the granulating step the granules may be sieved and dried.

The granules are then blended with a diluent and tableting aid. The diluent may be any material usually used for making tablets, such as microcrystalline cellulose. The tableting aid may be any material usually for making tablets, such as magnesium stearate.

The tablets thus obtained may then be coated with a hydrophilic cellulose polymer and talc. The hydrophilic cellulose polymer may be 2-hydroxypropyl methylcellulose.

The following examples and tests illustrate the present invention.

5

Example 1

A tablet of metformin/glibenclamide has been prepared as follows:

66.6 g of polyvinylpyrrolidone are mixed with 246 g of purified water
10 with a stirrer. 1500 g metformin hydrochloride, 7.5 g of glibenclamide (with
a 10 to 90% size range between 2 to 60 μm), 42 g croscarmellose sodium
and 284.4 g of microcrystalline cellulose are mixed in a granulator. The
polyvinylpyrrolidone solution is added to the granulator and the wet
mass is granulated. The granules are extruded through a 1 mm mesh.
15 The granules are emptied into a preheated fluidised bed dryer and the
granules are dried. 97.5 g of microcrystalline cellulose is mixed into the
granules using a tumbling mixer. 12 g of magnesium stearate is added to
the tumbling mixer and mix. The granule mix is tableted using a suitable
tablet press. The tablets are coated with a 2% hydroxypropyl
20 methylcellulose coat in a coating machine.

Example 2

A tablet of metformin/glibenclamide has been prepared as follows:

25 5.83 g of glibenclamide (with a 10 to 90% size range between 2 to
60 μm), are preblended with 32.67 g of croscarmellose sodium. 46.67 g of
polyvinylpyrrolidone are mixed with 93.33 g of purified water with a stirrer.
The glibenclamide-croscarmellose sodium blend is mixed with 1166.6 g of
metformin hydrochloride in a granulator. The polyvinylpyrrolidone solution
30 is added to the granulator and the wet mass is granulated. The granules
are emptied into a preheated fluidised bed dryer and the granules are

dried. The particle size of the granules is reduced by passing through a 1 mm mesh. 131.83 g of microcrystalline cellulose are mixed into the granules in the granulator. 16.3 g of magnesium stearate are added to the granulator and mixed. The granule mix is tabletted using a suitable tablet
5 press. The tablets are coated with a 2% hydroxypropyl methylcellulose coat in a coating machine.

Test 1

10 In-vivo bioavailability tests were performed with tablets prepared as disclosed in example 2, using two batches of glibenclamide. The two batches have the following 10 to 90% particle size range:

batch A: 3.47-38.08 μm

batch B: 15.63-91.6 μm .

15 The distribution of the particle size of batches A and B are illustrated in figure 1.

The two batches of tablets were administered to healthy patients in comparison to co-administered glibenclamide (marketed under the trade name Daonil) and metformin hydrochloride (16 patients for each group).

20 The comparative concentrations of glibenclamide in a tablet comprising a combination of metformin and respectively the batch A and the batch B of glibenclamide and with the co-administration are shown respectively in figures 2 and 3.

The area under the curve (AUC) are the following:

25

	AUC (ng/ml/h)
combination with batch A	790.5
combination with batch B	353.0
co-administration	869.3

30

It appears that with the combination according to the invention with batch A the AUC is substantially the same as in the case of co-administration, whereas with the combination with batch B the AUC is more clearly different.

5

Test 2

Careful examination of blood levels of glibenclamide in humans following administration of a series of tablet formulations of metformin hydrochloride combined with glibenclamide (identified as formulations Combo 1, 2, 3 and 4), where the formulation are identical save for the particle size characteristics of the glibenclamide used, compared with commercially available reference formulations of metformin hydrochloride (Glucophage™, Bristol-Myers Squibb) and glibenclamide (Micronase™, Upjohn) dosed together, allowed definition of particle characteristics for glibenclamide that would assure appropriate bioavailability of the glibenclamide component from the combination formulation. This means that disease control when patients are first treated with such a combination formulation will be predictable, based on prior physician knowledge of treatments employing either single drug.

Alternatively, if patients have undergone prior stabilisation of their disease by adding treatment with a commercial product like Micronase™ to existing treatment with Glucophage™ (or vice versa), then the switch over to a more convenient treatment employing the combination in a single tablet (and where the appropriate bioavailability of the glyburide component is assured) will result in the desired level of disease control being maintained.

Data from the studies with metformin hydrochloride/glibenclamide tablets formulated with glibenclamide of different particle size characteristics allowed the development of a correlation between drug particle size and the *in vivo* performance. The properties of the lots of

glyburide used in the series of combination tablets employed are shown in the table below:

Tablet batch	glibenclamide particle size (microns)		
	25 % undersize	50 % undersize	75 % undersize
Combo 1	15	33	62
Combo 2	28	58	88
Combo 3	10	25	52
Combo 4	6	11	19

- 5 When four compositionally-identical individual batches of tablets of metformin hydrochloride-glyburide 500/2.5mg were prepared using each of these lots of glibenclamide and dosed to humans, the following pharmacokinetic parameters were found on analysis of the glibenclamide plasma concentration-time curves:

10

Tablet batch	Pharmacokinetic parameters glibenclamide			
	C _{max} (ng/ml, geo. mean)	AUC (ng/ml/hr, geo. mean)	C _{max} (ng/ml, arith. mean)	AUC (ng/ml/hr, arith. mean)
Combo 1	71	478	76	493
Combo 2	52	345	54	339
Combo 3	64	513	67	531
Combo 4	88	642	93	716

- A reasonable correlation can be obtained between particle size and the maximum attained geometric mean glibenclamide plasma concentration, C_{max}, and also with the geometric mean area under the glibenclamide plasma concentration-time curve, AUC.

From these correlations, projected limits on particle size for glyburide that would give predicted C_{max} and AUC values $\pm 25\%$ of a

mean value for batches of the reference glibenclamide formulation, Micronase™ utilised in the *in vivo* studies become:

	<u>25% undersize limits</u>	<u>50% undersize limits</u>	<u>75% undersize limits</u>
Cmax	<0-18 microns	<0-37 microns	<0-63 microns
AUC	<0-11 microns	<0-25 microns	<0-46 microns

5 Accommodating both Cmax and AUC requirements, the projected limits then become:

<u>25% undersize limits</u>	<u>50% undersize limits</u>	<u>75% undersize limits</u>
≤ 11 microns	≤ 23 microns	≤ 46 microns

Glibenclamide having these particle size characteristics have
10 powder surface area values in the range 1.7 to 2.2 m²g⁻¹ as determined by nitrogen adsorption. Therefore material of these properties when formulated as described in this work is distinct from the material disclosed in US 3 979 520 which required glibenclamide of powder surface area in excess of 3m²g⁻¹ (preferably 5 to 10 m²g⁻¹) to yield appropriate
15 glibenclamide bioavailability. The glibenclamide of particle size properties detailed in this work, when formulated as described here produces appropriate glibenclamide bioavailability in humans as described in the next test.

20 Test 3

A batch of metformin hydrochloride-glibenclamide tablets 500/5mg was prepared as follows. Glibenclamide (1.0kg) with the above defined size was tumble mixed with 2.8kg of croscarmellose sodium and this
25 mixture was then blended in a high shear mixer with metformin hydrochloride (100kg) to which 0.5% by weight of magnesium stearate had been added.

This dry mix was wet granulated in a high shear mixer with 12.1kg of an aqueous solution of povidone (containing 4kg of povidone). The wet granules were dried in a fluid bed drier at 60°C to a defined moisture content. The dried (loss on drying 2-3% w/w) granules were size reduced in a oscillator (1.0mm screen aperture) then tumble mixed with 10.8kg of microcrystalline cellulose, followed by mixing with 0.9kg of the tablet lubricant magnesium stearate. The lubricated granules were compressed using 16mm x 8mm capsule shaped tooling and the tablet cores were film coated (weight gain approximately 2% w/w) with the proprietary film coat material Opadry 32920 to yield the final yellow, capsule-shaped tablets. In a human pharmacokinetic study volunteer either were dosed with one of these tablets or with a treatment being one 500mg Glucophage™ tablet plus one 5mg Micronase™ tablet co-administered. Glibenclamide plasma levels following dosing were analysed and the following pharmacokinetic were found for this component:

Treatment	Parameter	Mean	Adjusted geometric mean	Ratio of means (Point estimate)
Combination Tablet 500/5	Cmax	122	116	1.14
	AUC (O-T)	859	831	1.07
Glucophage + Micronase	Cmax	113	101	-
	AUC (O-T)	842	780	-

Glibenclamide bioavailability from the combination tablet is comparable to that from the reference glibenclamide formulation, Micronase™. This would thus allow patients to conveniently take one tablet of the combination product instead of two tablets of existing therapies together, without concern that low glibenclamide blood levels would result, which might occur with prior art formulations and lead to loss of control of disease.

Example 3

Instead of compressing into tablet granulation as prepared for test 3
5 was filled into size 00 capsules to either provide for metformin
hydrochloride/glibenclamide 500mg/5mg product or the 500mg/2.5mg
product. Granulation was filled into size 1 capsules to provide the
250mg/2.5mg product.

These capsule exhibited acceptable physical properties and
10 provide an alternative to the tablets. Formulations as described in WO
97/17975 could not be filled in capsules of a size acceptable to most
patients because of the larger amount of excipients employed the
formulations they described.

CLAIMS

1. A solid oral dosage form comprising a combination of metformin and glibenclamide in which the size of glibenclamide is such that the
5 glibenclamide bioavailability is comparable to the glibenclamide bioavailability obtained with a separate administration of metformin and glibenclamide .

2. A solid oral dosage form comprising a combination of metformin and glibenclamide in which the size of the glibenclamide is such that at
10 most 10% of the particles are less than 2 μm and at most 10% of the particles are greater than 60 μm .

3. A solid oral dosage form as claimed in claim 2 in which the size of the glibenclamide is such that at most 10% of the particles are less than 3 μm at most 10% of the particles are greater than 40 μm .

15 4. A solid oral dosage form comprising a combination of metformin and glibenclamide in which the size of glibenclamide is such that at most 25 % of the particles are less than 11 μm and at most 25 % of the particles are greater than 46 μm .

5. A solid oral dosage form in which 50 % of particles are less than
20 23 μm .

6. A solid oral dosage form as claimed in any one of claims 1 to 4 in which metformin is present as metformin salt and the weight ratio of metformin salt to glibenclamide is 50/1 to 250/1.

7. A solid oral dosage form as claimed in any one of claims 1 to 6
25 which is a tablet.

8. A tablet as claimed in claim 7 which is obtained by a process comprising:

- a) forming granules by wet granulation of a mixture of metformin and glibenclamide;
- 30 b) blending the granules with a tableting aid
- c) tableting the blend thus obtained into tablets.

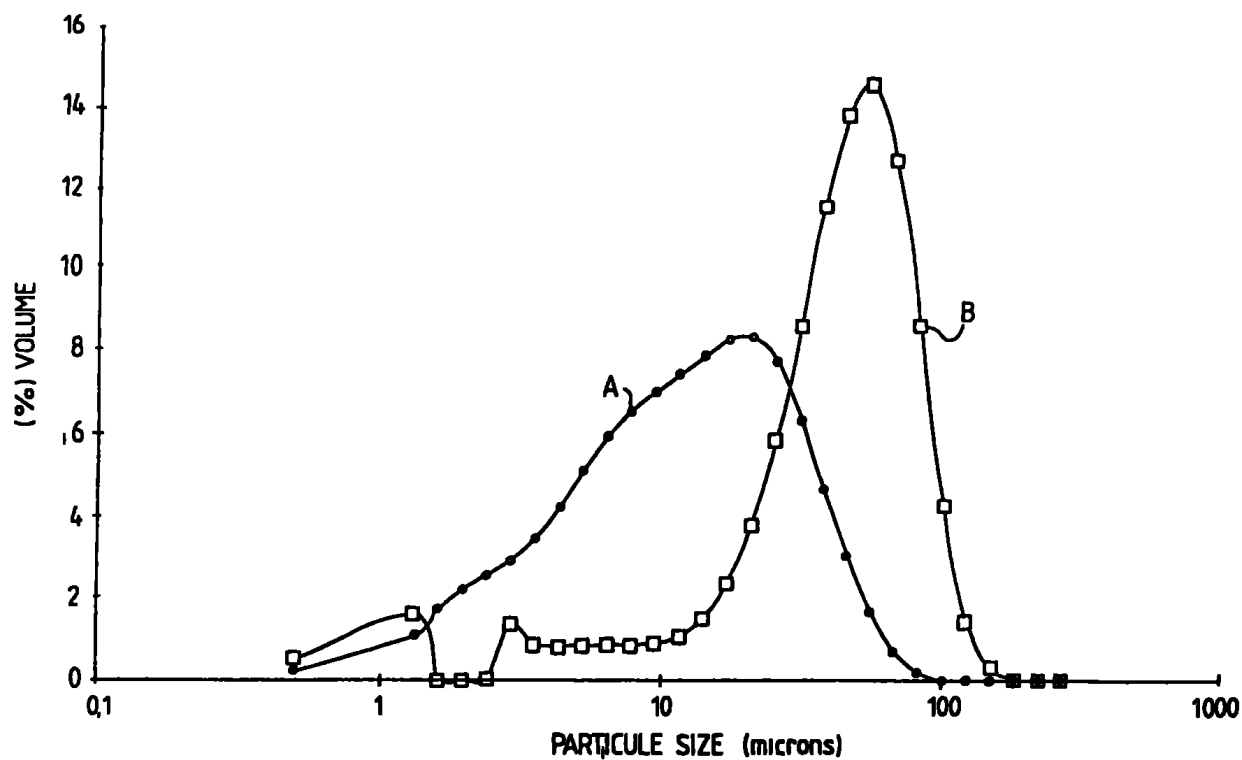
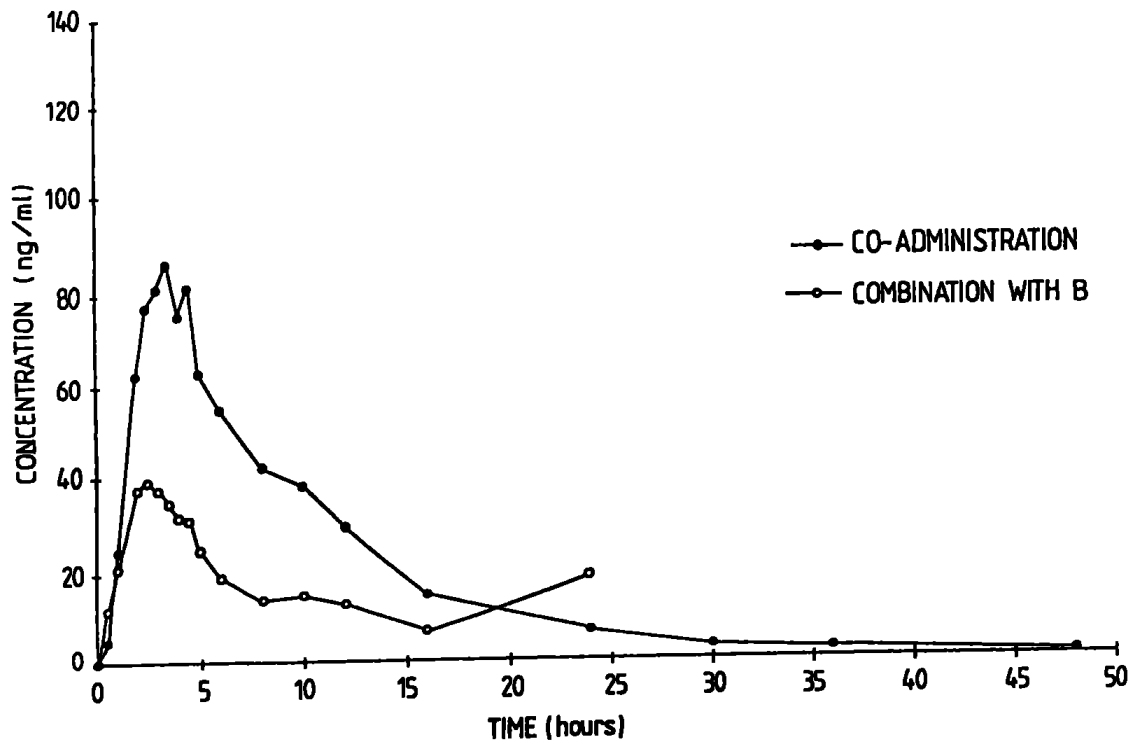


FIG 1

FIG. 2

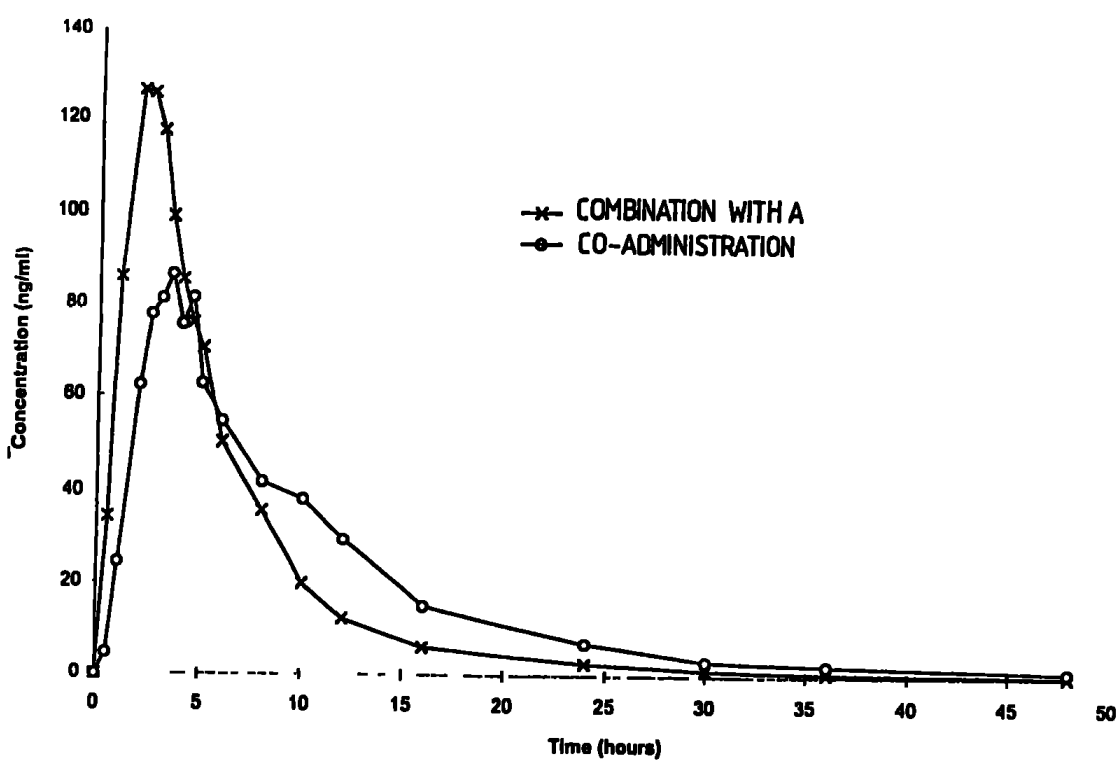


FIG 3



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/64 // (A61K 31/64, 31:155)	A3	(11) International Publication Number: WO 00/03742 (43) International Publication Date: 27 January 2000 (27.01.00)
(21) International Application Number: PCT/EP99/05571 (22) International Filing Date: 12 July 1999 (12.07.99) (30) Priority Data: 98401781.4 15 July 1998 (15.07.98) EP (71) Applicant (for all designated States except US): LIPHA [FR/FR]; 34, rue Saint-Romain, F-69008 Lyon (FR). (72) Inventors; and (75) Inventors/Applicants (for US only): BONHOMME, Yves [FR/FR]; Le Bucley, 21, avenue de la Paix, F-69260 Charbonnières les Bains (FR). NICHOLSON, Geoffrey [GB/GB]; 48 Langdon Avenue, Aylesbury, Buckinghamshire HP21 9UT (GB). CAVE, Gillian [GB/GB]; 26 Hilbre Drive, Ellesmere Port CH65 9JQ (GB). NICHOLSON, Sarah, J. [GB/GB]; 4 Redstone Hill, Helsby, Cheshire WA6 9PE (GB). (74) Agent: OBOLENSKY, Michel; Cabinet Levolz, 2, place d'Estienne d'Orves, F-75441 Paris Cedex 09 (FR).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 20 April 2000 (20.04.00)	
(54) Title: SOLID ORAL DOSAGE FORM COMPRISING A COMBINATION OF METFORMIN AND GLIBENCLAMIDE (57) Abstract The present invention relates to a solid oral dosage form comprising a combination of metformin and glibenclamide in which the size of glibenclamide is such that the glibenclamide bioavailability is comparable to the glibenclamide bioavailability obtained with a separate administration of metformin and glibenclamide.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SE	Sweden
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	NL	Netherlands	TR	Turkey
BG	Bulgaria	HU	Hungary	NL	Netherlands	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LJ	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/05571

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/64 //(A61K31/64,31:155)

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 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 17975 A (GENTILI IST SPA ;BARELLI GIULIO (IT); REGIS MASSIMO DE (IT)) 22 May 1997 (1997-05-22) claims	1-4
Y	US 4 060 634 A (ROTHER WERNER ET AL) 29 November 1977 (1977-11-29) column 4, line 32 - line 49	1-4

☐ 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
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document relating 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.
- "Z" document member of the same patent family

Date of the actual completion of the International search

15 February 2000

Date of mailing of the International search report

23/02/2000

Name and mailing address of the ISA

European Patent Office, P.O. Box 5010 Patentstrasse 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 840-2040, Tx. 31 651 opo nl,
Fax (+31-70) 840-2016

Authorized officer

Leherte, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

Original Application No

PCT/EP 99/05571

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9717975 A	22-05-1997	IT MI952337 A	14-05-1997
		AU 7566896 A	05-06-1997
		BR 9611448 A	23-03-1999
		CA 2237571 A	22-05-1997
		EP 0869796 A	14-10-1998
		US 5922769 A	13-07-1999
US 4060634 A	29-11-1977	DE 2348334 A	27-03-1975
		AT 330954 B	26-07-1976
		AT 762374 A	15-10-1975
		AU 7365374 A	01-04-1976
		BE 820254 A	24-03-1975
		CA 1029661 A	18-04-1978
		FI 275574 A,B,	27-03-1975
		FR 2244455 A	18-04-1975
		GB 1420907 A	14-01-1976
		JP 1089246 C	23-03-1982
		JP 50058216 A	21-05-1975
		JP 56032967 B	31-07-1981
		NL 7412393 A,B,	01-04-1975
		SE 402210 B	26-06-1978
		SE 7412044 A	27-03-1975
		US 3979520 A	07-09-1976
		ZA 7405967 A	26-11-1975



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/64 // (A61K 31/64, 31:155)	A1	(11) International Publication Number: WO 97/17975 (43) International Publication Date: 22 May 1997 (22.05.97)
(21) International Application Number: PCT/EP96/04860 (22) International Filing Date: 7 November 1996 (07.11.96) (30) Priority Data: MI95A002337 14 November 1995 (14.11.95) IT (71) Applicant (for all designated States except US): ISTITUTO GENTILI S.P.A. [IT/IT]; Via Mazzini, 112, I-56125 Pisa (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): BARELLI, Giulio [IT/IT]; Via Mazzini, 112, I-56125 Pisa (IT). DE REGIS, Massimo [IT/IT]; Via Mazzini, 112, I-56125 Pisa (IT). (74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: A GLIBENCLAMIDE-METFORMIN COMBINATION FOR THE TREATMENT OF DIABETES MELLITUS OF TYPE II (57) Abstract A combination of glibenclamide and metformin such that, when administered in the form of pharmaceutical composition in the treatment of diabetes mellitus of type II, the ratio between the two active principles allows to obtain an optimum therapeutical effect at any time of the progression of the disease, avoiding to make use of the insulin therapy in the most severe cases.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

A GLIBENCLAMIDE-METFORMIN COMBINATION FOR THE TREATMENT OF DIABETES MELLITUS OF TYPE II

The present invention relates to the use of a combination consisting of glibenclamide and metformin in one specific ratio as medicament for the treatment of diabetes mellitus of type II.

5 Non-insulin dependent diabetes of type II (NID) is known to be a frequent metabolic disease and the main cause of hyperglycemia. In recent years, diabetes mellitus of type II has been proved to be a heterogeneous disease, with complex, unclarified
10 metabolic aspects, which disease is characterized by three main metabolic abnormalities contributing to hyperglycemia: the partial or complete decrease in insulin secretion, the resistance of the peripheral tissues to insulin and the increased hepatic production
15 of glucose in fasting conditions.

Diet and physical exertion are unanimously recognized to be the foundation of the therapy of diabetes of type II: both of them lead to a reduction in insulin-resistance and, in the long run, to an
20 improvement in the pancreas secretive deficit.

However, these provisions are insufficient and a pharmacological aid with oral hypoglycemic agents is necessary. At present, the two main families of oral hypoglycemic agents available are sulfonylureas and
25 biguanides.

The use of sulfonylureas and biguanides in monotherapy, in most cases, allows to obtain an effective glycometabolic control for some years, if an

appropriate diet and behavioural regimen are kept. Nevertheless, the efficacy of the therapy with oral hypoglycemic agents can decrease with time.

After a positive starting response which can last 4-5 years, monotherapy becomes ineffective in a considerable percentage of patients. These are the so-called "secondary failures" of the therapy with oral hypoglycemic agents. Such a failure is estimated to occur each year in 5-10% of the patients under therapy with sulfonylureas, therefore after 10 years, only 50% of the patients still show a satisfactory response.

The secondary failure in patients under treatment with metformin appears to have an incidence superimposable to the above mentioned one.

Recent studies show that besides a qualitative/quantitative deficiency of insulin secretion, the combined occurrence of insulin-resistance conditions is at the bottom of NID diabetes.

Since sulfonylureas are capable of stimulating insulin release, but are not capable of acting on insulin resistance, and biguanides are able to act on insulin resistance, whereas they are not able to stimulate insulin secretion, the therapeutical rationale of said studies suggested the use of combined formulations of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin-resistance condition.

Vigneri et al. (Diabete & Metabolisme, 1991, (17), 232-234), faced the problem of secondary failure to sulfonylurea therapy in NID diabetes. The authors proposed a combination of glibenclamide-metformin in a

3

daily dosage of 15 mg and 1500 mg, respectively, in alternative to insulin therapy in addition to glibenclamide.

The combined therapy (sulfonylurea + biguanide) plays therefore a specifically important therapeutical role, since it allows to obtain an effective metabolic control in those patients with diabetes of type II, in which the therapy with only sulfonylureas or only biguanides becomes ineffective with time.

Two biguanides are used in the oral therapy of diabetes of type II: phenformin and metformin. Although the former is still widely used, a number of data in literature clearly show that metformin exerts an effective normoglycemic action with no risk of lactic acidosis in the patients, as it can occur in some cases when using phenformin. Therefore, it is generally accepted that metformin is the preferred biguanide in the therapy of diabetes of type II.

The Applicant found, during clinical experiments, that the sulfonylurea maximum daily dose considered optimum for the most severe, barely controllable cases is 15 mg. However, such a dose has to be combined with a biguanide maximum daily dose of 1500 mg in order to obtain the maximum therapeutical effect together with the reduction of untoward effects.

At present 4 combinations are marketed which use a combination of metformin with glibenclamide (Table 1). In the first combination, glibenclamide dose is 2.5 mg and metformin (expressed as the hydrochloride) dose is 500 mg for each tablet, namely a weight ratio of 1:200. In the other combinations, doses are respectively: 2.5

4

mg of glibenclamide and 400 mg of metformin, namely a weight ratio of 1:160.

TABLE I

Ready-to-use preparations of sulfonylurea (S) -
5 Metformin (M) available at present:

	Name	Manufacturer	S (dose/cp)	M (dose/cp)

10	Glucomide	Lipha	Glibenclamide	Metformin
			(2.5 mg)	(500 mg)
	Glibomet	Guidotti	Glibenclamide	Metformin
			(2.5 mg)	(400 mg)
	Suguan M	Hoechst	Glibenclamide	Metformin
			(2.5 mg)	(400 mg)
15	Bi-Euglucon M	Boehringer M	Glibenclamide	Metformin
			(2.5 mg)	(400 mg)

It should be noted, however, that none of these formulations attain the optimum therapeutical effect due
20 to the quantitative unbalance of the medicaments in combination. In fact, using the above mentioned formulations, in order to obtain the sulfonylurea maximum dose of 15 mg, which we consider optimum for the most severe, barely controllable cases, 6 tablets of the
25 medicament should be taken, thus receiving 2400-3000 mg of metformin, which is a dose markedly higher than the maximum one we recommend (1500 mg).

Therefore, the still unsolved problem is to find a combination capable of obtaining the maximum increase in
30 the therapeutical effect with balanced doses of the single medicaments, thereby decreasing in parallel their

untoward effects.

Such a research is of paramount importance, taking into account that in diabetes of type II it is often necessary to progressively increase with time the hypoglycemic medicament doses.

The present invention solves the problem to provide medicament effective for the treatment of diabetes mellitus of type II in cases of secondary failure to a combination of glibenclamide-metformin currently used in therapy.

Abstract of the invention

Now it has been found that a combination of glibenclamide and metformin (expressed as the hydrochloride) in a 1:100 weight ratio, so as to allow a daily administration of 15 mg of glibenclamide and 1500 mg of metformin, is suitable to the preparation of a medicament useful for the treatment of diabetes mellitus of type II at any time of the progression of the disease, from its onset to the most severe cases.

Therefore, it is an object of the present invention the use of the above mentioned combination in admixture with conventional carriers and excipients for the preparation of a medicament for the treatment of diabetes mellitus of type II, particularly in the cases of "secondary failure" to a combination of glibenclamide-metformin currently used in therapy.

Detailed disclosure of the invention

According to a first preferred embodiment of the present invention, the combination of the two active ingredients is used in a medicament in the form of tablets with a dosage of 5 mg of glibenclamide and 500

mg of metformin. This medicament is useful for the treatment of diabetes mellitus of type II.

The balance of said doses makes the therapeutical effect optimum at any time of the progression of the disease, starting from minor cases to the most severe ones, and particularly, when it is necessary to increase progressively with time the doses of the two substances.

On the contrary, when combination ratios different from those of the present invention are used, the following cases are likely to occur:

- when the ratios are lower than the recommended ones, the number of metabolically controlled diabetic patients will definitely be lower;
- when the recommended doses are exceeded, there will be an actual risk of untoward effects.

Therefore, the target area of the patients responding to the therapy will increase and at the same time the onset of therapeutical risks will be highly decreased only when the two medicaments are administered in combination at the doses present in the tablet, or at multiple and submultiple doses of the same.

Moreover, it has been proved that a dose increase beyond the maximum limits herein recommended of 15 mg of glibenclamide and 1500 mg of metformin daily causes a further favourable therapeutical effects.

Finally, it should be stressed that the above mentioned doses can theoretically be attained also using the two medicaments separately. However, this involves the need of taking twice as many tablets a day, with clear compliance problems, especially in the elderly patients which require concomitant therapies for other

pathologies which are frequently connected with diabetes, such as hypertension and vascular diseases.

Said combination of dosages can be used starting from the onset of the disease in NID diabetics since the
5 ratio of 5 mg of glibenclamide + 500 mg of metformin will always be balanced, in both the multiple and submultiple dosages. In fact, when the tablets are subdivided, thus obtaining minor and/or fractional daily dosages, the fixed ratio, which is the balanced one, is
10 always maintained. Therefore, according to a second embodiment of the present invention, the medicament is in the form of a divisible tablet containing the combination described above.

Alternatively, tablets containing fractions of the
15 preferred dosage can be prepared, always keeping the 1:100 ratio between the two active principles.

Analogously, in the most severe cases of diabetes with metabolic decompensation, which cannot be controlled with the commercially available combination
20 medicaments, (so that the patients should turn to insulin therapy), the combination of the invention allows to treat them, still and for a long time, with the oral therapy, with obvious benefits for the patients themselves.

25 In confirmation of what stated above, the study profile and the results of the experimentation carried out are reported in the following.

Study profile

Sample size

30 About 100 diabetics of type II (non insulin-dependent) have been studied. The sample was calculated

so that a clinically significant average reduction of the values of glycated hemoglobin A1c equal to or higher than 0.6% and an average reduction of glycemia equal to or higher than 18 mg/dl in the 16 weeks of treatment could be detected. The standard deviations envisaged for HbA1c and for fasting glycemia are 1.46% and 44 mg/dl. The analysis makes use of a significance level of 0.05 and a test power of 0.80 (two-tail test).

Description of the studied panel

98 Patients with diabetes mellitus of type II (non insulin-dependent) were studied. The average age of the subjects was 57.3 ± 6.6 years.

The panel consisted of 45 males (46%) and 53 females (54%) of superimposable age.

Starting metabolic profile

The fasting glycemia measured at examination 1 was 219 ± 37 mg/dl (95% confidence limits: 211-226 mg/dl; 10-90th percentile: 184-272 mg/dl), 24 hour glycosuria 25 ± 36 g (95% confidence limits: 18-33 g; 10-90 percentile 7-64 g), no acetonuria in all of the patients, glycated hemoglobin A1c $9.1 \pm 0.9\%$ (95% confidence limits 8.9-9.2%; 10-90th percentile: 8-10.1%).

25

30

TABLE A

Metabolic profile of the subjects studied in each centre.

5	Centre	1	2	3	4	ANOVA
						Oneway p=
	N	9	31	38	20	
	Fasting					
10	glycemia (mg/dl)	219±41	211±33	221±42	226±29	ns
	24 hour					
	glycosuria (g/24 hours)	11±14*	25±15	37±54	* *	0.026
15	Acetonuria	0	0	0	0	--
	Glycated					
	hemoglobin A1c (%)	8.8±1,1	9.1±0.7	8.8±1,0	9.6±0.4*	0.002
20	* p < 0.05 Centre 1 vs Centre 3					
	** At the Centre 4, glycosuria was doses with a semiquantitative procedure					
	* p < 0.05 Centre 4 vs Centres 1, 2. 3					
	<u>Evaluation of the efficacy of the treatment</u>					
25	The parameters the evaluation of the efficacy of the treatment is based on are:					
	1.	fasting glycemia;				
	2.	post-prandial glycemia;				
	3.	24 hour glycosuria;				
30	4.	presence of acetone in the urines;				
	5.	glycated hemoglobin (HbA1c).				

10

Other important parameters evaluated during the study are:

1. body weight
2. total cholesterol plasma levels;
- 5 3. HDL cholesterol plasma levels;
4. LDL cholesterol plasma levels;
5. arterial pressure values.

Fasting glycemia

The average values of the fasting glycemia
10 evidenced during the study are reported in Table B.

TABLE B[illegible]

12

* $p < 0.001$ vs Examination 1 and Examination 2

§ $p < 0.001$ vs Examination 1. $p < 0.01$ vs Examination 2

$p < 0.05$ vs Examination 1

5 § $p < 0.01$ vs Examination 2

In the whole panel, the fasting glycemia underwent a significant reduction already after two weeks of treatment ($p < 0.001$); said reduction was maintained subsequently during all the study (16 weeks). Similar results were obtained from the analysis carried out at the single Centres (Centres 2-4). Only in Centre 1, no reduction in glycemia was detected, partly probably due to the small number (n. 9) of the studied subjects (Table B).

15 Table C reports the results of the glycemia course in subjects stratified as a function of the Body Mass Index (BMI; normal weight: $BMI < 25 \text{ kg/m}^2$. $n = 21$; overweight $BMI 25-30 \text{ kg/m}^2$. $n = 52$; obesities $BMI \geq 30 \text{ kg/m}^2$. $n = 259$).

TABLE C

Fasting glycemia changes during the study
The subjects were stratified depending on BMI (Body Mass Index)

Examinations	1	2	2b	3	4	5	6	Variance
Weeks	-3	0	2	4	8	12	16	for analysis repeated measurements p <
BMI	1 Factor analysis							
< 25 kg/m ²	214	212	180*	167*	173*	175*	168*	0 0001
25-30 kg/m ²	220	223	192*	196*	194*	186*	182*	0 0001
≥ 30 kg/m ²	227	247	208§	208§	207§	196§	205§	0 035
Anova	ns	ns	ns	0 02	ns	ns		
Oneway (p <)	2 Factor analysis							
among groups	0 0001							
among examinations	0 0001							

13

46

14

* $p < 0.001$ vs Examination 1 and Examination 2

§ $p < 0.05$ vs Examination 2

The effects of the treatment are clear (variance analysis for repeated measurements, $p < 0.0001$) in the subjects with normal body weight and in the overweight subjects (BMI 25-30 kg/m²), which are less sensitive, but still statistically significant ($p < 0.035$ in the obese subgroup (BMI > 30 kg/m²)).

Post-prandial glycemia

The mean values of the fasting glycemia evidenced during the study are reported in Table D. The post-prandial glycemia, measured at the beginning and at the end of the study, underwent a significant reduction both in the whole panel (318 to 267/mg/dl) and in each of the subgroups defined depending on the Body Mass Index.

15

TABLE D

Post-prandial glycemia: changes during the study.

In the second part of the table the subjects were stratified depending on the BMI (Body Mass Index).

5	-----			
	Examinations	2	6	Student's t test for coupled data weeks (p <)
		0	16	

10	Whole	318	267	0.0001
	Panel:	(64)	(79)	

	BMI:			Variance analysis for measurements (1 factor)
15	<25 kg/m ²	317	252	0.0001
	25-30 kg/m ²	320	263	0.0001
	≥30 kg/m ²	313	287	0.001
	Anova	ns	ns	
	Oneway (p <)			
20				2 Factor analysis
	among groups			ns
	among examinations			0.0001

Adverse events

- 25 The untoward effects were infrequent and slight; in practice, only gastro-intestinal untoward effects such as nausea, abdomen pains and diarrhoea, more or less combined together, occurred.

Conclusions about the therapeutical efficacy

- 30 In the clinical study carried out, the proposed combination (glibenclamide 5 mg - metformin 500 mg) was

administered for 16 weeks to patients with diabetes of type II, in which the combined treatment with glibenclamide-metformin at the presently available dosages gave no longer an acceptable metabolic control.

5 The main result from the evaluation of the efficacy consists in the significant decrease in the fasting glycemia (-35 mg/dl), in the glycemia 2 hours after meals (-51 mg/dl) and in the HbA1c (-0.9%).

10 These results are of particular value when considering that:

1. Whereas the patients with a more severe diabetic condition (so as to be necessary the use of high dosages of glibenclamide and metformin), actually were no longer responsive to the sulfonylurea-metformin combinations commercially available and as a consequence it was necessary to start the subsequent therapeutical option, i.e. the addition of insulin to the oral therapy or the complete substitution of the latter with insulin itself.

15 These cases were treated successfully and the obtained results prove that the combination glibenclamide 5 mg + metformin 500 mg is an important therapeutical tool, which allows to obtain an effective control of glycid metabolism still making use of the only hypoglycemizing oral therapy, thus obtaining a further favourable effect on life-quality of the patients themselves.

20 2. On the contrary, for the less severe cases, the ratio 5 mg of glibenclamide + 500 mg of metformin, can be subdivided as desired, thereby having lower and/or fractional daily dosages thus allowing to

25 30

17

treat the disease from its onset, as the glibenclamide to metformin ratio, even when fractioned, will turn out to be very well balanced.

As far as the industrial applicability aspects are concerned, the medicaments according to the invention are provided in the form of pharmaceutical composition, which can be prepared according to conventional techniques known to those skilled in the art, for example as described in Remington's Pharmaceutical Sciences Handbook, Mack. Pub., N.Y., U.S.A.

Among the pharmaceutical compositions intended for the treatment of diabetes mellitus of type II, those which are administered orally are preferred, such as coated or non-coated tablets, capsules, sugar-coated pills, granulates, oral suspensions, microgranules, controlled-release tablets.

Metformin is used preferably in the form of metformin hydrochloride salt. Of course, it is also possible to use equivalent amounts of other phosphate, solfite, dithionate, acetate, benzoate, citrate salts and the like, optionally together with suitable buffers.

On the contrary, glibenclamide is an insoluble substance.

Since said compound has to be administered in comparatively high dosages (5 mg of Glibenclamide + 500 mg of Metformin HCl) and for long times in order to obtain a complete action, the oral route was considered the simplest administration method.

In the galenic study carried out to accomplish the most suitable pharmaceutical form, the following objectives were taken into account:

18

- ready contact of the active ingredient in the dispersed state with gastroenteral mucosae
- easiness of swallowing
- posology flexibility
- 5 - optimization of the technological characteristics of the granulate for the working up with fast devices
- choice of the material suitable for the preservation of the product
- 10 - manufacturing process easy to carry out and economical.

Considering the high unitary dosage required, the pharmaceutical formulation in lozenge-shaped tablets, with a central breaking division, has been chosen since
15 it is considered the most suitable one. Such a tablet can have the composition as shown in Example 1.

In fact this allows, with comparatively limited sizes, to carry suitably the active ingredient, so as to combine a favourable working-up with optimum bio-
20 pharmaceutical and technical characteristics besides an improved swallowability.

The tablets were subjected to wet-granulation; the excipients reported hereinbelow were selected, after a number of laboratory tests in order to find the amount
25 of each excipient to attain the best workability together with biopharmaceutical and technological characteristics of the tablets:

- maize starch: diluent and disintegrant;
- precipitated silica: it promotes the cohesion of
30 the granulates improving their flowability;
- microcristalline cellulose (Avicel PH 101): a

diluent, which favours the formation of compact granules and therefore of more resistant tablets contributing at the same time to disaggregation of the pharmaceutical form, promoting the penetration of liquid inside it by capillarity;

- gelatin: a binder used in solution to wet the granular mixture;
- glycerin: it is used in the gelatin solution to promote wetting and as a plasticizer;
- talc: a lubricant;
- magnesium stearate: a solid lubricant which is effective in amounts which do not significantly affect the disaggregation time of the tablets.

In order to improve handling and swallowing, a coating was moreover applied onto the tablets, which consists of a methylhydroxypropyl cellulose film as a film-forming agent, titanium dioxide as an opacifier and polyethylene glycol 400 as a plasticizer. The compatibility among the active ingredient and the selected excipients was ascertained by preliminary accelerated stability studies.

Finally, for the choice of the container, the physico-chemical characteristics of the active ingredient and of the tablet were considered in order to guarantee a safe preservation; the medicament of the invention showed a very good stability in an opaque blister consisting of PVC/PVDC and aluminium.

The manufacturing process was carried out by wet granulation both by means of kneading in a fast granulator and drying in air-circulation drier, and in fluidized bed granulator-drier. In both cases, tablets

20

with the desired characteristics were obtained.

The following examples further illustrate the invention.

EXAMPLE 1

5 **A coated tablet contains:**

	Glibenclamide	mg	5.00
	Metformin hydrochloride	mg	500.00
	Maize starch	mg	57.50
	Precipitate silica	mg	20.00
10	Microcrystalline cellulose	mg	65.00
	Gelatin	mg	40.00
	Glycerin	mg	17.50
	Talc	mg	17.50
	Magnesium stearate	mg	7.50
15	Methylhydroxypropylcellulose	mg	12.50
	Titanium dioxide	mg	6.25
	Polyethylene glycol 400	mg	1.25
	Unitary theor. average weight	mg	750.0

EXAMPLE 2

20 **Granulate sachets:**

	Glibenclamide:	mg	5.00
	Metformin hydrochloride	mg	500.00
	Polyvinylpyrrolidone	mg	22.00
	Saccharose	mg	1000.00
25	Mannitol	mg	821.00
	Sodium saccharinate	mg	10.00
	Orange flavour	mg	37.00
	Lemon flavour	mg	10.00
	Unitary theor. average weight	mg	2405.00

30

21

EXAMPLE 3Suspension:

	Glibenclamide	g	10.100
	Metformin hydrochloride	g	0.047
5	Sodium carboxymethylcellulose	g	0.079
	Microcrystalline cellulose	g	0.300
	Wild black cherry essence	g	0.089
	Anise essence	g	0.050
	Glycerol	g	10.000
10	Methyl p-hydroxybenzoate	g	0.050
	Saccharose	g	77.470
	Depurated water q.s. to	ml	100

CLAIMS

1. The use of a combination of glibenclamide-metformin hydrochloride in a 1:100 weight ratio for the preparation of a single-dose medicament useful for the treatment of diabetes mellitus of type II in cases of secondary failure to a combination of glibenclamide-metformin hydrochloride in a weight ratio higher than 1:100.
2. The use of a combination of glibenclamide-metformin hydrochloride in a 1:100 weight ratio for the preparation of a single-dose medicament useful for the treatment of diabetes mellitus of type II in cases of secondary failure to a combination of glibenclamide-metformin hydrochloride in a weight ratio of 1:160 or 1:200.
3. The use according to claim 1 or claim 2, characterized in that the medicament is suitable to the administration of a daily dosage of up to 15 mg of glibenclamide and 1500 mg of metformin.
4. The use according to claim 1 or 2, characterized in that, in the medicament, the unitary dose contains 5 mg of glibenclamide and 500 mg of metformin.
5. The use according to claim 4, wherein the medicament is in the form of a tablet.
6. The use according to claim 5, wherein the medicament is in the form of divisible tablet.
7. The use according to claims 1 or 2 and any one of claims 3-7, characterized in that in the medicament metformin hydrochloride is replaced with an equivalent amount of another pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/04860

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K31/64 //(A61K31/64,31:155)		
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 6 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)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to class No.
X	BIOSCI REP, 9 (3). 1989. 347-350., XP000570541 AL-AHMED F A A ET AL: "INTERACTION BETWEEN DIAZEPAM AND ORAL ANTIDIABETIC AGENTS ON SERUM GLUCOSE INSULIN AND CHROMIUM LEVELS IN RATS" see abstract	1-9
X	DIABETE METABOL., 1991, 17/1 BIS (232-234), FRANCE, XP000570538 VIGNERI R. ET AL: "Treatment of NIDDM patients with secondary failure to glyburide: comparison of the addition of either metformin or bed-time NPH insulin to glyburide" cited in the application see page 233, column 1, paragraph 3	1-9
☐ 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 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "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 18 February 1997		Date of mailing of the international search report 28.02.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer Leherte, C

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(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

(43) International Publication Date
8 November 2001 (08.11.2001)

PCT

(10) International Publication Number
WO 01/82875 A2

(51) International Patent Classification⁷: A61K
(21) International Application Number: PCT/US01/00044
(22) International Filing Date: 2 January 2001 (02.01.2001)
(25) Filing Language: English
(26) Publication Language: English

(74) Agent: ROSENSTOCK, Jerome; Frommer Lawrence & Haug LLP, 745 Fifth Avenue, New York, NY 10151 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(30) Priority Data:
60/201,057 1 May 2000 (01.05.2000) US
09/702,263 31 October 2000 (31.10.2000) US

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant: AEROPHARM TECHNOLOGY, INC.
[US/US]: 18 Mayfield Avenue, Campus Plaza 9, Raritan Center, Edison, NJ 08837 (US).

Published:
— *without international search report and to be republished upon receipt of that report*

(72) Inventors: CUTIE, Anthony, J.; 10 Tillman Court, Bridgewater, NJ 08807 (US). ADJEI, Akwete, L.; 15 Tillman Court, Bridgewater, NJ 08807 (US). SEXTON, Frederick, A.; 161 Kempt Avenue, Fair Haven, NJ 07704 (US).

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.



WO 01/82875 A2

(54) Title: A CORE FORMULATION

(57) Abstract: This invention relates to a combination drug product comprising proglitazone hydrochloride and a biguanide, e.g. metformin. In particular, the product comprises a core of the biguanide, e.g. metformin, at least a portion thereof has a layer or coat thereon of proglitazone.

A CORE FORMULATION

This application claims priority from U.S. provisional application Serial No. 60/201,057 filed May 1, 2000, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a core formulation, and, more particularly, to a core formulation comprising a first layer comprising pioglitazone, which covers at least a portion of a core comprising the biguanide, metformin (i.e., glucophage).

Description of the Related Art

Metformin and pioglitazone, or their salts such as the hydrochlorides, malcates, tartrates, etc., are two active ingredients of anti-diabetic drugs that are used to treat diabetic patients, e.g. human beings. These two active agents are administered orally to patients in need thereof in protocols calling for the single administration of either ingredient. Heretofore, there has not been revealed or hinted at combining both ingredients and certainly not a physically combined core formulation comprising both ingredients. The use of such a core formulation is advantageous to patients and prescribers because both medicaments are synergistic to each other in the body when used in the management of blood glucose control, i.e., diabetes.

SUMMARY OF THE INVENTION

This invention relates to a core formulation, and, more particularly, to a core formulation comprising a first layer comprising pioglitazone hydrochloride, which covers at least a portion of a core comprising a biguanide. A typical biguanide is metformin. It typically is used clinically as a pharmaceutically acceptable salt, preferably the hydrochloride salt. A commercial form of metformin hydrochloride is available as glucophage. Its chemical name is N,N-dimethylimidodicarbonimidic diamide hydrochloride. Metformin hydrochloride is a hydrochloride salt of metformin base, and as used herein, "metformin" means the base compound as well as its pharmaceutically acceptable salts. Metformin is used clinically to manage non-insulin dependent diabetes mellitus or "NIDDM", particularly in patients who are not effectively treated with a sulfonylurea. While it is not chemically related to the sulfonylureas, it is routinely utilized in combination with a sulfonylurea, and has been shown to be synergistic in some cases. Other

biguanides such as phenformin, buformin etc. can also be used. Additionally, in the treatment of a diabetic patient the metformin, for example, and the pioglitazone hydrochloride are present in effective amounts to provide such treatment.

DETAILED DESCRIPTION OF THE INVENTION

5 Metformin is an active ingredient for a commercially available drug employed to treat diabetes mellitus in a host or mammal, e.g. a human being, another animal. The typical daily effective dose for the oral treatment of a mammal, i.e., a human, ranges from 500 mg to 2550 mg. Typically, the dose is a single dose of 500 mg to 850 mg.

10 Pioglitazone hydrochloride, (ACTOS®), is an active ingredient for a commercially available drug employed to treat diabetes mellitus in a host, e.g. a human being. The typical daily effective dose for the oral administration to a mammal, e.g. a human being, ranges from 15 mg to 45 mg, given as a single dose.

 Heretofore, the metformin and pioglitazone hydrochloride have not
15 been administered together to try to improve the effectiveness of either drug, although co-administration of the two has been proposed [*Whitcomb; et al., United States Patent No. 6,011,049*]. However, a combined form of the drugs, i.e. a single integral unit thereof has not heretofore been reported. The present invention provides such a single integral unit in the form of a core formulation.

20 As indicated above, the relative concentrations of each drug is such that a first layer comprising metformin is prepared. The first layer covers at least a portion of a core comprising metformin. Depending upon the rate of administration and metabolism of the patient destined to be treated, and the concentrations of each ingredient desired for each drug, the first layer may cover only a portion of the core
25 or encompass the entire core. For example, one quarter of the core to about three fourths of the tablet core. The first layer should comprise pioglitazone hydrochloride because its dose requirement is lower compared to metformin. Additionally, it is slightly non-polar, its solubility rate slower, and its absorption rate thus dependent on its dissolution rate in the contents of the gastrointestinal tract
30 compared with metformin.

 It is to be understood, depending upon the rate of administration to the patient desired, either the first layer or the core may contain a mixture of the two active ingredients or both the first layer and the core may contain the two active

ingredients with different and varying concentrations of one or both active ingredients.

The first layer of the core comprises pioglitazone hydrochloride in an amount of 0.01 % to 20% of the total weight of the core formulation, whereas, the metformin in the core is present in an amount of 10% to 97.5% of the total weight of the core formulation.

Where combinations of the two active ingredients are present in the first layer and/or the core, the amounts of pioglitazone hydrochloride ranges from 1 mg to 45 mg whereas the metformin ranges from 100 mg to 2550 mg.

Finally, it is to be understood that a third pharmacologically active material, e.g. a drug, such as for example sulfonylureas, α -glucosidase inhibitors, meglitinides, and ACE inhibitors may be employed in an admixture with the active ingredients in the first layer and/or the core.

The α -glucosidase inhibitors [Jean-Bernard Ducep et al., US Patent No. 5,504,078], bisglucosylmoranoline derivatives [UK Patent No. GB 2 088 365 A], and glucosylmoranoline derivatives [European Patent No. 87112480.6] include the following medicaments: 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[6,7-dideoxy-7-D-glucoheptopyranosyl]imino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(1-deoxy-D-fructofuranosyl)imino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-4-D-glucopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[6-deoxy-1-(6-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[6,7-dideoxy-1-(6-O-D-glucopyranosyl)-7-.alpha.-D-glucoheptopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-4-D-glucopyranosyl)methylimino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(4-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-{[2(1-D-arabinofuranose)ethyl]imino}-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(6-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-{[4-deoxy-1-(4-O-D-glucopyranosyl)-4-.alpha.-D-glucopyranosyl]methyl}-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-{[4-deoxy-1-(6-O-D-

- glucopyranosyl)-4-.alpha.-D -glucopyranosyl)methyl}-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(6-deoxy-1-O-methyl-6-β-D-glucopyranosyl)-imino-D -glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(6,7-dideoxy-1-O-methyl-7-β-D-glucoheptopyranosyl) imino]-D-glucitol; 1.5-
- 5 Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(1-deoxy-2-O-methyl-β-D-fructofuranosyl)imino]-D-glucitol,
- 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-1-O-methyl-4-β-D-glucopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[6-deoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-.alpha.-D -glucopyranosyl]-1,5-
- 10 imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[6,7-dideoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-7-.alpha.-D-glucoheptopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-1-O-methyl-4-β-D-glucopyranosyl)methylimino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-
- 15 glucopyranosyl)-N-[4-deoxy-1-(1-O-methyl-4-O-8-D-glucopyranosyl)-.alpha.-D -glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[[2-(1-O-methyl-1-β-D-arabinofuranosyl)ethyl]imino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(1-O-methyl-6-O-β-D-
- 20 glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[[4-deoxy-1-(1-O-methyl-4-O-β-D-glucopyranosyl)-4-.alpha.-D-glucopyranosyl)methyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[6,7-dideoxy-7-D-
- 25 glucoheptopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(1-deoxy-D-fructofuranosyl)imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-4-D-glucopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[6-deoxy-1-(6-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-
- 30 O(.alpha.,D-glucopyranosyl)-N-[6,7-dideoxy-1-(6-O-D-glucopyranosyl)-7-.alpha.-D-glucoheptopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-4-D-glucopyranosyl)methylimino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(4-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-

glucopyranosyl)-1,5-{{2(1-D-arabinofuranose)ethyl}imino}-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(6-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-{{4-deoxy-1-(4-O-D-glucopyranosyl)-4-.alpha.-D-glucopyranosyl}methyl}-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-{{4-deoxy-1-(6-O-D-glucopyranosyl)-4-.alpha.-D-glucopyranosyl}methyl}-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(6-deoxy-1-O-methyl-6-β-D-glucopyranosyl)-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(6,7-dideoxy-1-O-methyl-7-β-D-glucoheptopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(1-deoxy-2-O-methyl-β-D-fructofuranosyl)imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-1-O-methyl-4-β-D-glucopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[6-deoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[6,7-dideoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-7-.alpha.-D-glucoheptopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-1-O-methyl-4-β-D-glucopyranosyl)methylimino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(1-O-methyl-4-O-β-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-{{2-(1-O-methyl-1-β-D-arabinofuranosyl)ethyl}imino}-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[(4-deoxy-1-(1-O-methyl-4-O-β-D-glucopyranosyl)-4-.alpha.-D-glucopyranosyl)methyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[(4-deoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-4-.alpha.-D-glucopyranosyl)methyl]-1,5-imino-D-glucitol.

The list of medicaments includes acid addition salt forms with such inorganic acids such as, for example, hydrochloric, hydrobromic, sulfuric, phosphoric and like acids: with organic carboxylic acids such as, for example, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, maleic, tartaric, citric, ascorbic, maleic, hydroxymaleic and dihydroxymaleic, benzoic, 2-

acetoxybenzoic, mandelic and like acids; and with organic sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acid.

The sulfonylureas are a class of compounds that have been widely employed to treat diabetes. Such compounds are well known, for example as described in U.S. Pat. Nos. 3,454,635; 3,669,966; 2,968,158; 3,501,495; 3,708,486; 3,668,215; 3,654,357; and 3,097,242. Especially preferred sulfonylureas to be employed in the combinations of this invention are glyburide, glipizide, tolbutamide, tolazamide, glisoxepid, chlorpropamide, glibornuride, gliclazide, glimepiride, phenbutamide, and tolcyclamide. Other medicaments, such as, for example an antibiotic, a vitamin, a drug that works on the heart, or in the liver, may be admixed with the active ingredients in the first layer and/or the core.

The resultant core having the first layer thereon is prepared by any conventional means known in the pharmaceutical art, e.g. compression, tableting technology, spraying technology, or encapsulation in a pharmaceutically acceptable presentation, such as a gelatin capsule. In particular, typically the core formulation of the present invention is preferably fabricated by compression into a tablet.

The resultant core formulation of the present invention is useful to treat diabetes mellitus. Surprisingly the resultant core formulation of the invention is as user friendly and clinically effective as compared to the administration of metformin alone or pioglitazone hydrochloride as demonstrated by co-administration of the two agents [*Whitcomb; et al., United States Patent No. 6,011,049*], where in general, the incidence of adverse events was not influenced by age or menopausal status, and further, patients treated with the combination therapy attained better glycemic control than with either monotherapy.

It is to be understood, however, that for any particular subject being treated, e.g., a mammal, specific dosage regimens should be adjusted according to the individual need. It is further to be understood that the dosages set forth herein are exemplary only and that they do not, to any extent limit the scope of the practice of the present invention.

The core formulation of the present invention may be administered orally, for example, with inert diluent or with an edible carrier. For the purpose of oral therapeutic administration, the core formulation may have excipients incorporated therein. The subject core formulation may also contain the following

adjuvants: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel®, corn starch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring.

The subject core formulation of the invention may contain other various materials which modify the physical form of the dosage unit (the subject core formulation), for example, as coatings. Thus, the subject core formulation of the present invention may be coated with sugar, shellac or other enteric coating agents. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

In an alternative embodiment of the present invention. The resultant core formulation (having a first layer completely or partially covering the core), is treated whereby an outer shell, at least a portion of which comprises a biodegradable material having a predetermined rate of degradation or metabolism in the host being treated, is formed which encloses the particles of the first layer and/or the core.

The biodegradable material is a high molecular weight compound, which is physiologically acceptable and decomposes in the body of the human being or other animal and is absorbed.

The biodegradable material, comprising the outer shell, having a predetermined rate of degradation or metabolism or break down, is selected from those materials well known in the art, which do not react with metformin and/or pioglitazone hydrochloride. Such materials include, biodegradable polymers, such as polyorthoesters, polyanhydrides, polyamides based on glutamic acid, polyalkyl cyanoacrylates, polyesters of lactic and glycolic acid, polylactide polymers, cellulosic polymers, polyvinyl acetate, polyvinyl alcohol, polyvinylchloride, natural and synthetic rubbers, polyacrylates, polystyrene, etc. Additionally, reference is made to U.S. Patents Nos. 4,166,800, and 4,389,330. which disclose additional shell forming materials and are incorporated hereinto by reference in their entirety.

The shell encapsulating the particles of pioglitazone hydrochloride of the first layer and/or the particles of metformin of the core is obtained by any conventional microencapsulation process whereby microspheres of metformin

and/or pioglitazone hydrochloride are formed, e.g. a solvent removal process, a phase separation technique, coacervation etc. In this regard reference is made to U.S. Patents Nos. 4,166,800 and 4,389,330, Conte et al, *J. Controlled Release*, vol. 26, (1993), pages 39-47; and U.S. Patent No. 4,839,177; all of which are

5 incorporated hereinto by reference in their entirety.

In a variation of the above alternative embodiment, the resultant core formulation is treated whereby only the top surface area of the first layer comprising metformin has a shell coating thereon. In this regard, reference is made to U.S. Patent No. 5,916,584, incorporated hereinto by reference in its entirety, which

10 describes the process for forming such a shell. The resulting core formulation having the first layer encapsulated by the shell comprising the shell material, is one which provides a delay time prior to release of the active ingredients, i.e. pioglitazone hydrochloride and metformin, to the patient being treated for diabetes mellitus.

15 It is to be understood that for either metformin or pioglitazone, any pharmaceutically acceptable form thereof can be employed. Such a form encompasses the free acids, free bases, salts and various hydrate forms, including semi-hydrate forms of these medicaments, as well as other pharmaceutical materials which are used in the formulation process as acceptable excipient materials

20 generally known to those skilled in the art.

It is understood that any one of the biguanides, i.e. drugs having the action of the stimulation of anaerobic glycolysis, is covered by this invention as these, like metformin, increase the sensitivity to insulin in peripheral tissues of the host, e.g. a human being or another animal. These compounds also are involved in the inhibition

25 of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of other typical biguanides included in this application are phenformin, buformin etc.

We claim:

1. A core formulation comprising,
 - (a) a first layer comprising pioglitazone hydrochloride or a pharmaceutically acceptable salt thereof as active ingredient,
 - 5 (b) a core, at least a portion of which is enclosed by said first layer, comprising a biguanide as active ingredient.
2. The formulation as defined in claim 1 wherein said biguanide is metformin.
3. The formulation as defined in claim 2 wherein said
10 pioglitazone hydrochloride is present in an amount ranging from 1 mg to 45 mg and, said metformin is present in an amount ranging from 10 mg to 4000 mg.
4. The formulation as defined in claim 2 which further comprises a biodegradable shell having a predetermined rate of degradation covering at least a portion of said first layer to provide a predetermined delay in the
15 time period of release of at least said pioglitazone hydrochloride.
5. The formulation as defined in claim 2, wherein said pioglitazone hydrochloride and/or said metformin are present as biodegradable microspheres having a biodegradable shell coating and where said shell coating has a predetermined rate of degradation.
- 20 6. A method of administering pioglitazone hydrochloride and metformin to a mammal, which comprises treating the mammal with the formulation defined in claim 2.
7. A method for producing a controlled release formulation, which comprises:
25 (a) producing a hollow outer shell comprising a biodegradable material having a predetermined rate of degradation to provide a predetermined delay in the time period of release of the contents destined to be enclosed by said shell;
- (b) inserting a core comprising metformin and having an outer
30 layer comprising pioglitazone hydrochloride partially enclosing said core, into said hollow outer shell; and
- (c) sealing said core within said hollow outer shell.

8. A method of producing a combined formulation of pioglitazone hydrochloride and metformin, which comprises:

- (a) forming a core of the metformin; and
- (b) depositing a layer of pioglitazone hydrochloride on at least a
5 portion of a surface of said core.

9. A method of treating diabetes mellitus in a patient in need thereof, which comprises administering to the patient the formulation of claim 1 wherein said active ingredients are each present in an effective amount.

10. A pharmaceutical composition comprising an effective
10 amount of pioglitazone hydrochloride combined with an effective amount of metformin.

11. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 10.

12. A pharmaceutical composition comprising an effective
15 amount of pioglitazone hydrochloride combined with an effective amount of phenformin.

13. A pharmaceutical composition comprising an effective amount of pioglitazone hydrochloride combined with an effective amount of buformin.

20 14. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 12.

15. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 13.

25 16. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 1 wherein the biguanide is phenformin.

17. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 1 wherein the biguanide is buformin.

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
18 July 2002 (18.07.2002)

PCT

(10) International Publication Number
WO 02/055009 A1(51) International Patent Classification⁷: A61J 3/07,
A61K 9/22

(21) International Application Number: PCT/IN02/00005

(22) International Filing Date: 11 January 2002 (11.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

37/MUM/2001	12 January 2001 (12.01.2001)	IN
323/MUM/2001	10 April 2001 (10.04.2001)	IN
324/MUM/2001	10 April 2001 (10.04.2001)	IN
326/MUM/2001	10 April 2001 (10.04.2001)	IN
325/MUM/2001	10 April 2001 (10.04.2001)	IN

(71) Applicant (for all designated States except US): SUN
PHARMACEUTICAL INDUSTRIES LIMITED
[IN/IN]; ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (EAST), 400059 MUMBAI (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SHANGHVI,
Dilip, Shantilal [IN/IN]; SUN PHARMACEUTICAL
INDUSTRIES LIMITED, ACME PLAZA, AND-
HERI-KURLA ROAD, ANDHERI (EAST), 400059
MUMBAI (IN). GANORKAR, Kirti, Wardhaman
[IN/IN]; SUN PHARMACEUTICAL INDUSTRIES
LIMITED, ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (EAST), 400059 MUMBAI (IN). ZALA,
Yashoraj, Rupsinh [IN/IN]; SUN PHARMACEUTICAL
ADVANCED RESEARCH CENTER, BOMBAY COL-
LEGE OF PHARMACY BUILDING, 2ND FLOOR, C.S.T
ROAD, KALINA, SANTACRUZ (EAST), 400098 MUM-
BAI (IN). DHARMADHIKARI, Nitin, Bhalachandra
[IN/IN]; SUN PHARMACEUTICAL ADVANCED
RESEARCH CENTER, BOMBAY COLLEGE OF
PHARMACY BUILDING, 2ND FLOOR, C.S.T ROAD,
KALINA, SANTACRUZ (EAST), 400098 MUMBAI (IN).
KHANNA, Satish, C [CH/CH]; KHANNA PHARMA
CONSULTANTS, SPITZACKERSTRASSE 6, 4103,
BOTTMINGEN, CH-4103 BASLE (CH).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i)) for the fol-
lowing designations AE, AG, AL, AM, AT, AU, AZ, BA, BB,
BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK,
DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,
NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW; ARIPO patent
(GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG)
- as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
ZA, ZW; ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL,
SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG,
KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY,

[Continued on next page]

(54) Title: SPACED DRUG DELIVERY SYSTEM

(57) Abstract: The present invention provides to a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system wherein the time of release of the two or more therapeutically active agents is designed to provide desired control on the disease condition. The present invention also provides a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system at a specified time prior to food intake by the patient. The present invention further provides a spaced drug delivery system that releases two or more antidiabetic agents at different times after oral administration, for the treatment of diabetes mellitus or conditions associated with diabetes mellitus. More particularly, the present invention provides a spaced drug delivery system that immediately releases one or more antidiabetic agents after oral administration of the system, and releases as a pulse one or more antidiabetic agents in a reliable manner at about a predetermined time after oral administration of the system.

WO 02/055009 A1

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.

SPACED DRUG DELIVERY SYSTEM

FIELD OF THE INVENTION

5

The present invention relates to a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system wherein the time of release of the two or more therapeutically active agents is designed to provide desired control on the disease condition

10

The present invention also relates to a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system at a specified time prior to food intake by the patient.

15

The present invention also relates to a spaced drug delivery system that releases two or more antidiabetic agents at different times after oral administration, for the treatment of diabetes mellitus or conditions associated with diabetes mellitus.

20

More particularly, the present invention relates to a spaced drug delivery system that immediately releases one or more antidiabetic agents after oral administration of the system, and releases as a pulse one or more antidiabetic agents in a reliable manner at about a predetermined time after oral administration of the system.

BACKGROUND OF THE INVENTION

25

Patients are often required to take multiple medications for the prophylaxis or treatment of diseases. Often patients are required to take different medications at different specified times. This results in patient inconvenience and consequently patient non-compliance to the prescribed dosage regimen.

30

A combination of two different medications could be taken at specified different times to obtain the desired control on the symptoms of the disease or a measurable indicator of the disease condition. For example, a specific antidiabetic agent may be orally administered at a specific time period prior to food intake to control post-prandial glucose and a second antidiabetic agent

may be more useful in controlling glucose levels when given with food. However, there are no prior art spaced drug delivery systems that enable one to administer medications in a convenient manner. Thus, there is a need for a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system, wherein at
5 least one first therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system and at least one second therapeutically active agent is released as a pulse at a predetermined time after oral administration, wherein the two or more therapeutic agents act on the disease condition by similar or dissimilar, but complementary mechanisms, to control the symptoms of the disease, or a measurable indicator of the disease condition, and
10 further wherein the time of release of the two or more therapeutically active agents is designed to provide desired control on the disease condition.

A combination of two different medications could also be taken at specified different times when one medication is required to be given on an empty stomach and the other with meals. Reasons
15 for giving certain medications on an empty stomach or with meals are well known to those skilled in the art and include for example, different rate or extent of absorption of the drug on an empty stomach versus in presence of food, difference in extent of degradation of the drug in gastric fluids when given with food versus without food, gastric irritation due to the drug and thus, there is a need for a method of administration of two or more therapeutically active agents comprising
20 orally administering to a patient a spaced drug delivery system at a specified time prior to food intake by the patient, wherein at least one therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system and at least one therapeutically active agent is released as a pulse after a delay at about the time when food is taken i.e. either immediately prior to meals, or at the time of meals, or after meals.

25 Maximum reduction in post-prandial blood-glucose can be obtained by administering antidiabetic agents such as glipizide about 30 minutes before meals, and hence, an immediate release of such antidiabetic agents is essential. On the other hand, an antidiabetic agent such as metformin is given with food. A spaced drug delivery system that immediately releases an antidiabetic agent,
30 such as glipizide, after oral administration of the system prior to meals, and releases as a pulse, after a delay, antidiabetic agents such as metformin, at the time the meal is taken, would provide improved patient compliance to the dosage regimen and optimum clinical benefits.

Non-insulin dependent diabetes mellitus (NIDDM), also known as maturity-onset diabetes or diabetes mellitus type 2, is a frequent metabolic disease and the main cause of hyperglycemia. It is a heterogeneous disease with complex, unclarified metabolic aspects. Insulin secretion may appear normal or even excessive, but it is insufficient to compensate for insulin resistance. The disease is characterized by three main abnormalities of metabolism contributing to hyperglycemia. These include the partial or complete decrease in insulin secretion, resistance of the peripheral tissues to insulin and increased hepatic production of glucose in fasting conditions. Insulin resistance may also be responsible for the obesity associated with NIDDM, although obesity itself has a reciprocal effect on insulin resistance; excess weight worsens insulin resistance, while weight loss lowers blood glucose levels. Diet and physical exercise cause a reduction in insulin-resistance and lead to an improvement in the pancreas deficit over a period of time.

The treatment goal of NIDDM is to normalize blood-glucose level in an attempt to prevent or reduce complications that may arise due to chronic hyperglycemia. The effect of regular exercise supplementing diet in patients with NIDDM causes a reduction in insulin-resistance and leads to an improvement in the pancreas deficit over a period of time. When these provisions are not sufficient, a pharmacological agent needs to be taken for control of hyperglycemia. Oral medications work either to reduce the body's resistance to its own insulin, or work to increase insulin secretion to meet the demand. Sulfonylureas and biguanides have been used in oral antidiabetic therapy. Other classes of oral antidiabetic agents include the alpha-glucosidase inhibitors, aldose reductase inhibitors, thiazolidinediones, insulin secretagogues and others. The use of these classes of compounds in monotherapy has been effective in obtaining a glycometabolic control in diabetic patients.

Biguanide derivatives like metformin, phenformin and buformin, generally in the form of their hydrochloride salt, have been used as anti-hyperglycemic agents in the treatment of non-insulin dependent diabetes mellitus. The mechanism of action of the drugs belonging to this class includes reduction in hepatic glucose production, decrease in intestinal absorption of glucose, and increase in glucose uptake and utilization. Biguanides improve glucose tolerance in patients with diabetes mellitus type 2, lowering both basal and post-prandial plasma glucose. With biguanide therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease. Although phenformin is still used widely as an anti-hyperglycemic agent, metformin is the preferred biguanide, as it exerts a better normoglycemic

action with a lower risk of lactic acidosis – a common side-effect with phenformin therapy. Metformin is also known to lower blood triglyceride levels and assist in weight reduction.

- 5 The sulfonyl ureas used in the treatment of diabetes mellitus type 2 include acetohexamide, carbutamide, chlorpropamide, glipizide, glyburide (glibenclamide), glimepiride, gliclazide, glibornuride, gliquidone, glisoxepid, glyhexamide, phenbutamide, tolazamide, tolbutamide, tolcyclamide, etc. These sulfonyl ureas are used as their bases and not as salts. The mechanism of action of these drugs involves lowering of blood glucose concentration mainly by stimulating release of endogenous insulin from beta cells of the pancreas, and thus they act as hypoglycemic agents. The sulfonyl ureas are used as an adjunct to diet for the management of non-insulin dependent diabetes mellitus in patients whose hyperglycemia cannot be controlled by diet alone. To achieve maximum reduction in post-prandial blood-glucose concentration, the sulfonyl urea is administered 30 minutes prior to each meal.
- 15 The 55th edition of the Physicians' Desk Reference, copyright 2001, suggests that the monotherapy with metformin hydrochloride, commercially available under the trade name Glucophage[®] from Bristol-Myers Squibb Co., may be effective in patients who have not responded to sulfonyl ureas or who have only a partial response to sulfonyl ureas or who have ceased to respond to sulfonyl ureas. In such patients, if adequate glycemic control is not attained with Glucophage[®] monotherapy, the combination of Glucophage[®] and a sulfonyl urea may have a synergistic effect. Also, monotherapy with the sulfonyl ureas has been found to give a positive response, which lasts for 4-5 years, but it becomes ineffective in a large number of patients over a period of time. This is referred to as the "secondary failure" associated with the oral therapy with hypoglycemic agents. In both these cases, a combination of biguanides and sulfonyl ureas is used.
- 20 The biguanides are able to act on insulin resistance but cannot stimulate insulin secretion, while the sulfonyl ureas can stimulate insulin release but are unable to act on insulin resistance. A combination therapy of a biguanide and a sulfonyl urea has a synergistic effect on glucose control, since both agents act by different but complementary mechanisms.
- 25 The biguanides are able to act on insulin resistance but cannot stimulate insulin secretion, while the sulfonyl ureas can stimulate insulin release but are unable to act on insulin resistance. A combination therapy of a biguanide and a sulfonyl urea has a synergistic effect on glucose control, since both agents act by different but complementary mechanisms.
- 30 Diabetes mellitus is a chronic disease with diverse pathologic manifestations and is accompanied by lipid metabolism disorders and circulatory disorders, as well as glycometabolism disorders. As a result, the disease tends to progress entailing complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual

drug cannot bring sufficient effects in some disease states and there are various problems such as side effects caused by an increased dose or long-term administration of a single drug or agent. Hence, there is a need to include combination therapy in NIDDM.

- 5 Alpha glucosidases are essential for the breakdown of starches, dextrins, maltose and sucrose. Alpha glucosidase inhibitors act by delaying glucose absorption from a carbohydrate load by inhibiting the glucosidases. The compounds of this class have the ability to prevent or attenuate diabetic nephropathic lesions. The common drugs of this class include acarbose, miglitol, emgilitate and voglibose. Inhibition of alpha glucosidase causes a delay in the digestion of
- 10 sucrose and other polysaccharides, thus retarding the rate of absorption of glucose and fructose. Acarbose is a complex oligosaccharide, which competitively inhibits intestinal brush border alpha glucosidases including glucoamylase, sucrase, maltase and isomaltase. It is the preferred alpha glucosidase inhibitor for use as an antihyperglycemic because it does not cause hypoglycemia. The drug also has weight lowering action. The alpha glucosidase inhibitors may be administered
- 15 along with other oral antidiabetic drugs for a better control on the blood-glucose levels. The 55th edition of the Physicians' Desk Reference, copyright 2001, states that acarbose diminishes the insulinotropic and weight increasing effects of sulfonyl ureas, when administered together.

- The thiazolidinediones is another class of antidiabetic agents which are thought to act by
- 20 enhancing insulin action, thus promoting glucose utilization in the peripheral tissues, possibly by stimulating non-oxidative glucose metabolism in muscle, and suppressing gluconeogenesis in the liver. The drugs belonging to this class stimulate adipogenesis and reduce plasma triglyceride and free fatty acid concentrations. The examples of thiazolidinediones commonly used in diabetes mellitus include troglitazone, pioglitazone, rosiglitazone, ciglitazone, darglitazone and
- 25 englitazone. Although thiazolidinediones enhance insulin action at the cellular level, they do not stimulate insulin release nor do they mimic its action. The therapeutic benefits of thiazolidinedione treatment depend on the availability of adequate amounts of insulin. The addition of a thiazolidinedione antidiabetic agent to concurrent sulfonyl urea treatment provides a balance of stimulated release of insulin while ameliorating insulin resistance.

- 30 A new class of insulinotropic agents (secretagogues) called meglitinide analogs or prandial glucose regulators, is now being used in the management of NIDDM. The compounds of this class are fast acting, short acting, non-sulfonyl urea, oral hypoglycemic agents that act by regulating prandial glucose. The prandial glucose regulation is aimed at restoring the first-phase

insulin response that follows consumption of a meal, which is missing in NIDDM patients. Repaglinide, the most commonly used agent of this class, provides a tighter glycemic control, while reducing the risk of hypoglycemic events. The drug lowers blood-glucose levels by stimulating the secretion of insulin from the pancreas. This action is dependent on the functioning β -cells in the pancreatic islets. Repaglinide closes ATP-dependent potassium channels in the β -cell membrane by binding at characterisable sites. This potassium channel blockade depolarizes the β -cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion-channel mechanism is highly tissue selective, with low affinity for heart and skeletal muscle. Repaglinide is rapidly absorbed and rapidly eliminated, ensuring quick return of post-prandial insulin levels to preprandial levels. Insulin release is glucose dependent and diminishes at low glucose concentrations. Repaglinide also offers increased mealtime flexibility and safety. As a result of the short plasma half-life and lack of accumulation of repaglinide with repeated dosing, the risk of between-meal and nocturnal hypoglycemia is substantially reduced. The drug acts synergistically with biguanides and thiazolidinediones, especially metformin and troglitazone. The dose of repaglinide ranges from 0.5 to 4mg, administered before each meal.

The prior art includes a number of systems that use a combination of antidiabetic agents for the treatment of non-insulin dependent diabetes mellitus. United States Patent No. RE 37330 (a reissue of US 5,922,769) claims a method of treating non-insulin dependent diabetes mellitus in cases of secondary failure to a treatment utilizing a combination of glibenclamide-metformin hydrochloride, in a weight ratio higher than 1:100, comprising administering to a subject in need of same a combination of glibenclamide and metformin, expressed as the hydrochloride, in a weight ratio of 1:100. The patent also discloses the results of a clinical study, which indicates that the maximum dose of glibenclamide, which does not cause any side-effects, is 15mg/day, while that for metformin is 1500 mg/day, and that the use of such a combination in a ratio lower than that claimed would result in formulations that do not attain the optimum therapeutic effect. The patent claims the combination of glibenclamide and metformin in a tablet form. The patent does not disclose a formulation wherein the sulfonyl urea is released immediately and the biguanide is released after a delay period, particularly after a predetermined delay period.

United States Patent No. 6,031,004 (004) discloses the use of a combination of novel salts of metformin and glyburide, in the treatment of diabetes mellitus type 2. In this invention, both metformin salt and glyburide are released immediately. The patent does not disclose a

composition wherein the sulfonyl urea is released immediately and the biguanide is released after a delay period, particularly after a predetermined delay period.

5 United States Patent No. 6,099,862 ('862) claims a controlled release pharmaceutical tablet which consists essentially of (a) a core consisting essentially of: (i) metformin or a pharmaceutically acceptable salt thereof, (ii) glipizide, (iii) polyvinylpyrrolidone, and (iv) sodium lauryl sulfate, (b) optionally a seal coat around the core, (c) a semipermeable membrane coating covering said core comprising - (i) cellulose acetate, (ii) polyethylene glycol with an average molecular weight between 380 and 420, and (iii) a plasticiser, and (d) at least one passageway in the semipermeable
10 membrane to allow the release of the metformin and glipizide from the core to the environment of use to provide therapeutic levels of metformin and glipizide from twelve to twenty-four hour periods. In this invention, both metformin salt and glipizide are released slowly upon oral administration. The patent does not disclose a composition wherein the sulfonyl urea is released immediately and the biguanide is released after a delay period, particularly after a predetermined
15 delay period.

PCT applications WO 98/57649 and WO 99/03476 both claim a combination of an insulin sensitiser such as a thiazolidinedione and an insulin secretagogue such as a sulfonyl urea. The system of the PCT application WO 99/03477 claims a method for the treatment of diabetes
20 mellitus and conditions associated with it, using a combination of an insulin sensitiser, an insulin secretagogue and a biguanide antihyperglycemic agent. The insulin sensitiser used in this combination is a thiazolidinedione like troglitazone, ciglitazone, rosiglitazone, pioglitazone or englitazone, and the insulin secretagogue is a sulfonyl urea or repaglinide. The application thus claims the combination of a thiazolidinedione, a sulfonyl urea or repaglinide, and a biguanide.
25 The application discloses that the claimed combinations exhibit synergism when given as a unit dosage form, and therefore the amount of each agent required is reduced. However, all the agents are released in a conventional manner, thereby reducing the flexibility of administration.

PCT application WO 99/03478 claims a method for the treatment of diabetes mellitus and
30 conditions associated with it, using a combination of an insulin sensitiser, an insulin secretagogue and an alpha glucosidase inhibitor. The insulin sensitiser used is a thiazolidinedione, the insulin secretagogue is a sulfonyl urea or repaglinide, while the alpha glucosidase inhibitor is selected from acarbose, emiglitate and miglitol. The application discloses that such a combination has a beneficial effect on the glycemic control as a result of a synergistic effect, and also has minimum

side effects. The invention, however, does not provide spaced drug delivery of a combination of two or more antidiabetic agents, wherein one antidiabetic agent is released immediately and the other antidiabetic agent(s) is/are released at a predetermined time interval.

5 The system of the United States Patent No. 6,011,049 claims a composition comprising a combination of synergistic amounts of a sulfonyl urea, a thiazolidinedione (glitazone) antidiabetic agent and a biguanide. The patent teaches that since the unstimulated insulin secretory capacity of the β -cells is very low in NIDDM, reversing insulin resistance alone would be of partial benefit. Therefore, the system maintains a level of stimulated insulin secretion with a sulfonyl urea while
10 adding glitazone to improve insulin sensitivity, thereby providing a level of glycemic control unattainable by either medication alone. However, the invention does not provide a spaced drug delivery system of a combination of the two or more antidiabetic agents.

The system claimed in the PCT application WO 98/56378 uses a short-acting hypoglycemic agent
15 capable of stimulating insulin secretion from β -cells, for the manufacture of a medicament adapted to stimulate meal-related insulin secretion, for the treatment of post-prandial hyperglycemia in NIDDM patients. The system uses repaglinide or a combination of repaglinide with long-acting hypoglycemic agents like metformin, a sulfonyl urea or troglitazone. The application teaches that repaglinide stimulates endogenous secretion of insulin in connection with
20 meals, while metformin enhances tissue sensitivity towards insulin, the combination providing a significant improvement in glycemic control. The combination is administered prandially. The invention, however, does not provide spaced drug delivery of a combination of two or more antidiabetic agents, wherein one antidiabetic agent is released immediately and the other antidiabetic agent(s) is/are released at a predetermined time interval.

25 United States Patent No. 6,166,043 ('043) claims a method for reducing the amounts of active components administered to a diabetic patient, which comprises administering a therapeutically effective amount of an insulin sensitivity enhancer in combination with a biguanide. The insulin sensitivity enhancer claimed in the system is a thiazolidinedione selected from pioglitazone and troglitazone, while the biguanide is selected from metformin, phenformin and buformin. The
30 combination is administered as an admixture or the agents are administered independently, wherein both the agents are released immediately.

United States Patent No. 6,172,090 (090) claims a method for reducing side effects of active components administered to a diabetic patient, which comprises administering to the said patient a therapeutically effective amount of an insulin sensitivity enhancer in combination with a biguanide. Similar to the V43 system, the patent claims a combination of a thiazolidinedione like pioglitazone or troglitazone, and a biguanide like metformin, phenformin or buformin, which is administered independently or as an admixture. In this invention, the thiazolidinedione and the biguanide are available immediately after oral administration of the dosage form as a conventional release.

United States Patent No. 6,153,632 (632) claims a composition for the treatment of diabetes mellitus comprising a therapeutic amount of an insulin sensitiser and a therapeutic amount of an antidiabetic agent, the latter being selected from the group consisting of orally ingestible insulin, injectable insulin, a sulfonyl urea, a biguanide and an alpha glucosidase inhibitor. The insulin sensitiser used in the invention is a thiazolidinedione. Both the antidiabetic agents are released immediately after oral administration of the composition in a conventional manner.

PCT application WO 98/57634 (634) claims a method for treating diabetes mellitus and conditions associated with it comprising administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and a biguanide antihyperglycemic agent. The insulin sensitiser used in the invention is a thiazolidinedione. In this invention both the antidiabetic agents are released immediately.

PCT application WO 00/28989 claims a pharmaceutical composition comprising an insulin sensitiser and another antidiabetic agent, and a pharmaceutically acceptable carrier therefore, wherein the composition is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetic agent. The modified release claimed may be a delayed release using gastric resistant formulation, or a sustained release using disintegrating, non-disintegrating or eroding matrices, or a controlled release formulation. The insulin sensitiser used in the invention is a thiazolidinedione, while the other antidiabetic agent is selected from an alpha glucosidase inhibitor, biguanide and an insulin secretagogue, the insulin secretagogue being a sulfonyl urea, repaglinide or nateglinide. The application teaches that the combination provides an advantageous delivery of the antidiabetic agents, maintaining effective glycemic control and has no observed adverse effects. The invention, however, does not provide spaced drug delivery

of a combination of two or more antidiabetic agents, wherein one antidiabetic agent is released immediately and the other antidiabetic agent(s) is/are released at a predetermined time interval.

A plethora of prior arts relate to pharmaceutical compositions that release a drug after a delay.

5 Some prior arts that relate to release of drug after a predetermined time include United States Patent No. 3,247,066; Irish patent application no IE 902533; United States Patent No. 4,871,549; United States Patent No. 5,229,131; PCT Publication no WO 99/18938 and PCT Publication no WO 00/74655. All of these relate to systems comprising a core that swells upon imbibing fluid from the surrounding and a coat that ruptures due to the pressure exerted upon it by the swelling

10 core. However, none of these prior arts disclose a spaced drug delivery system designed to provide desired control on the disease condition, comprising

- a. a first composition comprising one or more first therapeutically active agents, and
- b. a second composition comprising one or more second therapeutically active agents,

15 wherein at least one first therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system, and at least one second therapeutically active agent is released as a pulse at a predetermined time after oral administration, wherein the two or more therapeutic agents act on the disease condition by similar or dissimilar, but complementary mechanisms, to control the symptoms of the disease, or a measurable indicator of the disease condition, and further wherein the time of release of the two or more therapeutically active agents

20 is designed to provide desired control on the disease condition. More specifically and particularly, none of the prior arts suggest that it would benefit the treatment of diabetes mellitus by oral administration of a spaced drug delivery system comprising one or more therapeutically active antidiabetic agents wherein at least one first therapeutically active antidiabetic agent is released immediately upon oral administration of the spaced drug delivery system, and at least one second

25 therapeutically active antidiabetic agent is released as a pulse at a predetermined time after oral administration. Further, they do not disclose a spaced drug delivery system that immediately releases at least one first therapeutically active agent after oral administration of the spaced drug delivery system at a specified time prior to meals and releases at least one second therapeutically active antidiabetic agent at about the time the meal is taken. Prior arts such as United States

30 Patent No. 3,247,066, European Patent Application 1123700, United States Patent No. 5,260,069, and United States Patent No. 4,871,549 are distinct from the present invention in that they relate to controlled release dosage forms. Herein the dose of the drug is divided in multiple units and there is no specific and particular requirement of assurance that a unit ruptures at a predetermined time in a reliable manner. Statistically, different units rupture at different times and thereby

provide controlled release of the active ingredient, on an average, over a period of time. In the present invention, the total amount of active ingredient is contained in one single unit and is intended to be released at the predetermined time. An important requirement for using such systems in a large number of patients is that the system should deliver the drug at about the predetermined time in a reliable manner to the large number of patients to whom the system is administered. Thus, the coat rupture should occur reliably and consequently drug should be released reliably. For instance, if in five to ten out of a hundred times the coatings do not open or rupture at about the predetermined time, but rupture at a significantly prolonged time when tested by agitation over a range of agitational conditions and aqueous compositions, then the desired release at the predetermined time is not achieved reliably. Also, if the release prior to rupture may be influenced by changes in pH, then the desired release at the predetermined time is not achieved reliably. Also, if the coat rupture occurs but the therapeutically active agent is not released as a pulse in all or some of the units, then the desired release as a pulse at a predetermined time is not achieved reliably. Prior arts such as WO 99/18938, WO 00/74655, and IE 902533 make no reference to reliability of rupture or release from a large number of tablets or to the process for optimizing the compositions to obtain the reliability of rupture or reliability of release over a large number of tablets. United States Patent No. 5,229,131 presents a large amount of data giving the percent tablets splitting at 30 min and 60 min and the percent tablets releasing their contents at 60 min and 120 min in Tables 12 to 18. The tablets do not provide reliable manner of rupture as provided by the composition of the present invention, wherein 36 out of 36 tablets rupture within $\pm 50\%$ of the coating failure time. Despite the plethora of prior art, there are no commercially successful systems that provide spaced drug delivery in a reliable manner.

25 The prior art does not mention any formulations or systems containing combinations of two or more therapeutically active antidiabetic agents, wherein at least one therapeutically active antidiabetic agent is released immediately and at least one therapeutically active agent is released after a lag period or a predetermined spacing interval.

30 OBJECT OF THE INVENTION

It is an object of the present invention to provide a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system wherein at least one first therapeutically active agent is released immediately upon oral

administration of the spaced drug delivery system and at least one second therapeutically active agent is released as a pulse at a predetermined time after oral administration, wherein the two or more therapeutic agents act on the disease condition by similar or dissimilar, but complementary mechanisms, to control the symptoms of the disease, or a measurable indicator of the disease condition, and further wherein the time of release of the two or more therapeutically active agents is designed to provide desired control on the disease condition.

It is another object of the present invention to provide a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system at a specified time prior to food intake by the patient, wherein at least one therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system, and at least one therapeutically active agent is released, as a pulse, after a delay at about the time when food is taken.

It is a particular object of the present invention to provide above referred methods for the administration of two or more therapeutically active antidiabetic agents.

It is an object of the present invention to provide a spaced drug delivery system designed to provide desired control on the disease condition, comprising

- a. a first composition comprising one or more first therapeutically active agents, and
- b. a second composition comprising one or more second therapeutically active agents,

wherein at least one first therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system, and at least one second therapeutically active agent is released as a pulse at a predetermined time after oral administration, wherein the two or more therapeutic agents act on the disease condition by similar or dissimilar, but complementary mechanisms, to control the symptoms of the disease, or a measurable indicator of the disease condition, and further wherein the time of release of the two or more therapeutically active agents is designed to provide desired control on the disease condition.

It is yet another particular object of the present invention to provide a spaced drug delivery system for the treatment of diabetes mellitus or conditions associated with diabetes mellitus, comprising

- a. a first composition comprising one or more therapeutically active antidiabetic agent(s), which is/are released as a pulse after a delay, and

- b. a second composition comprising one or more therapeutically active antidiabetic agent(s), which is/are released immediately upon oral administration of the spaced drug delivery system.

- 5 It is yet another particular object of the present invention to provide a spaced drug delivery system as referred above, wherein the first composition is a timed pulse release composition that releases as a pulse an antidiabetic agent after a predetermined time spacing or interval after oral administration of the spaced drug delivery system.
- 10 It is a further object to provide a spaced drug delivery system containing a timed pulse release composition comprising a core composition comprising one or more therapeutically active antidiabetic agents, a swelling agent, and optionally water soluble compound(s) for inducing osmosis, and a coat composition comprising one or more film forming polymers, wherein upon swelling of the core the coat ruptures and releases as a pulse the therapeutically active agent in a
- 15 reliable manner at about a predetermined time after oral administration of the spaced drug delivery system.

SUMMARY OF THE INVENTION

- 20 The present invention provides a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system, wherein at least one first therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system, and at least one second therapeutically active agent is released as a pulse at a predetermined time after oral administration, wherein the two or more therapeutically
- 25 active agents act on the disease condition by similar or dissimilar, but complementary mechanisms, to control the symptoms of the disease, or a measurable indicator of the disease condition, and further wherein the time of release of the two or more therapeutically active agents is designed to provide desired control on the disease condition.
- 30 The present invention also provides a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system at a specified time prior to food intake by the patient, wherein at least one therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system, and at least

one therapeutically active agent is released, as a pulse, after a delay at about the time when food is taken.

Particularly, the present invention provides above referred methods of administration for two or
5 more therapeutically active antidiabetic agents.

Further, the present invention provides a spaced drug delivery system designed to provide desired control on the disease condition, comprising

- a. a first composition comprising one or more first therapeutically active agents, and
 - 10 b. a second composition comprising one or more second therapeutically active agents,
- wherein at least one first therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system, and at least one second therapeutically active agent is released as a pulse at a predetermined time after oral administration, wherein the two or more therapeutic agents act on the disease condition by similar or dissimilar, but complementary
15 mechanisms, to control the symptoms of the disease, or a measurable indicator of the disease condition, and further wherein the time of release of the two or more therapeutically active agents is designed to provide desired control on the disease condition.

The present invention, in particular, provides a spaced drug delivery system for the treatment of
20 diabetes mellitus or conditions associated with diabetes mellitus, comprising -

- a. a first composition comprising one or more therapeutically active antidiabetic agent(s), which is/are released as a pulse after a delay, and
- b. a second composition comprising one or more therapeutically active antidiabetic agent(s), which is/are released immediately upon oral administration of the spaced drug
25 delivery system.

Preferably, in the spaced drug delivery system as referred above, the first composition is a timed pulse release composition that releases as a pulse an antidiabetic agent after a predetermined time spacing or interval after oral administration of the spaced drug delivery system.

30 More particularly and specifically, the present invention provides a spaced drug delivery system containing a timed pulse release composition comprising a core composition comprising one or more therapeutically active antidiabetic agents, a swelling agent, and optionally water soluble compound(s) for inducing osmosis, and a coat composition comprising one or more film forming

polymers, wherein upon swelling of the core the coat ruptures and releases as a pulse the therapeutically active agent in a reliable manner at about a predetermined time after oral administration of the composition.

- 5 As referred to herein, 'conditions associated with diabetes mellitus' include those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus. When used herein the term 'conditions associated with pre-diabetic state' includes conditions such as insulin resistance, including hereditary insulin resistance, impaired glucose tolerance, obesity and hyperinsulinaemia.
- 10 'Conditions associated with diabetes mellitus' itself include hyperglycemia, insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational
- 15 diabetes. 'Complications associated with diabetes mellitus' includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy. Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephritic syndrome, hypertensive nephrosclerosis and end stage renal disease.

20 DETAILED DESCRIPTION OF THE INVENTION

- The present invention provides a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system, wherein at least one first therapeutically active agent is released immediately upon oral administration of the
- 25 spaced drug delivery system, and at least one second therapeutically active agent is released as a pulse at a predetermined time after oral administration, wherein the two or more therapeutic agents act on the disease condition by similar or dissimilar, but complementary mechanisms, to control the symptoms of the disease, or a measurable indicator of the disease condition; and further wherein the time of release of the two or more therapeutically active agents is designed to
- 30 provide desired control on the disease condition. The spaced drug delivery system can be suitably optimized to provide improved control on the disease condition when there is an easily measurable indicator of the disease condition such as blood pressure, pulse, blood glucose level, frequency of urination, ophthalmic pressure, etc. However, based on clinical observation of the

symptoms of the disease coupled with the blood level profile of the therapeutically active agent, the optimization of the system can also be suitably achieved.

The therapeutically active agent may be selected from the therapeutic class viz. alcohol abuse preparations, drugs used for Alzheimer's disease, anesthetics, acromegaly agents, analgesics, antiasthmatics, anticancer agents, anticoagulants, antithrombotic agents, anticonvulsants, antidiabetics, antiemetics, antiglaucoma agents, antihistamines, anti-infective agents, antiparkinsons agents, antiplatelet agents, antirheumatic agents, antispasmodics, anticholinergic agents, antitussives, carbonic anhydrase inhibitors, cardiovascular agents, cholinesterase inhibitors, agents for the treatment of CNS disorders, CNS stimulants, cystic fibrosis management agents, dopamine receptor agonists, agents for endometriosis management, erectile dysfunction therapy, fertility agents, gastrointestinal agents, immunomodulators, immunosuppressives, memory enhancers, migraine preparations, muscle relaxants, nucleoside analogues, osteoporosis management agents, parasympathomimetics, prostaglandins, psychotherapeutic agents, sedatives, hypnotics, tranquilizers, drugs used for skin ailments, steroids and hormones.

The term "release as a pulse" refers to release characteristic of conventional tablets and capsules that are devoid of design characteristics that result in slow, extended, controlled or retarded release of the therapeutically active agent. For example, in a particular embodiment where the predetermined time of pulse release is about 70 min, the "release of therapeutically active agent as a pulse" comprises release of not more than 10% of the active ingredient at 45 min and at least 70% of the active ingredient at 2 hrs, when tested by subjecting the tablets to USP dissolution test using pH 6.8 buffer at $37 \pm 0.5^\circ\text{C}$, in a USP Type II apparatus at an rpm of 75.

The present invention also provides a method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system at a specified time prior to food intake by the patient, wherein at least one therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system, and at least one therapeutically active agent is released as a pulse after a delay at about the time when food is taken i.e. either immediately prior to meals, or at the time of meals, or after meals.

Particularly, the present invention provides above referred methods of administration for two or more therapeutically active antidiabetic agents.

Further, the present invention provides a spaced drug delivery system designed to provide desired control on the disease condition, comprising -

- a. a first composition comprising one or more first therapeutically active agents, and
 - b. a second composition comprising one or more second therapeutically active agents,
- 5 wherein at least one first therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system, and at least one second therapeutically active agent is released as a pulse at a predetermined time after oral administration, wherein the two or more therapeutic agents act on the disease condition by similar or dissimilar, but complementary mechanisms, to control the symptoms of the disease, or a measurable indicator of the disease
- 10 condition, and further wherein the time of release of the two or more therapeutically active agents is designed to provide desired control on the disease condition. None of the prior arts disclose such spaced drug delivery systems.

The present invention, in particular, provides a spaced drug delivery system for the treatment of

15 diabetes mellitus or conditions associated with diabetes mellitus, comprising -

- a. a first composition comprising one or more therapeutically active antidiabetic agent(s), which is/are released as a pulse after a delay, and
 - b. a second composition comprising one or more therapeutically active antidiabetic agent(s), which is/are released immediately upon oral administration of the spaced drug delivery
- 20 system.

Preferably, in the spaced drug delivery system as referred above, the first composition is a timed pulse release composition that releases as a pulse an antidiabetic agent after a predetermined time spacing or interval after oral administration of the spaced drug delivery system.

25 More particularly and specifically, the present invention provides a spaced drug delivery system containing a timed pulse release composition comprising a core composition comprising one or more therapeutically active antidiabetic agents, a swelling agent, and optionally water soluble compound(s) for inducing osmosis, and a coat composition comprising one or more film forming

30 polymers, wherein upon swelling of the core the coat ruptures and releases as a pulse the therapeutically active agent.

In the present invention, the total amount of active ingredient is contained in one single unit of the timed pulse release composition and is intended to be released as a pulse at the predetermined

time. An important requirement for using such systems in a large number of patients is that the system should deliver the drug as a pulse at about the predetermined time in a reliable manner to the large number of patients to whom the system is administered. Thus, the coat rupture should occur reliably, the core should disintegrate immediately, and consequently the drug should be released as a pulse reliably. For instance, if in five to ten out of a hundred times the coatings do not open or rupture at about the predetermined time but rupture at a significantly prolonged time when tested by agitation over a range of agitational conditions and aqueous compositions, then the desired release at the predetermined time is not achieved reliably. Also, if the release prior to rupture or the rupture time is significantly influenced by changes in pH, composition of the surrounding fluids and the agitation conditions, then the desired release at the predetermined time is not achieved reliably. Also, if the coat rupture occurs but the therapeutically active agent is not released as a pulse in all or some of the units, then the desired release as a pulse at a predetermined time is not achieved reliably. The timed release composition in the spaced drug delivery system of the present invention has these desirable attributes such that the coat ruptures and releases as a pulse the therapeutically active agent in a reliable manner at about a predetermined time after oral administration of the composition.

Particularly, in the spaced drug delivery system of the present invention, the timed pulse release composition is optimized as follows:

- a. the core composition is capable of swelling at a desired rate to a sufficient extent,
 - b. the coat composition has the desirable film strength, plasticity, and water permeability, and
 - c. the amount of coat composition applied is adjusted,
- such that upon swelling of the core the coat ruptures and releases as a pulse the therapeutically active agent in a reliable manner at about the predetermined time after oral administration of the composition, wherein the reliable manner of rupture comprises rupturing of 36 tablets out of a total of 36 tablets at about the predetermined time, when tested by subjecting the tablets to USP dissolution test using an aqueous media at $37 \pm 0.5^\circ\text{C}$, in a USP Type I or Type II apparatus at an rpm selected from the range of about 50 rpm to about 100 rpm. Further wherein the predetermined time is in the range of about 1 hr to about 4 hr, the 36 out of the 36 tablets rupture within $\pm 50\%$ of the predetermined time; and wherein the predetermined time is in the range of about >4 hr to about 12 hr, the 36 out of the 36 tablets rupture within $\pm 25\%$ of the predetermined time.

In specific preferred embodiments, the spaced drug delivery system of the present invention includes -

1. A spaced drug delivery system wherein the antidiabetic agent in the first composition is a biguanide antidiabetic agent, and the antidiabetic agent in the second composition is a sulfonyl urea.
2. A spaced drug delivery system wherein the antidiabetic agents in the first composition are selected from the group consisting of an alpha glucosidase inhibitor, a thiazolidinedione, and an insulin secretagogue; and the antidiabetic agent in the second composition is an insulin secretagogue; further wherein the insulin secretagogues, if present in both first and second compositions, are not the same.
3. A spaced drug delivery system wherein the antidiabetic agent in the first composition is a biguanide antidiabetic agent, and the antidiabetic agent in the second composition is selected from the group consisting of insulin secretagogue and a thiazolidinedione, optionally in combination with an alpha glucosidase inhibitor.
4. A spaced drug delivery system wherein the antidiabetic agent in the first composition is a biguanide antidiabetic agent, and the antidiabetic agent in the second composition is an alpha glucosidase inhibitor.

In the present invention, the timed pulse release composition imbibes fluids from the environment of use causing the swelling agent in the core to swell. The therapeutically active antidiabetic agent is then released after the timed pulse release coat ruptures under the influence of mechanical pressure exerted by the swelling of the swelling agent(s) present in the core. The time of rupture of the coat can be controlled by varying (a) the degree and rate of swelling of the core; (b) the timed pulse release coat composition, by using different components and ratios of these components; and (c) the thickness of the coat.

The swelling agent used in the timed pulse release composition includes one or more swellable hydrophilic polymers. The quantity or relative proportion of the polymers is subject to considerable variation. However, a sufficient quantity of the material is present in the core to provide, upon uptake of water, a swelling pressure in excess of the cohesive strength of the coating surrounding the tablet or core. Preferably, the polymers are employed in the dry state or in a form that has substantial capacity for water uptake. Examples of swellable hydrophilic polymers that may be used in the timed pulse release composition of the present invention as the swelling agent include vinylpyrrolidone polymers such as povidone, or crosslinked

polyvinylpyrrolidone such as crospovidone; cellulose and cellulose derivatives such as microcrystalline cellulose, methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, carboxyalkyl celluloses or crosslinked carboxyalkylcelluloses and their alkali salts; sodium starch glycolate, starch and starch derivatives, ion-exchange resins and mixtures thereof. Preferably, the swelling agent used comprises a swelling agent that swells considerably but does not form a strong gel and may be selected from the group consisting of crosslinked sodium carboxymethyl cellulose, crosslinked polyvinylpyrrolidone and sodium starch glycolate. The preferred swelling agents also have a strong wicking action and are capable of swelling to several times their original volume on imbibing water from the surroundings.

The alkali salt of crosslinked carboxyalkyl cellulose, i.e. crosslinked sodium carboxymethyl cellulose, also known as croscarmellose sodium or Ac-Di-Sol, is available commercially as Nymcel[®] ZSX, Pharmacel[®] XL, Primellose[®] or Solutab[®]. The amount of swelling agent that may be used is dependent on the desired time of rupture of the timed pulse release coat, nature and amounts of other components in the core, as well as the composition and thickness of the coat. Generally, croscarmellose sodium may be used as the polymeric swelling agent, in an amount ranging from about 0.5% to about 50% by weight of the core, preferably from about 2% to about 40% by weight of the core, more preferably from about 5% to about 20% by weight of the core. In specific preferred embodiments croscarmellose sodium is used in a range from about 6% to about 10% by weight of the core, more preferably from about 7% to about 9% by weight of the core.

Vinyl pyrrolidone polymers or polyvinyl pyrrolidone (PVP), also referred to as Povidone, are synthetic polymers consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights, the molecular weight ranging between 2500 and 3,000,000 Daltons. PVP is commercially available as Kollidon[®] (BASF), Plasdone[®] and Peristone[®] (General Aniline). PVP is classified into different grades on the basis of its viscosity in aqueous solution. Different grades of PVP available are PVP K-12, PVP K-15, PVP K-17, PVP K-25, PVP K-30, PVP K-60, PVP K-90 and PVP K-120. The K-value referred to in the above nomenclature is calculated from the viscosity of the PVP in aqueous solution, relative to that of water. Crospovidone or cross-PVP, the synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone, may also be used as a swellable hydrophilic polymer. It is commercially available as Kollidon CL and Polyplasdone XL, and has a molecular weight higher than 1,000,000 Daltons. Crospovidone is used in the present invention in an amount

5 ranging from about 2% to about 5% by weight of the core. The preferred vinyl pyrrolidone polymer for use as a swellable hydrophilic polymer is PVP K-30, having an approximate molecular weight of 50,000 Daltons. It may be used in an amount ranging from about 0.5% to about 5% by weight of the core, more preferably from about 1% to about 2% by weight of the core.

10 Sodium starch glycolate, the sodium salt of carboxymethyl ether of starch, may also be used as the polymeric swelling agent. It has a molecular weight ranging between 500,000 and 1,000,000 Daltons, and is commercially available as Explotab and Primojel. Sodium starch glycolate may be used in the present invention in an amount ranging from about 0.5% to about 40% by weight of the core, preferably from about 2% to about 40% by weight of the core, more preferably from about 2% to about 10% by weight of the core.

15 Preferably, the timed pulse release composition in the spaced drug delivery system of the present invention contains a wicking agent. The term wicking agent as used herein implies a broader definition than a conventional wicking agent and includes any pharmaceutical excipient that provides influx of water into the core by any suitable mechanism, preferably by capillary action as is typical of conventional wicking agents. Materials suitable for use as wicking agents in the timed pulse release composition include, but are not limited to, colloidal silicon dioxide, kaolin, 20 titanium dioxide, fumed silicon dioxide, alumina, sodium lauryl sulfate, microcrystalline cellulose, low molecular weight polyvinyl pyrrolidone, bentonite, magnesium aluminum silicate, and the like.

25 Microcrystalline cellulose (MCC) is used in the preferred embodiment as the wicking agent. It is made up of a chain of about 250 glucose molecules in the form of a microcrystal, consisting primarily of crystallite aggregates obtained by removing amorphous regions of a pure cellulose source material by hydrolytic degradation using mineral acid. MCC has an average molecular weight of about 36,000 Daltons and is available in various grades, which differ in bulk density, particle size and moisture content. It is commercially available as Vivapur[®], Avicel[®], Vivacel[®], 30 Emcocel[®], Fibrocel[®] and Tabulose[®]. Avicel[®] PH 102, having a mean particle size of 100 μ m, i.e. 8% or less of the particles are retained on a # 60 sieve (as defined by ASTM, American Society for Testing and Materials), and 45% or more of the particles are retained on a #200 sieve (as defined by ASTM), and having a moisture content $\leq$ 5%, is used in more preferred embodiments

of the timed pulse release composition, in an amount ranging from about 2% to about 5% by weight of the core, more preferably from about 2% to about 3% by weight of the core.

Water-soluble compounds suitable for inducing osmosis, i.e. osmotic agents or osmogents, are generally used in the core of the timed pulse release composition when the drug itself does not exert sufficient osmotic pressure in order to imbibe fluid from the surroundings. Osmogents that may be present in the core of the timed pulse release composition include all pharmaceutically acceptable and pharmacologically inert water-soluble compounds referred to in the pharmacopoeias such as United States Pharmacopoeia, as well as in Remington: The Science and Practice of Pharmacy, edition 20, Lippincott Williams and Wilkins, Philadelphia (2000). Pharmaceutically acceptable water-soluble salts of inorganic or organic acids, or non-ionic organic compounds with high water solubility, e.g. carbohydrates such as sugar, or amino acids, are generally preferred. The examples of agents used for inducing osmosis include inorganic salts such as magnesium chloride or magnesium sulfate, lithium, sodium or potassium chloride, lithium, sodium or potassium hydrogen phosphate, lithium, sodium or potassium dihydrogen phosphate, salts of organic acids such as sodium or potassium acetate, magnesium succinate, sodium benzoate, sodium citrate or sodium ascorbate; carbohydrates such as mannitol, sorbitol, arabinose, ribose, xylose, glucose, fructose, mannose, galactose, sucrose, maltose, lactose, raffinose; water-soluble amino acids such as glycine, leucine, alanine, or methionine; urea and the like, and mixtures thereof. The amount of osmogents that may be used depends on the particular osmogent that is used and may range from about 1% to about 60% by weight of the core.

In addition to the above ingredients, the core of the timed pulse release composition may optionally contain pharmaceutically acceptable excipients such as binders, disintegrants, lubricants and the like. Examples of binders used commonly include starch, gelatin, sugars like sucrose, glucose, dextrose, molasses and lactose; acacia, sodium alginate, cellulose derivatives like methyl cellulose, ethyl cellulose, carboxymethyl cellulose and the like; polymers such as polyvinyl pyrrolidone, Veegum, polyethylene glycol, waxes and the like. The timed pulse release composition of the present invention may be optimized to obtain the reliable manner of rupture without the use of a wicking agent. However, the use of a wicking agent has been found to be useful in that the task of optimization to obtain the reliable manner of rupture is made easier.

Examples of lubricants that may be used in the timed pulse release composition include talc, magnesium stearate, calcium stearate, aluminium stearate, stearic acid, hydrogenated vegetable

oils, colloidal silicon dioxide, polyethylene glycol, cellulose derivatives such as carboxyalkyl cellulose and its alkali salts, or mixtures thereof. Hydrophobic or water insoluble lubricants may reduce the water imbibing properties of the core whereas hydrophilic or water soluble lubricants do not, and are preferred. A more preferred lubricant is colloidal silicon dioxide. A mixture of
5 colloidal silicon dioxide and magnesium stearate may be used as the preferred lubricant. More preferred embodiments use a combination of microcrystalline cellulose and colloidal silicon dioxide as the wicking agents, with colloidal silicon dioxide also functioning as a lubricant. Colloidal silicon dioxide is available commercially as Aerosil® from Degussa-Huls, Nippon and Fischer GmbH. The preferred colloidal silicon dioxide lubricant is Aerosil® 200, with an
10 approximate external surface area of 200m²/g. The colloidal silica may be used in amounts in the range of about 0.5 % to about 5% by weight of the core.

In a preferred embodiment, the core of the timed pulse release composition is obtained by mixing the therapeutically active agent and the swelling agent with the binder in a rapid mixer granulator
15 and granulating the mixture. In more preferred embodiments of the present invention, only a part of the total swelling agent is included in the composition and the remaining is mixed at the lubrication stage with the dried granules. The granules obtained using a suitable granulating solvent are wet milled through a screen and then dried in a fluidised bed drier at 40-50°C to a moisture content of 2-3%. The dried granules are then milled through a 2mm screen and are
20 mixed with one or more lubricants and the wicking agent. In more preferred embodiments, as described above, the remaining part of the swelling agent is mixed at this stage. The lubricated granules may be filled in hard gelatin capsules, or may be compressed to obtain the compressed tablets or cores.

25 The therapeutically active agent comprising compressed cores/capsules are covered with a coat composition comprising one or more film forming polymers, to provide a timed pulse release composition. The film forming polymers that may be used to form this timed pulse release composition are selected from the group consisting of water insoluble polymers, pH dependent polymers, and mixture of water soluble and water insoluble polymers, or mixtures thereof.
30 Examples of film forming polymers that may be used include cellulose ester derivatives like methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, cellulose acetate, cellulose acetate phthalate, pH-independent copolymers of methacrylic acid and methacrylic acid esters commercially available as Eudragit®, or mixtures thereof. The time of release of the therapeutically active agent of the first composition may be varied by varying the

components used to form the coat, and/or by varying the ratio in which these components are used. By selecting the suitable components and by using them in suitable ratios, the release can be obtained at about a predetermined time after oral administration of the spaced drug delivery system. A preferred embodiment of the invention uses a mixture of a water-insoluble polymer and a water soluble polymer to form the delayed release coat. In preferred embodiments ethyl cellulose is used as the water-insoluble polymer and hydroxypropyl methylcellulose (HPMC) is used as the water soluble polymer. The mixture is used in a preferred weight ratio of 0:20 to 20:0 of ethyl cellulose : HPMC, more preferably 6:3 to 9:3.

10 The compressed cores/capsules containing the therapeutically active agent are coated with the coating solution, comprising the film forming polymers in a suitable solvent system, to a defined weight gain, the thickness of the coat depending on the predetermined time of release of the active agent. The coating material may be applied by any procedure which provides a continuous film of essentially uniform thickness. One method of coating involves rotating a bed of uncoated
15 cores in a conventional tablet coating pan and applying a solution or dispersion of the coating agent in a suitable solvent by pouring or spraying the solution onto the moving cores. Other coating procedures such as fluid bed coating, vertical spray coating, and the like can also be employed. The coated cores are dried by exposing them to warm, dry air and may be cured, if necessary, by air drying, baking or force drying. In one embodiment of the present invention, the
20 compressed core is coated with a ethyl cellulose : HPMC solution to a weight gain in the range of about 2% to about 20% by weight of the compressed core, preferably from about 5% to about 10% by weight of the core; more preferably from about 9% to about 10% by weight of the compressed core. The cores are coated in an automated perforated coating pan followed by drying and curing of the coated cores in a tray drier for 24 hours at 40-50°C.

25 The present invention covers any spaced drug delivery system in which the first composition comprising the therapeutically active antidiabetic agent, and the second composition comprising the therapeutically active antidiabetic agent, are physically separated, or compartmentalized, so as to achieve different release rates of the two active agents. Such separation, or
30 compartmentalization, may be on a macro-scale, for instance, with the agents being incorporated into separate units (such as tablets, powder, granules, pellets etc) for simultaneous or sequential administration, or separation of the agents may be on a micro-scale, for instance, with the agents being present within the same unit. Two separate units when present are formed into a single unit spaced drug delivery system by filling them into capsules.

In the spaced drug delivery system of the present invention, the first and second composition may be in the form of either multiparticulates such as particles, pellets or granules, or present as concentric or laminar tablet layers or as single units such as a compressed tablet. The multiparticulates may be made by any of the conventional methods, including mixing, granulation, extrusion, spheronisation, layering of non-pareil seeds, etc, and various other methods known to a person skilled in the art. A compressed tablet core may be obtained by compressing the multiparticulates in a tablet die. The first composition is surrounded by a delayed release coating comprising delayed release material selected from the group consisting of enteric polymers, water insoluble polymers, hydrophobic compounds, hydrophilic non-polymeric compounds, hydrophilic polymers and the like, and mixtures thereof, using conventional coating methods. The coated multiparticulates or tablets of the first composition and the uncoated multiparticulates or tablets of the second composition, may be filled into capsules. Alternatively, tablets of the first composition may be surrounded by the second composition and compressed in a compression coating tablet machine or a second layer of the second composition may be compressed onto the compressed first composition to form bilayer tablets.

The second composition used in the spaced drug delivery system is in the form of multiparticulates or tablets, which may be filled into capsules along with the first timed pulse release composition. Alternatively, tablets of the first timed pulse release composition may be surrounded by the second composition and compressed in a compression coating tablet machine to obtain a single unit dose form with timed pulse release core composition and an immediate release coat composition comprising the therapeutically active agent of the second composition. The second composition may be included in the spaced drug delivery system of the present invention in different ways. Multiparticulates of the therapeutically active agent of the second composition may be obtained by mixing the agent with pharmaceutically acceptable excipients, such as binders, fillers, disintegrants and the like, or by further granulating the mixture. The granules so obtained are dried and lubricated with one or more lubricants.

The immediate release layer of the second composition may be introduced by mixing the therapeutically active antidiabetic agent with pharmaceutical adjuvants such as film-forming agents, plasticisers and the like, in a suitable solvent or solvent system, and coating the timed pulse release composition, using conventional coating methods known to a person skilled in the art. Examples of film-forming agents that may be used in the present invention include cellulose

derivatives such as cellulose acetate phthalate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose, ethyl cellulose, methyl cellulose, microcrystalline cellulose, methacrylic acid/methacrylate esters, polyvinyl acetate phthalate, shellac and the like, or mixtures thereof. Hydroxypropyl methylcellulose (HPMC) is used as the preferred film-
5 forming agent along with the therapeutically active agent in the present invention, in an amount ranging from about 2% to about 20% by weight of the timed pulse release composition, more preferably from about 2% to about 5% by weight of the composition. Examples of plasticisers that may be used in the present invention include, but are not limited to glycerol, propylene glycol, polyethylene glycol, sorbitol, triacetin, diethyl phthalate, mineral oil, petrolatum, lanolin
10 and the like. In a preferred embodiment of the present invention, polyethylene glycol (PEG) 4000 is used as the plasticiser in an amount ranging from 0% to about 5% by weight of the core, more preferably from about 0.1% to about 1% by weight of the core. The therapeutically active agent, HPMC and PEG 4000 are mixed in a suitable solvent or solvent system. The solution thus obtained is used to coat the core of the timed pulse release composition to a desired weight gain,
15 in a conventional tablet coating pan. The tablets are then dried in a tray drier at a temperature of 40-50°C for 24 hours.

The spaced drug delivery system is designed to allow immediate release of at least one therapeutically active antidiabetic agent and a delayed release of at least one therapeutically
20 active antidiabetic agent.

The present invention is further described with reference to a specific embodiment wherein one antidiabetic agent that is released immediately upon oral administration is a biguanide antidiabetic agent and one antidiabetic agent that is release as a pulse after a predetermined time
25 after administration is a sulfonyl urea; however this is meant only for the purpose of illustration and is by no means intended to limit the spirit and scope of the present invention.

Examples of biguanide antidiabetic agents that may be used in the present invention include metformin, phenformin and buformin, and their pharmaceutically acceptable salts.
30

Examples of sulfonyl ureas that may be used in the present invention include acetohexamide, carbutamide, chlorpropamide, glipizide, glyburide (glibenclamide), glimepiride, gliclazide, glibornuride, gliquidone, glisoxepid, glyhexamide, phenbutamide, tolazamide, tolbutamide, tolcyclamide, and the like.

71

The amounts of the biguanide antidiabetic agent and the sulfonyl urea are selected such that the combination provides optimum benefits in cases of diabetes mellitus or conditions associated with diabetes mellitus, while reducing the untoward effects. The RE 37330 patent claims use of a combination of glibenclamide and metformin in a method of treating non-insulin dependent diabetes mellitus, in a ratio of 1:100. The results of the clinical study mentioned in the RE 37330 patent indicate that a maximum daily dose of sulfonyl urea considered optimum for the most severe, barely controllable cases is 15mg. However, such a dose has to be combined with a biguanide maximum daily dose of 1500mg in order to obtain the maximum therapeutical effect together with the reduction of untoward effects. The patent claims use of the combination in other ratios such as those having a weight ratio of 1:160 to 1:200.

In preferred embodiments, the sulfonyl urea used in the second composition is glipizide. In yet another preferred embodiment, the sulfonyl urea of the second composition is glibenclamide. Metformin, or its pharmaceutically acceptable salt, preferably the hydrochloride salt, is used as the preferred biguanide antidiabetic agent in the present invention. The metformin hydrochloride and glipizide are preferably used in a metformin hydrochloride to glipizide weight ratio ranging from about 250:1 to about 50:1. Glipizide is used in an amount ranging from about 2mg to about 15mg, while metformin hydrochloride is used in an amount ranging from about 200mg to about 1.5gm. For instance, the unit spaced drug delivery system comprises 250 mg metformin hydrochloride and 2.5 mg glipizide, or 850 mg metformin hydrochloride and 5mg glipizide, or 1 g metformin hydrochloride and 10 mg glipizide. In preferred embodiments the unit spaced drug delivery system comprises 500mg metformin hydrochloride and 5mg glipizide. The metformin hydrochloride-glibenclamide combination is used in a metformin hydrochloride to glibenclamide weight ratio ranging from about 250:1 to about 50:1, more preferably in a ratio of 100:1. Glibenclamide is used in an amount ranging from about 1mg to about 10mg, while metformin hydrochloride is used in an amount ranging from about 200mg to about 1.5gm. In preferred embodiments the unit spaced drug delivery system comprises 250mg metformin hydrochloride and 1.25mg glibenclamide, or 5000 mg metformin hydrochloride and 2.5 mg glibenclamide, more preferably 250mg metformin hydrochloride and 2.5mg glibenclamide, still more preferably 500mg metformin hydrochloride and 5mg glibenclamide.

The following examples do not limit the scope of the invention and are presented as illustrations.

Example 1

The spaced drug delivery system of the present invention is obtained as mentioned in Table 1 below.

Table 1

Ingredients	Quantity (mg)	Percent (%) w/w.
A. Immediate release sulfonyl urea granules -		
Glipizide	5.0	6.67
Microcrystalline cellulose (MCC)	13.0	17.33
Lactose monohydrate	51.175	68.23
Polyvinyl pyrrolidone (PVP K-30)	1.5	2.0
Sodium starch glycolate	3.5	4.67
Sodium lauryl sulfate	0.075	0.1
Magnesium stearate	0.75	1.0
Total	75	100.0
B. Delayed release biguanide core -		
Core -		
Metformin hydrochloride	500.0	83.33
Croscarmellose sodium (Ac-Di-Sol)	50.0	8.33
Corn starch, plain (as 10% starch paste)	17.0	2.83
Microcrystalline cellulose (MCC)	13.5	2.25
Colloidal silicon dioxide	13.5	2.25
Magnesium stearate	6.0	1.0
Total	600.0	100.0
Coat -		
Ethyl cellulose	40.7	coated to a weight gain of 9.5% by weight of the core.
Hydroxypropyl methylcellulose	16.3	

- 5
- The immediate release sulfonyl urea granules were obtained by sifting glipizide, lactose monohydrate and microcrystalline cellulose (MCC) and sodium starch glycolate through a # 40 sieve (as defined by American Society for Testing and Materials, ASTM) and blending the powders suitably. A solution of PVP K-30 in water was used to granulate the dry powder blend.
- 10
- The granules thus obtained were dried to a moisture content of not more than 3%. These granules were then passed through a # 25 sieve (as defined by ASTM). The granules were finally mixed with talc and magnesium stearate to obtain the final granules. The method of preparation of the delayed release biguanide core included sifting the metformin hydrochloride and croscarmellose sodium through a suitable sieve and mixing them in a rapid mixer granulator. The dry powder blend was then granulated using 10% starch paste, followed by wet milling the wet mass through a Fitz mill. The granules so obtained were dried to a moisture content of 3-4%. The dry granules are then milled in a Fitz mill through a 1.5mm screen, followed by sifting of the granules through
- 15

a # 16 sieve (as defined by ASTM). These granules of metformin hydrochloride were then mixed with MCC, colloidal silicon dioxide and magnesium stearate, and the lubricated mixture thus obtained was compressed on a rotary compression machine using oblong shaped punches. The tablets were then coated in a conventional coating pan using a solution of ethyl cellulose and HPMC in a mixture of methanol and dichloromethane.

The delayed release biguanide core was then mixed with 75mg of the immediate release sulfonyl urea granules and encapsulated in a size '0' hard gelatin capsule. The delayed release biguanide composition and 75mg of sulfonyl urea granules were subjected to dissolution studies using pH 6.8 buffer at 37±0.5°C, in a USP Type II apparatus (rpm = 75). The release profile for metformin is recorded in Table 2 below, while that for glipizide is recorded in Table 3 below. The rupture time of the timed pulse release coating on the biguanide core was observed for 30 tablets, which were subjected to dissolution testing. It was found that all the tablets opened reliably at about 1 hour to about 1.3 hour after start of the dissolution test.

Table 2

Time (mins)	% metformin released (± S.D.)
45	1 ± 0.5
105	91 ± 6.89
120	98 ± 4.26

Table 3.

Time (min)	% glipizide released (± S.D.)
45	88 ± 2.19

The tablets were tested in different media, using different conditions of pH and apparatus, and the opening time was recorded. The observations are recorded in Table 4 below.

Table 4

No.	Medium used	Conditions used	Opening time of 6 tablets (hours.min)
1.	pH 6.8	USP Type I apparatus, rpm of 100	1.08, 1.25, 1.13, 1.16, 1.02, 1.12
2.	pH 6.8	USP Type I apparatus, rpm of 100	1.04, 1.14, 1.18, 1.09, 1.09, 1.25
3.	pH 6.8	USP Type I apparatus, rpm of 100	1.23, 1.05, 0.59, 1.12, 0.58, 1.25
4.	pH 6.8	USP Type I apparatus, rpm of 100	1.18, 1.26, 1.24, 1.01, 1.12, 1.06
5.	pH 6.8	USP Type II apparatus, rpm of 75	1.28, 1.30, 1.21, 1.17, 1.09, 1.03
6.	0.1N HCl	USP Type II apparatus, rpm of 75	1.07, 1.18, 1.21, 1.10, 1.03, 1.30
7.	pH 6.8	USP Type II apparatus, rpm of 50	1.02, 1.39, 1.28, 1.21, 1.03, 1.26
8.	0.1N HCl	USP Type II apparatus, rpm of 50	1.24, 1.10, 1.05, 1.12, 1.29, 0.50

Example 2

The spaced drug delivery system of the present invention is obtained as mentioned in Table 5 below.

Table 5

Ingredients	Quantity (mg)	Percent (%) w/w.
A. Immediate release sulfonyl urea granules -		
Glipizide	5.0	6.67
Lactose monohydrate	64.175	85.56
Sodium starch glycolate	3.5	4.67
Polyvinyl pyrrolidone (PVP K-30)	1.5	2.0
Sodium lauryl sulfate (SLS)	0.075	0.1
Magnesium stearate	0.75	1.0
Total	75	100.0
B. Delayed release biguanide core -		
Core -		
Metformin hydrochloride	500.0	83.33
Croscarmellose sodium (Ac-Di-Sol)	50.0	8.33
Corn starch, plain (as 10% starch paste)	17.0	2.83
Microcrystalline cellulose (MCC)	13.5	2.25
Colloidal silicon dioxide	13.5	2.25
Magnesium stearate	6.0	1.0
Total	600.0	100.0
Coat -		
Ethyl cellulose	42.0	coated to a weight gain of 9.8% by weight of the core.
Hydroxypropyl methylcellulose	16.8	

5

The immediate release sulfonyl urea granules were obtained by sifting glipizide, lactose monohydrate and MCC through a # 40 sieve (as defined by American Society for Testing and Materials, ASTM) and blending the powders suitably. A solution of PVP K-30 and SLS in water was used to granulate the dry powder blend. The rest of the procedure remains the same as for Example 1 above. The delayed release biguanide cores were also prepared as per the method given in Example 1 above.

10

The immediate release sulfonyl urea granules (75mg) were mixed with the delayed release biguanide core and the mixture was encapsulated. The delayed release biguanide composition and the sulfonyl urea granules were subjected to dissolution studies using pH 6.8 buffer at 37±0.5°C, in a USP Type II apparatus (rpm = 75). The release profile for metformin is recorded in Table 6 below, while that for glipizide is recorded in Table 7 below. The rupture time for timed pulse release coating on the biguanide core was observed for 30 tablets, which were subjected to

15

dissolution testing. It was found that all tablets opened reliably at about 1 hour to about 1.3 hour after start of the dissolution test.

Table 6

Time (min)	% metformin released
45	1
120	91 ± 5.33

5

Table 7

Time (min)	% glipizide released
45	98 ± 1.55

The tablets obtained as per example 2 of the present invention were tested in water, using different conditions of pH and apparatus, and the opening time was recorded. The observations are recorded in Table 8 below.

10

Table 8

No.	Medium	Conditions used	Opening time of 6 tablets (hours.min)
1.	pH 6.8	USP Type I apparatus, with rpm of 100	1.15, 1.04, 1.16, 1.13, 1.21, 1.16
2.	pH 6.8	USP Type I apparatus, with rpm of 100	1.37, 1.18, 1.20, 1.12, 1.00, 1.15
3.	pH 6.8	USP Type I apparatus, with rpm of 100	1.02, 1.15, 1.07, 1.10, 1.15, 0.53
4.	0.1N HCl	USP Type II apparatus, with rpm of 75	1.11, 1.10, 0.50, 0.58, 0.59, 0.45
5.	pH 6.8	USP Type II apparatus, with rpm of 50	1.00, 1.09, 0.55, 1.09, 1.09, 1.22
6.	0.1N HCl	USP Type I apparatus, with rpm of 100	1.02, 1.00, 1.23, 1.23, 1.26, 1.01

Example 3

The spaced drug delivery system of the present invention is obtained as mentioned in Table 9 below.

Table 9

Ingredients	Quantity (mg)	Percent (%) w/w.
A. Immediate release sulfonyl urea granules -		
Glibenclamide	5.0	6.67
Lactose monohydrate	64.175	85.48
Sodium starch glycolate	3.5	4.67
Polyvinyl pyrrolidone (PVP K-30)	1.5	2.0
Sodium lauryl sulfate (SLS)	0.075	0.1
Magnesium stearate	0.75	1.0
Total	75	100.0
B. Delayed release biguanide core -		
Core -		
Metformin hydrochloride	500.0	83.33
Croscarmellose sodium (Ac-Di-Sol)	50.0	8.33
Corn starch, plain (as 10% starch paste)	17.0	2.83
Microcrystalline cellulose (MCC)	13.5	2.25
Colloidal silicon dioxide	13.5	2.25
Magnesium stearate	6.0	1.0
Total	600.0	100.0
Coat -		
Ethyl cellulose	42.0	coated to a weight gain of 9.8% by weight of the core.
Hydroxypropyl methylcellulose	16.8	

5

The spaced drug delivery system was prepared by a procedure similar to Example 2. The immediate release sulfonyl urea granules (75mg) were mixed with the delayed release biguanide core and the mixture was encapsulated.

- 10 The delayed release biguanide composition and the sulfonyl urea granules were subjected to dissolution studies. The release profile for metformin is similar to that obtained in Example 2 above. The dissolution studies for glibenclamide were carried out using 0.025M tris buffer pH 9.01 at 37±0.5°C, in a USP Type II apparatus (rpm = 50) and is recorded in Table 10 below.

Table 10

Time (min)	% glibenclamide released
15	93 ± 2.09
30	95 ± 1.72
45	96 ± 1.53

15

74

Example 4

The spaced drug delivery system of the present invention is obtained as mentioned in Table 11 below.

Table 11

Ingredients	Quantity (mg)	Percent (%) w/w.
A. Immediate release granules -		
Rosiglitazone maleate (equivalent to 8mg of rosiglitazone base)	10.6	11.04
Lactose monohydrate	78.09	81.25
Sodium starch glycolate	4.5	4.69
PVP K-30	1.92	2.0
Magnesium stearate	0.96	1.0
Total	95.98	99.98
B. Delayed release biguanide core :-		
Core -		
Metformin hydrochloride	500.0	83.33
Croscarmellose sodium (Ac-Di-Sol)	50.0	8.33
Corn starch, plain (as 10% starch paste)	17.0	2.83
Microcrystalline cellulose (MCC)	13.5	2.25
Colloidal silicon dioxide	13.5	2.25
Magnesium stearate	6.0	1.0
Total	600.0	100.0
Coat -		
Ethyl cellulose	42.0	coated to a weight gain of 9.8% by weight of the core.
Hydroxypropyl methylcellulose	16.8	

5

The spaced drug delivery system was prepared by a procedure similar to Example 2. The immediate release rosiglitazone maleate granules were mixed with the delayed release biguanide core and the mixture was encapsulated.

- 10 The delayed release biguanide composition and the rosiglitazone maleate granules were subjected to dissolution studies. The release profile for metformin is similar to that obtained in Example 2 above. The dissolution studies for rosiglitazone maleate were carried out using 0.1N HCl at 37±0.5°C, in a USP Type II apparatus (rpm = 50) and are recorded in Table 12 below.

Table 12

Time (min)	% rosiglitazone released
10	97 ± 2.72
20	96 ± 3.00
30	96 ± 2.82

15

Example 5

The delayed release biguanide core of the present invention was subjected to radiological studies to determine the coat rupture time in vivo. The compositions of Example 2 with the addition of 25mg barium sulfate in the core, was used for the radiological studies. The delayed release metformin tablet cores containing barium sulfate were prepared as per the method given in Example 1 above, with the barium sulfate being mixed with the starch paste to ensure its uniform distribution in the core.

A single dose, open label study was carried out using six healthy male volunteers. The subjects were fasted overnight before dosing and for 4 hours thereafter. Drinking water was prohibited for 2 hours before dosing and 2 hours thereafter. A single barium sulfate containing delayed release metformin tablet core was administered to each volunteer as the test product along with 240ml of drinking water. Standard meals were provided at 4 hours after dosing. X-rays were taken at the following time points after dosing : 30, 45, 60, 75 and 90 minutes. The result of the radiological follow-up at the above-mentioned time intervals is given in Table 13 below.

Table 13

Vol. No.	Position of the tablet (minutes)				
	30	45	60	75	90
1	Proximal small bowel (intact)	Proximal small bowel (intact)	Obscure (intact)	Left hyponchondrion of colon (intact)	Disappeared completely
2	Not observed	Not observed	Not observed	Not observed	Not observed
3	Small bowel (intact)	Small bowel (intact)	Obscure	Small bowel (intact)	Disappeared completely
4	Stomach fundus (intact)	Pyloric antrum (intact)	Pyloric antrum (intact)	Pyloric antrum (intact)	Proximal jejunal loop (Disintegrating)
5	Distal jejunal loop (intact)	Proximal ileal loop (intact)	Ileal loop (Disintegrating)	Ileal loop (Disintegrating)	Disappeared completely
6	Pyloric antrum (intact)	Pyloric antrum (intact)	Duodenojejunal flexure (intact)	Distal duodenum (disintegrating)	Disappeared completely

As seen in Table 13 above, the tablet was not observed in volunteer no. 2, perhaps due to insufficient barium sulfate in the core. In four of the five remaining volunteers, the tablet was completely disintegrated in 90 minutes, and in volunteer no. 4 the tablet started disintegrating at 90 minutes.

75

Example 6

Comparative example 1

This example illustrates the process of optimization of the composition to obtain, at about the predetermined time, a reliable manner of coat rupture.

5

Tablet cores were prepared according to the composition given in Table 14. The target coat rupture time was 1 hr.

Table 14

Ingredients	Quantity (mg)
Metformin hydrochloride	500.0
Croscarmellose sodium (Ac-Di-Sol)	34.5
PVP K-90F	10.0
Magnesium stearate	5.5
Total	550.0

10 The above cores were coated with a combination of ethylcellulose and hydroxypropyl methylcellulose dissolved in methylene chloride : methanol (4:1) solvent system. The ratio of ethylcellulose to hydroxypropyl methylcellulose was varied to evaluate its effect on the coat rupture time. When the ratio was 9:2 and the gain in weight upon coating was 4% by weight of the total weight of the core, the coat rupture time was about 2 hours. The coat rupture time could
15 be decreased by decreasing the amount of coat applied. However, at a ethylcellulose to hydroxypropyl methylcellulose ratio of 9:2, the coat rupture time was sensitive to this factor and this could lead to coat rupture time changing with variations in amount of coat applied from batch to batch. It was found that by a small change from 4% to 3% weight gain upon coating the coat rupture time decreased to 45-60 minutes. Increase in proportion of hydroxypropyl
20 methylcellulose decreased the coat rupture time. Ratio of ethylcellulose to hydroxypropyl methylcellulose in the range of 8:3 to 7:3 were evaluated and it was surprisingly found that at these ratios coat rupture time of about 1 hr was obtained and the coat rupture time was not sensitive to the amount of coat applied. However, the coat did not rupture in a reliable manner as is evident from the results on the dissolution test evaluation for coat rupture time given in Table
25 15 below. The test was conducted in a USP type II apparatus in pH 6.8 buffer at 50 rpm.

Table 15

% weight gain on application of coat of EC: HPMC ratio of 7.5:3	No of tablets tested	Opening time (minutes)
9%	18	60, 53, 60, <u>> 135</u> , 60, 58, 48, 50, <u>>135</u> , 50, 75, 55, 65, 64, 55, 55, 55, 48
11%	18	90, 71, 78, 80, <u>> 150</u> , 79, 60, 66, 73, 60, 91, 70, 76, 85, <u>did not open</u> , 76, 76, <u>did not open</u>
14.6%	6	66, 65, 78, 180, 86, 60

It is seen that on an average the coat rupture time meets the target rupture time of about 1 hr, however, the reliability of rupture is low in that some tablets the coat rupture is unduly prolonged.

5 The coat composition was then kept fixed and the core composition was optimized, for example, to compositions in Examples 1 and 2, to achieve coat rupture and drug release in a reliable manner.

Comparative example 2

The following example is generated as per example 1 of European patent 408496, equivalent to 10 IE 902533. The tablets were made as per the following formula in Table 16 below--

Table 16

Ingredients	Quantity (mg/tablet)
Core	
Diclofenac sodium	50mg
Polyvinylpyrrolidone (crosslinked)	100mg
Sodium chloride	50mg
Silica aerogel (Aerosil® 200)	7mg
Magnesium stearate	3mg
Coating	
Cellulose acetate (containing 32% acetyl)	31mg
Cellulose acetate (containing 32.9% acetyl)	32.33mg
Hydroxypropyl methylcellulose	3.33mg

15 The core components were mixed in a tumbler mixer and compressed in a tableting press using a 8mm concave punch. The coating components were dissolved in a mixture of methylene chloride and methanol. This solution was used to coat the cores by a fluidized bed method. Three different batches were obtained by coating the cores to a weight gain of 4% and 9.8% (by weight of the core). The tablets were then dried for 48 hours.

20 The tablets obtained by this formula were tested in 900ml of water at 37°C and the opening time is recorded in Table 17 below.

76

Table 17

Coating (% by weight of the core)	Observations	Target opening time as per Table 1 of example 1 of IE 902533
4% (before drying)	One tablet opened at about 45 minutes. Remaining tablets did not open till 3 hours and 20 minutes.	65 minutes
4% (after drying for 48 hours at 40°C)	One tablet opened at about 30 minutes, and another opened at about 50 minutes. Remaining tablets did not open till 2 hours and 15 minutes.	65 minutes
9.8%	No tablet opened till 2 hours and 56 minutes.	120 minutes

The above observations indicate that the tablets obtained by the formula mentioned in IE 902533 do not provide opening of the tablets at a specific predetermined time, as claimed in the main claim of the patent, in a reliable manner.

While the invention has been described with reference to specific embodiments, this was done for purposes of illustration only and should not be considered to limit the scope of the invention.

We claim –

1. A method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system, wherein at least one first therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system, and at least one second therapeutically active agent is released as a pulse at a predetermined time after oral administration, wherein the two or more therapeutic agents act on the disease condition by similar or dissimilar, but complementary mechanisms, to control the symptoms of the disease, or a measurable indicator of the disease condition, and further wherein the time of release of the two or more therapeutically active agents is designed to provide desired control on the disease condition.
2. A method of administration of two or more therapeutically active agents comprising orally administering to a patient a spaced drug delivery system at a specified time prior to food intake by the patient, wherein at least one therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system and at least one therapeutically active agent is released as a pulse after a delay at about the time when food is taken.
3. A method of administration of two or more therapeutically active agents as claimed in claim 1 or 2, wherein the two or more therapeutically active agents are therapeutically active antidiabetic agents.
4. A spaced drug delivery system designed to provide desired control on the disease condition, comprising
 - a. a first composition comprising one or more first therapeutically active agent(s), and
 - b. a second composition comprising one or more second therapeutically active agent(s),wherein at least one first therapeutically active agent is released immediately upon oral administration of the spaced drug delivery system, and at least one second therapeutically active agent is released as a pulse at a predetermined time after oral administration, wherein the two or more therapeutic agents act on the disease condition by similar or dissimilar, but complementary mechanisms, to control the symptoms of the disease, or a measurable indicator of the disease condition, and further wherein the time of release of the two or more therapeutically active agents is designed to provide desired control on the disease condition.
5. A spaced drug delivery system for the treatment of diabetes mellitus or conditions associated with diabetes mellitus, comprising -

- a. a first composition comprising one or more therapeutically active antidiabetic agent(s), which is/are released as a pulse after a delay, and
- b. a second composition comprising one or more therapeutically active antidiabetic agent(s), which is/are released immediately upon oral administration of the spaced drug delivery system.
6. A spaced drug delivery system as claimed in claim 5, wherein the first composition is a timed pulse release composition that releases as a pulse an antidiabetic agent after a predetermined time spacing or interval after oral administration of the spaced drug delivery system.
7. A spaced drug delivery system as claimed in claim 5, wherein the antidiabetic agent in the first composition is a biguanide antidiabetic agent, and the antidiabetic agent in the second composition is a sulfonyl urea.
8. A spaced drug delivery system as claimed in claim 5, wherein the antidiabetic agents in the first composition are selected from the group consisting of an alpha glucosidase inhibitor, a thiazolidinedione, and an insulin secretagogue; and the antidiabetic agent in the second composition is an insulin secretagogue; further wherein the insulin secretagogues, if present in both first and second compositions, are not the same.
9. A spaced drug delivery system as claimed in claim 5, wherein the antidiabetic agent in the first composition is a biguanide antidiabetic agent, and the antidiabetic agent in the second composition is selected from the group consisting of insulin secretagogue and a thiazolidinedione, optionally in combination with an alpha glucosidase inhibitor.
10. A spaced drug delivery system as claimed in claim 5, wherein the antidiabetic agent in the first composition is a biguanide antidiabetic agent, and the antidiabetic agent in the second composition is an alpha glucosidase inhibitor.
11. A spaced drug delivery system as claimed in claim 7 comprising metformin hydrochloride and glipizide in a weight ratio ranging from 250:1 to 50:1.
12. A spaced drug delivery system as claimed in claim 11 comprising metformin hydrochloride in an amount ranging from about 200mg to about 1.5gm, and glipizide in an amount ranging from about 2mg to about 15mg.
13. A spaced drug delivery system as claimed in claim 7, comprising metformin hydrochloride and glibenclamide in a weight ratio ranging from 250:1 to 50:1.
14. A spaced drug delivery system as claimed in claim 13, comprising metformin hydrochloride and glibenclamide in a weight ratio of 100:1.

15. A spaced drug delivery system as claimed in claim 7, comprising metformin hydrochloride in an amount ranging from about 200mg to about 1.5gm, and glibenclamide in an amount ranging from about 1mg to about 10mg.
- 5 16. A spaced drug delivery system as claimed in claim 4 comprising a timed pulse release composition comprising a core composition comprising one or more therapeutically active antidiabetic agents, a swelling agent, and optionally water soluble compound(s) for inducing osmosis, and a coat composition comprising one or more film forming polymers, wherein upon swelling of the core the coat ruptures and releases the therapeutically active agent in a reliable manner at about a predetermined time after oral administration of the composition.
- 10 17. A spaced drug delivery system as claimed in claim 16 wherein the timed pulse release composition is optimized as follows:
- a. the core composition is capable of swelling at a desired rate to a sufficient extent,
 - b. the coat composition has the desirable film strength, plasticity, and water permeability, and
 - 15 c. the amount of coat composition applied is adjusted,
- such that upon swelling of the core the coat ruptures and releases as a pulse the therapeutically active agent in a reliable manner at about the predetermined time after oral administration of the composition wherein the reliable manner of rupture comprises rupturing of 36 tablets out of a total of 36 tablets at about the predetermined time, when tested by subjecting the tablets to USP dissolution test using an aqueous media at $37 \pm 0.5^\circ\text{C}$, in a USP Type I or Type II apparatus at an rpm selected from the range of about 50 rpm to about 100 rpm.
- 20 18. A spaced drug delivery system as claimed in claim 17 wherein the predetermined time is in the range from about 1 hr to about 4 hr, and the 36 out of the 36 tablets rupture within $\pm 50\%$ of the predetermined time.
- 25 19. A spaced drug delivery system as claimed in claim 18 wherein the predetermined time is about 70 min.
- 30 20. A spaced drug delivery system as claimed in claim 19, wherein the "release of therapeutically active agent as a pulse" comprises release of not more than 10% of the active ingredient at 45 min and at least 70% of the active ingredient at 2 hrs when tested by subjecting the tablets to USP dissolution test using pH 6.8 buffer at $37 \pm 0.5^\circ\text{C}$, in a USP Type II apparatus at an rpm of 75.

21. A spaced drug delivery system as claimed in claim 16, wherein the swelling agent is selected from the group consisting of croscarmellose sodium, crosslinked polyvinylpyrrolidone and sodium starch glycolate.
22. A spaced drug delivery system as claimed in claim 21, wherein the core further comprises a wicking agent.
23. A spaced drug delivery system as claimed in claim 22, wherein the wicking agent is selected from microcrystalline cellulose and colloidal silicon dioxide.
24. A spaced drug delivery system as claimed in claim 23, wherein the core further comprises starch.
25. A spaced drug delivery system as claimed in claim 16, wherein the film forming polymers in the coat comprise a mixture of a water insoluble polymer and a water soluble polymer.
26. A spaced drug delivery system as claimed in claim 25, wherein the water insoluble polymer is ethyl cellulose and the water soluble polymer is hydroxypropyl methylcellulose (HPMC).
27. A spaced drug delivery system as claimed in claim 26, wherein the predetermined time of release is about 70 min and the weight ratio of ethyl cellulose to hydroxypropyl methylcellulose is in a range from about 6:3 to about 9:3.
28. A spaced drug delivery system as claimed in claim 26, wherein the core is coated to a weight gain of about 5% to about 10%.
29. A spaced drug delivery system as claimed in claim 27, wherein the core is coated to a weight gain of about 9% to about 10%.
30. A spaced drug delivery system as claimed in claim 17 wherein the predetermined time is in the range of about >4 hr to about 12 hr, the 36 out of the 36 tablets rupture within $\pm 25\%$ of the predetermined time.
31. A method for treating diabetes mellitus or conditions associated with diabetes mellitus in a human, which method comprises administering a spaced drug delivery system claimed in claim 5 or 6.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 02/00005

CLASSIFICATION OF SUBJECT MATTER

IPC⁷: A61J 3/07, A61K 9/22

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)

IPC⁷: A61J, A61K, 9/00

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 practicable, search terms used)

EPO: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6117450 A (DITTGEN et al.) 12 September 2000 (12.09.00) <i>the whole document.</i>	4
Y	<i>the whole document.</i>	5,16
A	US 4681583 (URQUHART et al.) 21 July 1987 (21.07.87) <i>the whole document.</i>	4

☐ Further documents are listed in the continuation of Box C.☒ See patent family 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 application or patent but published on or after the international filing date
- ..I- document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- ..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

22 April 2002 (22.04.2002)

Date of mailing of the international search report

28 May 2002 (28.05.2002)

Name and mailing address of the ISA/AT

Austrian Patent Office
Kohlmarkt 8-10; A-1014 Vienna
Facsimile No. 1/53424/535

Authorized officer

SLABY

Telephone No. 1/53424/348

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 02/00005

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1,2,3,31
because they relate to subject matter not required to be searched by this Authority, namely:
claims 1,2,3,31 are directed to methods of treatment of the human body, which cannot be granted of Rule 39.1 (iv) PCT.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: It is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 02/00005-0

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
US	A	4681583	21-07-1987	US	A	4578075	25-03-1986
				US	A	4773907	27-09-1988
US	A	6117450	12-09-2000	AU	A1	80099/98	24-11-1998
				BR	A	9809328	04-07-2000
				DE	C1	19718012	08-10-1998
				EP	A1	979069	16-02-2000
				HU	A8	00003121	28-02-2001
				PL	A1	336572	03-07-2000
				SK	A3	1479/99	11-07-2000
				WO	A1	9848782	05-11-1998

PCT/ISA/210 (patent family annex) (July 1998)

PATENT COOPERATION TREATY

88

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GERVASI, Gemma
NOTARBARTOLO & GERVASI
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

15.12.2003

Applicant's or agent's file reference
3063PTWO/a

IMPORTANT NOTIFICATION

International application No.
PCT/EP02/13497

International filing date (day/month/year)
29.11.2002

Priority date (day/month/year)
29.11.2001

Applicant

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the International
preliminary examining authority:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Janzing, M

Tel. +31 70 340-4140



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3063PTWO/a	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/16)	
International application No. PCT/EP02/13497	International filing date (day/month/year) 29.11.2002	Priority date (day/month/year) 29.11.2001
International Patent Classification (IPC) or both national classification and IPC A61K9/20		
Applicant MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.		
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 opinion 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 Rule 66.2(a)(ii) 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 26.06.2003	Date of completion of this report 15.12.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Boulois, D Telephone No. +31 70 340-3678 	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP02/13497

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

1-22 as originally filed

Claims, Numbers

1-19 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.:
- ☐ 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:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP02/13497**

**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	1-19
	No: Claims	
Inventive step (IS)	Yes: Claims	1-19
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-19
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP02/13497

1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: FR-A-2244481

D2: WO-A-0003742 (cited in the application)

D3: WO-A-9717975 (cited in the application)

E1: WO-A-0255009

2. The subject-matter claimed in claims 1-19 can be regarded as novel (Article 33(2) PCT) since the described composition and its use are not disclosed in the prior art.

The content of the document WO-A-0255009 (E1) will have to be taken in account in the regional phase for the judgement of novelty. This document seems to be relevant for the novelty of claims 1, 6-8, 19.

3. The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-19 involves an inventive step.

The layered compositions of the present application offer a better dissolution of the active agents than when the two compounds are mixed together and a comparable or better dissolution when the two compounds are maintained in separate compositions (see the examples of the present application), while offering a better compliance.

The document D1, appears to be of particular relevance as far as inventive step is concerned and can be considered as the closest prior art. This document solves indeed the same problem than the present application, namely the improvement of the bioavailability of glibenclamide when it is in combination with a biguanide (see D1, p. 1, l. 35-41; p. 2, l. 24-40; p. 5-9, the examples).

The present application differs from the disclosure of D1 by the use of metformine which is used as the biguanide, instead of phenformine in D1.

D1 also presents the biguanide in a retard form, and the dosage of phenformine (25-50 mg) is much lower than the dosage of metformine (200-1000 mg) of the present application.

The problem to be solved by the present invention may therefore be regarded as how to increase the bioavailability of glibenclamide when it is administered with metformine,

while improving the compliance by a unique administration of both compounds.

The solution proposed in claim 1 of the present application is considered as involving an inventive step.

The replacement of a known biguanide by another known biguanide is not obvious in this case. The association of the active ingredients metformine/glibenclamide must be made in a high ratio, which causes a heavy reduction in the bioavailability of glibenclamide. The use of metformine implies a mass-effect which cannot be foreseen in the light of use of phenformine in document D1.

The replacement of a biguanide in a known composition by an another biguanide is therefore not envisageable for the resolution of the problem of the present application. The subject-matter of claims 1-19 is therefore inventive over D1.

PATENT C PERATI N TREATY

From the RECEIVING OFFICE

PCT

To:

Gerli, Paolo
NOTARBARTOLO & GERVASI
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE

NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing
(day/month/year)

- 7. 01. 2003

Applicant's or agent's file reference

3063PTWO/Er/fe

IMPORTANT NOTIFICATION

International application No.

PCT/EP 02/ 13497

International filing date (day/month/year)

29/11/2002

Priority date (day/month/year)

29/11/2001

Applicant

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.

3. ☐ Other: _____

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the Receiving Office



European Patent Office, P.B. 5818 Patentplan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

M. Peis
Tel: (070) 340 34 20
The Hague

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 0 2 / 1 3 4 9 7	
International Application No.	
2 9 NOV 2002	(29 11 2002)
International Filing Date	
EUROPEAN PATENT OFFICE	
PCT INTERNATIONAL APPLICATION	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if distinct) (12 characters maximum) 3063PTWO/Er/fe	

Box No. I TITLE OF INVENTION Pharmaceutical compositions for the treatment of Type II Diabetes Mellitus	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A. 1. Avenue de la Gare 1611 LUXEMBOURG - Luxembourg	
Telephone No.	
Facsimile No.	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: LU	State (that is, country) of residence: LU
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) TOSETTI Alessandro Via F. Paoletti, 13 50012 BAGNO A RIPOLI - Italy	
This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.)	
Applicant's registration No. with the Office	
State (that is, country) of nationality: IT	State (that is, country) of residence: IT
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) GERLI: Paolo c/o NOTARBARTOLO & GERVASI Corso di Porta Vittoria, 9 20122 MILAN - ITALY	
Telephone No. +39025417991	
Facsimile No. +390254179928	
Teleprinter No.	
Agent's registration No. with the Office	
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Sheet No. ...2...

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) GUIDUCCI Mauro Via Tullio Levi Civita, 1 52100 AREZZO - Italy	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: IT	State (that is, country) of residence: IT
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) VITI Giovanni Viale A. Guidoni, 179 50127 FIRENZE Italy	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: IT	State (that is, country) of residence: IT
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) (Empty)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) (Empty)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V

DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☐ AP

ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)

☐ EA

Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☐ EP

European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☐ OA

OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

☐ AE United Arab Emirates	☐ GM Gambia	☐ NZ New Zealand
☐ AG Antigua and Barbuda	☐ HR Croatia	☐ OM Oman
☐ AL Albania	☐ HU Hungary	☐ PH Philippines
☐ AM Armenia	☐ ID Indonesia	☐ PL Poland
☐ AT Austria	☐ IL Israel	☐ PT Portugal
☐ AU Australia	☐ IN India	☐ RO Romania
☐ AZ Azerbaijan	☐ IS Iceland	☐ RU Russian Federation
☐ BA Bosnia and Herzegovina	☐ JP Japan	
☐ BB Barbados	☐ KE Kenya	☐ SD Sudan
☐ BG Bulgaria	☐ KG Kyrgyzstan	☐ SE Sweden
☐ BR Brazil	☐ KP Democratic People's Republic of Korea	☐ SG Singapore
☐ BY Belarus	☐ KR Republic of Korea	☐ SI Slovenia
☐ BZ Belize	☐ KZ Kazakhstan	☐ SK Slovakia
☐ CA Canada	☐ LC Saint Lucia	☐ SL Sierra Leone
☐ CH & LI Switzerland and Liechtenstein	☐ LK Sri Lanka	☐ TJ Tajikistan
☐ CN China	☐ LR Liberia	☐ TM Turkmenistan
☐ CO Colombia	☐ LS Lesotho	☐ TN Tunisia
☐ CR Costa Rica	☐ LT Lithuania	☐ TR Turkey
☐ CU Cuba	☐ LU Luxembourg	☐ TT Trinidad and Tobago
☐ CZ Czech Republic	☐ LV Latvia	
☐ DE Germany	☐ MA Morocco	☐ TZ United Republic of Tanzania
☐ DK Denmark	☐ MD Republic of Moldova	☐ UA Ukraine
☐ DM Dominica		☐ UG Uganda
☐ DZ Algeria		☐ US United States of America
☐ EC Ecuador	☐ MG Madagascar	
☐ EE Estonia	☐ MK The former Yugoslav Republic of Macedonia	☐ UZ Uzbekistan
☐ ES Spain		☐ VN Viet Nam
☐ FI Finland	☐ MN Mongolia	☐ YU Yugoslavia
☐ GB United Kingdom	☐ MW Malawi	☐ ZA South Africa
☐ GD Grenada	☐ MX Mexico	☐ ZM Zambia
☐ GE Georgia	☐ MZ Mozambique	☐ ZW Zimbabwe
☐ GH Ghana	☐ NO Norway	

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ VC Saint Vincent and the Grenadines

☐ SC Seychelles

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that these additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Form PCT/RO/101 (second sheet) (July 2002)

See Notes to the request form

Sheet No. ...4...

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 29/11/2001	FI2001A000230	IT		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(4)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

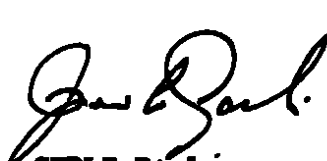
Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- | | | |
|---|--|---|
| ☐ Box No. VIII (i) | Declaration as to the identity of the inventor | : |
| ☐ Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| ☐ Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| ☐ Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| ☐ Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : |

Sheet No. 5

Box No. IX CHECK LIST; LANGUAGE OF FILING		
This international application contains: (a) the following number of sheets in paper form: request (including declaration sheets) : 5 description (excluding sequence listing part) : 22 claims : 4 abstract : 1 drawings : _____ Sub-total number of sheets : 32 sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) : _____ Total number of sheets : 32 (b) sequence listing part of description filed in computer readable form (i) ☐ only (under Section 801(a)(i)) (ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii)) Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(II), in right column): _____	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): 1. ☐ fee calculation sheet : _____ 2. ☐ original separate power of attorney : _____ 3. ☐ original general power of attorney : _____ 4. ☐ copy of general power of attorney; reference number, if any: _____ : _____ 5. ☐ statement explaining lack of signature : _____ 6. ☐ priority document(s) identified in Box No. VI as item(s): _____ : _____ 7. ☐ translation of international application into (language): _____ : _____ 8. ☐ separate indications concerning deposited microorganism or other biological material : _____ 9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other)) (i) ☐ copy submitted for the purposes of international search under Rule 134ter only (and not as part of the international application) : _____ (ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 134ter : _____ (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column : _____ 10. ☒ other (specify): Accompanying Letter : 1	Number of items
Figure of the drawings which should accompany the abstract: _____	Language of filing of the international application: ENGLISH	
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i>		
 Milan, Italy, November 28, 2002 GERLI Paolo		
For receiving Office use only		
1. Date of actual receipt of the purported international application: 29 NOV 2002 (29.11.02) 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: _____ 4. Date of timely receipt of the required corrections under PCT Article 11(2): _____ 5. International Searching Authority (if two or more are competent): ISA /	2. Drawings: ☐ received: ☐ not received: 6. ☐ Transmittal of search copy delayed until search fee is paid	
For International Bureau use only		
Date of receipt of the record copy by the International Bureau: _____		

From the INTERNATIONAL BUREAU

PCT**NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES**

(PCT Rule 47.1(c), first sentence)

To:

GERLI, Paolo
c/o Notarbartolo & Gervasi
Corso di Porta Vittoria, 9
I-20122 Milan
ITALIE

NOTARBARTOLO & GERVASI MILANO	
R E C E I V E D	
19 GIU. 2003	
AR	RS

IMPORTANT NOTICE

Date of mailing(day/month/year) 05 June 2003 (05.06.03)		
Applicant's or agent's file reference 3063PTWO/Er/fe		
International application No. PCT/EP02/13497	International filing date(day/month/year) 29 November 2002 (29.11.02)	Priority date(day/month/year) 29 November 2001 (29.11.01)
Applicant MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

CH, KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 05 June 2003 (05.06.03) under No. 03/045355

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Judith Zahra

Facsimile No.(41-22) 740.14.35

Telephone No.(41-22) 338.91.11

Form PCT/IB/308 (April 2002)

NOTARBARTOLO & GERVASI MILANO	
RECEIVED	
21/ABU. 2003	
[Signature]	

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

GERVASI, GEMMA
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria 9
20122 Milan
Italy

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year) 22 July 2003 (22.07.03)		IMPORTANT INFORMATION	
Applicant's or agent's file reference 3063PTWO/Er/fe			
International application No. PCT/EP02/13497	International filing date (day/month/year) 29 November 2002 (29.11.02)	Priority date (day/month/year) 29 November 2001 (29.11.01)	
Applicant MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A. et al			

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR
National : AU, BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SC, SD, SE, SG, SI, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

[Signature]

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: R. Boudraa
Facsimile No. (41-22) 338-7080	Telephone No. (41-22) 338 8335

REPORTE DEL EXAMEN

Solic. Internacional No.

PRELIMINAR INTERNACIONAL

PCT/EP02/13497

I. Base del Reporte

1. Con respecto a los elementos de la solicitud internacional (Las hojas reemplazadas las cuales han sido suministradas a la Oficina receptora en respuesta a una invitación bajo el Artículo 14, se mencionan en este reporte como "presentada originalmente" y no se anexan a este reporte ya que no contienen enmiendas (Reglas 70.16 y 70.17).):

Descripción, páginas:

1-22 como se presentaron originalmente

Reivindicaciones, Nos:

1-19 como se presentaron originalmente

2. Con respecto al lenguaje, todos los elementos marcados más arriba están disponibles o suministrados a esta Autoridad en el lenguaje en la cual la solicitud internacional se presentó, a menos que se indique de otra forma este punto.

Estos elementos están disponibles o suministrados a esta Autoridad en el lenguaje siguiente: , que es:

REPORTE DEL EXAMEN

Solic. Internacional No.

PRELIMINAR INTERNACIONAL

PCT/EP02/13497

-
- [] el lenguaje de una traducción suministrada para los propósitos de la búsqueda internacional (bajo la regla 23.1(b)).
 - [] el lenguaje de la publicación de la solicitud internacional (bajo la Regla 48.3(b)).
 - [] el lenguaje de una traducción suministrada para los propósitos del examen preliminar internacional (bajo la Regla 55.2 y/o 55.3).

3. Con respecto a cualquier nucleótido y/o secuencia de aminoácidos descritos en la solicitud internacional, se llevó a cabo el examen preliminar internacional en base al listado de secuencias:

- [] contenido en la solicitud internacional en forma escrita,
- [] presentado con la solicitud internacional en forma leíble por computadora,
- [] suministrada subsecuentemente a esta Autoridad en forma escrita,
- [] suministrada subsecuentemente a esta Autoridad en forma leíble por computadora,

REPORTE DEL EXAMEN**Solic. Internacional No.****PRELIMINAR INTERNACIONAL****PCT/EP02/13497**

☐ El testimonio que el listado de secuencias escritas subsecuentemente suministradas no llevan más allá de la descripción en la solicitud internacional como se presentó, ha sido suministrado,

☐ El testimonio que la información registrada en forma leíble por computadora es idéntica al listado de secuencias escritas ha sido suministrado.

4. Las enmiendas han resultado en la cancelación de:

☐ la descripción, páginas:

☐ las reivindicaciones, Nos:

☐ los dibujos, hojas:

5. ☐ Este reporte ha sido establecido como si (algunas de) las enmiendas han sido hechas, ya que se han considerado para ir más allá de la descripción como se presentó (Regla 70.2(c)):

(Cualquier hoja de reemplazo que contiene tales enmiendas debe ser mencionada bajo el punto 1 y anexadas a este reporte.)

6. Observaciones adicionales, si es necesario:

REPORTE DEL EXAMEN
PRELIMINAR INTERNACIONAL

Solic. Internacional No.
PCT/EP02/13497

V. Testimonio razonado bajo el Artículo 35(2) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que apoyan tal testimonio

1. Testimonio

Novedad (N)	Sí:	Reivindicaciones 1-19
	No:	Reivindicaciones
Etapa Inventiva (EI)	Sí:	Reivindicaciones 1-19
	No:	Reivindicaciones
Aplicabilidad Industrial (AI)	Sí:	Reivindicaciones 1-19
	No:	Reivindicaciones

2. Citas y explicaciones

ver hoja por separado

1. Los siguientes documentos (D) están designados en esta comunicación; la numeración será adherida en el resto del procedimiento:

D1: FR-A-2244481

D2: WO-A-0003742 (citado en la solicitud)

D3: WO-A-9717975 (citado en la solicitud)

E1: WO-A-0255009

2. La materia objeto reclamada en las reivindicaciones 1-19 puede considerarse como novedosa (Artículo 33(2) del PCT) ya que la composición descrita y su uso no están descritos en la técnica anterior.

El contenido del documento WO-A-0255009 (E1) tendría que ser tomado en cuenta en la fase regional para el dictamen de novedad. Este documento parece ser relevante para la novedad de las reivindicaciones 1, 6-8, 19.

3. La presente solicitud no cumple los requerimientos del Artículo 33(3) del PCT, debido a que la materia objeto de las reivindicaciones 1-19 implica una etapa inventiva.

Las composiciones constituidas por capas de la presente solicitud ofrecen una mejor disolución de los agentes activos que cuando los dos compuestos son mezclados juntos y una mejor o comparable disolución cuando los dos compuestos son mantenidos en composiciones por separado (ver los ejemplos de la presente solicitud), mientras que ofrecen una mejor docilidad.

El documento D1, parece ser de relevancia particular hasta que la etapa inventiva sea interesada y pueda ser considerada como la técnica anterior más cercana. Este documento soluciona en realidad el mismo problema que la presente solicitud, a saber el mejoramiento de la biodisponibilidad de la glibenclamida cuando está en combinación con una biguanida (ver D1, p. 1, l. 35-41; p. 2, l. 24-40; p. 5-9, los ejemplos).

La presente solicitud difiere de la descripción de D1 mediante el uso de metformina que se utiliza como la biguanida, en lugar de fenformina en D1.

D1 también presenta la biguanida en una forma retardada, y la dosificación de fenformina (25-50 mg) es muy inferior que la dosificación de la metformina (200-1000 mg) de la presente solicitud.

El problema a resolver por la presente solicitud puede por lo tanto ser considerada de cómo aumentar la biodisponibilidad de la glibenclamida cuando se suministra con metformina, mientras que mejora la docilidad mediante un único suministro de ambos compuestos.

La solución propuesta en la reivindicación 1 de la presente solicitud se considera que implica una etapa inventiva.

El reemplazo de una biguanida conocida por otra biguanida conocida no es obvio en este caso. La asociación de los ingredientes activos de metformina/glibenclamida debe hacerse en una alta relación, que provoque una fuerte reducción en la biodisponibilidad de la glibenclamida. El uso de metformina implica un efecto en masa que puede no ser prevista en la luz del uso de fenformina en el documento D1.

El reemplazo de una biguanida en una composición conocida por otra biguanida es por lo tanto no concebible para la resolución del problema de la presente solicitud. Por lo tanto la materia objeto de las reivindicaciones 1-19 es inventiva sobre D1.

ORGANIZACIÓN MUNDIAL DE LA PROPIEDAD INTELECTUAL
Oficina Internacional

SELLO

(CÓDIGO DE BARRAS)

(43) Fecha de publicación internacional:
5 de Junio del 2003 (05.06.2003)

PCT

(10) Número de Publicación Internacional:
WO 03/045355 A1

(51) Clasificación⁷ de Patente Internacional: A61K 9/20, 31/64
(21) Número de solicitud internacional: PCT/EP02/13497
(22) Fecha de presentación internacional: 29 de Noviembre del 2002 (29.11.2002)
(25) Idioma de Presentación: Inglés
(26) Idioma de Publicación: Inglés
(30) Fecha de Prioridad: 29 de Noviembre del 2001 (29.11.2001) IT
F12001A000230

(51) Estados designados (nacionales): AE, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KR, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(54) Estados Designados (regionales): Patente ARIPO (CH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eusemítica (AM, AZ, BY, EG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TO).

Declaración bajo la Regla 4.17:
- entidad inventiva (Regla 4.17(iv)) para US únicamente

Publicada
- Con reporte de búsqueda internacional
- Antes de la expiración del tiempo límite para enmendar las reivindicaciones y volver a publicar en el caso de recepción de enmienda.

Para códigos de dos letras y otras abreviaciones, se refiere a las "Notas Guía en Códigos y Abreviaciones" que aparecen al principio de cada edición regular de la Gaceta del PCT.

(71) Solicitante (para todos los Países designados excepto los US): MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A. [LU/LU]; 1, avenue de la Gare, L-1611 Luxembourg (LU).

(72) Inventores y
Inventores/Solicitantes (únicamente para los US): TOSETTI, Alessandro [IT/IT]; Via F. Paoletti, 13, I-50012 Bagno A Ripoli (IT). GUIDUCCI, Mauro [IT/IT]; Via Tullio Levi Civita, 1, I-S2100 Arezzo (IT). VITI, Giovanni [IT/IT]; Viale A. Guidoni, 179, I-50127 Firenze (IT).

(74) Agentes: GERLI, Paolo s/o Notabartolo & Garvani, Corso di Porta Vittoria, 9, I-20122 Milán (IT).

(54) Título: COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN METFORMINA Y GLIBENCLAMIDA PARA EL TRATAMIENTO DE LA DIABETES MELLITUS TIPO II

(57) Resumen: Se describen composiciones farmacéuticas que son suministrables por la vía oral en forma de comprimidos para el tratamiento de la diabetes mellitus tipo II, que comprenden glibenclamida y metformina, o sus sales farmacéuticamente aceptables, como ingredientes activos, mantenidos en forma separada entre sí dentro de la misma composición.

PCT
PETITORIO

El abajo firmante solicita que la presente solicitud Internacional sea procesada de acuerdo al Tratado de Cooperación en Materia de Patentes

PCT/EP 02/13497
No. de Solicitud Internacional
29 DE NOVIEMBRE DEL 2002 (29.11.2002)
Fecha de presentación internacional
OFICINA DE PATENTES EUROPEA
SOLICITUD INTERNACIONAL DE PCT
Nombre de la oficina receptora y "Solicitud Internacional de PCT"

Referencia de archivo del solicitante o agente
(si se desea) (12 caracteres máximo) 3063PTWO/Er/fe

Cuadro No. I TITULO DE LA INVENCIÓN

Composiciones farmacéuticas para el tratamiento de la Diabetes Mellitus Tipo II

Cuadro No. II SOLICITANTE

☐ Esta persona es también inventor

Nombre y dirección: (Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país. El país de la dirección indicada en este cuadro es la del estado solicitante (es decir el país) de residencia si no del estado de residencia indica en seguida).

MENARINI INTERNATIONAL OPERATIONS
LUXEMBOURG S.A.
1. Avenue de la Gare
1611 LUXEMBURGO - Luxemburgo

No. de teléfono

No. de facsímil

No. de teleimpresora

No. de Registro del Solicitante con la Oficina

Estado (esto es, país) de nacionalidad:

LU

Estado (esto es, país) de residencia:

LU

Esta persona es solicitante para los propósitos de

☒ todos los países designados

☐ todos los países designados excepto los Estados Unidos de Norteamérica

☐ los Estados Unidos de Norteamérica solamente

☐ los países indicados en el cuadro complementario

Cuadro No. III SOLICITANTES ADICIONALES Y/O INVENTORES (ADICIONALES)

Nombre y dirección: (Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país. El país de la dirección indicada en este cuadro es la del estado solicitante (es decir el país) de residencia si no del estado de residencia indica en seguida).

TOSETTI Alessandro
Via F. Paoletti, 13
50012 BAGNO A RIPOLI - Italia

Esta persona es:

☐ solicitante solamente

☒ solicitante e inventor

☒ inventor solamente (si se marca este cuadro, no llenar lo que sigue)

No. de Registro del Solicitante con la Oficina

Estado (esto es, país) de nacionalidad:

IT

Estado (esto es, país) de residencia:

IT

Esta persona es solicitante para los propósitos de

☐ todos los países designados

☐ todos los países designados excepto los Estados Unidos de Norteamérica

☒ los Estados Unidos de Norteamérica solamente

☐ los países indicados en el cuadro complementario

☐ Los solicitantes adicionales y/o inventores (adicionales) se indican en una hoja de continuación.

Cuadro No. IV AGENTE O REPRESENTANTE COMÚN; O DIRECCIÓN PARA CORRESPONDENCIA

La persona identificada posteriormente es/ha sido citada para actuar en nombre del(los) solicitante(s) ante las Autoridades Internacionales competentes como: ☒ agente ☐ representante común

Nombre y dirección: (Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país).

GERLI, Paolo
c/o NOTARBARTOLO & GERVASI
Corso di Porta Vittoria, 9
20122 MILAN - ITALIA

No. de teléfono

+39025417991

No. de facsímil

+390254179928

No. de teleimpresora

No. de Registro del Agente con la Oficina

☐ Dirección para la Correspondencia: Marque este recuadro cuando ningún agente o representante común es/ha sido citado y el espacio anterior se usa en su lugar para indicar una dirección especial a la cual se debe enviar la correspondencia.

Hoja No. 2

Cuadro No. III SOLICITANTES ADICIONALES Y/O INVENTORES (ADICIONALES)	
Si alguno de los siguientes subcuadros es utilizado, esta hoja no deberá incluirse en la solicitud	
Nombre y dirección (Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país. El país de la dirección indicada en este cuadro es la del estado solicitante (es decir el país) de residencia si no del estado de residencia indica en seguida). GUIDUCCI Mauro Via Tullio Levi Civita, 1 52100 AREZZO - Italia	Esta persona es: ☐ solicitante solamente ☒ solicitante e inventor ☐ inventor solamente (si se marca este cuadro, no llenar lo que sigue) No. de Registro del Solicitante con la Oficina
Estado (esto es, país) de nacionalidad: IT	Estado (esto es, país) de residencia: IT
Esta persona es solicitante para los propósitos de ☐ todos los países designados ☐ todos los países designados excepto los Estados Unidos de Norteamérica ☒ los Estados Unidos de Norteamérica solamente ☐ los países indicados en la cuadro complementario	
Nombre y dirección (Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país. El país de la dirección indicada en este cuadro es la del estado solicitante (es decir el país) de residencia si no del estado de residencia indica en seguida). VITI Giovanni Viale A. Guidoni, 179 50127 FIRENZE Italia	Esta persona es: ☐ solicitante solamente ☒ solicitante e inventor ☐ inventor solamente (si se marca este cuadro, no llenar lo que sigue) No. de Registro del Solicitante con la Oficina
Estado (esto es, país) de nacionalidad: IT	Estado (esto es, país) de residencia: IT
Esta persona es solicitante para los propósitos de ☐ todos los países designados ☐ todos los países designados excepto los Estados Unidos de Norteamérica ☒ los Estados Unidos de Norteamérica solamente ☐ los países indicados en la cuadro complementario	
Nombre y dirección (Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país. El país de la dirección indicada en este cuadro es la del estado solicitante (es decir el país) de residencia si no del estado de residencia indica en seguida).	Esta persona es: ☐ solicitante solamente ☐ solicitante e inventor ☐ inventor solamente (si se marca este cuadro, no llenar lo que sigue) No. de Registro del Solicitante con la Oficina
Estado (esto es, país) de nacionalidad:	Estado (esto es, país) de residencia:
Esta persona es solicitante para los propósitos de ☐ todos los países designados ☐ todos los países designados excepto los Estados Unidos de Norteamérica ☐ los Estados Unidos de Norteamérica solamente ☐ los países indicados en la cuadro complementario	
Nombre y dirección (Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país. El país de la dirección indicada en este cuadro es la del estado solicitante (es decir el país) de residencia si no del estado de residencia indica en seguida).	Esta persona es: ☐ solicitante solamente ☐ solicitante e inventor ☐ inventor solamente (si se marca este cuadro, no llenar lo que sigue) No. de Registro del Solicitante con la Oficina
Estado (esto es, país) de nacionalidad:	Estado (esto es, país) de residencia:
Esta persona es solicitante para los propósitos de ☐ todos los países designados ☐ todos los países designados excepto los Estados Unidos de Norteamérica ☐ los Estados Unidos de Norteamérica solamente ☐ los países indicados en la cuadro complementario	

☐ Solicitantes adicionales y/o inventores (adicionales) se indican en una hoja de continuación.

Recuadro No. V DESIGNACIÓN DE ESTADOS Márquese las casillas adecuadas; debe marcarse por lo menos una.

A continuación se hacen las designaciones siguientes bajo la Regla 4.9(a)

Patente Regional

- ☒ **AP** Patente ARIPO: GH Ghana, GM Gambia, KE Kenia, LS Lesoto, MW Malawi, MZ Mozambique, SD Sudán, SL Sierra Leona, SZ Swazilandia, TZ República Unida de Tanzania, UG Uganda, ZM Zambia, ZW Zimbabue, y cualquier otro Estado que sea un Estado Contratante del Protocolo de Harare y del PCT (si se desea otra forma de protección o de tramitación, especifíquese en la línea de puntos).....
- ☒ **EA** Patente Euroasiática: AM Armenia, AZ Azerbaiyán, BY Belarús, KG Kirguistán, KZ Kazajistán, MD República de Moldova, RU Federación Rusa, TJ Tayikistán, TM Turkmenistán, y cualquier otro Estado que sea un Estado Contratante del Convenio de la Patente Euroasiática y del PCT
- ☒ **EP** Patente Europea: AT Austria, BE Bélgica, BG Bulgaria, CH y LI Suiza y Liechtenstein, CY Chipre, CZ República Checa, DE Alemania, DK Dinamarca, EE Estonia, ES España, FI Finlandia, FR Francia, GB Reino Unido, GR Grecia, IE Irlanda, IT Italia, LU Luxemburgo, MC Mónaco, NL Países Bajos, PT Portugal, SE Suecia, SK Eslovaquia, TR Turquía, y cualquier otro Estado que sea un Estado Contratante del Convenio de la Patente Europea y del PCT
- ☒ **OA** Patente OAPI: BF Burkina Faso, BJ Benin, CF República Centroafricana, CG Congo, CI Côte d'Ivoire, CM Camerún, GA Gabón, GN Guinea, GQ Guinea Ecuatorial, GW Guinea-Bisáu, ML Malí, MR Mauritania, NE Níger, SN Senegal, TD Chad, TG Togo, y cualquier otro Estado que sea un Estado miembro de la OAPI y que sea un Estado Contratante del PCT (si se desea otra forma de protección o de tramitación, especifíquese en la línea de puntos).....

Patente Nacional (si se desea otra forma de protección o de tramitación, especifíquese en la línea de puntos):

- | | | |
|---|--|--|
| ☒ AE Emiratos Árabes Unidos | ☒ GM Gambia | ☒ NZ Nueva Zelanda |
| ☒ AG Antigua y Barbuda | ☒ HR Croacia | ☒ OM Omán |
| ☒ AL Albania | ☒ HU Hungría | ☒ PH Filipinas |
| ☒ AM Armenia | ☒ ID Indonesia | ☒ PL Polonia |
| ☒ AT Austria | ☒ IL Israel | ☒ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Rumania |
| ☒ AZ Azerbaiyán | ☒ IS Islandia | ☒ RU Federación Rusa |
| ☒ BA Bosnia y Herzegovina | ☒ JP Japón | |
| ☒ BB Barbados | ☒ KE Kenia | ☒ SD Sudán |
| ☒ BG Bulgaria | ☒ KG Kirguistán | ☒ SE Suecia |
| ☒ BR Brasil | ☒ KP República Popular Democrática de Corea | ☒ SG Singapur |
| ☒ BY Belarús | ☒ KR República de Corea | ☒ SI Eslovenia |
| ☒ BZ Belice | ☒ KZ Kazajistán | ☒ SK Eslovaquia |
| ☒ CA Canadá | ☒ LC Santa Lucía | ☒ SL Sierra Leona |
| ☒ CH & LI Suiza y Liechtenstein | ☒ LK Sri Lanka | ☒ TJ Tayikistán |
| ☒ CN China | ☒ LR Liberia | ☒ TM Turkmenistán |
| ☒ CO Colombia | ☒ LS Lesoto | ☒ TN Túnez |
| ☒ CR Costa Rica | ☒ LT Lituania | ☒ TR Turquía |
| ☒ CU Cuba | ☒ LU Luxemburgo | ☒ TT Trinidad y Tobago |
| ☒ CZ República Checa | ☒ LV Letonia | |
| ☒ DE Alemania | ☒ MA Marruecos | ☒ TZ República Unida de Tanzania |
| ☒ DK Dinamarca | ☒ MD República de Moldova | ☒ UA Ucrania |
| ☒ DM Dominica | | ☒ UG Uganda |
| ☒ DZ Argelia | ☒ MG Madagascar | ☒ US Estados Unidos de América |
| ☒ EC Ecuador | ☒ MK La primera República Yugoslava de Macedonia | |
| ☒ EE Estonia | ☒ MN Mongolia | ☒ UZ Uzbekistán |
| ☒ ES España | ☒ MW Malawi | ☒ VN Vietnam |
| ☒ FI Finlandia | ☒ MX México | ☒ YU Yugoslavia |
| ☒ GB Reino Unido | ☒ MZ Mozambique | ☒ ZA Sudáfrica |
| ☒ GD Granada | ☒ NO Noruega | ☒ ZM Zambia |
| ☒ GE Georgia | | ☒ ZW Zimbabue |
| ☒ GH Ghana | | |

Casillas reservadas para designar Estados que han pasado a formar parte del PCT después de la publicación de la presente hoja:

- | | | |
|---|--------------------------|--------------------------|
| ☒ VC San Vicente y las Granadinas | ☐ | ☐ |
| ☒ SC Seychelles | ☐ | ☐ |

Declaración de la Designación Preventiva: Además de las designaciones arriba efectuadas, el solicitante efectuará también, en virtud de la Regla 4.9(b), todas las designaciones que estén permitidas con arreglo al PCT, salvo la designación o designaciones indicadas en el Recuadro Suplemental que sean excluidas a partir del alcance de esta declaración. El Solicitante declara que estas designaciones adicionales están sujetas a confirmación y que cualquier designación que no se confirme antes de que expiren los 15 meses a partir de la fecha prioritaria se considerará retirada por el solicitante al expirar el tiempo límite. (La confirmación (incluyendo derechos) deberá llegar a la Oficina receptora dentro de este plazo de 15 meses).

Cuadro No. VI REIVINDICACIÓN DE PRIORIDAD.				
La prioridad de la o las solicitudes anteriores siguientes es reivindicada:				
Fecha de presentación de la solicitud anterior (día/mes/año)	Número de solicitud anterior	De donde la solicitud anterior es:		
		Solicitud nacional: país	Solicitud regional: * Oficina regional	Solicitud internacional: Oficina receptora
cuadro (1) 29/11/2001	FI2001A000230	IT		
cuadro (2)				
cuadro (3)				
cuadro (4)				
cuadro (5)				

☐ Las reivindicaciones de prioridad adicionales se indican en el Cuadro Complementario.

La Oficina receptora es notificada mediante la presente para que prepare y transmita a la Oficina Internacional una copia certificada de la(s) solicitud(es) anterior(es) identificada(s) anteriormente (únicamente si la solicitud anterior fue presentada con la Oficina la cual para los propósitos de la presente solicitud internacional es la Oficina receptora) identificada como cuadro(s):

☐ todos los cuadros ☐ cuadro (1) ☐ cuadro (2) ☐ cuadro (3) ☐ cuadro (4) ☐ cuadro (5) ☐ otros, ver el cuadro complementario

**Donde la solicitud anterior es una solicitud ARIPO, es obligatorio indicar en el Cuadro Complementario por lo menos un país parte de la Convención de París para la Protección de la Propiedad Industrial para la cual la solicitud anterior fue presentada (Regla 4.10(b)(1)).*

Cuadro No. VII AUTORIDAD DE BÚSQUEDA INTERNACIONAL		
Elección de la Autoridad de Búsqueda Internacional (ISA) (Si dos o más Autoridades de Búsqueda Internacional son competentes para llevar a cabo la búsqueda internacional, indique la Autoridad escogida; se puede utilizar el código de dos letras): ISA/		
La petición para el uso de los resultados de la búsqueda anterior; con referencia a la búsqueda (si la búsqueda anterior se ha llevado acabo por o solicitaria de la Autoridad de Búsqueda Internacional):		
Fecha (día/mes/año)	Número	País (u Oficina regional)

Cuadro No. VIII DECLARACIONES	
Las declaraciones siguientes figuran en los cuadros No. VIII.(i) a v) (marcar la o las casillas apropiadas e indicar la columna de la derecha el nombre del tipo de cada declaración):	Nombre de las declaraciones
☐ cuadro no. VIII.(i) declaración con relación a la identidad del inventor	:
☐ cuadro no. VIII.(ii) declaración con relación al derecho de depósito, a la fecha de depósito internacional, para solicitar y obtener una solicitud	:
☐ cuadro no. VIII.(iii) declaración con relación al derecho de depósito, a la fecha de depósito internacional, para reivindicar la prioridad de una solicitud anterior	:
☐ cuadro no. VIII.(iv) declaración con respecto a la calidad inventiva (solamente con fines de la designación de los Estados Unidos de Norteamérica)	:
☐ cuadro no. VIII.(v) declaración con relación a las descripciones que tienen algunos accesos que no se oponen o tienen excepciones al defecto de novedad	:

Hoja No. 5

Cuadro No. IX HOJA DE DECLARACIÓN: IDIOMA DE DEPÓSITO

La presente solicitud internacional contiene: a) el número de hojas siguientes bajo la forma de pago: Petitorio (y comprende la o las hojas para declaración) : 5 Descripción (a excepción de la parte reservada para el listado de secuencias) : 22 Reivindicaciones : 4 Extracto : 1 Dibujos : _____ Total del número de hojas : 32 Parte de la descripción reserva un listado de secuencias (<i>nombre real de las hojas si son parte de este depósito, bajo la forma de pago, que está o no igualmente depositada bajo la forma legible en computadora; ver b) siguiente</i>): _____ Número total de hojas : 32 b) parte de la descripción se reserva al listado de secuencias depositado bajo la forma legible en computadora i) ☐ solamente (en virtud de la instrucción 801.a)ii)) ii) ☐ e igualmente bajo la forma de pago (en virtud de la instrucción 801.a)ii)) Tipo u nombre de soporte (disquete, CD-ROM, CR-R y otros) los cuales representan la parte reservada al listado de secuencias (<i>copias complementarias e indicadas en el punto 9.ii</i>), en la columna de la derecha):	☒ o los elementos siguientes están acompañados por la presente solicitud internacional (verificar el o los casos apropiados e indicarlos en la columna de la derecha el número de elementos verificados): 1. ☐ costo de la hoja de cálculo 2. ☐ poder del apoderado firmado separado 3. ☐ original del poder general 4. ☐ copia del poder general del apoderado, número de referencia, si la hay 22363 5. ☐ declaración que explique carencia de firma 6. ☐ documento(s) de prioridad identificado en el cuadro No. VI como en el cuadro(s): 7. ☐ traducción de la solicitud internacional en (idioma): 8. ☐ indicaciones separadas concernientes a los microorganismos depositados u otro material biológico. 9. ☐ listado de secuencia bajo la forma legible en computadora (indicar también el tipo y el nombre de soporte (disquete, CD-ROM, CD-R u otros)) i) ☐ copia proporcionada al final de la búsqueda internacional en virtud de la regla 13ava únicamente (y no como parte de la solicitud internacional) ii) ☐ (únicamente cuando el caso d)i) o b)ii) de la columna de la izquierda es marcada) hojas complementarias, incluyendo si fuera necesario, la hoja del descuento al final de la búsqueda internacional en virtud de la regla 13ava iii) ☐ con la declaración pertinente con respecto a la identidad de la copia o copias complementarias y la parte reservada para el listado de secuencias mencionado en la columna de la izquierda. 10. ☒ otros elementos (<i>especificar</i>). Carta Anexa	No. de elementos
---	--	-------------------------

La figura de los dibujos la cual debe acompañar al extracto;	Idioma del archivo de la Solicitud internacional: Inglés
---	---

Cuadro No. X FIRMA DEL SOLICITANTE, AGENTE O REPRESENTANTE COMUN

Enseñada de cada firma, indique el nombre de la persona que firma y la capacidad en la cual la persona firma (si tal capacidad no es obvia de la lectura del petitorio).

Milán, Italia, 28 de Noviembre del 2002 (Firma) GERLI Paolo

Para uso de la Oficina receptora solamente

1. Fecha del recibo real de la solicitud internacional alegada: 29 DE NOVIEMBRE DEL 2002 (29.11.02)	2. Dibujos ☐ recibidos: ☐ no recibidos:
3. Fecha corregida del vencimiento del recibo real a los documentos o dibujos recibidos posteriormente pero a tiempo que complementan la solicitud internacional alegada:	
4. Fecha del recibo a tiempo de las correcciones requeridas bajo el artículo 11(2) de PCT:	
5. Autoridad de Búsqueda Internacional especificada por la solicitante: ISA/	
6. ☐ Transmisión de copia de búsqueda retardada hasta que la cuota de búsqueda sea pagada	

Para uso de la Oficina Internacional solamente

Fecha del recibo de la copia de registro por la Oficina Internacional:

Forma PCT/RO/101 (última hoja) (Marzo del 2001; reimpresión Julio del 2002)

Urbano: notar con relevancia a la forma de sustituirlo

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/EP 02/13497

A. CLASIFICACION DEL TEMA

TPC 7 A61K9/20 A61K31/64

De acuerdo a la Clasificación de Patentes Internacional (IPC) o a la clasificación nacional y a la IPC.

R. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación)

IPC 7 A61K

Documentación buscada diferente a la documentación mínima, a la extensión que tales documentos están incluidos en los campos buscados

Base de datos electrónicos consultada durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría*	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv. No.
Y	FR 2 244 481 A (HOECHST AG) 18 de Abril de 1975 (1975-04-18) página 3, línea 35 – línea 41 página 2, línea 24 – línea 40 página 5 –página 9; ejemplos	1-19
Y	WO 00 03742 A (BONHOMME YVES ;LIPHA (FR); NICHOLSON SARAH J (GB); CAVE GILLIAN (G) 27 de Enero del 2000 (2000-01-27) citado en la solicitud el documento completo	1-19
A	WO 97 17975 A (GENTILI IST SPA ;BARELLI GIULIO (IT); REGIS MASSIMO DE (IT)) 22 de Mayo de 1997 (1997-05-22) citado en la solicitud el documento completo	1-19

☒ Documentos adicionales se enlistan en la continuación del cuadro C. ☒ Véase familia de patentes anexa.

* Categorías especiales de los documentos citados

"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia.

"E" documento anterior publicado en o después de la fecha de presentación internacional.

7.- documento el cual puede arrojar dudas sobre la(s) reivindicación(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)

"O" documento que se refiere a una descripción oral, uso, exhibición u otro medio

7º documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.

T documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.

"X" documento de relevancia particular; la invención reivindicada no puede ser considerada nueva o no se puede considerar que involucre una etapa inventiva cuando el documento es considerado de manera síndica.

"Y" documento de particular relevancia; no se puede considerar que la invención involucre una etapa inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica.

"E" documento miembro de la misma familia de notarios.

Fecha de la terminación real de la búsqueda internacional
23 de Abril del 2003

Fecha de envío del reporte de búsqueda internacional
06/05/2003

Nombre y dirección postal de la ISA Oficina de Patentes Europea. P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx 31 651 nl, Fax: (31+70) 340-3016	Oficial autorizado0 Boulois, D
--	--

Forma PCT/ISA/210 (segunda hoja) (julio de 1992)

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/EP 02/13497

C (Continuación) DOCUMENTOS CONSIDERADOS RELEVANTES		
Categoría*	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante a la reivindicación No.
A	WO 01 82875 A (AEROPHARM TECHNOLOGY INC) 8 de Noviembre del 2001 (2001-11-08) página 3, línea 10 – línea 13 -----	1-19
P, X	WO 02 055009 A (KHANNA SATISH C ;ZALA YASHORAJ RUPSINH (IN); DHARMADHIKARI NITIN B) 18 de Julio del 2002 (2002-07-18) página 23, línea 21 – línea 23 página 25, línea 27 – línea 28 página 27, línea 13 – línea 31 -----	1,6-8,19

ANEXO DE LA FAMILIA DE PATENTES
Información de los miembros de la familia de patentes

No. de solicitud internacional
PCT/EP 02/13497

Documento de patente citado en el Reporte de Búsqueda		Fecha de publicación	Miembro(s) de la familia de patente(s)		Fecha de publicación
FR 2244481	A	18-04-1975	DE	2347531 A1	30-04-1975
			AU	7349374 A	25-03-1976
			BE	820222 A1	24-03-1975
			DK	496774 A	26-05-1975
			FI	274174 A	22-03-1975
			FR	2244481 A1	18-04-1975
			JP	50053521 A	12-05-1975
			NL	7412254 A	25-03-1975
			NO	743394 A	14-04-1975
			SE	7411852 A	24-03-1975
			ZA	7405981 A	29-10-1975
WO 0003742	A	27-01-2000	EP	0974356 A1	26-01-2000
			AU	753604 B2	24-10-2002
			AU	5417999 A	07-02-2000
			BR	9906600 A	18-07-2000
			CA	2303537 A1	27-01-2000
			CN	1275082 T	29-11-2000
			WO	0003742 A2	27-01-2000
			EP	1011684 A2	28-06-2000
			JP	2002520371 T	09-07-2002
			NZ	503248 A	27-09-2002
			US	6303146 B1	16-10-2001
WO 9717975	A	22-05-1997	IT	M1952337 A1	14-05-1997
			AU	7566896 A	05-06-1997
			BR	9611448 A	23-03-1999
			CA	2237571 A1	22-05-1997
			DE	869796 T1	19-04-2001
			WO	9717975 A1	22-05-1997
			EP	0869796 A1	14-10-1998
			ES	2150889 T1	16-12-2000
			US	5922769 A	13-07-1999
			US	RE37330 E1	14-08-2001
WO 0182875	A	08-11-2001	AU	2753501 A	12-11-2001
			WO	0182875 A2	08-11-2001
			US	6403121 B1	11-06-2002
			US	2001046515 A1	29-11-2001
WO 02055009	A	18-07-2002	WO	02055009 A1	18-07-2002
			WO	02080887 A2	17-10-2002

TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 del PCT)

Referencia de archivo del solicitante o agente 3063PTWO/1a	PARA ACCION ADICIONAL	Véase la Notificación de transmisión del reporte de examen preliminar internacional (Forma PCT/IPEA416)
No. de solicitud internacional PCT/EP 02/13497	Fecha de presentación internacional (día/mes/año) 29.11.2002	Fecha de prioridad (día/mes/año) 29.11.2001
Clasificación de Patente Internacional (IPC) o clasificación nacional e IPC A61K9/20		
Solicitante MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.		

1. Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional y se transmite al solicitante de acuerdo al Artículo 36.

2. Este REPORTE consiste de un total de 5 hojas que incluyen esta portada.

- ☐ Este reporte también está acompañado de ANEXOS, esto es, hojas de la descripción, reivindicaciones y/o dibujos los cuales han sido enmendados y son la base de este reporte y/u hojas que contienen rectificaciones hechas ante esta Autoridad. (véase Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT).

Estos anexos consisten de un total de _____ Hojas.

3. Este reporte contiene indicaciones y páginas correspondientes que se relacionan con los siguientes ítems:

- I ☒ Base del reporte
- II ☐ Prioridad
- III ☐ No se establece opinión con respecto a la novedad, paso o etapa inventiva y aplicabilidad industrial
- IV ☐ Carencia de unidad de la invención
- V ☒ Declaración justificada bajo el Artículo 35(2) con respecto a novedad, etapa o paso inventivo o aplicabilidad industrial; citas y explicaciones que apoyan tal declaración.
- VI ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos en la solicitud internacional
- VIII ☐ Ciertas observaciones en la solicitud internacional

Fecha de presentación de la demanda 26.06.2003	Fecha de consumación de este reporte 15.12.2003
Nombre y dirección de correspondencia de la IPEA  Oficina de Patentes Europea P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk - Países Bajos Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Oficial autorizado Boulois, D (SELLO)

Teléfono No. +31 70 340-3878

Forma PCT/IPEA/409 (portada) (Enero de 1994)

**COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN METFORMINA Y
GLIBENCLAMIDA PARA EL TRATAMIENTO DE LA DIABETES MELLITUS
TIPO II**

5

CAMPO DE LA INVENCION

La presente invención se refiere a nuevas composiciones farmacéuticas que comprenden glibenclamida y metformina, eficaces para el tratamiento de la diabetes mellitus tipo II, en la cual los dos ingredientes activos son
10 mantenidos en forma separada entre ellos si bien se encuentran dentro de la misma composición.

ESTADO DE LA TÉCNICA

La diabetes mellitus tipo II dependiente de la insulina es un trastorno metabólico caracterizado por la
15 hiperglucemia, vinculada a una deficiencia de insulina, a una resistencia de los tejidos periféricos a la misma insulina, a un incremento de la producción de glucosa por parte del hígado, a una reducida tolerancia a la glucosa.

Existen dos categorías principales de medicamentos
20 antidiabéticos: las sulfonilureas entre las cuales recordamos a las glibenclamidas, clorpropamida, glicacida, tolacemida, gliquidona, glipicida, tolbutamida, y las biguanidas, entre las cuales recordamos la fenformina y la metformina. Mientras que las sulfonilureas actúan a través de la estimulación de
25 la producción de insulina por parte del páncreas, por lo que

(Ref. 155534)

es necesaria una actividad residual de este órgano a fin que esta categoría de fármacos pueda tener una cierta eficacia, las biguanidas actúan mediante el aumento de la utilización de la glucosa reduciendo la resistencia a la insulina y la gluconeogenesis hepática.

Por lo tanto para que esta categoría de fármacos pueda ser eficaz, es necesaria una producción residual de insulina por parte de la célula beta del páncreas.

Es conocido que el tratamiento inicial de la diabetes tipo II se puede basar únicamente sobre el control de la dieta y sobre el ejercicio físico, pero a menudo estas modificaciones de las costumbres de vida resultan insuficientes para un control óptimo de la glucemia de modo que se torna necesario la utilización de los fármacos antidiabéticos orales.

El tratamiento de la diabetes mellitus tipo II mediante monoterapia con un fármaco antidiabético oral puede ser eficaz a largo plazo pero, para un amplio porcentaje de pacientes la efectividad se reduce progresivamente con el transcurso de los años.

Se ha demostrado que siempre más a menudo en pacientes con diabetes tipo II existe una corcondancia entre el déficit de producción de insulina y la resistencia periférica a la insulina, de modo que las sulfonilureas y las biguanidas poseen un mecanismo de acción complementario, es

evidente que la causa por la que se ha consolidado hoy en día el tratamiento que consiste en la asociación de las dos categorías de fármacos. Además, para mejorar la aceptación por el paciente, se han realizado comprimidos que contienen ya en si mismas la asociación de los dos fármacos.

El tratamiento combinado de sulfonilureas y biguanidas asume por lo tanto un importante rol en la terapia de la diabetes tipo II, puesto que permite un control metabólico mejorado en aquellos pacientes en los cuales únicamente las biguanidas o las sulfonilureas han resultado ineficaces con el paso del tiempo.

Entre las dos categorías de fármacos, las biguanidas y las sulfonilureas, aquellos que son utilizados mayormente para el tratamiento de la diabetes mellitus tipo II, son respectivamente la metformina y la glibenclamida.

La asociación de metformina y glibenclamida presenta notables ventajas con relación al suministro de los ingredientes activos por separado, ya que mejora significativamente la facilidad de uso y además, especialmente en pacientes ancianos y/o pacientes sometidos a politerapias con otros fármacos, reduce el riesgo de errores en el suministro.

En la actualidad están presentes en el comercio cinco combinaciones que prevén la presencia de un único comprimido de glibenclamida y metformina, con diferentes

dosificaciones, en particular:

- 1) glibenclamida en una dosis de 1.25 mg y clorhidrato de metformina en una dosis de 250 mg (relación en peso de glibenclamida/metformina de 1:200);
- 5 2) glibenclamida en una dosis de 2.5 mg y clorhidrato de metformina en una dosis de 500 mg (relación en peso de glibenclamida/metformina de 1:200);
- 3) glibenclamida en una dosis de 5 mg y clorhidrato de metformina en una dosis de 1000 mg (relación en peso de
- 10 glibenclamida/metformina de 1:200);
- 4) glibenclamida en una dosis de 2.5 mg y clorhidrato de metformina en una dosis de 400 mg (relación en peso de glibenclamida/metformina de 1:160);
- 5) glibenclamida en una dosis de 5 mg y clorhidrato de
- 15 metformina en una dosis de 500 mg (relación en peso de glibenclamida/metformina de 1:100).

En los datos de la literatura más recientes emerge que la dosificación diaria máxima recomendada para la glibenclamida para tratar a los pacientes más graves y

20 escasamente controlados es de 20 mg en uno o más suministros. Esta dosis con el fin de obtener un efecto terapéutico óptimo puede ser combinada con una dosis diaria de metformina incluida entre 1000 y 2000 mg. La metformina es eliminada sin modificaciones en la orina; en realidad no es sometida a

25 metabolismo hepático (en realidad no se han encontrado

metabolitos en humanos) o a excreción biliar. En sujetos con
disminución de la función renal (basadas en el aclaramiento o
depuración de la creatinina) la vida media plasmática de la
metformina es prolongada y la depuración renal es disminuida
5 en proporción con la reducción de la depuración de la
creatinina.

En vista de las diversas dosificaciones óptimas, es
evidente que la relación entre metformina y glibenclamida en
asociación entre ellas debe ser mantenida en una relación de
10 alrededor de 100:1 o superior, por lo tanto están en general
en presencia de una dosis masiva de metformina asociada a
dosis relativamente modestas de glibenclamida.

También la solubilidad en agua es notablemente
distinta entre los dos ingredientes activos y mientras la
15 metformina es extremadamente soluble en agua, la
glibenclamida es relativamente muy poco soluble.

La forma más simple de realizar una asociación
entre los dos ingredientes activos es la de mezclarlos
íntimamente junto con excipientes apropiados.

20 Vignieri et al (Diabete & Metabolisme, 1991, 17,
232-234) han propuesto una asociación de los dos compuestos
en una dosificación diaria de 1500 mg de metformina y 15 mg
de glibenclamida.

En WO9717975 se reivindica el uso de una asociación
25 de los dos ingredientes en relación de 100:1 para el

tratamiento de la diabetes mellitus tipo II en caso de que no obtenga éxito debido a combinaciones con una relación más alta de metformina.

En WO0003742, los inventores de LIPHA SA han
5 demostrado claramente que la simple mezcla de metformina y glibenclamida en relación de 100:1 con ciertos excipientes, resultaba en una gran reducción en la biodisponibilidad de la glibenclamida, que se puede visualizar en el área por debajo de la curva (AUC) con relación a lo que es obtenible con uno
10 co-suministro de los mismos ingredientes activos en las mismas dosificaciones. Los inventores pudieron evitar este problema micronizando la glibenclamida antes de agregarla a la mezcla.

La técnica de micronización es seguida también por
15 Bristol-Myers Squibb para la preparación de la asociación comercializada con la marca Glucovance® en la cual, usando partículas de glibenclamida con dimensiones promedio aún más reducidas que aquellas descritas en WO0003742, consiguen obtener una AUC que resulta superior, aunque por poco, a la
20 de la glibenclamida no micronizada, vendida con la marca Micronase, cuando se da en co-suministro con metformina (Summary of Product Characteristics of Glucovance distribuido por Bristol-Myers Squibb mediante su sitio en Internet, como soporte a la comercialización, a partir del
25 31/07/2000).

Ya que las ventajas del suministro en asociación de la metformina y la glibenclamida, o sus sales, son ahora evidentes, se torna importante sentir la necesidad de resolver el problema de la reducida biodisponibilidad de la glibenclamida cuando la misma es mezclada con la metformina.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

La Solicitante ha encontrado ahora de modo sorprendente que preparando composiciones farmacéuticas que comprenden como ingredientes activos metformina y glibenclamida, o sus sales, de forma tal que los dos ingredientes activos se mantengan separados entre ellos, no se produce, como consecuencia de la asociación de estos ingredientes activos con alta relación en metformina/glibenclamida, una gran reducción en la biodisponibilidad de las glibenclamas.

Un modo eficaz para mantener separados los dos ingredientes activos se ha encontrado por la Solicitante en la preparación de comprimidos, por ejemplo comprimidos policapa (dos o más capas, en cada una de las cuales se encuentra exclusivamente uno de los dos fármacos) o comprimidos de metformina uniformemente recubiertos con glibenclamida.

Las características ventajosas de las formulaciones en la invención han sido además ulteriormente mejoradas con la selección de excipientes apropiados farmacéuticamente aceptables.

Por lo tanto el objeto de la presente invención son las formulaciones farmacéuticas suministrables por vía oral en forma de comprimidos, que comprenden como ingredientes activos glibenclamida y metformina, o sus sales
5 farmacéuticamente aceptables, caracterizadas por el hecho que dichos ingredientes activos son incluidos en capas separadas entre ellas.

Las características y ventajas de las composiciones farmacéuticas de acuerdo con la presente invención serán
10 ilustradas en la descripción detallada que sigue.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

El modo más simple para la preparación de una asociación de dos fármacos para los cuales no está previsto un distinto sitio o método de absorción es seguramente la de
15 mezclarlos íntimamente, pero en el caso de la glibenclamida con la metformina, como se menciona anteriormente, la absorción de la glibenclamida resulta inexplicablemente obstaculizada por la masiva presencia de la metformina.

La evaluación de la absorción es siempre bastante
20 compleja, pero, en una primera aproximación, se puede considerar el porcentaje de disociación del comprimido que contiene el ingrediente activo como un indicador de la absorción que se puede esperar (J. Pharm. Pharmacol. 2000, 52, 831-838, Drug Development and Industrial Pharmacy, 1993,
25 19 (20), 2713-2741).

La sola micronización de la glibenclamida, como cualquier persona que conozca el arte podría deducir en base a la solución propuesta en la Solicitud de Patente Internacional No. WO0003742 y por aquella descrita por Bristol Myers Squibb, no parece ser en general satisfactoria; en nuestro caso la micronización de la glibenclamida de acuerdo con las especificaciones adoptadas por nosotros, aunque distinta de las condiciones usadas en los dos métodos anteriormente mencionados, no fue suficiente para disolver los comprimidos que contienen una mezcla de glibenclamida y metformina en forma comparable a aquellos comprimidos donde la glibenclamida y la metformina están separados.

Manteniendo en cambio los dos ingredientes activos separados entre sí, pero en la misma formulación farmacéutica, ha sido sorprendentemente posible resolver el problema permitiendo la disolución de la glibenclamida en forma comparable o aún mejor a la que se habría obtenido suministrando los dos ingredientes activos con dos formulaciones completamente separadas. El mantenimiento de los dos ingredientes activos en una única formulación garantiza una mejora "aceptación" por parte del paciente y al mismo tiempo puede garantizar un tratamiento terapéutico comparable al que utiliza los dos ingredientes activos separados, sin peligro de subdosificación para la glibenclamida (en el cambio de una terapia con dos fármacos

separados a aquella con los dos fármacos mezclados juntos).

Para obtener formulaciones en las cuales los dos ingredientes activos son mantenidos separados entre sí es técnicamente un poco más complejo que mezclarlos simplemente, pero las ventajas que se han obtenido sorprendentemente tornan de gran interés a las formulaciones de la invención.

No todas las formulaciones en las cuales los dos ingredientes activos son mantenidos separados constituyen soluciones igualmente satisfactorias para la presente invención. Sería en efecto deseable que la parte que contiene la glibenclamida se disuelva en el medio en forma rápida. Uno de los modos para tratar de alcanzar esta velocidad de disolución, es el de tener una amplia superficie de erosión y mantener esta superficie lo mas posible amplia en el tiempo hasta lograr la disolución completa.

Existen dos formas farmacéuticas preferidas de acuerdo con la presente invención:

- 1) comprimidos policapa, preferentemente seleccionados entre:
 - a) comprimidos bicapa en donde la glibenclamida está comprimida en una capa relativamente delgada sobre un comprimido de metformina, y
 - b) comprimidos tricapa en donde la glibenclamida está comprimida en dos capas ubicadas arriba y debajo de la capa central de metformina;

2) comprimidos recubiertos preferentemente seleccionados entre:

a') comprimidos de metformina recubiertos uniformemente por una capa delgada que contiene glibenclamida que se encuentra
5 comprimida a su alrededor, y

b') comprimidos de metformina barnizadas o revestidas externamente con una solución de glibenclamida que se estratifica sobre la misma.

En la modalidad de las formulaciones farmacéuticas
10 presentes, puede ser utilizada indiferentemente la glibenclamida en forma micronizada o de otra manera.

Puede entenderse mejor que lo mencionado anteriormente observando el diagrama esquemáticamente ejemplificado que sigue a continuación.

15



A



B

20 A y B representan las secciones transversales de dos comprimidos cilíndricos: A representa una bicapa en la cual la parte oscura es la capa que contiene glibenclamida, y B representa un comprimido de solamente glibenclamida, pero con el mismo volumen total de la parte que contiene glibenclamida
25 de A.

Los comprimidos esquematizados como B, actualmente en el mercado o comúnmente realizable por cualquier experto en la técnica que contienen de 1.25 a 5 mg de glibenclamida (por peso total, incluyendo los excipientes, de 100-150 mg con un máximo de 200 mg) presentan una superficie expuesta a la erosión menor que o al máximo comparable a, la superficie ofrecida por la capa de glibenclamida comprimida sobre el soporte de metformina, como se esquematiza en A. Pero lo que es más importante es que la superficie de erosión de B se reduce rápidamente al efectuarse la disolución, mientras que en el caso de A la reducción de la superficie es completamente insignificante en el inicio del proceso y es discernible solo en las fases avanzadas de la disolución. Como consecuencia la cinética de disolución de la glibenclamida en A será más rápida que en B y la diferencia en disolución entre los dos comprimidos se incrementarán con el tiempo, en la medida en que la diferencia entre la superficie erosionable de A y de B se incrementa.

También las otras soluciones descritas e los puntos 1 y 2 muestran ventajas cinéticas análogas a aquellas descritas por los comprimidos bicapa de la figura A.

Por los motivos establecidos anteriormente es particularmente eficaz para los fines de la invención, y debe por lo tanto considerarse al comprimido policapa como una solución particularmente preferida de la invención, más

preferentemente el comprimido bicapa o tricapa de tipo I.

Como se ha mencionado previamente, la biodisponibilidad de la glibenclamida en asociación con metformina tiene un comportamiento complejo que puede ser
5 influenciado también por otros factores, además del que resulta de la mezcla con metformina: en efecto es otro objeto de la presente invención también la selección de excipientes y/o aditivos apropiados que sirvan para incrementar la disolución de la parte que contiene a la glibenclamida y
10 consecuentemente su biodisponibilidad.

Además, la selección fundamental de mantener los dos ingredientes activos separados permite además dosificar los excipientes y/o los aditivos necesarios para obtener la deseada biodisponibilidad de la glibenclamida, solamente en
15 la capa que comprende la glibenclamida reduciendo por lo tanto su empleo a lo que es estrictamente necesario, evitando potenciales problemas con la metformina.

Los comprimidos realizables de acuerdo con la presente invención son además para cantidades de
20 glibenclamida que varían entre 1 y 20 mg por cada comprimido, de preferencia entre 2.5 y 5 mg; y para cantidades de metformina que varían entre 200 y 1000 mg por cada comprimido, y de preferencia entre 500 y 850 mg.

Las presentes formulaciones en forma de comprimido
25 pueden ser preparadas de acuerdo con las metodologías

comúnmente utilizadas en las técnicas farmacéuticas. Los comprimidos bicapa de la invención, por ejemplo, pueden ser preparados de la siguiente forma: se preparan separadamente las composiciones de la capa que contiene metformina y de la
5 que contiene glibenclamida; la primera puede ser obtenida mezclando polvos previamente tamizados de metformina y excipientes apropiados farmacéuticamente aceptables, después granulando tal mezcla junto con uno o más agentes dispersantes, desecando el granulado obtenido así, que luego
10 es calibrado y agregado con uno o más agentes lubricantes. La composición de la capa de glibenclamida puede en cambio ser preparada mezclando directamente tal ingrediente activo con excipientes apropiados farmacéuticamente aceptables y tamizando luego los polvos mezclados. Utilizando después una
15 máquina comprimidora adecuada para la producción de comprimidos bicapa se logra la compresión de las composiciones mencionadas anteriormente.

Los comprimidos recubiertos de la invención pueden ser realizados preparando un núcleo de metformina obtenido
20 por compresión de la composición mencionada anteriormente, recubriéndolo luego uniformemente con una capa delgada que contiene glibenclamida mediante compresión de la composición mencionada anteriormente que contiene glibenclamida o mediante barnizado o revestimiento del núcleo con una
25 solución de glibenclamida.

DA

Excipientes preferidos para la parte que comprende glibenclamida en forma de comprimidos de acuerdo con la invención son los tensioactivos y los agentes dispersantes hidrosolubles.

5 En el caso de los tensioactivos, puede ser empleada una cantidad que varía entre 0.1 y 10 mg en la parte que contiene glibenclamida de cada comprimido, de preferencia entre 0.5 y 2 mg; los tensioactivos preferidos de acuerdo con la invención son seleccionados entre las sales alcalinas o
10 alcalinotérreas del laurilsulfato y del Polisorbato 80. Un tensioactivo particularmente preferido el laurilsulfato de sodio.

 En el caso de los agentes dispersantes hidrosolubles, los mismos pueden ser usados en cantidades
15 comprendidas entre 20 y 100 mg en la parte que contiene glibenclamida de cada comprimido, de preferencia entre 45 y 55 mg; los agentes dispersantes hidrosolubles preferidos son seleccionados del grupo de polietilenglicoles, entre los cuales particularmente preferido es el Macrogol 6000.

20 Cuando es empleado un tensioactivo sólido, tal como una sal de laurilsulfato, se puede eventualmente dispersar el tensioactivo en forma húmeda en el agente lubricante (por ejemplo el estearato de Mg) antes de utilizarlos en la granulación para mejorar el efecto humectante del
25 tensioactivo mismo.

Cuando es utilizado un agente dispersante hidrosoluble, puede especialmente ser preferible fundir el agente dispersante (por ejemplo el Macrogol 6000), luego dispersar en el mismo a la glibenclamida, dejar solidificar
5 nuevamente, pulverizar el sólido obtenido así y utilizarlo para la sucesiva preparación del granulado.

Los siguientes ejemplos son presentados para los propósitos de ilustración no limitantes de la presente invención.

10 EJEMPLO 1 (COMPARACIÓN)

Preparación de comprimidos de Glibenclamida de 5 mg

Composición de cada comprimido en mg:

	Glibenclamida	5
	Almidón de maíz pregelatinizado	58.3
15	Sílice coloidal hidratado	0.5
	Lactosa monohidrato	96.2
	Laurilsulfato de Na	1
	Talco	0.5
	Estearato de magnesio	0.5

20 Preparación:

La mezcla de los ingredientes activos y de los excipientes es sometida a granulación y el granulado resultante es secado, luego sometido a compresión hasta obtener comprimidos que contienen cada uno 5 mg de glibenclamida y que tienen la
25 composición presentada anteriormente.

EJEMPLO 2 (COMPARACIÓN)

Preparación de comprimidos de Metformina de 400 mg

Composición de cada comprimido en mg:

	Metformina HCl	400
5	Celulosa microcristalina	65
	Almidón de maíz	60
	Sílice coloidal anhidro	20
	Gelatina	40
	Glicerina	17.5
10	Talco	17.5
	Estearato de magnesio	7.5
	Celulosa acetato-ftalato	2

La mezcla de los ingredientes activos y de los excipientes es sometida a granulación y el granulado resultante es secado, luego sometido a compresión para obtener comprimidos que contienen cada uno 400 mg de metformina y que tienen la composición presentada anteriormente.

EJEMPLO 3 (COMPARACIÓN)

Preparación de comprimidos que contienen la mezcla de

20 Glibenclamida + Metformina (5 + 400 mg)

Composición para cada comprimido en mg:

	Metformina HCl	400
	Glibenclamida	5
	Celulosa microcristalina	65
25	Almidón de maíz	55

	Almidón de maíz pregelatinizado	58.3
	Sílice coloidal anhidro	20
	Sílice coloidal hidratada	0.5
	Lactosa monohidrato	96.2
5	Gelatina	40
	Glicerina	17.5
	Talco	18
	Estearato de magnesio	8
	Celulosa acetato-ftalato	2
10	Laurilsulfato de Na	1
	Ftalato de dietilo	0.5

Los dos ingredientes activos y los excipientes han sido granulados juntos. El granulado obtenido así es secado y, una vez terminado el secado es calibrado. Se agrega al granulado calibrado el estearato de Mg y se mezcla. La mezcla obtenida se somete a granulación fina para obtener comprimidos, que contienen cada uno la composición presentada anteriormente.

EJEMPLO 4 (COMPARACIÓN)

Preparación de comprimidos separados de 5 mg de Glibenclamida y 400 mg de Metformina

	Comprimido de metformina	
	Metformina HCl	500
	Macrogol 4000	24.7
	Sílice coloidal anhidro-Aerosil 200-	5
25	Polivinilpirrolidona K25	20

	Estearato de Mg	5.9
	Comprimidos de Glibenclamida	
	Glibenclamida	5
	Lactosa mono-granulada	128
5	Almidón de maíz	40
	Cell. Microg.-Avicel® PH 102-	15
	HPMC-5-	4.8
	Croscarmelosa de Na	13
	Sílice coloidal anhidro-Aerosil® 200-	0.7
10	Polisorbato 80	0.5
	Estearato de Mg	1
	Óxido de hierro amarillo	1
	Óxido de hierro rojo	1

Los comprimidos separados se han preparado como se describe
 15 anteriormente en los Ejemplos 1 y 2.

EJEMPLO 5 (COMPARACIÓN)

Preparación de comprimidos que contienen la mezcla de
Glibenclamida + Metformina (5 + 400 mg) granulación separada)

Composición de cada comprimido en mg:

20	Metformina HCl	500
	Macrogol 4000	24.7
	Sílice coloidal anhidro-Aerosil® 200-	5
	Polivinilpirrolidona K25	20
	Estearato de Mg	5.9
25	Glibenclamida	5

	Lactosa mono-granulada	128
	Almidón de maíz	40
	HPMC-5-	4.8
	Croscarmelosa de Na	13
5	Sílice coloidal anhidro-Aerosil® 200-	0.7
	Polisorbato 80	0.5
	Estearato de Mg	1
	Óxido de hierro amarillo	1
	Óxido de hierro rojo	1
10	Los dos ingredientes activos han sido granulados por separado, cada uno con sus respectivos excipientes (en forma análoga al Ejemplo 4), pero luego han sido mezclados juntos y sometidos a compresión para formar comprimidos que tienen cada uno la composición anteriormente presentada.	
15	<u>EJEMPLO 6 (COMPARACIÓN)</u>	
	<u>Preparación de comprimidos que contienen la mezcla de</u>	
	<u>Glibenclamida + Metformina (5 + 500 mg)</u>	
	Composición de cada comprimido en mg:	
	Metformina HCl	500
20	Macrogol 4000	24.7
	Polivinilpirrolidona K25	20
	Glibenclamida	5
	Lactosa mono-granulada	40
	Cell. Microg.-Avicel PH 102-	15
25	HPMC-5-	4.8

	Croscarmelosa de Na	13
	Sílice coloidal anhidro-Aerosil® 200-	5.7
	Polisorbato 80	0.5
	Estearato de Mg	6.9
5	Óxido de hierro amarillo	1
	Óxido de hierro rojo	1

La preparación es análoga a la que está presentada anteriormente para el Ejemplo 3.

EJEMPLO 7

10 Preparación de comprimidos bicapa de Glibenclamida + Metformina (5 + 500 mg)

Composición de la capa de Metformina para cada comprimido, en mg:

	Metformina HCl	500
15	Macrogol 4000	24.7
	Polivinilpirrolidona	20
	Sílice coloidal anhidro	5

Composición de la capa de Glibenclamida para cada comprimido, en mg:

20	Glibenclamida	5
	Lactosa monohidrato	50.75
	Laurilsulfato de Na	0.75
	Celulosa microcristalina	100
	Croscarmelosa de sodio	5.5
25	Sílice coloidal anhidro	0.5

Estearato de magnesio	3.4
Color óxido de hierro amarillo E 172	1
Color óxido de hierro rojo E 172	1

Preparación:

5 Capa con Metformina

- Solución granulante: disolver bajo agitación el Macrogol 4000
- Granulación: tamizar la metformina, la Polivinilpirrolidona y el sílice coloidal anhidro.
- 10 - Mezclar los polvos tamizados, luego granular utilizando la solución granulante preparada previamente. Secar el granulado obtenido así y, una vez que se completó el procedimiento de secado, calibrar el mismo.
- Mezcla final: agregar el estearato de Mg al granulado
- 15 calibrado y mezclar.

Capa con Glibenclamida

- Preparación de la mezcla: mezclar el sílice coloidal anhidro, glibenclamida, laurilsulfato de Na, croscarmelosa de Na, color óxido de hierro amarillo, color óxido de hierro
- 20 rojo y aproximadamente 20% de lactosa monohidrato. Tamizar los polvos mezclados, Celulosa Microcristalina y la restante lactosa monohidrato. Mezclar, agregar el estearato de Mg y mezclar nuevamente.

Comprimido bicapa

- 25 Utilizando una máquina comprimidora adecuada para la

producción de comprimidos bicapa, se comprimen las dos capas.

Los comprimidos realizados de esta forma tienen los siguientes valores en la prueba de disgregación:

Capa de glibenclamida: disgregación completa en menos de un
5 minuto (30 segundos en promedio)

Capa de metformina: disgregación completa en 10 minutos en promedio.

EJEMPLO 8

Preparación de comprimidos bicapa de Glibenclamida +

10 Metformina (5 + 500 mg)

Composición de la capa de Metformina para cada comprimido, en mg:

Metformina HCl	500
Macrogol 4000	24.7
15 Sílice coloidal anhidro-Aerosil® 200-	5.0
Polivinilpirrolidona K 25	20
Estearato de Mg	5.9

Composición de la capa de Glibenclamida para cada comprimido, en mg:

20 Glibenclamida	5
Macrogol 6000	50
Lactosa monohidrato S.D.	34
Cell. Microgr.-Avicel® PH 102-	70
Croscarmelosa de Na	5
25 Sílice coloidal anhidro-Aerosil 200-	0.5

Estearato de Mg 0.5

La preparación es análoga a la presentada anteriormente para el Ejemplo 7.

EJEMPLO 9

5 Preparación de comprimidos bicapa de Glibenclamida + Metformina (5 + 500 mg)

Composición de la capa de Metformina para cada comprimido, en mg:

	Metformina HCl	500
10	Macrogol 4000	24.7
	Sílice coloidal anhidro-Aerosil® 200-	5
	Polivinilpirrolidona K 25	20
	Estearato de Mg	5.9

15 Composición de la capa de Glibenclamida para cada comprimido, en mg:

	Glibenclamida	5
	Cell. Microgr.-Avicel® PH 102-	100
	Croscarmelosa de Na	5.25
	Sílice coloidal anhidro-Aerosil® 200-	0.5
20	Laurilsulfato de Na	0.5
	Estearato de Mg	0.5
	Óxido de hierro amarillo	1
	Óxido de hierro rojo	0.75

25 La preparación es análoga a la presentada anteriormente para el Ejemplo 7.

EJEMPLO 10

Preparación de comprimidos bicapa de Glibenclamida + Metformina (5 + 400 mg)

Composición de la capa de Metformina para cada comprimido, en mg:

5	Metformina HCl	400
	Celulosa microcristalina	65
	Almidón de maíz	60
	Sílice coloidal anhidro	20
10	Gelatina	40
	Glicerina	17.5
	Talco	17.5
	Estearato de magnesio	7.5
	Celulosa acetato-ftalato	2
15	Ftalato de dietilo	0.5

Composición de la capa de Glibenclamida para cada comprimido, en mg:

	Glibenclamida	5
	Almidón de maíz pregelatinizado	58.3
20	Sílice coloidal hidratada	0.5
	Lactosa monohidrato	96.2
	Laurilsulfato de Na	1
	Talco	0.5
	Estearato de magnesio	0.5

25 La preparación es análoga a la presentada anteriormente para

el Ejemplo 7.

EJEMPLO 11

Preparación de comprimidos bicapa de Glibenclamida + Metformina (5 + 500 mg)

5 Composición de la capa de Metformina para cada comprimido, en mg:

	Metformina HCl	500
	Macrogol 4000	24.7
	Sílice coloidal anhidro-Aerosil® 200-	5
10	Polivinilpirrolidona K 25	20
	Estearato de Mg	5.9

Composición de la capa de Glibenclamida para cada comprimido, en mg:

	Glibenclamida	5
15	Lactosa monogranulada	128
	Almidón de maíz	40
	Cell. Microgr.-Avicel® PH 102-	15
	HPMC-5-	4.8
	Croscarmelosa de Na	13
20	Sílice coloidal anhidro-Aerosil® 200-	0.7
	Polisorbato 80	0.5
	Estearato de Mg	1
	Óxido de hierro amarillo	1
	Óxido de hierro rojo	1

25 La preparación es análoga a la presentada anteriormente para

el Ejemplo 7.

EJEMPLO 12

Preparación de comprimidos bicapa de Glibenclamida +
Metformina (2.5 + 500 mg)

5 Composición de la capa de Metformina para cada comprimido,
en mg:

	Metformina HCl	500
	Macrogol 4.000	24.7
	Sílice coloidal anhidro	8.2
10	Polivinilpirrolidona	20
	Estearato de magnesio	5.9

Composición de la capa de Glibenclamida para cada comprimido,
en mg:

	Glibenclamida	2.5
15	Lactosa monohidrato	89
	Laurilsulfato de sodio	0.750
	Celulosa microcristalina	150
	Croscarmelosa de sodio	5.500
	Sílice coloidal anhidro	0.750
20	Estearato de Magnesio	0.750
	Óxido de hierro amarillo E 172	0.750

El procedimiento de preparación es como se describe en el
Ejemplo 7.

Los comprimidos pueden estar revestidos con sustancias bien
25 conocidas en el campo farmacéutico.

EJEMPLO 13

Preparación de comprimidos bicapa de Glibenclamida + Metformina (5 + 500 mg)

Composición de la capa de Metformina para cada comprimido,

5 en mg:

Metformina HCl	500
Macrogol 4.000	24.7
Sílice coloidal anhidro	8.2
Polivinilpirrolidona	20
10 Estearato de magnesio	5.9

Composición de la capa de Glibenclamida para cada comprimido,

en mg:

Glibenclamida	5
Lactosa monohidrato	86.75
15 Laurilsulfato de sodio	0.750
Celulosa microcristalina	150
Croscarmelosa de sodio	5.500
Sílice coloidal anhidro	0.750
Estearato de Magnesio	0.750
20 Óxido de hierro amarillo E 172	0.125
Óxido de hierro rojo E 172	0.375

El procedimiento de preparación es como se describe en el Ejemplo 7.

Los comprimidos pueden estar revestidos con sustancias bien

25 conocidas en el campo farmacéutico.

EJEMPLO 14**Preparación de comprimidos bicapa de Glibenclamida + Metformina (2.5 + 850 mg)**

Composición de la capa de Metformina para cada comprimido,

5 en mg:

Metformina HCl	850
Macrogol 4.000	42
Sílice coloidal anhidro	14
Polivinilpirrolidona	34
10 Estearato de magnesio	10

Composición de la capa de Glibenclamida para cada comprimido,
en mg:

Glibenclamida	2.5
Lactosa monohidrato	89
15 Laurilsulfato de sodio	0.750
Celulosa microcristalina	150
Croscarmelosa de sodio	5.500
Sílice coloidal anhidro	0.750
Estearato de Magnesio	0.750
20 Óxido de hierro amarillo E 172	0.750

El procedimiento de preparación es como se describe en el
Ejemplo 7.

Los comprimidos pueden estar revestidos con sustancias bien
conocidas en el campo farmacéutico.

25 **EJEMPLO 15**

Preparación de comprimidos bicapa de Glibenclamida + Metformina (5 + 850 mg)

Composición de la capa de Metformina para cada comprimido, en mg:

5	Metformina HCl	850
	Macrogol 4.000	42
	Sílice coloidal anhidro	14
	Polivinilpirrolidona	34
	Estearato de magnesio	10

10 Composición de la capa de Glibenclamida para cada comprimido, en mg:

	Glibenclamida	5
	Lactosa monohidrato	86.75
	Laurilsulfato de sodio	0.750
15	Celulosa microcristalina	150
	Croscarmelosa de sodio	5.500
	Sílice coloidal anhidro	0.750
	Estearato de Magnesio	0.750
	Óxido de hierro amarillo E 172	0.125
20	Óxido de hierro rojo E 172	0.375

El procedimiento de preparación es como se describe en el Ejemplo 7.

Los comprimidos pueden estar revestidos con sustancias bien conocidas en el campo farmacéutico.

25 PRUEBA DE DISOLUCIÓN

El estudio sobre la biodisponibilidad de la glibenclamida en las diversas formulaciones puede ser inútilmente complejo, por lo que para el estudio de las diversas formulaciones se ha considerado la prueba de la disolución asumiendo como primera aproximación que a una mayor disolución en un período definido de tiempo corresponde una mayor biodisponibilidad (J. Pharm. Pharmacol., 2000, 52, 831-838; Drug Development and Industrial Pharmacy, 1993, 19 (20), 2713-2741).

El comprimido bajo prueba es agregado en una solución acuosa (900 ml) que contiene un tampón fosfato 0.05 M a pH 7.4 a 37°C y se disuelve utilizando un agitador con aspas (Paddle) a 35 rpm. A menos que se especifique de otra manera, una muestra de la solución es separada luego de 45 minutos y la glibenclamida dosificada mediante HPLC (método interno). La prueba de disolución se repite por lo menos 6 veces sobre comprimidos del mismo lote y se considera el valor promedio.

Experimento 1) Disolución de compuestos comerciales

a)

-	Glibenclamida 5 mg (DAONIL®)	37%
-	Glibenclamida 5 mg + Metformina 500 mg (DAONIL® + GLUCOPHAGE®)	42%
-	Glibenclamida 5 mg + Metformina 500 mg	39%

HA

(EUGLUCON® + GLUCOPHAGE®)

Como se puede observar en los resultados anteriormente presentados, la disolución de comprimidos comerciales de Glibenclamida (Daonil® o Euglucon®) en presencia de un comprimido de Metformina 500 mg comercial (Glucophage®), no parece ser distinto de la disolución de comprimidos de Glibenclamida únicamente.

b)

	- Glibenclamida 5 mg	58%
10	(GLIBORAL®)	
	- Glibenclamida 5 mg + Metformina 500 mg	52%
	(GLIBORAL® + SIOFOR®)	
	- Mezcla de Glib+Met (5 mg+500 mg)	26%
	(GLIBOMET®)	

La disolución de comprimidos comerciales de glibenclamida (Gliboral®) únicamente o en presencia de un comprimido de metformina 500 mg comercial (Siofor®) es comparable, mientras que la disolución de la glibenclamida en mezcla con la metformina en un solo comprimido comercial (Glibomet®) es muy reducida. Los productos comerciales han sido seleccionados sobre la base de su semejanza de la composición y del tipo de excipientes utilizados para minimizar su influencia.

Experimento 2)

25	- Glib. 5 mg (Ejemplo 1)	88%
----	--------------------------	-----

- Glib. 5 mg + Met. 400 mg (Ejemplos 1 + 2) 92%
- Glib. + Met. 5 + 400 mg (Ejemplo 3) 15%
- Glib. + Met. 5 + 400 mg (Ejemplo 10) 89%

Los comprimidos tienen la composición descrita en los ejemplos específicamente indicados. Los excipientes que constituyen los comprimidos de glibenclamida (Ejemplo 1) son idénticos cualitativamente y cuantitativamente a los que constituyen la capa de glibenclamida en el comprimido bicapa (Ejemplo 10). En forma análoga, los excipientes que constituyen los comprimidos de metformina (Ejemplo 2) son idénticos cualitativamente y cuantitativamente a los que constituyen la capa de metformina en el comprimido bicapa. Los excipientes en el comprimido de la mezcla glibenclamida/metformina (Ejemplo 3) son cualitativamente/-
 15 cuantitativamente iguales a la suma de los excipientes de los comprimidos de metformina y de glibenclamida (Ejemplos 1 y 2). De esta forma se ha tratado de minimizar el efecto de los excipientes entre la disolución de un comprimido y del otro.

La glibenclamida, cuando se mezcla con la metformina tiene una notable reducción en el porcentaje de disolución con relación a cuando los dos compuestos son mantenidos en composiciones separadas (como ya se ha observado en los comprimidos comerciales en el experimento 1b). En forma sorprendente la utilización de un comprimido
 25 bicapa elimina el problema y la glibenclamida se disuelve en

porcentajes comparables con relación a los dos productos separados.

Experimento 3)

Composición		5'	15'	45%
5	- Glib 5 + Met 500 (Ejemplo 4))	54%	65%	66%
	- Glib + Met 5+500 (Ejemplo 5)	11%	44%	64%
	- Glib + Met 5+500 (Ejemplo 6)	27%	53%	53%
	- Glib + Met 5+500 (Ejemplo 11)	52%	86%	103%

En el experimento 3) se han medido los valores de disolución en tres tiempos distintos, es decir a 5, 15 y 45 minutos. Las formulaciones usadas en el presente experimento, en forma análoga al experimento precedente 2, tienen un contenido de excipientes entre ellos comparables en forma que se pueden eliminar sus efectos en el interior del grupo específico examinado.

Se puede efectivamente notar que los excipientes pueden jugar un rol importante en la disolución comparando la disolución obtenida con la mezcla de los Ejemplos 5 y 6 en relación con el Ejemplo 3 o con los ejemplos comerciales. Con el uso de excipientes apropiados es posible obtener también para mezclas de Glib + Met, valores de disolución comparables a los de Glib + Met dados separadamente al tiempo final de 45'. Un análisis se puede intentar como una función del tiempo, sin embargo se muestra que en tiempos breves (luego de 5') la disolución de las mezclas es aún muy inferior a la

de los comprimidos separados (11% y 27% contra 54%), pero esto resulta evidente también luego de 15' (44% y 53% contra 65%). Estos datos podrían no permitir un igual perfil de biodisponibilidad *in vivo* y por lo tanto un comportamiento y farmacodinamia distintos. Una cierta importancia se deriva también del método de preparación de las mezclas, en efecto, en tiempos breves se disuelve más rápidamente la glibenclamida cuando la granulación es efectuada sobre la mezcla ya preparada (Ejemplo 6) antes que cuando los dos ingredientes activos son granulados separadamente y luego mezclados (Ejemplo 5).

Aparece sin embargo muy clara la superioridad de los correspondientes comprimidos bicapa (Ejemplo 11), cuyo porcentaje en la disolución es prácticamente comparable en 5 minutos a la de los comprimidos separados, y siempre superior en todos los demás casos.

Experimento 4): Comprimidos bicapa

-	Ejemplo 7	66%
-	Ejemplo 8	86%
20	- Ejemplo 9	53%
-	Ejemplo 10	89%
-	Ejemplo 11	103%

La disolución de la glibenclamida en los comprimidos bicapa resulta siempre muy buena, siempre comparable o superior a la obtenida con comprimidos separados.

Se hace constar que con relación a esta fecha, el mejor método conocido por la solicitante para llevar a la práctica la citada invención, es el convencional para la manufactura de los objetos o productos a que la misma se
5 refiere.

REIVINDICACIONES

Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes reivindicaciones:

5 1. Formulaciones farmacéuticas para el suministro por vía oral en forma de comprimidos, que comprenden glibenclamida y metformina, o sus sales farmacéuticamente aceptables, como ingredientes activos, caracterizadas por el hecho que los ingredientes activos están comprimidos en capas
10 separadas entre sí.

 2. Las formulaciones farmacéuticas de conformidad con la reivindicación 1, caracterizadas porque los comprimidos se seleccionan de comprimidos policapa y comprimidos recubiertos en donde la glibenclamida se encuentra siempre en
15 al menos una capa exterior de los comprimidos policapa o en la cobertura de los comprimidos recubiertos.

 3. Las formulaciones farmacéuticas de conformidad con la reivindicación 2, caracterizadas porque los comprimidos policapa se selecciona de:

20 a) comprimidos bicapa en donde la glibenclamida está comprimida en una capa relativamente delgada sobre un comprimido de metformina, y

b) comprimidos tricapa en donde la glibenclamida está comprimida en dos capas ubicadas arriba y debajo de la capa
25 central de metformina.

4. Las formulaciones farmacéuticas de conformidad con la reivindicación 3, caracterizadas porque los comprimidos policapa son comprimidos bicapa en donde la glibenclamida está comprimida en una capa relativamente delgada sobre un comprimido de metformina.

5. Las formulaciones farmacéuticas de conformidad con la reivindicación 2, caracterizadas porque los comprimidos recubiertos se seleccionan de:

a') comprimidos de metformina recubiertos uniformemente por una capa delgada que contiene glibenclamida que se encuentra comprimida a su alrededor, y

b') comprimidos de metformina barnizadas o revestidas externamente con una solución de glibenclamida que se estratifica sobre la misma.

6. Las formulaciones farmacéuticas de conformidad con las reivindicaciones 1 a 5, caracterizadas porque la cantidad de glibenclamida en cada comprimido varía entre 1 y 20 mg y la cantidad de metformina en cada comprimido varía entre 200 y 1000 mg.

7. Las formulaciones farmacéuticas de conformidad con la reivindicación 6, caracterizadas porque la cantidad de glibenclamida en cada comprimido varía entre 2.5 y 5 mg y la cantidad de metformina en cada comprimido varía entre 500 y 850 mg.

8. Las formulaciones farmacéuticas de conformidad

con las reivindicaciones 1 a 7, caracterizadas porque comprenden además excipientes farmacéuticamente aceptables.

5 9. Las formulaciones farmacéuticas de conformidad con la reivindicación 8, caracterizadas porque la parte de la formulación que comprende glibenclamida incluye al menos como excipiente un tensioactivo o un agente dispersante hidrosoluble.

10 10. Las formulaciones farmacéuticas de conformidad con la reivindicación 9, caracterizadas porque la parte de la formulación que comprende glibenclamida incluye como excipiente un tensioactivo a una concentración desde 0.1 a 10 mg.

11. Las formulaciones farmacéuticas de conformidad con la reivindicación 10, caracterizadas porque la concentración del tensioactivo está incluido de entre 0.5 a 2 mg.

15 12. Las formulaciones farmacéuticas de conformidad con la reivindicación 9, caracterizadas porque el tensioactivo se selecciona de las sales alcalinas o alcalinotérreas de laurilsulfato y Polisorbato 80.

20 13. Las formulaciones farmacéuticas de conformidad con la reivindicación 12, caracterizadas porque el tensioactivo es laurilsulfato de sodio.

25 14. Las formulaciones farmacéuticas de conformidad con la reivindicación 9, caracterizadas porque la parte de la formulación que comprende glibenclamida incluye como excipiente un agente dispersante hidrosoluble a una

concentración de entre 20 a 100 mg.

15. Las formulaciones farmacéuticas de conformidad con la reivindicación 14, caracterizadas porque la concentración del agente dispersante hidrosoluble está
5 incluido de entre 45 y 55 mg.

16. Las formulaciones farmacéuticas de conformidad con la reivindicación 9, caracterizadas porque el agente dispersante hidrosoluble se selecciona a partir de los polietilenglicoles.

10 17. Las formulaciones farmacéuticas de conformidad con la reivindicación 16, caracterizadas porque el agente dispersante hidrosoluble es Macrogol 6000.

18. Las formulaciones farmacéuticas de conformidad con la reivindicación 1, caracterizadas porque son:

15 - Glib + Met (5+500 mg)

Capa de metformina: Metformina HCl, 500; Macrogol 4000, 24.7; Polivinilpirrolidona, 20; Sílice coloidal anhidro, 5;

Capa de Glibenclamida: Glibenclamida, 5; Lactosa monohidrato, 50.75; Laurilsulfato de Na, 0.75; Celulosa microcristalina,
20 100; Croscarmelosa de sodio, 5.5; Sílice coloidal anhidro, 0.5; Estearato de magnesio, 3.4; Color óxido de hierro amarillo E 172, 1; Color óxido de hierro rojo E 172, 1;

- Glib + Met (5+500 mg)

Capa de Metformina: Metformina HCl, 500; Macrogol 4000, 24.7;
25 Sílice coloidal anhidro-Aerosil 200, 5; Polivinilpirrolidona

K 25, 20; Estearato de Mg, 5.9;

Capa de Glibenclamida: Glibenclamida, 5; Macrogol 6000, 50; Lactosa monohidrato S.D., 34; Cell. Microgr.-Avicel® PH 102, 70; Croscarmelosa de Na, 5; Sílice coloidal anhidro-Aerosil

5 200, 0.5; Estearato de Mg, 0.5

- Glib + Met (5+500 mg)

Capa de Metformina: Metformina HCl, 500; Macrogol 4000, 24.7; Sílice coloidal anhidro-Aerosil 200, 5; Polivinilpirrolidona K 25, 20; Estearato de Mg, 5

10 Capa de Glibenclamida: Glibenclamida, 5; Cell. Microgr.-Avicel PH 102, 100; Croscarmelosa de Na, 5.25; Sílice coloidal anhidro-Aerosil 200, 0.5; Laurilsulfato de Na, 0.5; Estearato de Mg, 0.5; Óxido de hierro amarillo, 1; Óxido de hierro rojo, 0.75

15 -Glib + Met (5+400 mg)

Capa de Metformina: Metformina HCl, 400; Celulosa microcristalina, 65; Almidón de maíz, 60; Sílice coloidal anhidro, 20; Gelatina, 40; Glicerina, 17.5; Talco, 17.5; Estearato de magnesio, 7.5; Celulosa acetato-ftalato, 2; Ftalato de

20 dietilo, 0.5;

Capa de Glibenclamida: Glibenclamida, 5; Almidón de maíz pregelatinizado, 58.3; Sílice coloidal hidratada, 0.5; Lactosa monohidrato, 96.2; Laurilsulfato de Na, 1; Talco, 0.5; Estearato de magnesio, 0.5;

25 - Glib + Met (5+500 mg)

Capa de Metformina: Metformina HCl, 500; Macrogol 4000, 24.7; Sílice coloidal anhidro-Aerosil 200, 5; Polivinilpirrolidona K 25, 20; Estearato de Mg, 5.9;

Capa de Glibenclamida: Glibenclamida, 5; Lactosa monogranulada, 128; Almidón de maíz, 40; Cell. Microgr.-Avicel PH 102, 15; HPMC-5, 4.8; Croscarmelosa de Na, 13; Sílice coloidal anhidro-Aerosil 200, 0.7; Polisorbato 80, 0.5; Estearato de Mg, 1; Óxido de hierro amarillo, 1; Óxido de hierro rojo, 1;

10 - Glib + Met (2.5 + 500 mg)

Capa de Metformina: Metformina HCl, 500; Macrogol 4000, 24.7; Sílice coloidal anhidro, 8.2; Polivinilpirrolidona, 20; Estearato de magnesio, 5.9;

Capa de Glibenclamida: Glibenclamida, 2.5; Lactosa monohidrato, 89; Laurilsulfato de sodio, 0.75; Celulosa microcristalina, 150; Croscarmelosa de sodio, 5.5; Sílice coloidal anhidro, 0.75; Estearato de Magnesio, 0.75; Óxido de hierro amarillo E 172, 0.75;

- Glib + Met (5 + 500 mg)

20 Capa de Metformina: Metformina HCl, 500; Macrogol 4000, 24.7; Sílice coloidal anhidro, 8.2; Polivinilpirrolidona, 20; Estearato de magnesio, 5.9;

Capa de Glibenclamida: Glibenclamida, 5; Lactosa monohidrato, 86.75; Laurilsulfato de sodio, 0.750; Celulosa microcristalina, 150; Croscarmelosa de sodio, 5.5; Sílice coloidal

25

anhidro, 0.75; Estearato de Magnesio, 0.75; Óxido de hierro amarillo E 172, 0.125; Óxido de hierro rojo E 172m 0.375;

- Glib + Met (2.5 + 850 mg)

Capa de Metformina: Metformina HCl, 850; Macrogol 4000, 42;

5 Sílice coloidal anhidro, 14; Polivinilpirrolidona, 34; Estearato de magnesio, 10;

Capa de Glibenclamida: Glibenclamida, 2.5; Lactosa monohidrato, 89; Laurilsulfato de sodio, 0.75; Celulosa microcristalina, 150; Croscarmelosa de sodio, 5.5; Sílice

10 coloidal anhidro, 0.750; Estearato de Magnesio, 0.750; Óxido de hierro amarillo E 172, 0.750

- Glib + Met (5 + 850 mg)

Capa de Metformina: Metformina HCl, 850; Macrogol 4000, 42;

Sílice coloidal anhidro, 14; Polivinilpirrolidona, 34;

15 Estearato de magnesio, 10;

Capa de Glibenclamida: Glibenclamida, 5; Lactosa monohidrato, 86.75; Laurilsulfato de sodio, 0.75; Celulosa microcristalina, 150; Croscarmelosa de sodio, 5.5; Sílice coloidal anhidro, 0.75; Estearato de Magnesio, 0.75; Óxido de hierro

20 amarillo E 172, 0.125; Óxido de hierro rojo E 172, 0.375;

19. Uso de glibenclamida y metformina, o sus sales farmacéuticamente aceptables, para la preparación de composiciones farmacéuticas como se describe de conformidad con las reivindicaciones 1 a 18 para el tratamiento de la

25 diabetes mellitus tipo II.

RESUMEN DE LA INVENCION

Se describen composiciones farmacéuticas que son suministrables por la vía oral en forma de comprimidos para el tratamiento de la diabetes mellitus tipo II, que comprenden glibenclamida y metformina, o sus sales farmacéuticamente aceptables, como ingredientes activos, mantenidos en forma separada entre sí dentro de la misma composición.

SUPERINDUSTRIA Y COMERCIO
Radacion: 04061363 00000000 Folios 156
Fecha (RND) 2004-06-29 08:52 36
Tramite 011 PCT-PATENT 379 FREE INCI 411 PRESENTAC
Dependencia 2029 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION 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 se 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 o fotográfica 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 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 Claudia M Neva

Fecha

2020
Bogotá D C

Doctor(a)
DORA MARÍA GOMEZ DIAZ

Oficio N° 68274

Apoderado
MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.

ASUNTO:

Radicación N°	04-61363
Solicitud internacional	PCT/EP02/13497
Fecha inicio fase nacional	29/06/2004
Trámite	011
Evento	379
Actuación	416
Folios	001

Como resultado del examen de forma, realizado con fundamento en 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 copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de 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 éste fuere una 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 CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 10-9 SEP 2004
202044