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**FORMULARIO UNICO DE OPOSICION
2000-12**

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OPOSICION A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

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**SOLICITUD
PUBLICADA**

Número del expediente: 07-096-487
Solicitante: WATSON PHARMACEUTICALS, INC. Y TAKEDA
PHARMACEUTICAL COMPANY LIMITED.
Apoderado: DILIA MARÍA RODRÍGUEZ D'ALEMÁN
Título de la nueva creación o denominación del signo:
FORMULACIÓN FARMACÉUTICA NOVEDOSA QUE CONTIENE
BIGUANIDA Y UN DERIVADO DE TIAZALIDINODIONA.
Gaceta 592 de 30 de Mayo de 2008, número de publicación 422.

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OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: TECNOQUIMICAS S.A., Sociedad comercial organizada y existente a las leyes Colombianas, con domicilio y sede principal en la Ciudad de Cali Valle. Dirección: Calle 23 # 7-39 Cali - Valle Teléfono: 882 5555 Fax: 883 8859 E-mail: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890.300.466-5
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: (1) 621.26.31 E-mail: info@reyes-abogados.com Fax: (1) 621.25.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaqué TP 44655

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FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial) 16 y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia)). Artículo 30 (Reivindicaciones) y artículo 42 (oposiciones) de la Decisión 486 de la Comisión de la Comunidad Andina.

Justificación: Ver Anexo

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Comprobante de pago No. 08-68471
08-68476(Oposición) Fecha Agosto 28 de 2008
(Prórroga) Fecha Agosto 28 de 2008

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Anexos:

Comprobante de pago de la tasa



Poderes, si fuere el caso



Pruebas de los fundamentos de la oposición



Documentos que acrediten el legítimo interés, si fuere el caso



Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas



Copia de la oposición para el traslado al solicitante.

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: 

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 07-096-487

TÍTULO SOLICITADO: FORMULACIÓN FARMACÉUTICA NOVEDOSA QUE
CONTIENE BIGUANIDA Y UN DERIVADO DE
TIAZALIDINODIONA.

PUBLICACIÓN: Gaceta 592 de 30 de Mayo de 2008, número de
publicación 422.

PRIORIDAD: US 60/093,742 de Marzo 30 de 2005.

SOLICITANTE: WATSON PHARMACEUTICALS, INC. Y TAKEDA
PHARMACEUTICAL COMPANY LIMITED

APODERADO: DILIA MARÍA RODRÍGUEZ D'ALEMÁN

TRÁMITE: PRESENTACIÓN DE OPOSICION

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al
pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655
del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la
sociedad **TECNOQUÍMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de
la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente **07-096-487**, por no cumplir con lo dispuesto por los artículos 14, 16 y 18 de la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplían los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTO DE LA OPOSICIÓN

La solicitud colombiana en trámite que reivindica una forma de dosificación farmacéutica que contiene una primera y segunda droga activa y que comprende un núcleo de liberación controlada que comprende una droga antihiperglicémica (biguanida) y una cubierta de liberación inmediata que contiene un derivado de tiazolidinodiona, incumple con los requisitos indispensables para otorgársele el privilegio de patente de invención, tal y como se demuestra con los siguientes argumentos:

3.1. Para comenzar, es necesario tener en cuenta que la primera reivindicación de la solicitud colombiana en trámite hace referencia a:

"Una forma de dosis farmacéutica que tiene una primera y segunda droga activa, dicha forma de dosis comprende:

(a) un núcleo de liberación controlado que comprende una droga antihiperglicémica y por lo menos un excipiente aceptable; y

(b) un derivado de tiazolidinodiona de liberación inmediata que contiene un componente que comprende un derivado de tiazolidinodiona y un ligador soluble en agua de viscosidad baja;

En donde no menos del 85%, de la tiazolidinodiona es liberada de forma de dosis dentro de los 45 minutos cuando se prueba de acuerdo con la farmacopea (USP) 26, con un aparato 1 a 100rpm, 37°C y 900ml de KCl 0.3M-amortiguador HCl pH 2.0." (cursiva fuera del texto)

es del caso mencionar en primer término y llamar la atención del despacho a la generalidad e indeterminación de la gran mayoría de las reivindicaciones contenidas, empezando por dicha reivindicación 1, toda vez que son muy amplias las posibilidades que podrían ser protegidas mediante patente no solo para excipientes o vehículos de la formulación sino para la sustancias

activas que forman parte de la misma, ya que abarcan toda clase de principios activos señalados como antihiperglicémicos y como tiazolidinodiona.

Sin perjuicio de la existencia de reivindicaciones dependientes¹, resulta claro que la primera reivindicación pretende obtener exclusiva sobre una composición farmacéutica para uso oral de dos sustancias activas que comprende a) un núcleo de liberación controlado con un fármaco antihiperglicémico y b) un derivado de tiazolidinadiona de liberación inmediata. No hacen falta mayores disquisiciones para concluir que la reivindicación en cuestión, en caso de ser concedida cubriría, sin determinarlos, TODOS LOS COMPUESTOS QUE SEAN ANTIHIPERGLICÉMICOS Y DERIVADOS DE TIAZOLIDINODIONA, y EXCIPIENTES CON LAS CARACTERÍSTICAS ANTES MENCIONADAS.

Además de ser indeterminada, la reivindicación primera carece de claridad en tanto pretende amparar un número indefinido de compuestos, sin mencionar siquiera sus nombres específicos o incluir sus fórmulas químicas.

- 3.2. Igualmente es importante señalar que la combinación de antihiperglicémicos como las biguanidas y derivados de tiazolidinodiona para el tratamiento de trastornos diabéticos del tipo II es una combinación farmacológica reconocida en el estado de la técnica, debido a que el mecanismo de acción de las biguanidas (Tendencia a reducir la gluconeogénesis en el hígado, reduciendo así los niveles de glucosa en sangre y facilitar la reabsorción de glucosa del plasma por los tejidos) y de dichos derivados de tiazolidinodiona (Actúan por unión a los receptores PPARs, específicamente a los del tipo PPAR γ , cuya activación conlleva a que la resistencia a insulina decrezca) resultan, como cualquier persona medianamente versada en la materia reconoce, complementarios.

Lo anteriormente expuesto puede verificarse a través de diversas publicaciones de carácter científico, veamos:

¹ Se recuerda que no sólo a la luz del artículo 30 de la Decisión 486 de 2000, sino al tenor del Manual de Examen de la Oficina Europea de Patentes, Parte C, capítulo III, apartado 4-4.1, Art. 84, página 28, (Guidelines for Examination in the European Patent Office – Published by EPO, 1999), el requisito de claridad debe cumplirse tanto en las reivindicaciones individualmente consideradas, como en éstas como un todo. (Según traducción libre del opositor). No resulta de recibo en este caso excusar la indeterminación y falta de claridad de la primera y más importante reivindicación con base en sus dependencias.

Efficacy And Metabolic Effects Of Metformin And Troglitazone In Type II Diabetes Mellitus².

Abstract: **BACKGROUND:** Combination therapy is logical for patients with non-insulin-dependent (type 2) diabetes mellitus, because they often have poor responses to single-drug therapy. We studied the efficacy and physiologic effects of metformin and troglitazone alone and in combination in patients with type 2 diabetes. **METHODS:** We randomly assigned 29 patients to receive either metformin or troglitazone for three months, after which they were given both drugs for another three months. Plasma glucose concentrations during fasting and postprandially and glycosylated hemoglobin values were measured periodically during both treatments. Endogenous glucose production and peripheral glucose disposal were measured at base line and after three and six months. **RESULTS:** During metformin therapy, fasting and postprandial plasma glucose concentrations decreased by 20 percent (58 mg per deciliter [3.2 mmol per liter], $P<0.001$) and 25 percent (87 mg per deciliter [4.8 mmol per liter], $P<0.001$), respectively. The corresponding decreases during troglitazone therapy were 20 percent (54 mg per deciliter [2.9 mmol per liter], $P=0.01$) and 25 percent (83 mg per deciliter [4.6 mmol per liter], $P<0.001$). Endogenous glucose production decreased during metformin therapy by a mean of 19 percent ($P=0.001$), whereas it was unchanged by troglitazone therapy ($P=0.04$ for the comparison between groups). The mean rate of glucose disposal increased by 54 percent during troglitazone therapy ($P=0.006$) and 13 percent during metformin therapy ($P=0.03$ for the comparison within the group and between groups). In combination, metformin and troglitazone further lowered fasting and postprandial plasma glucose concentrations by 18 percent (41 mg per deciliter [2.3 mmol per liter], $P=0.001$) and 21 percent (54 mg per deciliter [3.0 mmol per liter], $P<0.001$), respectively, and the mean glycosylated hemoglobin value decreased 1.2 percentage points. **CONCLUSIONS:** Metformin and troglitazone have equal and additive beneficial effects on glycemic control in patients with type 2 diabetes. Metformin acts primarily by decreasing endogenous glucose production, and troglitazone by increasing the rate of peripheral glucose disposal.

Effect Of Metformin And Rosiglitazone Combination Therapy In Patients With Type 2 Diabetes Mellitus: A Randomized Controlled Trial³.

Abstract: **CONTEXT:** Most antidiabetic agents target only 1 of several underlying causes of diabetes. The complementary actions of the antidiabetic agents metformin hydrochloride and rosiglitazone maleate may maintain optimal glycemic control in patients with type 2 diabetes; therefore, their combined use may be indicated for patients whose diabetes is poorly controlled by metformin alone. **OBJECTIVE:** To evaluate the efficacy of metformin-rosiglitazone therapy in patients whose type 2 diabetes is inadequately controlled with metformin alone. **DESIGN:** Randomized, double-blind, placebo-controlled trial from April 1997 and March 1998. **SETTING:** Thirty-six outpatient centers in the United States. **PATIENTS:** Three hundred forty-eight patients aged 40 to 80 years with a mean fasting plasma glucose level of 12.0 mmol/L (216 mg/dL), a mean glycosylated hemoglobin level of 8.8%, and a mean body mass index of 30.1 kg/m² were randomized. **INTERVENTIONS:** Patients were assigned to receive 2.5 g/d of metformin plus placebo ($n = 116$); 2.5 g/d of metformin plus 4 mg/d of rosiglitazone ($n = 119$); or

² Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, Shulman GI. N Engl J Med. 1998 Mar 26;338(13):867-72.

³ Fonseca V, Rosenstock J, Patwardhan R, Salzman A. JAMA. 2000 Apr 5;283(13):1695-702.

2.5 g/d of metformin and 8 mg/d of rosiglitazone ($n = 113$) for 26 weeks. **MAIN OUTCOME MEASURES:** Glycosylated hemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and beta-cell function, compared between baseline and week 26, by treatment group. **RESULTS:** Glycosylated hemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and beta-cell function improved significantly with metformin-rosiglitazone therapy in a dose-dependent manner. The mean levels of glycosylated hemoglobin decreased by 1.0% in the 4 mg/d metformin-rosiglitazone group and by 1.2% in the 8 mg/d metformin-rosiglitazone group and fasting plasma glucose levels by 2.2 mmol/L (39.8 mg/dL) and 2.9 mmol/L (52.9 mg/dL) compared with the metformin-placebo group ($P < .001$ for all). Of patients receiving 8 mg/d of metformin-rosiglitazone, 28.1% achieved a glycosylated hemoglobin level of 7% or less [corrected]. Dose-dependent increases in body weight and total and low-density lipoprotein cholesterol levels were observed ($P < .001$ for both rosiglitazone groups vs placebo). The proportion of patients reporting adverse experiences was comparable across all groups. **CONCLUSIONS:** Our data suggest that combination treatment with once-daily metformin-rosiglitazone improves glycemic control, insulin sensitivity, and beta-cell function more effectively than treatment with metformin alone.

Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study⁴.

Abstract: **BACKGROUND:** Their complimentary mechanisms of action suggest that a combination of pioglitazone hydrochloride and metformin may have clinically beneficial effects in the treatment of patients with type 2 diabetes. **OBJECTIVE:** This study was undertaken to assess the efficacy and tolerability of pioglitazone in combination with metformin in patients with type 2 diabetes mellitus. **METHODS:** This was a 16-week, double-blind study with the option of enrollment in a separate open-ended, open-label study. It included patients with poorly controlled diabetes mellitus (glycated hemoglobin [HbA1c] $> \text{or} = 8.0\%$, fasting C-peptide > 1.0 ng/mL) who had been receiving a stable regimen of metformin for $> \text{or} = 30$ days. Patients with diabetic retinopathy, nephropathy, or neuropathy; impaired liver or kidney function; or unstable cardiovascular or cerebrovascular conditions were excluded. Patients were randomized to receive once-daily pioglitazone 30 mg + metformin or placebo + metformin. Patients in the open-label extension received pioglitazone 30 mg (with optional titration to 45 mg) + metformin. **RESULTS:** Three hundred twenty-eight patients were randomized to treatment (168 pioglitazone + metformin, 160 placebo + metformin), and 249 completed the study. Of these, 154 elected to enter the open-label extension study. Patients' mean age was 56 years; most (84%) were white and slightly more than half (57%) were male. Patients receiving pioglitazone 30 mg + metformin had statistically significant mean decreases in HbA1c (-0.83%) and fasting plasma glucose (FPG) levels (-37.7 mg/dL) compared with placebo + metformin ($P < \text{or} = 0.05$). Decreases in FPG levels occurred as early as the fourth week of therapy, the first time point at which FPG was measured. The pioglitazone + metformin group had significant mean percentage changes in levels of triglycerides (-18.2%) and high-density lipoprotein cholesterol (+8.7%) compared with placebo + metformin ($P < \text{or} = 0.05$). Mean percentage increases were noted in low-density lipoprotein cholesterol levels (7.7%, pioglitazone + metformin; 11.9%, placebo + metformin) and total cholesterol (4.1%, pioglitazone + metformin; 1.1%, placebo + metformin), with no significant differences between groups. In the extension study, patients treated with open-label pioglitazone + metformin for 72 weeks had mean changes from baseline of -1.36% in HbA1c and -63.0 mg/dL in FPG. The incidence of adverse events was

⁴ Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL. Clin Ther. 2000 Dec;22(12):1395-409.

similar in both groups. Throughout the study, no patient in either treatment group had an alanine aminotransferase (ALT) value > or =3 times the upper limit of normal, a commonly used marker of potential liver damage. Thus, no evidence of drug-induced hepatotoxicity or drug-induced elevations in serum ALT was observed. CONCLUSIONS: In this study in patients with type 2 diabetes mellitus, pioglitazone + metformin significantly improved HbA1c and FPG levels, with positive effects on serum lipid levels and no evidence of drug-induced hepatotoxicity. These effects were maintained for >1.5 years, including the open-label extension.

Como se puede apreciar, en estas publicaciones se revelan las ventajas de combinar biguanidas con derivados de tiazolidinodiona y además hace mención explícita de la combinación de Metformina (que es una biguanida) con pioglitazona, rosiglitazona o troglitazona, que son la mayoría de los derivados de tiazolidinodiona que menciona la solicitud colombiana en la combinación farmacológica que reivindica (reivindicaciones 22, 30); con lo cual queda claro que, por lo menos en este aspecto, combinar dichos tipos de fármacos en una misma formulación farmacéutica para administración concomitante, carece por completo de nivel inventivo.

En el mismo sentido, la razón de combinar dichos fármacos de manera concomitante no solo se limita a la adición de dosis terapéuticamente efectivas de ambas sustancias, sino que en el estado de la técnica ya se había previsto la necesidad de formular dichos compuestos en una formulación que permita la liberación sostenida de la biguanida, mientras que se liberaba de manera inmediata el derivado de tiazolidinodiona, con el fin de aumentar la efectividad de la combinación farmacológica, veamos:

La Patente americana US 6,296,874 publicada el 02 de Octubre de 2001 y titulada "CORE FORMULATION COMPRISING TROGLITAZONE AND A BIGUANIDE" revela:

1. Field of the Invention

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

(...)

1. A core formulation comprising

- (a) a first layer comprising troglitazone hydrochloride or a pharmaceutically acceptable salt thereof as active ingredient,
- (b) a core, at least a portion of which is covered said first layer, comprising a biguanide as an active ingredient. (...)

6. A method for producing a controlled release formulation, which comprises:

- (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 layer comprising troglitazone partially enclosing said core, into said hollow outer shell; and
- (c) sealing said core within said hollow outer shell.

7. A method of producing a combined formulation of troglitazone hydrochloride and metformin, which comprises:

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

15. 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.

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 buformin.

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 metformin.

Como se puede apreciar, en esta anterioridad al igual que en la solicitud colombiana en trámite se busca fabricar una forma farmacéutica sólida que contenga un núcleo interior de liberación controlada en donde se encuentre el fármaco antihiperlipidémico o más específicamente la biguanida, recubierto con una capa o cubierta que contenga el derivado de tiazolidinodiona (explícitamente troglitazona) para la liberación inmediata. Si

bien es cierto que el mecanismo a través del cual esta anterioridad genera el efecto de liberación controlada de la biguanida difiere del utilizado por la solicitud colombiana en trámite, el mismo demuestra que en el estado del arte ya se había planteado la necesidad de controlar la liberación de la biguanida y que por lo tanto la solicitud colombiana, por lo menos en este aspecto, también carece irrefutablemente de nivel inventivo.

- 3.3. No siendo suficiente la carencia de nivel inventivo demostrada con los argumentos expuestos anteriormente, existen documentos que además evidencian que el mismo tipo de formulación farmacéutica reivindicado por la solicitud colombiana en trámite ya se había descrito en el estado de la técnica con los mismos propósitos de combinar los mismos agentes farmacológicos, veamos:

❖ La Patente americana US 6,099,862 publicada el 08 de Agosto de 2000 y titulada "ORAL DOSAGE FORM FOR THE CONTROLLED RELEASE OF A BIGUANIDE AND SULFONYLUREA" revela:

A controlled release pharmaceutical tablet containing anti-hyperglycemic drug and a hypoglycemic drug that does not contain an expanding or gelling polymer layer and comprising a core containing the antihyperglycemic drug and the hypoglycemic drug, a semipermeable coating membrane surrounding the core and at least one passageway in the membrane to allow the drugs to be released from the core.

(...)

1. A controlled release pharmaceutical tablet which consisting essentially of:

(a) a core consisting essentially of:

- (i) metformin or a pharmaceutically acceptable salt thereof;
- (ii) glipizide

- (iii) polyvinyl pyrrolidone; 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 plasticizer; and
- (d) at least one passageway in the semipermeable 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.

En esta anterioridad se expone una formulación farmacéutica con un núcleo tipo tableta osmótica (presencia de canales de paso) que de igual manera que en la solicitud colombiana en trámite está sustancialmente libre de cualquier polímero gelificante o de expansión; comprende un enlazante "binder" como polivinilpirrolidona, un mejorador de la absorción tal como un ácido graso, lubricantes y otros excipientes; opcionalmente tiene un recubrimiento de sellante que rodea al núcleo, una membrana de liberación sostenida con por lo menos un pasaje formado allí para liberar el fármaco antihiperlipémico de tipo biguanida y que conforma una combinación farmacológica útil para el tratamiento de Diabetes tipo II, que si bien es cierto no es la combinación revelada en la solicitud colombiana en trámite (biguanida + tiazolidinodiona), es obvio para cualquier persona medianamente versada en la materia que incluir un principio activo distinto estructuralmente pero perteneciente al grupo de los antihiperlipémicos en una misma formulación farmacéutica, se traduce simplemente en la aplicación de los respectivos ensayos de formulación y preformulación que permitan obtener la estabilidad, seguridad, eficacia y eficiencia que se espera para un medicamento de este tipo.

En otras palabras, la solicitud colombiana carece por lo menos de nivel inventivo puesto que en el estado de la técnica ya se había descrito el mismo tipo de formulaciones que incluyen dos agentes antihiperlipémicos y que son útiles en el tratamiento de la diabetes tipo II.

❖ La patente americana US 2004/0161462 publicada el 19 de Agosto de 2004 y titulada "NOVEL PHARMACEUTICAL FORMULATION CONTAINING A BIGUANIDE AND A THIAZOLIDINEDIONE DERIVATIVE" revela:

A pharmaceutical dosage form comprising a controlled release component comprising an antihyperglycemic drug in combination with a second component comprising a thiazolidinedione derivative is herein disclosed and described. (...)

[0020] The foregoing objectives are met by a dosage form comprising a first and second active drug, wherein the first active drug is formulated as a controlled release core, preferably an osmotic tablet, with or without a gelling or expanding polymer. The second active ingredient may be part of the controlled release core or it may preferably be combined with the controlled release core in a manner that provides for immediate release of the second active ingredient. For example, the second active ingredient can be incorporated into a membrane that is applied to the core or the second active ingredient may be applied to a coated or uncoated controlled release core. (...)

FIRST ACTIVE DRUG		
Core:	Amount (% of core)	
drug	50-98%	(75-95% preferred)
binder	0.1-40%	(3-15% preferred)
absorption enhancer	0-20%	(2-10% preferred)
lubricant	0-5%	(0.5-1% preferred)
Coating:	Amount (% of coating)	
polymer	50-99%	(75-95% preferred)
flux enhancer	0-40%	(2-20% preferred)
plasticizer	0-25%	(2-15% preferred)

SECOND ACTIVE DRUG	Amount (% of total dosage form)	
drug	0.1-20%	(1-10% preferred)
binder	0.1-30%	(1-15% preferred)

-continued

SECOND ACTIVE DRUG	Amount (% of total dosage form)	
surfactant	0-20%	(0.1-15% preferred)
pore former	0-25%	(0.1-15% preferred)
polymer (optional)	0-30%	(0.1-20% preferred)

[0044] The dosage forms prepared according to the present invention exhibit the following dissolution profile when tested in a USP Type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37° C.:

(...)

[0048] Further the excipients for use in the thiazolidinedione component of the dosage form should be selected so that the total thiazolidinedione related compounds or impurities in the final dosage form are not more than 0.6%, preferably not more than 0.5% and most preferably not more than 0.25% and each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.25%, preferably not more than 0.2% and most preferably not more than 0.1%. The thiazolidinedione related compounds or impurities in the final dosage form are determined by High Performance Liquid Chromatography (HPLC) (...)

Esta anterioridad es en esencia idéntica a la solicitud colombiana en trámite y su equivalente WO 06/07528 ya que en estos documentos se expone una formulación farmacéutica que tiene un primer y segundo fármaco y que comprende con un núcleo de liberación controlada tipo tableta osmótica sustancialmente libre de cualquier polímero gelificante o de expansión con un agente antihiperlipémico junto con al menos otro excipiente y una capa que contiene un derivado de tiazolidinodiona de liberación inmediata que libera no menos del 85% a los 45 minutos según el test de la farmacopea USP 26; así mismo, la combinación farmacológica resulta útil para el tratamiento de Diabetes tipo II (idéntica a la de la solicitud colombiana (biguanida con derivado de tiazolidinodiona); los mismos fármacos derivados de tiazolidinodiona (troglitazona, rosiglitazona, pioglitazona y ciglitazona); los mismos intervalos de tiempo de liberación de

los respectivos fármacos, la misma clase compuestos que sirven como excipientes en cada una de las dos partes de componen dicha formulación farmacéutica y las mismas cantidades de impurezas relacionadas con la tiazolidinodiona.

En otras palabras, queda demostrado que la solicitud colombiana carece totalmente de novedad, puesto que en el estado de la técnica ya se había descrito completamente el mismo tipo de formulaciones; ahora bien, si la novedad es atribuida a la presencia de un enlazante soluble en agua de baja viscosidad (ver Reivindicación 1), es necesario entonces afirmar que lo contenido en la solicitud colombiana en trámite carece de nivel inventivo dados todos y cada uno de los argumentos expuestos hasta el momento.

Como complemento y para demostrar la gran similitud entre la anterioridad US 2004/0161462 y la WO 06/107528 (Equivalente a la solicitud colombiana 07-096-487 en trámite) me permito señalar el siguiente cuadro comparativo en donde se demuestra que las reivindicaciones 1 a 34 son idénticas con la excepción que en la anterioridad no se hace mención de un enlazante soluble en agua de baja viscosidad, pero, que a pesar de no incluirse en dicha formulación permite obtener entre otros, los mismos porcentajes de liberación de la tiazolidinodiona en los mismos tiempos revelados en la solicitud colombiana en trámite, desvirtuando por completo la novedad y en su defecto el nivel inventivo de la misma:

1. A pharmaceutical dosage form having a first and second active drug, said dosage form comprising: (a) a controlled release core comprising an antihyperglycemic drug and at least one pharmaceutically acceptable excipient; and (b) an immediate release thiazolidinedione derivative containing a component wherein not less than 85% of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	1. A pharmaceutical dosage form having a first and second active drug, said dosage form comprising: (a) a controlled release core comprising an antihyperglycemic drug and at least one pharmaceutically acceptable excipient; and (b) an immediate release thiazolidinedione derivative containing a component that comprises a thiazolidinedione derivative and a low viscosity water soluble binder; wherein not less than 85% of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
2. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90% of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	2. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90% of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
3. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95% of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	3. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95% of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

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4. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	4. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
5. The pharmaceutical dosage form as defined in claim 1 wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	5. The pharmaceutical dosage form as defined in claim 1 wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
6. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	6. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
7. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	7. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

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8. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	8. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
9. The pharmaceutical dosage form as defined in claim 1 wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	9. The pharmaceutical dosage form as defined in claim 1 wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
10. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	10. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
11. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	11. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

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12. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.	12. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
13. A pharmaceutical dosage form having a first and second active drug, said dosage form comprising: (a) a controlled release core comprising an antihyperglycemic drug and at least one pharmaceutically acceptable excipient; and (b) an immediate release thiazolidinedione derivative containing component that comprises a thiazolidinedione derivative and a low viscosity water soluble binder; wherein the total thiazolidinedione related compounds or impurities in the final dosage form are not more than 0.6 as determined by high performance liquid chromatography.	13. A pharmaceutical dosage form having a first and second active drug, said dosage form comprising: (a) a controlled release core comprising an antihyperglycemic drug and at least one pharmaceutically acceptable excipient; and (b) an immediate release thiazolidinedione derivative containing component that comprises a thiazolidinedione derivative and a low viscosity water soluble binder; wherein the total thiazolidinedione related compounds or impurities in the final dosage form are not more than 0.6 as determined by high performance liquid chromatography.
14. The pharmaceutical dosage form as defined in claim 13 wherein the total thiazolidinedione related compounds are not more than 0.5%. 15. The pharmaceutical dosage form as defined in claim 13 wherein the total thiazolidinedione related compounds are not more than 0.5%. 16. The pharmaceutical dosage form as defined in claim 13 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.25%.	14. The pharmaceutical dosage form as defined in claim 13 wherein the total thiazolidinedione related compounds are not more than 0.5%. 15. The pharmaceutical dosage form as defined in claim 13 wherein the total thiazolidinedione related compounds are not more than 0.5%. 16. The pharmaceutical dosage form as defined in claim 13 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.25%.

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17. The pharmaceutical dosage form as defined in claim 16 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.20%. 18. The pharmaceutical dosage form as defined in claim 17 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.10%. 19. The dosage form of claim 1 wherein said controlled release core is an osmotic tablet.	17. The pharmaceutical dosage form as defined in claim 16 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.20%. 18. The pharmaceutical dosage form as defined in claim 17 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.10%. 19. The dosage form of claim 1 wherein said controlled release core is an osmotic tablet.
20. The dosage form of claim 19 wherein the osmotic tablet comprises: (a) a core comprising: (i) 50-98% of said antihyperglycemic drug; (ii) 0.1-40% of a binding agent; (iii) 0-20% of an absorption enhancer; and (iv) 0-5% of a lubricant; (b) optionally a seal coat surrounding the core; and (c) a sustained release membrane comprising: (i) 50-99% of a polymer; (ii) 0-40% of a flux enhancer and (iii) 0-25% of a plasticizer, said membrane having at least one passageway formed therein for release of the antihyperglycemic drug.	20. The dosage form of claim 19 wherein the osmotic tablet comprises: (a) a core comprising: (i) 50-98% of said antihyperglycemic drug; (ii) 0.1-40% of a binding agent; (iii) 0-20% of an absorption enhancer; and (iv) 0-5% of a lubricant; (b) optionally a seal coat surrounding the core; and (c) a sustained release membrane comprising: (i) 50-99% of a polymer; (ii) 0-40% of a flux enhancer and (iii) 0-25% of a plasticizer, said membrane having at least one passageway formed therein for release of the antihyperglycemic drug.

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21. The dosage form of claim 1 wherein said antihyperglycemic drug is a biguanide.	21.	The dosage form of claim 1 wherein said antihyperglycemic drug is a biguanide.	
		22. The dosage form of claim 1 wherein said thiazolidinedione derivative is troglitazone, rosiglitazone, pioglitazone, ciglitazone or pharmaceutically acceptable salts, isomers or derivatives thereof.	
		23. The dosage form of claim 1 wherein said core is substantially free from any gelling or expanding polymer.	
24. The dosage form of claim 1 wherein said controlled release of said antihyperglycemic drug provides a Tmax of 8-12 hours. 25. The dosage form of claim 1 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-12 hours. 26. The dosage form of claim 25 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-4 hours.	24.	The dosage form of claim 1 wherein said controlled release of said antihyperglycemic drug provides a Tmax of 6-12 hours.	
		25. The dosage form of claim 1 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-12 hours.	
		26. The dosage form of claim 25 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-4 hours.	

En conclusión, y a través de los argumentos expuestos, queda demostrada la absoluta carencia de los requisitos fundamentales de novedad y de nivel inventivo por parte de la solicitud colombiana en trámite, puesto que todos los aspectos fundamentales que sustentan la invención ya habían sido tenido en cuenta y también podrían derivarse de manera obvia con la información disponible al respecto en el estado de la técnica

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16 y 18 de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- Abstracts de todas las publicaciones científicas mencionadas en el acápite de fundamentos de la oposición.
- La Patente americana US 6,296,874 publicada el 02 de Octubre de 2001 y titulada "CORE FORMULATION COMPRISING TROGLITAZONE AND A BIGUANIDE" columna 1 y capítulo reivindicatorio.
- La Patente americana US 6,099,862 publicada el 08 de Agosto de 2000 y titulada "ORAL DOSAGE FORM FOR THE CONTROLLED RELEASE OF A BIGUANIDE AND SULFONILUREA".
- La patente americana US 2004/0161462 publicada el 19 de Agosto de 2004 y titulada "NOVEL PHARMACEUTICAL FORMULATION CONTAINING A BIGUANIDE AND A THIAZOLIDINEDIONE DERIVATIVE".

- La publicación internacional WO 06/107528 publicada el 12 de octubre de 2006 y titulada ""NOVEL PHARMACEUTICAL FORMULATION CONTAINING A BIGUANIDE AND A THIAZOLIDINEDIONE DERIVATIVE", capítulo reivindicatorio.

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Tecnoquímicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. El mencionado en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 207, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A., las recibirá en la secretaría de su Despacho o en su sede localizada en la Calle 23 # 7-39, de la ciudad de Cali.

Señor Superintendente



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

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EFFICACY AND METABOLIC EFFECTS OF METFORMIN AND TROGLITAZONE IN TYPE II DIABETES MELLITUS

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ABSTRACT

Background Combination therapy is logical for patients with non-insulin-dependent (type II) diabetes mellitus, because they often have poor responses to single-drug therapy. We studied the efficacy and physiologic effects of metformin and troglitazone alone and in combination in patients with type II diabetes.

Methods We randomly assigned 29 patients to receive either metformin or troglitazone for three months, after which they were given both drugs for another three months. Plasma glucose concentrations during fasting and postprandially and glycosylated hemoglobin values were measured periodically during both treatments. Endogenous glucose production and peripheral glucose disposal were measured at base line and after three and six months.

Results During metformin therapy, fasting and postprandial plasma glucose concentrations decreased by 20 percent (58 mg per deciliter [3.2 mmol per liter], $P < 0.001$) and 25 percent (87 mg per deciliter [4.8 mmol per liter], $P < 0.001$), respectively. The corresponding decreases during troglitazone therapy were 20 percent (54 mg per deciliter [2.9 mmol per liter], $P = 0.01$) and 25 percent (83 mg per deciliter [4.6 mmol per liter], $P < 0.001$). Endogenous glucose production decreased during metformin therapy by a mean of 19 percent ($P = 0.001$), whereas it was unchanged by troglitazone therapy ($P = 0.04$ for the comparison between groups). The mean rate of glucose disposal increased by 54 percent during troglitazone therapy ($P = 0.006$) and 13 percent during metformin therapy ($P = 0.03$ for the comparison within the group and between groups). In combination, metformin and troglitazone further lowered fasting and postprandial plasma glucose concentrations by 18 percent (41 mg per deciliter [2.3 mmol per liter], $P = 0.001$) and 21 percent (54 mg per deciliter [3.0 mmol per liter], $P < 0.001$), respectively, and the mean glycosylated hemoglobin value decreased 1.2 percentage points.

Conclusions Metformin and troglitazone have equal and additive beneficial effects on glycemic control in patients with type II diabetes. Metformin acts primarily by decreasing endogenous glucose production, and troglitazone by increasing the rate of peripheral glucose disposal. (N Engl J Med 1998; 338:867-72.)

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HYPERGLYCEMIA in patients with non-insulin-dependent (type II) diabetes mellitus is caused by peripheral insulin resistance, which results in decreased insulin-mediated glucose disposal; increased endogenous glucose production, chiefly from the liver; and inadequate pancreatic insulin secretion.¹ Reversal of these defects, either individually or in concert, improves glycemic control. New drugs are now available that affect each of these defects separately, and an understanding of their mechanisms of action is important for their proper use, especially when they are administered in combination.

Until recently in the United States, the only oral drugs available for patients with type II diabetes were sulfonylureas. These increase insulin secretion,² but they often lead to weight gain and may cause hypoglycemia. Recently, metformin became available. Its exact mechanisms of action are poorly understood, but they include suppression of endogenous glucose output³ and increased peripheral insulin sensitivity.⁴ In patients with diabetes, metformin lowers plasma glucose concentrations both alone^{5,6} and in combination with a sulfonylurea,⁶⁻⁸ while simultaneously decreasing plasma insulin concentrations. A third category of drug, α -glucosidase inhibitors, decreases postprandial plasma glucose concentrations by delaying the absorption of carbohydrates.⁹ Troglitazone, the drug that has become available most recently, acts by increasing overall insulin sensitivity,¹⁰ with evidence of effects in both the liver,^{11,12} the primary glucose-producing organ, and skeletal muscle,^{13,14} the main site of glucose disposal. Troglitazone is effective both when given alone¹⁵⁻¹⁷ and when given in combination with either a sulfonylurea^{18,19} or insulin.²⁰ Given that metformin and troglitazone may have different metabolic actions, both with the theoretical advantage of reducing hyperglycemia without increasing insulin secretion, they are attractive prospects for combination therapy in patients with type II diabetes.

In this study, we evaluated the efficacy and phys-

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iologic effects of these two drugs during three months of monotherapy in a group of patients with type II diabetes and then during three months of combination therapy.

METHODS

Study Subjects

We studied 29 patients with type II diabetes, as defined by the National Diabetes Data Group,²¹ who had a glycosylated hemoglobin value above the upper limit of normal and a plasma C-peptide concentration of at least 1.5 ng per milliliter (0.50 nmol per liter) while receiving dietary therapy or treatment with a sulfonylurea. Patients were excluded if they had abnormal renal or hepatic function or had had a recent atherosclerotic event. Fifteen patients (8 women and 7 men) were randomly assigned to receive metformin for three months, and 14 (8 women and 6 men) to receive troglitazone for three months. They then were treated with both drugs for an additional three months. Both the patients and the investigators were aware of the treatment. One patient assigned to receive troglitazone withdrew from the study after two weeks because of persistent hyperglycemia (plasma glucose concentrations, >350 mg per deciliter [19.4 mmol per liter]). One patient in each treatment group elected not to continue into the combination phase. Finally, two patients assigned to receive troglitazone completed the monotherapy period but not the period of combination therapy, because of intervening illnesses. The protocol was approved by the human-investigation committee of Yale University, and all the patients gave informed consent.

Study Design

Monotherapy: Months 0 to 3

After a two-week washout period during which any previous drug therapy was discontinued, the patients received either 1000 mg of metformin twice daily orally or 400 mg of troglitazone once daily orally for three months. Plasma glucose, glycosylated hemoglobin, and routine hematologic and chemical values were measured at base line and monthly thereafter. At base line and month 3, the patients underwent an eight-hour mixed-meal tolerance test and a hyperinsulinemic-euglycemic clamp study²² with [6,6-²H]glucose to measure endogenous glucose production and glucose disposal rate.

Combination Therapy: Months 4 to 6

After the initial three-month period, the patients were invited to continue therapy for a second three months, during which they took both the original drug and the other drug in combination. The patients were again followed monthly as described above, and at the end of the study period they underwent a final mixed-meal tolerance test and hyperinsulinemic-euglycemic clamp study. During the course of the study, the patients were prescribed a diet designed to maintain base-line body weight, with a composition of 50 percent carbohydrate, 34 percent fat, and 16 percent protein.

Meal-Tolerance Test

At approximately 7 a.m., with the patients in bed after a 12-hour fast, an intravenous catheter was inserted into an antecubital vein for blood sampling. At 8 a.m., the patients drank a liquid formula breakfast (Sustacal-HC) containing 33 percent of their total daily caloric intake, followed four hours later by an identical liquid lunch. Blood samples were drawn before the breakfast and then hourly for eight hours for measurements of plasma glucose, insulin, and C peptide. After completing the test, the patients received an evening meal and then fasted until the end of the clamp study, which was performed the next day. The mean of all plasma glucose values after the first test was taken as the postprandial value.

Hyperinsulinemic-Euglycemic Clamp Study

Beginning at 6 a.m., a primed (corrected for ambient fasting plasma glucose concentration) [6,6-²H]glucose solution (2 mg per square meter of body-surface area per minute) was infused into the antecubital vein continuously for four hours. During the third hour, a retrograde cannula was inserted into a warmed vein of the contralateral hand for sampling of arterialized venous blood. Blood samples were drawn at 10-minute intervals during the final 40 minutes of the 4-hour basal period for the measurement of plasma glucose, insulin, and [²H]glucose. Then, a two-step priming dose of insulin was administered for 10 minutes (480 mU per square meter per minute for 5 minutes, followed by 240 mU per square meter per minute for 5 minutes), followed by a continuous infusion of insulin (120 mU per square meter per minute) for a total of 5 hours. The plasma glucose concentration was allowed to fall to 100 mg per deciliter (5.6 mmol per liter) and then maintained at that concentration by the administration of glucose (20 g of dextrose per 100 ml enriched to approximately 2.5 percent with [6,6-²H]glucose). The basal isotope infusion was stopped when the exogenous glucose infusion was started. During the final hour of the clamp study, additional blood samples were drawn at 10-minute intervals for the measurement of plasma insulin and steady-state glucose isotope enrichment.

Substrate and Hormone Measurements

Plasma samples were shipped frozen to Corning Nichols Institute for chemical analysis. Plasma insulin was determined by radioimmunoassay, with an interassay coefficient of variation of 12.3 percent and an intraassay coefficient of variation of 7.4 percent. Plasma C peptide was also measured by radioimmunoassay, with an interassay coefficient of variation of 12.0 percent and an intraassay coefficient of variation of 6.5 percent. Glycosylated hemoglobin was measured by high-performance liquid chromatography (Bio-Rad), with a normal reference range of 4.5 to 5.9 percent; the assay was linear up to a value of 14 percent. Plasma glucose was measured at the bedside with a Beckman glucose analyzer.

Gas chromatography-mass spectrometry of the [6,6-²H]glucose concentration in plasma was carried out at the Yale Stable Isotope Core Facility, with the pentaacetate derivative of glucose as described previously.²³ Basal endogenous glucose production was calculated with the following equation:

$$\text{Basal endogenous glucose production} = (f/BSA) \times ([\text{enrichment}_{\text{inf}}/\text{enrichment}_{\text{plasma}}] - 1),$$

where f is the basal [6,6-²H]glucose infusate rate (in milligrams per minute), BSA is the body-surface area (in square meters), $\text{enrichment}_{\text{inf}}$ is the percent enrichment of [6,6-²H]glucose infusate, and $\text{enrichment}_{\text{plasma}}$ is the percentage of basal plasma [6,6-²H]glucose enrichment. The glucose disposal rate during clamping was calculated with the following equation:

$$\text{Glucose disposal rate} = \text{cEGP} + \text{GIR},$$

where GIR is the mean rate of infusion of exogenous glucose from minutes 260 to 300 of the clamping period (in milligrams per square meter per minute), and cEGP is endogenous glucose production during clamping, calculated as follows:

$$\text{Endogenous glucose production during clamping} = \text{GIR} \times ([\text{enrichment}_{\text{inf}}/\text{enrichment}_{\text{plasma}}] - 1),$$

where $\text{enrichment}_{\text{inf}}$ is the percent [6,6-²H]glucose enrichment of infusate, and $\text{enrichment}_{\text{plasma}}$ is the steady-state percentage of plasma [6,6-²H]glucose enrichment during clamping.

Statistical Analysis

Descriptive and inferential statistical analyses were performed with Systat, version 5.2.1. The actual results at each time were compared with repeated-measures analysis of variance. All statistical tests were two-sided.

RESULTS

Characteristics of the Patients

The patients in the two groups were evenly matched with respect to age; body-mass index; fasting plasma glucose, insulin, and C-peptide concentrations; and glycosylated hemoglobin values (Table 1).

Monotherapy

At three months, metformin and troglitazone lowered the mean fasting plasma glucose concentration by 58 mg per deciliter (3.2 mmol per liter) ($P < 0.001$) and 54 mg per deciliter (3.0 mmol per liter) ($P = 0.01$), respectively, a decrease of 20 percent in both groups (Fig. 1A). The glycosylated hemoglobin values did not change significantly in either group from the values obtained before the two-week period of washout from former therapy. During the meal-tolerance test, the mean postprandial plasma glucose concentration decreased by 87 mg per deciliter (4.8 mmol per liter) in the metformin group ($P < 0.001$) and by 83 mg per deciliter (4.6 mmol per liter) in the troglitazone group ($P < 0.001$), a decrease of 25 percent in both groups (Fig. 1B). The mean fasting and postprandial plasma insulin and C-peptide concentrations decreased slightly but not significantly in both groups.

After three months of metformin therapy, mean endogenous glucose production decreased by 19 percent, from 108 to 87 mg per square meter per minute (6.0 to 4.8 mmol per square meter per minute, $P = 0.001$). In contrast, there was no significant change (–3 percent) in the troglitazone group ($P = 0.04$). The mean glucose-disposal rate increased in the troglitazone group by 54 percent, from 172 to 265 mg per square meter per minute (9.5 to 14.7 mmol per square meter per minute, $P = 0.006$). The increase with metformin therapy was comparatively less (13 percent; from 240 to 272 mg per square meter per minute [13.3 to 15.1 mmol per square meter per minute]; $P = 0.03$).

When the data were analyzed according to the mean percent changes in these values within subjects, endogenous glucose production decreased by a mean of 18 percent after three months of metformin therapy but was not significantly changed (–0.1 percent) by troglitazone therapy (Fig. 2). The mean increase in the glucose-disposal rate within subjects was 97 percent in the troglitazone group and 27 percent in the metformin group (Fig. 2). The changes in these results were also significantly different between the groups ($P = 0.04$ for the change in endogenous glucose production, and $P = 0.03$ for change in glucose disposal).

Combination Therapy

During combination therapy, the mean fasting plasma glucose concentration decreased by an addi-

TABLE 1. BASE-LINE CHARACTERISTICS OF PATIENTS WITH TYPE II DIABETES MELLITUS WHO COMPLETED THE THREE-MONTH MONOTHERAPY PHASE OF THE STUDY.*

CHARACTERISTIC	METFORMIN GROUP (N = 15)	TROGLITAZONE GROUP (N = 13)
Age (yr)	51 ± 13	56 ± 12
Duration of diabetes (yr)	6 ± 6	4 ± 3
Weight (kg)	99 ± 15	96 ± 26
Body-mass index†	33.7 ± 6.8	34.0 ± 8.1
Fasting plasma glucose after wash-out period (mg/dl)	287 ± 84	275 ± 73
Glycosylated hemoglobin at screening (%)	9.8 ± 1.7	9.3 ± 1.9
Fasting plasma insulin (μU/ml)	24 ± 13	35 ± 25
Fasting plasma C peptide (ng/ml)	1.9 ± 0.5	2.3 ± 0.7

*Plus-minus values are means ± SD. There were no significant differences between groups. To convert values for glucose to millimoles per liter, multiply by 0.056. To convert values for insulin to picomoles per liter, multiply by 6. To convert values for C peptide to nanomoles per liter, multiply by 0.33.

†Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

tional 41 mg per deciliter (2.3 mmol per liter) ($P = 0.001$), a reduction of 18 percent, between three and six months (Fig. 1A). The total mean decrease in fasting plasma glucose concentration in all patients during the six-month treatment period was 98 mg per deciliter (5.4 mmol per liter) ($P = 0.001$), a 35 percent reduction. During combination therapy the mean postprandial plasma glucose concentration decreased an additional 54 mg per deciliter ($P < 0.001$), a reduction of 21 percent (Fig. 1B). During the entire six-month study period, the mean postprandial plasma glucose concentration decreased by 140 mg per deciliter (7.8 mmol per liter) ($P < 0.001$), a 41 percent reduction. The mean glycosylated hemoglobin value also decreased during the three months of combination therapy, with a mean absolute fall of 1.2 percent from base line ($P < 0.001$) (Fig. 3). The mean fasting and postprandial plasma insulin and C-peptide concentrations were lower at six months than at base line, although the changes were small and not statistically significant.

The addition of troglitazone to metformin resulted in no further decrease in basal endogenous glucose production. At six months in this group, mean endogenous glucose production was 90 mg per square meter per minute (5.0 mmol per square meter per minute), representing a decrease of 17 percent from base line ($P = 0.002$) and one not significantly different from the 19 percent decrease after three months of metformin alone. Similarly, in the group given metformin in addition to troglitazone, there was no decrease in endogenous glucose production at six months (92 mg per square meter per minute

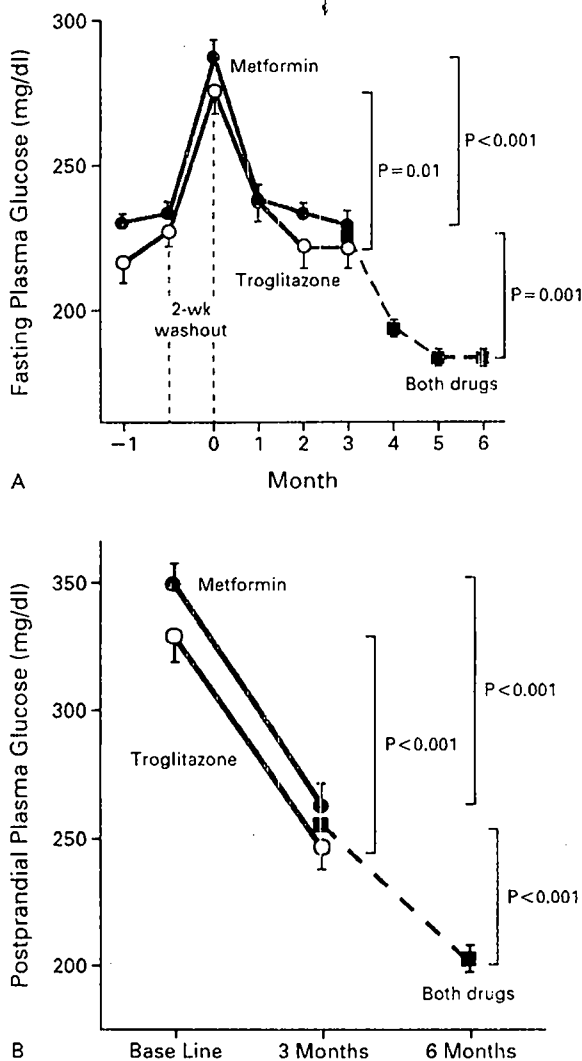


Figure 1. Mean ($\pm$ SE) Changes in Fasting Plasma Glucose Concentrations (Panel A) and Postprandial Plasma Glucose Concentrations (Panel B) during Therapy with Metformin or Troglitazone for Three Months Followed by Combined Therapy with Metformin and Troglitazone for Three Months.

The postprandial plasma glucose values are the means of eight hourly measurements made during the meal-tolerance test. To convert values for glucose to millimoles per liter, multiply by 0.056.

[5.1 mmol per square meter per minute]) as compared with base line (92 mg per square meter per minute) or after three months of troglitazone alone (89 mg per square meter per minute [4.9 mmol per square meter per minute]).

Adding troglitazone to metformin significantly increased the rate of glucose disposal to 337 mg per square meter per minute (18.7 mmol per square meter per minute), a mean increase of 24 percent over the three-month value ($P=0.04$). In contradistinction, when metformin was added to troglitazone, the rate of glucose disposal increased to 304 mg per square meter per minute (16.9 mmol per square meter per minute), a mean increase of only 15 percent from three months ($P=0.30$). The mean increase in the rate of glucose disposal between base line and six months was 40 percent ($P<0.001$) in the patients who received metformin first, with troglitazone added for the second three months, and it was 77 percent ($P<0.001$) in those initially treated with troglitazone, with metformin added for the second three months.

Body Weight and Adverse Events

There were no significant changes in body weight during either monotherapy or combination therapy. Intermittent diarrhea developed in one patient soon after metformin was added to troglitazone. She subsequently withdrew from the study. No other adverse events were ascribed to either monotherapy or combination therapy. The mean plasma lactate concentration was normal at all times in both groups, and no patient had any abnormalities on liver-function tests during the study.

DISCUSSION

In this small group of patients with moderate type II diabetes, metformin and troglitazone had nearly identical efficacy in reducing plasma glucose concentrations. Their mechanisms of action, however, differed. Metformin primarily lowered endogenous glucose production, presumably at the level of the liver, whereas troglitazone increased insulin-mediated peripheral glucose disposal, which occurs predominantly in skeletal muscle. Peripheral glucose disposal was also increased by metformin, but the increase was less than one quarter of that associated with troglitazone. Whereas all the glucose-lowering effect of troglitazone at this dosage may be attributed to this peripheral effect, the action of metformin is more difficult to categorize. The effect of metformin on endogenous glucose production appears to be primary and substantial, with the 19 percent reduction translating to a correction of more than two thirds of the increase described in patients with type II diabetes.^{24,25} The beneficial effect of metformin on glucose disposal, on the other hand, is in the same range as that which occurs in patients treated

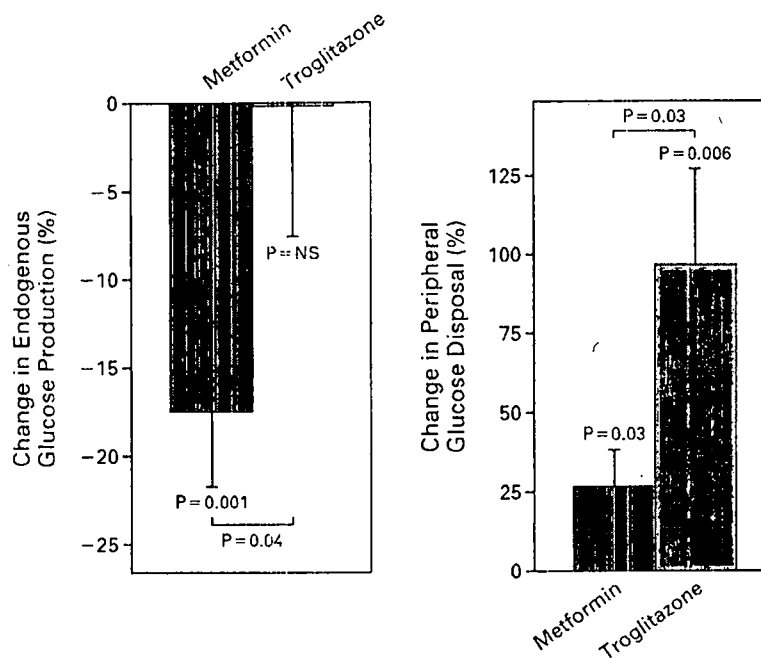


Figure 2. Mean ($\pm$ SE) Percent Changes within Subjects in Endogenous Glucose Production and the Glucose Disposal Rate under Hyperinsulinemic-Clamp Conditions after Three Months of Therapy with Metformin or Troglitazone.

NS denotes not significant.

with sulfonylurea drugs.^{26,27} Whether this is a direct effect of metformin or due to an overall decrease in glucose toxicity is not known.²⁸

The lack of effect of troglitazone at this dose on endogenous glucose production is in contrast to findings by others,^{10,12,13} but is in agreement with the results of a recently reported large, multicenter study.¹⁴ At higher doses (600 mg per day), troglitazone therapy does result in small decreases in hepatic glucose production.¹⁴

Although both drugs alone resulted in improved glycemic profiles, the mean fasting plasma glucose concentrations remained high in both groups at three months. In combination, these drugs further reduced both fasting and postprandial plasma glucose concentrations. The addition of troglitazone to metformin resulted in a significant further increase in peripheral glucose disposal. The small, insignificant increase in glucose disposal when metformin was added to troglitazone suggests that the peripheral action of metformin is minimal. By six months, peripheral glucose disposal had increased in both groups, but the increase was greater among the patients who were initially given troglitazone. This may reflect a delayed effect of troglitazone,²⁹ since the group with the greater increase had received troglitazone for a full six months.

When troglitazone was added to metformin, there

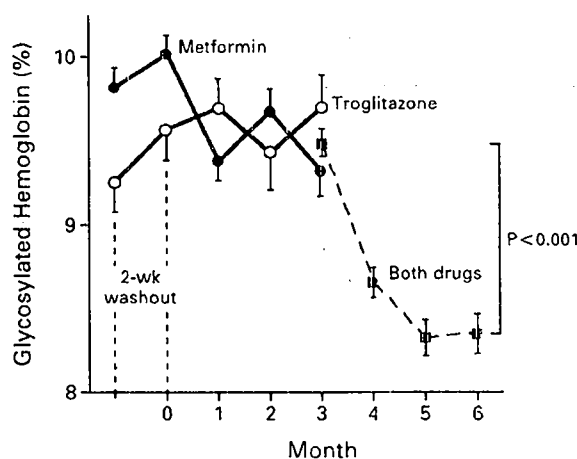


Figure 3. Mean ($\pm$ SE) Changes in Glycosylated Hemoglobin Values during Therapy with Metformin or Troglitazone for Three Months Followed by Combined Therapy with Metformin and Troglitazone for Three Months.

was no further decrease in endogenous glucose production, in keeping with our finding that troglitazone alone had no significant effect on this variable. However, the lack of further lowering of endogenous glucose production when metformin was added to troglitazone is more difficult to explain, particularly because these patients had a significant improvement in glycemic control during combined treatment.

In conclusion, metformin and troglitazone have different mechanisms of action, yet are equally effective in lowering plasma glucose concentrations in patients with type II diabetes. Combination metformin and troglitazone therapy results in further improvement in glucose control, without stimulation of insulin secretion and with reversal of the two principal pathophysiologic abnormalities in this disorder.

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Effect of Metformin and Rosiglitazone Combination Therapy in Patients With Type 2 Diabetes Mellitus

A Randomized Controlled Trial

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TYPE 2 DIABETES IS CHARACTERIZED by decreased insulin secretion^{1,2} and insulin sensitivity in liver, adipose tissue, and skeletal muscle. Together these abnormalities confound efforts to treat diabetes because most antidiabetic agents target only 1 underlying cause of the disease. Approximately 50% of patients treated with monotherapy require additional therapy to achieve target glycosylated hemoglobin (HbA_{1c}) levels 3 years after diagnosis.³

Rosiglitazone maleate, a member of the thiazolidinedione class of antidiabetic agents that was recently approved by the US Food and Drug Administration, targets insulin resistance by binding to the transcription factor peroxisome proliferator-activated receptor- γ , promoting synthesis of glucose transporters and activating adipocyte differentiation.⁴⁻⁶ In contrast, metformin hydrochloride promotes glucose lowering by reducing hepatic glucose production and gluconeogenesis and by enhancing peripheral glucose uptake.⁷⁻¹⁰

Because metformin and rosiglitazone act through different mechanisms, their combined use may be indicated in patients whose disease is poorly controlled with a maintenance dose of metformin. This study evaluated the efficacy and safety of adding

Context Most antidiabetic agents target only 1 of several underlying causes of diabetes. The complementary actions of the antidiabetic agents metformin hydrochloride and rosiglitazone maleate may maintain optimal glycemic control in patients with type 2 diabetes; therefore, their combined use may be indicated for patients whose diabetes is poorly controlled by metformin alone.

Objective To evaluate the efficacy of metformin-rosiglitazone therapy in patients whose type 2 diabetes is inadequately controlled with metformin alone.

Design Randomized, double-blind, placebo-controlled trial from April 1997 and March 1998.

Setting Thirty-six outpatient centers in the United States.

Patients Three hundred forty-eight patients aged 40 to 80 years with a mean fasting plasma glucose level of 12.0 mmol/L (216 mg/dL), a mean glycosylated hemoglobin level of 8.8%, and a mean body mass index of 30.1 kg/m² were randomized.

Interventions Patients were assigned to receive 2.5 g/d of metformin plus placebo (n = 116); 2.5 g/d of metformin plus 4 mg/d of rosiglitazone (n = 119); or 2.5 g/d of metformin and 8 mg/d of rosiglitazone (n = 113) for 26 weeks.

Main Outcome Measures Glycosylated hemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and β -cell function, compared between baseline and week 26, by treatment group.

Results Glycosylated hemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and β -cell function improved significantly with metformin-rosiglitazone therapy in a dose-dependent manner. The mean levels of glycosylated hemoglobin decreased by 1.0% in the 4 mg/d metformin-rosiglitazone group and by 1.2% in the 8 mg/d metformin-rosiglitazone group and fasting plasma glucose levels by 2.2 mmol/L (39.8 mg/dL) and 2.9 mmol/L (52.9 mg/dL) compared with the metformin-placebo group ($P < .001$ for all). Of patients receiving 8 mg/d of metformin-rosiglitazone, 28.1% achieved a glycosylated hemoglobin level of 7% or less. Dose-dependent increases in body weight and total and low-density lipoprotein cholesterol levels were observed ($P < .001$ for both rosiglitazone groups vs placebo). The proportion of patients reporting adverse experiences was comparable across all groups.

Conclusions Our data suggest that combination treatment with once-daily metformin-rosiglitazone improves glycemic control, insulin sensitivity, and β -cell function more effectively than treatment with metformin alone.

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4 mg/d and 8 mg/d of rosiglitazone maleate to maximal-dosage of metformin in patients with poorly controlled type 2 diabetes. Combined efficacy was assessed by comparing the level changes

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in HbA_{1c}, fasting plasma glucose (FPG), fructosamine, serum insulin, free fatty acids (FFA), lipids, lactate, and estimates of insulin sensitivity and β -cell function (BCF) between combined metformin-rosiglitazone treatment and metformin-placebo alone.¹¹

METHODS

Study Subjects

To detect a 0.75% absolute difference in HbA_{1c} between treatment groups, 65 evaluable patients per group would be required to achieve a power of 95%. Planned enrollment was 280 patients (approximately 93 per group). Persons between the ages of 40 and 80 years with type 2 diabetes as defined by the National Diabetes Data Group¹² with FPG concentrations of between 7.8 and 16.7 mmol/L (140 and 300 mg/dL) at screening and during the placebo-maintenance period while taking 2.5 g/d of metformin were eligible. All patients demonstrated insulin secretory capacity as determined by a fast-

ing C-peptide concentration of 0.27 nmol/L (0.8 ng/mL) or more at screening. Subjects were required to have a body mass index, calculated as weight in kilograms divided by the square of height in meters, of 22 to 38 and a weight change of no more than 10% between screening and baseline.

Patients were excluded if they had clinically significant renal or hepatic disease, angina, New York Heart Association Classification class III or IV cardiac insufficiency, symptomatic diabetic neuropathy, significant clinical abnormality on electrocardiogram, abnormal laboratory test results (blood chemistry, hematology, or urinalysis), use of chronic insulin therapy, participated in any rosiglitazone-related study, or used any investigational drug (excluding metformin) within 30 days of study (or 5 half-lives of the investigational drug, if longer than 30 days). Anorectic agents were discontinued at least 30 days before screening. Patients with hyperlipemia, elevated cholesterol or triglyc-

eride levels, or lipid metabolism disorders were eligible; lipid-lowering agents were maintained at the same dosage level throughout the study.

Study Design

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 36 sites in the United States between April 1997 and March 1998. Before the study, patients discontinued all antihyperglycemic medications, with the exception of metformin. Metformin dose tolerability was determined during a 3-week period in which metformin was titrated to 2.5 g/d; afterward, patients entered a 4-week, single-blind metformin-placebo maintenance period with a weight-maintenance diet. During this maintenance period, only investigators were aware that patients were receiving the metformin-placebo treatment. Patients previously treated with metformin at 2.5 g/d proceeded directly to maintenance; thus, with the exception of metformin, patients refrained from medication for a minimum of 4 weeks and a maximum of 7 weeks.

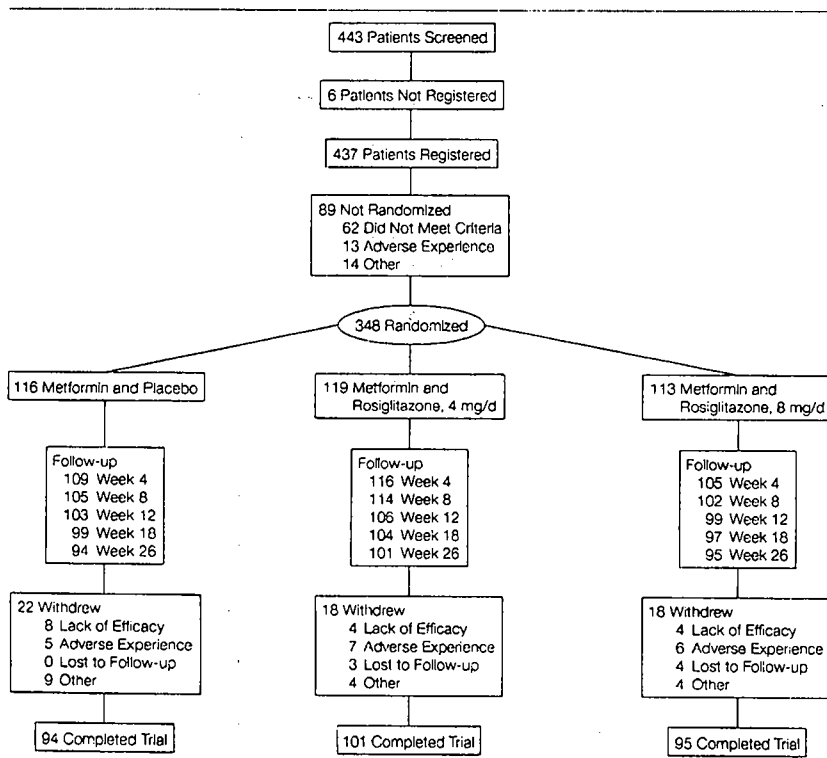
At the end of the maintenance period, patients with inadequate glycemic control (FPG concentration range, 7.7-16.7 mmol/L [140-300 mg/dL]) were randomly assigned (1:1:1 ratio) to receive double-blind metformin treatment in 1 of 3 combinations: placebo (control), 4 mg of rosiglitazone, or 8 mg of rosiglitazone once daily for 26 weeks. Randomization was computer generated with a fixed block size. No patient, investigator, or sponsor was aware of treatment allocation until study completion (FIGURE 1).

This study was conducted in accordance with the Declaration of Helsinki (as amended, 1989), Title 21 of the US Code of Federal Regulations, and Good Clinical Practice guidelines. The institutional review board at each center approved the protocol, and subjects provided informed consent before enrollment.

Efficacy and Safety Measurements

Laboratory measurements for efficacy and safety were performed by SmithKline Beecham Clinical Laboratories (Van Nuys,

Figure 1. Study Profile of Patients Randomized to Receive Metformin Hydrochloride Alone or With Rosiglitazone Maleate



Calif) on blood collected in the fasting state. Fasting plasma glucose concentrations, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were measured by an Olympus analyzer (Olympus Clinical Instruments Division, Lake Success, NY); levels of HbA_{1c} were measured by the high-performance liquid chromatography method (Variant, Bio-Rad, Hercules, Calif); C-peptide by radioimmunoassay (Diagnostic Products, Los Angeles, Calif); insulin by radioimmunoassay (Linco Research Inc, St Charles, Mo); fructosamine by colorimetric analysis (RoTAG fructosamine assay, Roche Diagnostic Systems, Indianapolis, Ind); and FFA by enzymatic/colorimetric analysis (Wako Diagnostic, Richmond, Va) using a COBAS analyzer (Roche Diagnostic Systems). Low-density lipoprotein cholesterol (LDL-C) concentrations were estimated from total cholesterol and HDL-C determinations using the Friedewald calculation.¹³ Lactate was measured by enzymatic spectrophotometric analysis using an Olympus analyzer (Olympus Clinical Instruments Division).

Estimates of insulin sensitivity determined by homeostasis model assessment (HOMA-S) and BCF (HOMA-B) were calculated using FPG and immunoreactive insulin values, or C-peptide levels. HOMA is a mathematical model based on glucose and insulin interaction in different organs, including the pancreas, liver, and peripheral tissues.¹¹ HOMA estimates of BCF and insulin sensitivity were calculated for each participant's FPG and insulin, or C-peptide levels, and expressed relative to values in a lean, nondiabetic reference population aged 18 to 25 years.¹⁴⁻¹⁶ HOMA-S determinations of insulin sensitivity or insulin resistance have been validated by comparison with results of glucose clamp studies,^{11,14} intravenous glucose tolerance tests,^{11,15} and continuous infusion of glucose with model assessment.¹⁵ The HOMA-B method has been validated by comparison with the intravenous glucose tolerance test and continuous infusion of glucose model assessment.¹⁷ Application of HOMA has also been used in epidemiological studies.^{18,19}

Safety monitoring included physical examination, vital sign assessment, weight measurement, electrocardiogram, adverse experience query, and laboratory tests.

Statistical Methods

The primary population for efficacy analysis was the intention-to-treat population, those with at least 1 value while receiving therapy (last observation was carried forward in the case of missing data or early withdrawals). Efficacy and safety parameters were measured at baseline and after 26 weeks of treatment. Safety parameters were assessed based on week 26 data (without the last observation carried forward).

Treatment groups were compared using analysis of covariance with terms for baseline, treatment, and center. The assumptions of the statistical model were tested before application. The Levene test of heterogeneity across treatments was applied at a significance level of $\alpha = .01$. If significant, the Shapiro-Wilk test of nonnormality ($\alpha = .01$) was examined. Parametric analysis or nonparametric analysis was used, depending on results of test assumptions. If prospectively defined assumptions for param-

etric analysis were not met, the Wilcoxon rank sum test was used. Pairwise comparisons to placebo used Dunnett multiple comparison procedure to maintain a 2-sided .05 significance level within each parameter. The statistical significance of the within-group change from baseline was tested by a paired *t* test or a signed rank test. Safety parameters, including clinical laboratory tests, vital signs, and body weight, were examined using 1-way analysis of variance. Statistical analyses were performed using statistical software (SAS/STAT Software, Release 6.12, SAS Institute Inc, Cary, NC).

RESULTS

Of 443 patients screened, 437 entered the titration and maintenance period and 348 were randomized to treatment (Figure 1). Most withdrawals were due to failing to meet inclusion criteria (69.7%). Baseline characteristics were similar among treatment groups (TABLE 1). Fifty-eight patients withdrew before completion of the double-blind phase: 22 from the placebo group and 18 from the 4-mg/d and 18 from the 8-mg/d rosiglitazone groups. Most participants withdrew because of adverse experiences or lack of efficacy (Figure 1).

Table 1. Baseline Demographic and Metabolic Characteristics of Randomized Patients (Intention-to-Treat Population)

Baseline Characteristics	Metformin Hydrochloride and Placebo (n = 113)	Metformin Hydrochloride and Rosiglitazone Maleate	
		4 mg/d (n = 116)	8 mg/d (n = 110)
Age, mean (SD), y	58.8 (9.2)	57.5 (10.5)	58.3 (8.8)
Sex, %			
Men	74.3	62.1	68.2
Women	25.7	37.9	31.8
Duration of diabetes, mean (SD), y	7.3 (5.7)	7.5 (6.3)	8.3 (6.3)
Prior treatment, %			
Diet and exercise only	4.4	6.0	4.5
Oral monotherapy	48.7	39.7	43.6
Oral combination therapy	46.9	54.3	51.8
Baseline HbA _{1c} , mean (SD), %*	8.6 (1.3)	8.9 (1.3)	8.9 (1.5)
Baseline fasting plasma glucose, mean (SD), mmol/L†	11.87 (2.91)	11.90 (3.17)	12.19 (3.05)
Body mass index, mean (SD), kg/m ²	30.3 (4.4)	30.2 (4.2)	29.8 (3.9)
Race, %			
White	81.4	80.2	77.3
Black	3.5	6.9	10.0
Other	15.0	12.9	12.7

*HbA_{1c} indicates glycosylated hemoglobin.

†To convert from millimoles per liter to milligrams per deciliter divide by 0.0555.

Glycemic Control

The mean HbA_{1c} levels decreased significantly from baseline in a dose-dependent fashion in both rosiglitazone groups by 0.56% in the 4-mg/d and by 0.78% in the 8-mg/d rosiglitazone groups. But the control group experienced a significant increase in HbA_{1c} levels (0.45%) (FIGURE 2). Furthermore, both rosiglitazone groups had HbA_{1c} levels lower than those in the control group by 1.0% in the 4-mg/d and 1.2% in the 8-mg/d rosiglitazone groups. In contrast to results observed in the control group, the mean HbA_{1c} levels in the rosiglitazone groups decreased after week 4 and plateaued by week 18 (FIGURE 3). The percentage who achieved a 1.0% reduction in HbA_{1c} concentrations was 32.8% in the 4-mg/d and 37.3% in the 8-mg/d rosiglitazone groups and 7.1% in the control group.

Twenty-five (28.1%) of 89 patients taking 8 mg/d of rosiglitazone achieved the target HbA_{1c} control levels of 7.0%, and 51 patients (57.3%) in the same group achieved HbA_{1c} levels of 8.0%, or below the American Diabetes Association action point. Yet only 7.6% of the patients in the control group achieved HbA_{1c} levels of 7.0% and 35.9% achieved an HbA_{1c} level of 8.0%.

The mean baseline fructosamine levels of 341.73 μ mol/L in the control group increased by 12.3 μ mol/L. But in the rosiglitazone groups the levels decreased by 27.9 μ mol/L from 340.9 μ mol/L in the

4-mg/d group and by 36.8 μ mol/L from 351.8 μ mol/L in the 8-mg/d group (reference range, 200-278 μ mol/L).

Although the mean FPG concentrations did not change significantly in the control group, they significantly decreased in a dose-dependent order from baseline in both rosiglitazone groups (1.8 mmol/L [-33.0 mg/dL], 4-mg/d rosiglitazone; -2.7 mmol/L [-48.4 mg/dL], 8-mg/d-rosglitazone; $P < .0001$). The mean FPG concentrations in both rosiglitazone groups also had decreased compared with the control group (-2.2 mmol/L [-39.8 mg/dL], 4-mg/d rosiglitazone; -2.9 mmol/L [-52.9 mg/dL], 8-mg/d rosiglitazone; $P < .0001$) (FIGURE 4). Furthermore, FPG concentrations in both rosiglitazone groups decreased during the first 4 weeks, plateaued at 12 to 18 weeks, and remained stable thereafter (FIGURE 5). Nine patients (7.9%) in the control group, 25 (21.6%) in the 4-mg/d and 33 (30.0%) in the 8-mg/d rosiglitazone groups achieved FPG concentrations of less than 7.8 mmol/L (140 mg/dL).

Effects on Insulin Sensitivity and BCF

Adding rosiglitazone to maximum doses of metformin significantly increased HOMA-S values. The median baseline HOMA-S values ranged from 46.6 to 49.0 units. The HOMA-S values increased dose-dependently by 1.7

units in the 4-mg/d and by 3.8 units in the 8-mg/d rosiglitazone groups compared with the control group.

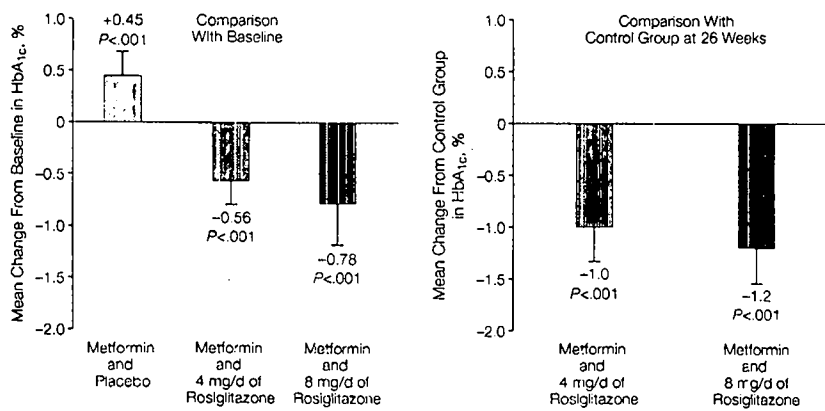
The metformin-rosglitazone combination increased HOMA-B in a dose-dependent fashion. The median baseline HOMA-B values ranged from 32.5 to 35.8 units and were significantly increased by 10.3 to 13.7 units in the rosiglitazone groups compared with the control group.

Other Metabolic Effects

In the control group, the insulin value decreased by 11.05 pmol/L from a baseline of 118.56 pmol/L after treatment ($P = .03$) and in the 4-mg/d and 8-mg/d rosiglitazone groups the insulin values respectively decreased by 12.98 pmol/L from 124.55 pmol/L ($P = .01$) and by 31.07 pmol/L from 136.73 pmol/L ($P = .14$). The C-peptide values respectively decreased by 0.10 nmol/L from 0.93 nmol/L ($P < .001$), by 0.07 nmol/L from 0.92 nmol/L ($P = .01$), and by 0.12 nmol/L from 0.93 nmol/L ($P < .001$).

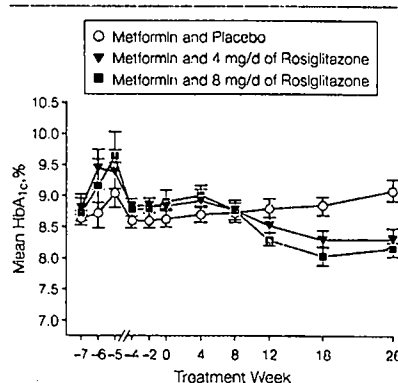
Mean total cholesterol-HDL-C, and LDL-C levels from baseline in both rosiglitazone groups achieved statistically significant increases in all treatment groups compared with the control group (TABLE 2). Total cholesterol-HDL-C ratios in the rosiglitazone groups were not significantly different from those in the control group.

Figure 2. Change in Glycosylated Hemoglobin (HbA_{1c}) Levels at Week 26 in Patients Taking Metformin Hydrochloride and Rosiglitazone Maleate Compared With Taking Metformin Alone



Error bars indicate 95% confidence interval.

Figure 3. Mean Change in Glycosylated Hemoglobin (HbA_{1c}) Levels Over Time in Patients Taking Metformin Hydrochloride Alone Compared With Patients Taking Metformin and Rosiglitazone Maleate Combined



Error bars indicate SE.

Changes in LDL-C levels were evaluated based on those at baseline. In that analysis, we identified 2 subgroups: those with levels lower than 3.37 mmol/L (<130 mg/dL) and those at that level or higher. We did not provide *P* values for any of the subgroups because the values were not large enough for statistical analyses and because the subgroups were not randomized, so significance could not be established. In the lower subgroup, the median baseline LDL-C value increased by 0.13 mmol/L (5 mg/dL) from 2.59 mmol/L (100 mg/dL) in 51 patients in the control group. In both rosiglitazone groups, the LDL-C values increased by 0.54 mmol/L (21 mg/dL) from a median baseline value of 2.69 mmol/L (104 mg/dL) in 57 patients taking 4-mg/d and from 2.64 mmol/L (102 mg/dL) in 60 patients taking 8-mg/d, resulting in medians that remained below 3.37 (<130 mg/dL) for all 3 treatment groups.

In the higher subgroup, the median baseline LDL-C value increased by 0.07 mmol/L (3 mg/dL) from 3.78 mmol/L (146 mg/dL) in 30 patients in the control group. In the rosiglitazone groups, the median baseline LDL-C value increased by 0.31 mmol/L (12 mg/dL) from 3.72 mmol/L (144 mg/dL) in 27 patients taking 4-mg/d and by 0.34-

mmol/L (13 mg/dL) from 4.20 mmol/L (162 mg/dL) in 20 patients taking 8-mg/d.

Changes in triglyceride levels also were evaluated based on baseline values, using 2 subgroups: those with levels lower than 2.26 mmol/L (<200 mg/dL) and those with that level or higher. In the lower subgroup, the median baseline triglyceride values increased by 0.15 mmol/L (13 mg/dL) from 1.44 mmol/L (128 mg/dL) in 52 patients in the control group. In the rosiglitazone groups, the median baseline triglyceride value increased by 0.16 mmol/L (15 mg/dL) from 1.67 mmol/L (148 mg/dL) in 56 patients taking 4-mg/d and by 0.07 mmol/L (6 mg/dL) from 1.34 mmol/L (119 mg/dL) in 55 patients taking 8-mg/d. The treatment values in all groups remained less than 2.25 mmol/L (200 mg/dL).

In the higher subgroup, the median baseline triglyceride values decreased by 0.12 mmol/L (11 mg/dL) from 3.24 mmol/L (287 mg/dL) in 41 patients in the control group. In the rosiglitazone groups, the baseline median triglyceride value increased by 0.15 mmol/L (13 mg/dL) from 3.50 mmol/L (310 mg/dL) in 43 patients taking 4-mg/d and decreased by 0.72 mmol/L (64 mg/dL) from 3.16 mmol/L (280 mg/dL) in the 8-mg/d rosiglitazone group.

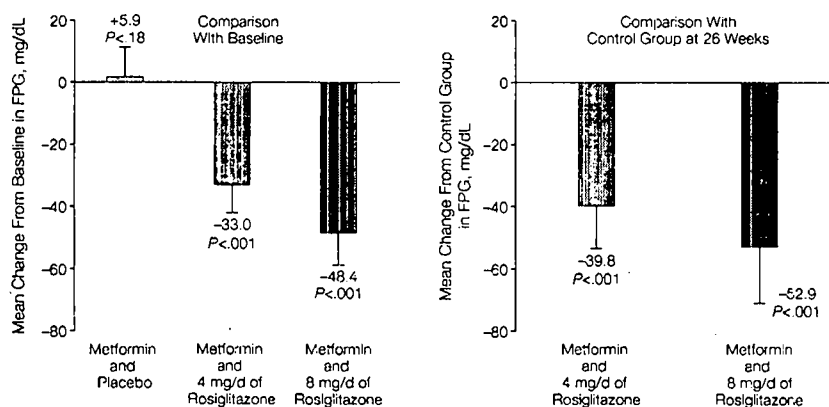
Mean fasting lactate levels decreased significantly in patients taking both dose levels of rosiglitazone compared with those in the control group (4-mg/d rosiglitazone, *P* = .012; 8-mg/d rosiglitazone, *P* = .002). Free fatty acids concentrations decreased significantly from baseline in both rosiglitazone groups. (TABLE 3).

Safety

The percentage of patients with at least 1 adverse event were comparable among each group (75.2%, 4-mg/d rosiglitazone; 78.2%, 8-mg/d rosiglitazone; 76.7%, control). The most frequently reported adverse events were upper respiratory tract infection, diarrhea, and headache. One death due to acute myocardial infarction occurred in the 4-mg/d rosiglitazone group but was judged to be unrelated to study medication. Serious non-fatal adverse events occurred in 5 (4.3%) of 116 patients in the control group and in 5 (4.2%) of 119 patients in the 4-mg/d and 5 (4.4%) of 113 patients in the 8-mg/d rosiglitazone groups, none considered related to study medication.

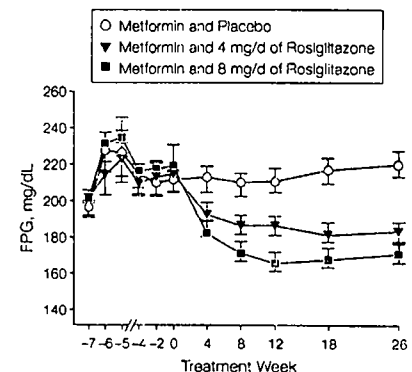
Symptomatic mild or moderate hypoglycemia was reported by 2 patients in the control group and by 3 patients in the 4-mg/d and by 5 patients in the 8-mg/d rosiglitazone groups. No patient required third-party interven-

Figure 4. Change in Fasting Plasma Glucose (FPG) Concentrations at Week 26 in Patients Taking Metformin Hydrochloride and Rosiglitazone Maleate Compared With Patients Taking Metformin Alone



To convert from milligrams per deciliter to millimoles per liter multiply by .0555. Error bars indicate 95% confidence interval.

Figure 5. Mean Fasting Plasma Glucose (FPG) Concentrations Over Time in Patients Taking Metformin Hydrochloride Alone Compared With Patients Taking Metformin and Rosiglitazone Maleate



To convert from milligrams per deciliter to millimoles per liter multiply by .0555. Error bars indicate SE.

COMBINATION THERAPY IN DIABETES

tion or hospitalization, but the metformin dose was reduced from 2.5 g/d to 2.0 g/d in 2 patients. No one withdrew because of hypoglycemia, and there were no biochemically documented instances of FPG levels of less than 2.78 mmol (<50 mg/dL).

Both rosiglitazone groups experienced small but statistically significant decreases in hemoglobin and hematocrit levels, which occurred primarily during the first 12 to 18 weeks of treatment, after which values for both parameters increased slightly. The mean

decreases in hemoglobin levels were -5.0 g/L in the 4-mg/d and -8.0 g/L in the 8-mg/d rosiglitazone groups ($P < .0001$ for both groups), and mean decreases in hematocrit were -1.8% in the 4-mg/d and -2.5% in the 8-mg/d rosiglitazone groups ($P < .0001$ for both groups). There were no significant changes in these parameters in the control group. One patient in each rosiglitazone group withdrew because of anemia, and 1 patient in the 4-mg/d rosiglitazone group with low hemoglobin and hematocrit levels was withdrawn from the study after week 8 because of evidence of gastrointestinal tract bleeding, considered by the investigator to be unrelated to the study medication.

There were no significant changes from baseline in vital signs or electrocardiogram parameters in the rosiglitazone groups compared with the control group. Although infrequent, edema was observed with greater frequency in the rosiglitazone groups (2.5%, 4-mg/d; 3.5%, 8-mg/d) than in the control group (0.9%). No one withdrew due to edema.

Those in the control group experienced a mean decrease in body mass of 1.2 kg from baseline, but those in the rosiglitazone groups experienced a mean body mass increase of 0.7 kg in the 4-mg/d and 1.9 kg in the 8-mg/d rosiglitazone groups ($P = .0001$ for both groups). There were no significant differences in waist-to-hip ratios among groups.

No one in the rosiglitazone groups experienced elevations of alanine aminotransferase (ALT) levels greater than 3 times the upper limit of the reference range. Mean changes in aspartate aminotransferase (AST), ALT, and total bilirubin levels were similar in all groups, with a slight decrease observed in mean ALT (-1.9 U/L, control; -1.9 U/L, 4-mg/d rosiglitazone; -3.4 U/L, 8-mg/d rosiglitazone). Mean alkaline phosphatase decreased in all groups (-3.5 U/L, control; -12.0 U/L, 4 mg/d rosiglitazone; -14.7 U/L, 8-mg/d rosiglitazone); the mean value for all groups was within the reference range. Two patients in the control group were

Table 2. Change in Lipid Parameters From Baseline at Week 26*

Lipid Parameter	Metformin Hydrochloride and Placebo	Metformin Hydrochloride and Rosiglitazone Maleate	
		4 mg/d	8 mg/d
Total cholesterol, mmol/L			
No. of patients	113	116	110
Baseline, mean (SD)	5.32 (1.02)	5.25 (0.92)	5.19 (1.22)
Week 26, mean (SD)	5.50 (1.03)	5.98 (1.05)	6.01 (1.41)
Mean (SD) change from baseline†	0.18 (0.61)	0.72 (0.74)	0.82 (1.07)
P value‡	.0018	<.0001	<.0001
Mean difference from placebo	...	0.53	0.60
P value§	...	<.0001	<.0001
HDL cholesterol, mmol/L			
No. of patients	112	116	110
Baseline, mean (SD)	1.14 (0.28)	1.18 (0.29)	1.20 (0.37)
Week 26, mean (SD)	1.20 (0.29)	1.32 (0.34)	1.36 (0.42)
Mean (SD) change from baseline†	0.06 (0.14)	0.13 (0.19)	0.16 (0.24)
P value‡	<.0001	<.0001	<.0001
Mean difference from placebo	...	0.08	0.10
P value§	...	.0002	.0002
Total cholesterol-HDL ratio			
No. of patients	112	116	110
Baseline, mean (SD)	4.86 (1.37)	4.62 (1.13)	4.58 (1.40)
Week 26, mean (SD)	4.79 (1.27)	4.80 (1.48)	4.77 (1.75)
Median change from baseline†	-0.015	0.115	0.130
P value‡	.73	.12	.18
Median difference from placebo	...	0.150	0.16
P value‡	...	.13	.16
LDL cholesterol, mmol/L			
No. of patients	104	108	102
Baseline, mean (SD)	3.03 (0.88)	2.99 (0.78)	2.91 (0.84)
Week 26, mean (SD)	3.13 (0.97)	3.46 (0.86)	3.45 (1.04)
Mean (SD) change from baseline†	0.10 (0.44)	0.46 (0.58)	0.53 (0.76)
P value‡	.02	<.0001	<.0001
Mean difference from placebo	...	0.36	0.40
P value§	...	<.0001	<.0001
Triglycerides, mmol/L			
No. of patients	113	116	110
Baseline, mean (SD)	2.77 (2.19)	2.54 (1.56)	2.57 (2.07)
Week 26, mean (SD)	2.78 (1.79)	2.62 (1.57)	2.57 (1.87)
Mean (SD) change from baseline†	0.008 (1.32)	0.08 (1.35)	-0.003 (1.72)
P value‡	.95	.53	.98
Mean difference from placebo	...	-0.06	-0.10
P value§	...	.73	.56

*To convert cholesterol levels from millimoles per liter to milligrams per deciliter divide by 0.0259. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and ellipses, not applicable. Data are rounded.

†Calculated only for patients with both a baseline and a week 26 value.

‡Significance level is .05.

§Significance level is .0259.

||To convert triglyceride levels from millimoles per liter to milligrams per deciliter divide by 0.0113.

noted to have liver function tests for potential clinical concern (>3 times the upper limit of the reference range) while in treatment. Both completed the study with elevated transaminase values.

COMMENT

This is the first large, multicenter, clinical trial demonstrating the efficacy and safety of combined rosiglitazone and metformin treatment in patients with type 2 diabetes. The combination treatment of metformin and rosiglitazone significantly reduced HbA_{1c} and FPG concentrations, in a dose-ordered fashion compared with baseline and with metformin alone. Conversely, treatment with metformin was associated with significant increases in HbA_{1c} concentrations, indicating that these agents complement each other to achieve optimal glycemic control and confirming the clinical utility of metformin in combination with a thiazolidinedione drug.²⁰

Consistent with the mechanisms of action of metformin and rosiglitazone, the reductions in FPG concentrations were proportionately smaller than those observed in HbA_{1c} concentrations. Maximum doses of metformin decrease hepatic gluconeogenesis, which principally affects FPG concentrations, whereas rosiglitazone enhances insulin sensitivity at the peripheral level and affects overall glucose disposal, including postprandial excursions. Because the relative contribution of postprandial glucose on glycemic control depends on the magnitude of FPG concentrations,²¹ rosiglitazone may have an effect on postprandial hyperglycemia, as demonstrated directly in a rosiglitazone trial that showed significant improvements in fasting and postprandial glucose concentrations and excursions.²²

The complementary actions of combined metformin and rosiglitazone is further supported by the effects of rosiglitazone on insulin sensitivity despite maximum doses of metformin. Rosiglitazone may provide added therapeutic value by reducing peripheral insulin resistance. While HOMA-S is an indirect method for determining insulin sensitivity, these results are consis-

Table 3. Change in Free Fatty Acid Levels at Week 26 (Compared With Baseline and Metformin Hydrochloride and Placebo)*

	Free Fatty Acids, mg/dL		
	Metformin and Placebo (n = 113)	Metformin and Rosiglitazone Maleate	
		4 mg/d (n = 116)	8 mg/d (n = 110)
Baseline, mean (SD)	18.26 (7.75)	18.39 (7.56)	18.44 (8.00)
Week 26, mean (SD)	18.17 (6.06)	15.78 (6.05)	14.15 (6.13)
Change from baseline, mean (SD)†	-0.09 (7.66)	-2.61 (6.69)	-4.30 (7.88)
P value‡	.90	<.0001	<.0001
Mean difference from control	...	-2.62	-4.22
P value§	...	.0003	<.0001

*Ellipses indicate not applicable.

†Calculated only for patients with both a baseline and a week 26 value.

‡Significance level is .05.

§Significance level is .0259.

tent with glucose-clamp studies using other thiazolidinedione drugs.^{23,24}

The improvements in HOMA-B with metformin-rosiglitazone treatment (not observed with metformin alone) were unexpected and introduce an important potential therapeutic benefit of rosiglitazone. Although the exact mechanism underlying this improvement remains to be determined, rosiglitazone-mediated reductions in glucotoxicity²⁵ and lipotoxicity secondary to elevated concentrations of circulating FFA or both^{26,27} are candidate mechanisms by which rosiglitazone may improve BCF. The effects of rosiglitazone on BCF and insulin sensitivity are consistent with its effects on long-term glycemic control and suggest that it may possibly delay or prevent disease progression.

Despite significant increases in total cholesterol, HDL-C, and LDL-C with the metformin-rosiglitazone treatments, the total cholesterol-HDL-C ratio, which did not change significantly, may be a better predictor of cardiovascular outcome than either total cholesterol or HDL-C levels alone.²⁸⁻³⁰ Since this study was not designed to assess long-term lipid effects, the long-term significance of these changes is unknown; however, patients with baseline plasma LDL-C levels lower than 3.37 mmol/L (<130 mg/dL) remained less than that level after therapy. No significant changes in triglyceride levels were noted in any treatment group, and segregation of patients

into subgroups revealed nonsignificant increases in patients with baseline triglyceride levels lower than 2.26 mmol/L (<200 mg/dL). Among patients in the 8-mg/d rosiglitazone group whose baseline was higher than 2.26 mmol/L (>200 mg/dL), there was a significant statistical decrease observed (64 mg/dL). The clinical significance of lipid level changes may be minimal, because lipid-lowering therapy may be often administered to patients with diabetes irrespective of prior heart disease history.^{31,32}

Elevated FFA may play a role in the development of insulin resistance, because it is associated with increased hepatic glucose output^{33,34} and may contribute to β -cell dysfunction via a lipotoxic effect.^{26,27} Elevated FFA has also been linked to endothelial dysfunction and hypertension^{35,36} and enhanced platelet aggregation and coagulation,^{37,38} which may increase cardiovascular risk. Therefore metformin-rosiglitazone treatment was significantly more effective in lowering FFA than the metformin alone.

The weight gain observed in those receiving metformin-rosiglitazone treatment may be attributed to increased adipocyte differentiation,^{39,40} fluid retention,^{39,41} or increased appetite.⁴² Despite weight increases, no significant differences in waist-to-hip ratio among groups were observed, suggesting that rosiglitazone treatment leads to increased energy storage in subcutaneous adipose sites that are not associated with

increased cardiovascular risk.⁴³ The small decreases in hemoglobin and hematocrit levels associated with metformin-rosiglitazone therapy may relate to plasma volume expansion derived from fluid retention and hemodilution.⁴⁴

Metformin-rosiglitazone therapy may be a safe alternative therapy to attain optimal glycemic control where monotherapy has failed because the statistically significant decreases in lactate levels associated with metformin-rosiglitazone treatment indicate that rosiglitazone may correct metabolic abnormalities beyond reducing hyperglycemia, and further suggest differing and complementary actions of metformin and rosiglitazone; and ALT elevations greater than 3 times the upper limit of the reference range were not observed in either of the rosiglitazone groups.

In summary, combination metformin-rosiglitazone treatment is effective and safe in reducing hyperglycemia in patients with type 2 diabetes. In patients whose fundamental abnormality is insulin resistance, such a combination raises the exciting possibility of treating diabetes by targeting the underlying cause of the disease, rather than the traditional approach of stimulating insulin secretion. Nearly 30% of patients taking the combination therapy achieved HbA_{1c} levels of 7% or less. This level of glycemic control is 3-fold greater than what was achieved among those taking metformin alone. Additional investigation is needed to determine whether this combination will alter the long-term risk of cardiovascular disease or delay disease progression.

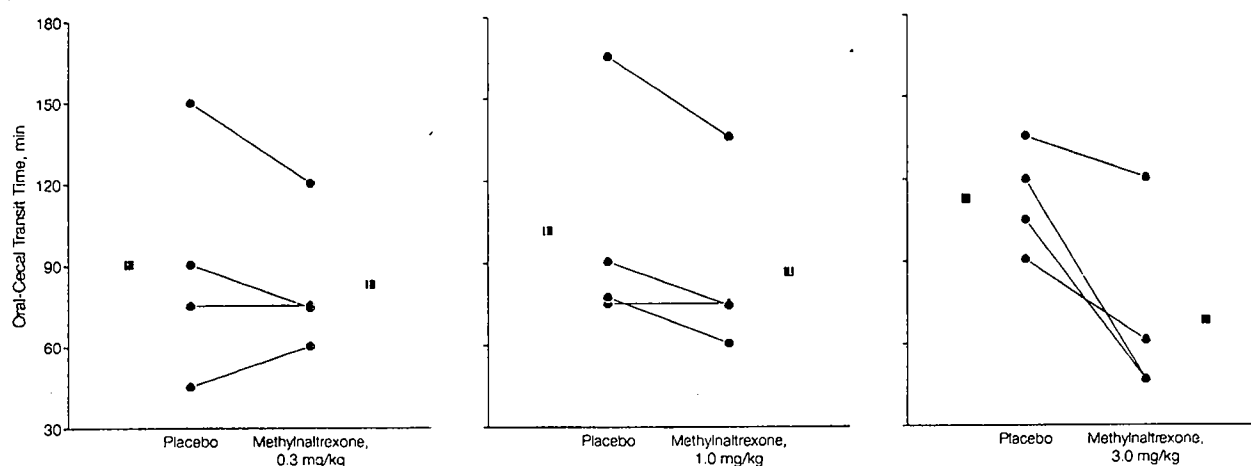
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Figure. Dose-Related Changes in Oral-Cecal Transit Times

Changes in individual oral-cecal transit times of 12 patients receiving long-term methadone treatment after placebo and 3 oral methylnaltrexone doses (4 patients in each dose group). Squares represent mean values.

methylnaltrexone levels. Mean (SD [range]) peak plasma level for the other 4 patients (1 from the 1.0 mg/kg group and 3 from the 3.0 mg/kg group) was 17.8 (6.6 [10-26]) ng/mL.

Comment. Tertiary opioid antagonists, such as naloxone, cross the blood-brain barrier and reverse both the pain-relieving benefits and the adverse effects of opiates. Although oral naloxone may relieve opioid-induced constipation, the therapeutic index is very narrow,³ and naloxone may induce opioid withdrawal symptoms. Many patients receiving opioid pain medications face a difficult choice between burdensome adverse effects or ineffective analgesia. Methylnaltrexone may allow for more aggressive use of opioid analgesics with fewer adverse effects. The low methylnaltrexone plasma levels observed in our study suggest that this charged compound acts directly in the gut. Oral methylnaltrexone has potential clinical utility in managing opioid-induced constipation with minimal adverse effects.

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Funding/Support: This work was supported in part by a grant from the International Anesthesia Research Society, National Institutes of Health grants R01 CA79042 and M01 RR00055. Methylnaltrexone was originally formulated and subsequently modified by faculty at the University of Chicago. The University of Chicago and Drs Yuan and Foss stand to benefit financially from the further development of methylnaltrexone.

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CORRECTIONS

Incorrect Wording and Footnote Symbol: In The Rational Clinical Examination entitled "Does This Patient Have Carpal Tunnel Syndrome?" published in the June 21, 2000, issue of THE JOURNAL (2000;283:3110-3117), there was incorrect wording in the abstract. In the Conclusion paragraph on page 3110, the first sentence should have read, "Hand symptom diagrams, hypalgesia, and thumb abduction strength testing are helpful in establishing the electrodiagnosis of CTS." Also, in Table 2 on pages 3114 and 3115, the "No. of Hands" columns should include dagger symbols (†) instead of asterisks (*) down the column to indicate which studies used subjects instead of individual hands.

Incorrect Wording and Data Presentation and Omitted Acknowledgment: In the Original Contribution entitled "Effect of Metformin and Rosiglitazone Combination Therapy in Patients With Type 2 Diabetes Mellitus: A Randomized Controlled Trial" published in the April 5, 2000, issue of THE JOURNAL (2000;283:1695-1702), incorrect wording and incorrect data presentation were printed. On page 1695, in the "Results" section of the Abstract, the sentence that read "28.1% achieved a glycosylated hemoglobin of less than 7%" should have read "7% or less." On page 1698, the last sentence in the "Glycemic Control" section should have read "Nine patients (7.9%) in the control group, 25 (21.6%) in the 4-mg/d, and 33 (30.0%) in the 8-mg/d rosiglitazone groups achieved FPG concentrations of less than 7.8 mmol/L (140 mg/dL)." On page 1699 in the "Other Metabolic Effects" section, in the penultimate paragraph, which reports triglyceride findings, the phrase that read "in the rosiglitazone groups, the median baseline triglyceride value increased. . . by 0.07 mmol/L (6 mg/dL) from 1.34 mmol/L (119 mg/dL) in 55 patients taking 8-mg/d," should have read "decreased by 0.72 mmol/L (64 mg/dL) from 9.16 mmol/L (280 mg/dL) in 37 patients taking 8 mg/d." The last sentence of the penultimate paragraph of the "Other Metabolic Effects" section was repeated from the prior paragraph and should be deleted. In Table 2, the "Total cholesterol-HDL ratio" section should not have been converted to mmol/L. To calculate the proper ratio, divide the values in that section by 0.0259. In the footnote of Table 2, the cholesterol conversion factor should have read "0.0259." On page 1701 in the "Comment" section in the third column, the line that read "Among patients in the 8-mg/d rosiglitazone group. . . there was a significant statistical decrease observed (6.4-mg/dL)" should have read "(64 mg/dL)." In addition, Sylvia K. Chai, PhD, should have been included in the acknowledgment for her significant contributions to the preparation and review of the article.

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Diabetes and Endocrine Associates and Sharp HealthCare, San Diego, California, USA.

BACKGROUND: Their complimentary mechanisms of action suggest that a combination of pioglitazone hydrochloride and metformin may have clinically beneficial effects in the treatment of patients with type 2 diabetes. **OBJECTIVE:** This study was undertaken to assess the efficacy and tolerability of pioglitazone in combination with metformin in patients with type 2 diabetes mellitus. **METHODS:** This was a 16-week, double-blind study with the option of enrollment in a separate open-ended, open-label study. It included patients with poorly controlled diabetes mellitus (glycated hemoglobin [HbA1c] > or =8.0%, fasting C-peptide >1.0 ng/mL) who had been receiving a stable regimen of metformin for > or =30 days. Patients with diabetic retinopathy, nephropathy, or neuropathy; impaired liver or kidney function; or unstable cardiovascular or cerebrovascular conditions were excluded. Patients were randomized to receive once-daily pioglitazone 30 mg + metformin or placebo + metformin. Patients in the open-label extension received pioglitazone 30 mg (with optional titration to 45 mg) + metformin. **RESULTS:** Three hundred twenty-eight patients were randomized to treatment (168 pioglitazone + metformin, 160 placebo + metformin), and 249 completed the study. Of these, 154 elected to enter the open-label extension study. Patients' mean age was 56 years; most (84%) were white and slightly more than half (57%) were male. Patients receiving pioglitazone 30 mg + metformin had statistically significant mean decreases in HbA1c (-0.83%) and fasting plasma glucose (FPG) levels (-37.7 mg/dL) compared with placebo + metformin ($P < or = 0.05$). Decreases in FPG levels occurred as early as the fourth week of therapy, the first time point at which FPG was measured. The pioglitazone + metformin group had significant mean percentage changes in levels of triglycerides (-18.2%) and high-density lipoprotein cholesterol (+8.7%) compared with placebo + metformin ($P < or = 0.05$). Mean percentage increases were noted in low-density lipoprotein cholesterol levels (7.7%, pioglitazone + metformin; 11.9%, placebo + metformin) and total cholesterol (4.1%, pioglitazone + metformin; 1.1%, placebo + metformin), with no significant differences between groups. In the extension study, patients treated with open-label pioglitazone + metformin for 72 weeks had mean changes from baseline of -1.36% in HbA1c and -63.0 mg/dL in FPG. The incidence of adverse events was similar in both groups. Throughout the study, no patient in either treatment group had an alanine aminotransferase (ALT) value > or =3 times the upper limit of normal, a commonly used marker of potential liver damage. Thus, no evidence of drug-induced hepatotoxicity or drug-induced elevations in serum ALT was observed. **CONCLUSIONS:** In this study in patients with type 2 diabetes mellitus, pioglitazone + metformin significantly improved HbA1c and FPG levels, with positive effects on serum lipid levels and no evidence of drug-induced hepatotoxicity. These effects were maintained for >1.5 years, including the open-label extension.

PMID: 11192132 [PubMed - indexed for MEDLINE]

Related Articles

Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. [Diabetes Care. 2000]

Triple therapy with glimepiride in patients with type 2 diabetes mellitus inadequately controlled by metformin and a thiazolidinedione: results of a 30-week, randomized, double-blind, placebo-controlled, parallel-group study. [Clin Ther. 2005]

Efficacy and safety of pioglitazone in type 2 diabetes: a randomised, placebo-controlled study in patients receiving stable insulin therapy. [Int J Clin Pract. 2002]

The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. [Coron Artery Dis. 2001]

Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. [Am J Med. 2001]

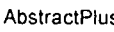
[» See all Related Articles...](#)**Patient Drug Information**

Metformin (Fortamet®, Glucophage®, Glucophage® XR, ...) Metformin is used alone or with other medications, including insulin, to treat type 2 diabetes (condition in which the body does not use insulin normally and, therefore, cannot control the amount of sugar in the blood) ...

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Pioglitazone (Actos®, ActoPL USMell® (as a combination product containing pioglitazone and metformin), Duolact® (as a combination product containing pioglitazone and glimepiride))

Pioglitazone is used with a diet and exercise program and sometimes with other medications, to treat type 2 diabetes (condition in which the body does not use insulin normally and therefore cannot control the amount of s...

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US006296874B1

(12) **United States Patent**
Cutie et al.

(10) **Patent No.:** **US 6,296,874 B1**
(45) **Date of Patent:** **Oct. 2, 2001**

(54) **CORE FORMULATION COMPRISING
TROGLITAZONE AND ABIGUANIDE**

(75) **Inventors:** **Anthony J. Cutie; Akwete L. Adjei,**
both of Bridgewater, NJ (US)

(73) **Assignee:** **Aeropharm Technology Incorporated,**
Edison, NJ (US)

(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** **09/703,023**

(22) **Filed:** **Oct. 31, 2000**

Related U.S. Application Data

(60) **Provisional application No. 60/201,233, filed on May 1,**
2000.

(51) **Int. Cl.⁷** **A61K 9/28; A61K 9/30;**
A61K 9/50

(52) **U.S. Cl.** **424/474; 424/468; 424/471;**
424/475; 424/490; 514/866

(58) **Field of Search** 424/474, 475,
424/479, 480, 481, 482, 491, 493, 494,
496, 497, 490, 471, 468, 463

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Primary Examiner—James M. Spear

(74) *Attorney, Agent, or Firm*—Frommer Lawrence &
Haug LLP

(57) **ABSTRACT**

This invention relates to a combination drug product com-
prising troglitazone, e.g. its hydrochloride, and a biguanide,
e.g. metformin. In particular, the product comprises a core of
metformin, at least a portion thereof has a layer or coat
thereon of troglitazone.

17 Claims, No Drawings

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**CORE FORMULATION COMPRISING
TROGLITAZONE AND ABIGUANIDE**

This application claims priority from U.S. provisional application Ser. No. 60/201,233 filed May 1, 2000, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION**1. Field of the Invention**

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

2. Description of the Related Art

Metformin and troglitazone, and 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 advantage 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 troglitazone or a derivative thereof, e.g. troglitazone 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 ("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 and the troglitazone, e.g. its hydrochloride, are present in effective amounts to A provide such treatment.

**DETAILED DESCRIPTION OF THE
INVENTION**

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.

Troglitazone hydrochloride, (Rezulin®), is an active ingredient for a commercially available drug employed to treat diabetes mellitus in a host, e.g. a human being. The

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typical daily effective dose for the oral administration to a mammal, e.g. a human being, ranges from 200 mg to 400 mg, given as a single dose.

Heretofore, the metformin and pioglitazone hydrochloride have not been administered together to try to improve the effectiveness of either drug, although co-administration of the two has been proposed [Whitcomb; et al., U.S. Pat. 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.

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 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 troglitazone 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 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 troglitazone, e.g. its 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 troglitazone, e.g. its 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 can admixed with the active ingredients in the first layer and/or the core.

The α -glucosidase inhibitors [Jean-Bernard Ducep et al., U.S. Pat. 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-(α ,D-glucopyranosyl)-1,5-[6,7-dideoxy-7-D-glucobioheptopyranosyl]imino-D-glucitol; 1,5-Dideoxy-4-O-(α ,D-glucopyranosyl)-1,5-[(1-deoxy-D-fructofuranosyl)imino]-D-glucitol; 1,5-Dideoxy-4-O-(α ,D-glucopyranosyl)-1,5-[(4-deoxy-4-D-glucopyranosyl)imino]-D-glucitol; 1,5-Dideoxy-4-O-(α ,D-glucopyranosyl)-N-[6-deoxy-1-(6-O-D-glucopyranosyl)- α ,D-glucopyranosyl]-1,5-imino-D-glucitol; 1,5-Dideoxy-4-O-(α ,D-glucopyranosyl)-N-[6,7-dideoxy-1-(6-O-D-glucopyranosyl)-7- α ,D-glucobioheptopyranosyl]-1,5-imino-D-glucitol; 1,5-Dideoxy-4-O-(α ,D-glucopyranosyl)-1,5-[(4-deoxy-4-D-glucopyranosyl)methylimino]-D-glucitol; 1,5-Dideoxy-4-O-(α ,D-glucopyranosyl)-N-[4-deoxy-1-(4-O-D-glucopyranosyl)- α ,D-glucopyranosyl]-1,5-imino-D-

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8. 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.

9. A pharmaceutical composition comprising an effective amount of troglitazone hydrochloride and an effective amount of metformin in a core formulation comprising a first layer of said troglitazone hydrochloride and a core, at least a portion of which is covered by said first layer, comprising said metformin.

10. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 9.

11. A pharmaceutical composition comprising an effective amount of troglitazone hydrochloride contained in a first layer of a core formulation which covers at least a portion of a core comprising an effective amount of phenformin.

12. A pharmaceutical composition comprising a first layer of a core formulation comprising an effective amount of troglitazone hydrochloride and a core, having at least a portion thereof covered by said first layer, comprising an effective amount of buformin.

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

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 1 wherein the biguanide is phenformin.

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 buformin.

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 metformin.

* * * * *



US006099862A

United States Patent [19][11] **Patent Number:** 6,099,862

Chen et al.

[45] **Date of Patent:** Aug. 8, 2000

[54] **ORAL DOSAGE FORM FOR THE CONTROLLED RELEASE OF A BIGUANIDE AND SULFONYLUREA**

[75] Inventors: Chih-Ming Chen; Xiu Xiu Cheng, both of Davie; Joseph Chou; Steve Jan, both of Coral Springs, all of Fla.

[73] Assignee: ANDRX Corporation, Fort Lauderdale, Fla.

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Primary Examiner—Thurman K. Page

Assistant Examiner—Brian K. Seidleck

Attorney, Agent, or Firm—Hedman, Gibson & Costigan, P.C.

[57]

ABSTRACT

A controlled release pharmaceutical tablet containing anti-hyperglycemic drug and a hypoglycemic drug that does not contain an expanding or gelling polymer layer and comprising a core containing the antihyperglycemic drug and the hypoglycemic drug, a semipermeable coating membrane surrounding the core and at least one passageway in the membrane to allow the drugs to be released from the core.

4 Claims, 2 Drawing Sheets

[21] Appl. No.: 09/143,876

[22] Filed: Aug. 31, 1998

[51] Int. Cl.⁷ A61K 9/24; A61K 9/36; A61K 9/20

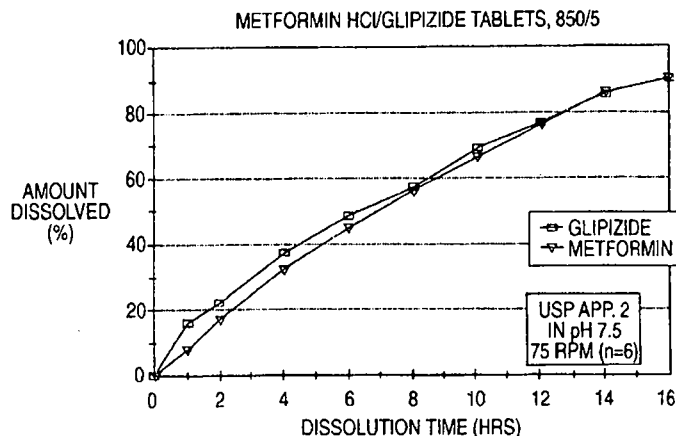
[52] U.S. Cl. 424/473; 424/468; 424/474; 424/475; 424/479; 424/480

[58] Field of Search 424/464, 468, 424/472, 473, 474, 475, 479, 480; 604/890.1, 892.1

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ORAL DOSAGE FORM FOR THE CONTROLLED RELEASE OF A BIGUANIDE AND SULFONYLUREA

BACKGROUND OF THE INVENTION

The present invention relates to controlled release unit dose formulations containing an antihyperglycemic drug and a hypoglycemic drug. As used in this specification the term "antihyperglycemic" refers to a drug that is useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM) by decreasing hepatic glucose production, decreasing intestinal absorption of glucose and/or improving insulin sensitivity. Biguanides are the preferred antihyperglycemic drugs. As used in this specification the term "hypoglycemic" refers to a drug that is useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM) by stimulating the release of insulin from the pancreas. Sulfonylureas are the preferred hypoglycemic drugs.

In a preferred embodiment, the present invention relates to an oral dosage form comprising a unique combination of a biguanide and a sulfonylurea. The biguanide is preferably metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride or the metformin salts described in U.S. Pat. Nos. 3,957,853 and 4,080,472 which are incorporated herein by reference. The sulfonylurea compound is preferably glipizide as described in U.S. Pat. No. 5,545,413 or glyburide. Other possible sulfonylurea compounds such as glibornuride, glisoxepide, gliclazide, acetohexamide, chlorpropamide, tolazamide, tolbutamide and tolbutamide which are described in U.S. Pat. Nos. 5,674,900 and 4,708,868, which are incorporated herein by reference, may also be employed.

The dosage form of the present invention can provide therapeutic levels of the drugs from twelve to twenty-four hour periods. In a preferred embodiment, the dosage form will be administered once a day and provide therapeutic levels of the drug throughout the day.

In the prior art, many techniques have been used to provide controlled and extended-release pharmaceutical dosage forms in order to maintain therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance.

In the prior art are extended release tablets which employ either a biguanide drug alone or a sulfonylurea drug alone. For example WO 96/08243 discloses a controlled release dosage form containing only metformin HCl, a biguanide, as the active ingredient and employs a hydrogel to push the active ingredient from the dosage form. Similarly, U.S. Pat. Nos. 5,545,413, 5,591,454 and 5,091,190 disclose controlled release dosage forms containing only the drug glipizide and employ a hydrogel to push the active ingredient from the dosage form.

The 50th edition of the Physicians' Desk Reference®, copyright 1996, suggests administering to a patient a metformin HCl dosage form commercially available from Bristol-Myers Squibb Co. under the tradename GLUCOPHAGE® and a dosage form of a sulfonylurea compound such as glyburide. More specifically, page 753 of the 50th edition of the Physicians' Desk Reference states that if adequate glycemic control is not attained with GLUCOPHAGE® monotherapy, the combination of GLUCOPHAGE® and a sulfonylurea such as glyburide may have a synergistic effect, since both active ingredients act to improve glucose tolerance by different mechanism. According to the 50th edition of the Physicians' Desk Reference, the GLUCOPHAGE®

dosage form is believed to function by decreasing hepatic glucose production, decreasing intestinal absorption of glucose and improving insulin sensitivity, while the sulfonylurea compound is believed to lower the blood glucose levels by stimulating the release of insulin from the pancreas.

Although the 50th edition of the Physicians' Desk Reference suggests the combined administration of metformin HCl and a sulfonylurea compound, it fails to suggest a single unitary controlled release dosage form comprising both an antihyperglycemic drug and a hypoglycemic drug that can provide continuous and non-pulsating therapeutic levels of an antihyperglycemic drug and a hypoglycemic drug to an animal in need of such treatment over a twelve hour or twenty-four hour period.

It is an object of the present invention to provide a controlled or sustained release formulation that contains both an antihyperglycemic drug and a hypoglycemic drug.

It is a further object of the present invention to provide a controlled or sustained release formulation that contains both an antihyperglycemic drug and a hypoglycemic drug that does not employ an expanding or gel forming material to push the drugs out.

It is a further object of the present invention to provide a controlled or sustained release formulation that contains both an antihyperglycemic drug and a hypoglycemic drug that can provide continuous and non-pulsating therapeutic levels of an antihyperglycemic drug to an animal in need of such treatment over a twelve hour or twenty-four hour period.

It is also an object of this invention to provide a controlled or sustained release pharmaceutical tablet having a homogeneous core wherein the core component may be made using ordinary tablet compression techniques.

SUMMARY OF THE INVENTION

The foregoing objectives are met by a controlled release dosage form which comprises:

- (a) a core which comprises:
 - (i) an antihyperglycemic drug;
 - (ii) a hypoglycemic drug;
 - (iii) a binding agent; and
 - (iv) optionally, an absorption enhancer;
- (b) optionally a seal coating layer around the core;
- (c) a semipermeable coating membrane surrounding the core; and
- (d) at least one passageway in the semipermeable membrane to allow release of the antihyperglycemic drug and the hypoglycemic drug.

In the preferred embodiment the antihyperglycemic drug is a biguanide such as metformin or a pharmaceutically acceptable salt and the hypoglycemic drug is a sulfonylurea, such as glipizide or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph which depicts the dissolution profile in simulated intestinal fluid (SIF), pH 7.5 phosphate buffer of the formulation described in Example 1 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 2 is a graph which depicts the dissolution profile in simulated intestinal fluid (SIF), pH 7.5 phosphate buffer of the formulation described in Example 2 as tested according

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to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

DETAILED DESCRIPTION OF THE INVENTION

The term antihyperglycemic drug as used in this specification refers to drugs that are useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM) by decreasing hepatic glucose production, decreasing intestinal absorption of glucose and/or improving insulin sensitivity. Preferably the antihyperglycemic drug is a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride.

The term hypoglycemic drug as used in this specification refers to drugs that are useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM) by stimulating the release of insulin from the pancreas. Preferably the hypoglycemic drug is a sulfonylurea compound such as glyburide, glipizide, glibornuride, glisoxepide, gliclazide, acetohexamide, chlorpropamide, tolazamide, tolbutamide, tolbutamide or mixtures thereof.

The binding agent may be any conventionally known pharmaceutically acceptable binder, but it is preferred that the binding agent be a water-soluble polymer such as polyvinyl pyrrolidone having a weight average molecular weight of 25,000 to 200,000. Other pharmaceutically acceptable water-soluble polymers include hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose and the like. Mixtures of the water-soluble binders may also be used. The water-soluble binders comprise approximately about 0 to about 40% of the total weight of the core and preferably about 3-15% of the total weight of the core.

The absorption enhancer employed in the core can be any type of absorption enhancer commonly known in the art such as a fatty acid, a surfactant, a chelating agent, a bile salt or mixtures thereof. Examples of some preferred absorption enhancers are fatty acids such as capric acid, oleic acid and their monoglycerides, surfactants, especially alkyl sulfates, such as sodium lauryl sulfate, sodium dodecyl sulfate and polysorbate 80, chelating agents such as citric acid and phytic acid. The core comprises approximately 1 to about 20% absorption enhancer based on the total weight of the core and most preferably about 2 to about 10% of the total weight of the core.

The core of the present invention which comprises the antihyperglycemic drug, the hypoglycemic drug, the binder which preferably is a pharmaceutically acceptable water-soluble polymer and the absorption enhancer is preferably formed by mixing and tableting techniques commonly known in the art. The core may also be formed by granulating the core ingredients and compressing the granules with or without the addition of a lubricant into a tablet. The tableting can be performed on a rotary press.

Other commonly known excipients may also be included into the core such as lubricants, pigments or dyes.

The homogeneous core is subsequently coated with a semipermeable membrane, preferably a modified polymeric membrane to form the controlled release tablet of the invention. The semipermeable membrane is permeable to the passage of an external fluid such as water and biological fluids and is impermeable to the passage of the antihyperglycemic drug and/or the hypoglycemic drug in the core. Materials that are useful in forming the semipermeable membrane are cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose

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acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, cellulose acetate butyrate and ethylcellulose. Other suitable polymers are described in U.S. Pat. Nos. 3,845,770, 3,916,899, 4,008,719, 4,036,228 and 4,112,10 which are incorporated herein by reference. The most preferred semipermeable membrane material is cellulose acetate comprising an acetyl content of 39.3 to 40.3%, commercially available under the tradename CA 398-10 or CA 398-3 from Eastman Fine Chemicals.

In an alternative embodiment, the semipermeable membrane can be formed from the above-described polymers and a flux enhancing agent. The flux enhancing agent increases the volume of fluid imbibed into the core to enable the dosage form to dispense substantially all of the antihyperglycemic drug and hypoglycemic drug through both the passageway and the porous membrane. The flux enhancing agent is a water-soluble component such as sodium chloride, potassium chloride, sugar, sucrose, sorbitol, mannitol, polyethylene glycol (weight av. molecular weight 380-3700), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methylcellulose and mixtures thereof. The preferred flux enhancer is PEG 400.

The flux enhancing agent comprises approximately 0 to 40% of the total weight of the coating, most preferably 2-20% of the total weight of the coating. The flux enhancing agent dissolves or leaches from the semipermeable membrane to form paths in the semipermeable membrane for the fluid to enter the core and dispense the active ingredients from the core.

The semipermeable membrane may also be formed with commonly known excipients such as a plasticizer. Some commonly known plasticizers include adipate, azelate, enzoate, citrate, stearate, isocubate, sebacate, triethyl citrate, tri-n-butyl citrate, acetyl tri-n-butyl citrate, citric acid esters, and those described in the Encyclopedia of Polymer Science and Technology, Vol. 10 (1969), published by John Wiley & Sons. The preferred plasticizer is triacetin but materials such as acetylated monoglyceride, rape seed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributylate, and the like. Depending on the particular plasticizer, amounts of from 0% to 25%, and preferably 2 to 15% of the plasticizer can be used based upon the total weight of the coating.

As used herein the term passage way includes an aperture, orifice, bore, hole, weakened area or an erodible element such as a gelatin plug that erodes to form an osmotic passage way for the release of the antihyperglycemic drug and hypoglycemic drug from the dosage form. A detailed description of the passageway can be found in U.S. Pat. Nos. 3,845,770, 3,916,899, 4,034,758, 4,077,407, 4,783,337 and 5,071,607.

Generally, the membrane coating around the core will comprise from about 1-10% (theoretically) and preferably about 2-6% (theoretically) based on the total weight of the core and coating.

In a preferred embodiment the dosage form will have the following composition:

	Preferred	Most Preferred
CORE:		
antihyperglycemic cpd	50-96%	75-93%
hypoglycemic cpd	0.05-3%	0.25-3%
binder	0-40%	3-15%
absorption enhancer	1-20%	2-10%
COATING:		
semipermeable polymer	50-99%	75-95%
plasticizer	0-25%	2-15%
flux enhancer	0-40%	2-20%

The dosage forms prepared according to the present invention should exhibit the following dissolution profile when tested in a USP type 2 (paddle) apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37° C.:

ANTIHYPERTENSIVE RELEASE		
Time (hours)	Preferred	Most Preferred
2	0-30%	0-25%
4	10-50%	20-45%
8	30-90%	45-90%
12	NLT 50%	NLT 60%
16	NLT 60%	NLT 70%

NLT = NOT LESS THAN

HYPOGLYCEMIC RELEASE		
Time (hours)	Preferred	Most Preferred
2	0-30%	0-25%
4	10-50%	20-45%
8	30-90%	45-90%
12	NLT 50%	NLT 60%
16	NLT 60%	NLT 70%

NLT = NOT LESS THAN

In the preparation of the tablets of the invention, various conventional well known solvents may be used to prepare the granules and apply the external coating to the tablets of the invention. In addition, various diluents, excipients, lubricants, dyes, pigments, dispersants etc. which are disclosed in Remington's Pharmaceutical Sciences, 1995 Edition may be used to optimize the formulations of the invention. In the alternative, dry granulation techniques may be used to prepare the granules for making compressed tablets.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

A once a day controlled release tablet containing 850 mg of metformin HCl and 5 mg of glipizide and having the following formula is prepared as follows:

I Core	Weight %
metformin HCl	88.10%
glipizide	0.52%
povidone ¹ , USP	6.33%
sodium lauryl sulfate	4.56%
magnesium stearate	0.50%

¹approximate molecular weight = 1,000,000; dynamic viscosity (10% w/v solution at 20° C.) = 300-700 mPa s.

(a) Granulation

1321.46 g of metformin HCl and 67.01 g of sodium lauryl sulfate are delumped by passing the compounds through a 40 mesh screen and then mixed. 94.92 g of povidone, K-90, and 1.34 g of sodium lauryl sulfate are dissolved in 1,803.5 g of purified water and then 7.76 g of glipizide is dispersed in the solution. The mixture of metformin HCl and sodium lauryl sulfate is then added to a top-spray fluidized bed granulator and granulated by spraying with the granulating solution of povidone, sodium lauryl sulfate and glipizide under the following conditions: product temperature: 35-45° C.; atomization pressure: 1-3 bar; spray rate: 10-150 ml/min. Once the granulating solution is depleted and the granules are dried in the fluidized bed coater until the loss on drying is less than 2%. The dried granules are then passed through a Comil equipped with a screen equivalent to 18 mesh.

(b) Tableting

7.50 g of magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl/glipizide granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 15/32" round standard concave punches.

(c) Seal Coating (optional)

The tablet or core is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry clear in purified water. The Opadry solution is then sprayed onto the tablet or core using a pan coater under the following conditions: exhaust air temperature of 38-42° C.; atomization pressure of 28-40 psi; and spray rate of 10-150 ml/min. The core tablets are coated with the seal coating until a theoretical coating level of approximately 2% is obtained.

II Sustained Release Coating	Weight %
cellulose acetate (398-10) ²	85%
triacetin	5%
PEG 400 ³	10%

²acetyl content 39.3-40.3%

³weight av. molecular weight 380-420

(d) Sustained Release Coating

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a homogenous solution is obtained. The coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 15-25° C.; atomization pressure of approximately 1-2 bar; and a spray rate of 10-30 ml/min. This coating process continues until a theoretical coating level of approximately 3% is obtained.

Once the theoretical coating level is obtained, the sustained release coated tablets are dried in the fluidized bed

coater for approximately 5 to 10 minutes. Then one hole is either mechanically drilled or laser drilled onto each side of the sustained release tablet.

The resulting tablets are tested in simulated intestinal fluid (pH 7.5) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 (paddle) @ 75 rpm and found to have the following release profile:

METFORMIN HCl RELEASE	
TIME (hours)	% Released (pH 7.5)
2	17
4	32
8	56
12	76
16	89

GLIPIZIDE RELEASE	
TIME (hours)	% Released (pH 7.5)
2	22
4	37
8	57
12	76
16	90

The release profile in simulated intestinal fluid (pH 7.5) of the sustained release product prepared in this Example is shown in FIG. 1.

EXAMPLE 2

A controlled release tablet containing 500 mg of metformin HCl and 5 mg of glipizide and having the following formula is prepared as follows:

I Core	Weight %
metformin HCl	87.77%
glipizide	0.88%
povidone ^a , USP	6.31%
sodium lauryl sulfate	4.54%
magnesium stearate	0.50%

^aapproximate molecular weight = 1,000,000 dynamic viscosity (10% w/v solution at 20° C.) = 300–700 mPa s.

(a) Granulation

5.266 kg of metformin HCl and 0.263 kg of sodium lauryl sulfate are delumped by passing the compounds through a 40 mesh screen and then mixed. 0.379 kg of povidone, K-90, 0.009 kg of sodium lauryl sulfate are dissolved in 7.201 kg of purified water and then 0.053 kg of glipizide is dispersed in the solution. The mixture of metformin HCl and sodium lauryl sulfate is then added to a top-spray fluidized bed granulator and granulated by spraying with the granulating solution of povidone, sodium lauryl sulfate and glipizide under the following conditions: product temperature: 35–45° C.; atomization pressure: 1–3 bar; spray rate: 10–150 ml/min. Once the granulating solution is depleted and the granules are dried in the fluidized bed coater until the loss on drying is less than 2%. The dried granules are then passed through a Comil equipped with a screen equivalent to 18 mesh.

(b) Tableting

The granules are pressed into tablets according to the procedure outlined in Example 1 with the exception that 0.030 kg of magnesium stearate is employed.

(c) Seal Coating (optional)

The tablets are seal coated with an Opadry material or other suitable water-soluble material according to the procedure outlined in Example 1.

II, Sustained Release Coating	Weight %
cellulose acetate (398-10) ⁵	85%
triacetin	5%
PEG 400 ⁶	10%

⁵acetyl content 39.3–40.3%

⁶weight av. molecular weight 380–420

(d) Sustained Release Coating

The sustained release coating solution is prepared and applied to the seal coated tablets according to the procedure outlined in Example 1, with the exception that the sustained release coating is applied to the seal coated tablets until a theoretical coating level of approximately 4.5% is obtained.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 (paddle) @ 75 rpm and found to have the following release profile:

METFORMIN HCl RELEASE	
TIME (hours)	% Released (pH 7.5)
2	23
4	41
8	70
12	92
16	98

GLIPIZIDE RELEASE	
TIME (hours)	% Released (pH 7.5)
2	23
4	35
8	56
12	75
16	90

The release profile in SIF of the sustained release product prepared in this Example is shown in FIG. 2.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

We claim:

1. A controlled release pharmaceutical tablet which consisting essentially of:

(a) a core consisting essentially of:

- (i) metformin or a pharmaceutically acceptable salt thereof;
- (ii) glipizide

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- (iii) polyvinyl pyrrolidone; 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 plasticizer; and
 - (d) at least one passageway in the semipermeable 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.
2. A controlled release pharmaceutical tablet as defined in claim 1 that exhibits the following dissolution profile when tested in a USP type 2 apparatus, paddle, at 75 rpm in 900 ml of simulated intestinal fluid, pH 7.5 phosphate buffer and at 37° C.:
- after 2 hours 0-30% of the metformin is released;
 - after 4 hours 10-50% of the metformin is released;
 - after 8 hours 30-90% of the metformin is released;
 - after 12 hours not less than 50% of the metformin is released; and
 - after 16 hours not less than 60% of the metformin is released; and
 - after 2 hours 0-30% of the glipizide is released;
 - after 4 hours 10-50% of the glipizide is released;

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- after 8 hours 30-90% of the glipizide is released;
 - after 12 hours not less than 50% of the glipizide is released; and
 - after 16 hours not less than 60% of the glipizide is released.
3. A controlled release pharmaceutical tablet as defined in claim 1 that exhibits the following dissolution profile when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid, pH 7.5 phosphate buffer and at 37° C.:
- after 2 hours 0-25% of the metformin is released;
 - after 4 hours 20-45% of the metformin is released;
 - after 8 hours 45-90% of the metformin is released;
 - after 12 hours not less than 60% of the metformin is released; and
 - after 16 hours not less than 70% of the metformin is released; and
 - after 2 hours 0-25% of the glipizide is released;
 - after 4 hours 20-45% of the glipizide is released;
 - after 8 hours 45-90% of the glipizide is released;
 - after 12 hours not less than 60% of the glipizide is released; and
 - after 16 hours not less than 70% of the glipizide is released.
4. A controlled release pharmaceutical tablet as defined in claim 1 wherein the plasticizer is triacetin.

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(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0161462 A1**
Kositprapa et al. (43) **Pub. Date: Aug. 19, 2004**(54) **NOVEL PHARMACEUTICAL
FORMULATION CONTAINING A
BIGUANIDE AND A THIAZOLIDINEDIONE
DERIVATIVE**(76) **Inventors: Unchalee Kositprapa, Davie, FL (US);
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New York, NY 10036 (US)**(21) **Appl. No.: 10/777,542**(22) **Filed: Feb. 12, 2004****Related U.S. Application Data**(63) Continuation-in-part of application No. 10/664,803,
filed on Sep. 19, 2003.(60) Provisional application No. 60/412,180, filed on Sep.
20, 2002. Provisional application No. 60/412,181,
filed on Sep. 20, 2002.**Publication Classification**(51) **Int. Cl.⁷ A61K 9/24; A61K 31/426**(52) **U.S. Cl. 424/471; 514/369**(57) **ABSTRACT**

A pharmaceutical dosage form comprising a controlled release component comprising an antihyperglycemic drug in combination with a second component comprising a thiazolidinedione derivative is herein disclosed and described.

**NOVEL PHARMACEUTICAL FORMULATION
CONTAINING A BIGUANIDE AND A
THIAZOLIDINEDIONE DERIVATIVE**

[0001] This is a continuation-in-part application of U.S. patent application Ser. No. 10/664,80 filed on Sep. 19, 2003 and provisional patent applications Serial Nos. 60/412,180 and 60/412,181 filed on Sep. 20, 2002.

BACKGROUND OF THE INVENTION

[0002] The present invention relates to a pharmaceutical dosage form comprising an antihyperglycemic drug, in combination with a thiazolidinedione derivative. More specifically, the present invention relates to an oral dosage form comprising a biguanide e.g. metformin or buformin or a pharmaceutically acceptable salt thereof e.g., metformin hydrochloride or the metformin salts described in U.S. Pat. Nos. 3,957,853 and 4,080,472 which are incorporated herein by reference in combination with a thiazolidinedione derivative as described in U.S. Pat. No. 4,687,777 also incorporated herein by reference.

[0003] Many techniques have been used to provide controlled and extended-release pharmaceutical dosage forms in order to maintain therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance.

[0004] For example, extended release tablets have been described which have an osmotically active drug core surrounded by a semi-permeable membrane. These tablets function by allowing the aqueous components of a fluid such as gastric or intestinal fluid to permeate the coating membrane and dissolve the active ingredient so the resultant drug solution can be released through a passageway in the coating membrane. Alternatively, if the active ingredient is insoluble in the permeating fluid, it can be pushed through the passageway by an expanding agent such as a hydrogel. Some representative examples of these osmotic tablet systems can be found in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,034,758; 4,077,407 and 4,783,337. U.S. Pat. No. 3,952,741 teaches an osmotic device wherein the active agent is released from a core surrounded by a semipermeable membrane only after sufficient pressure has developed within the membrane to burst or rupture the membrane at a weak portion of the membrane.

[0005] The basic osmotic device described in the above cited patents have been refined over time in an effort to provide greater control of the release of the active ingredient. For example, U.S. Pat. Nos. 4,777,049 and 4,851,229 describe osmotic dosage forms comprising a semipermeable wall surrounding a core. The core contains an active ingredient and a modulating agent wherein the modulating agent causes the active ingredient to be released through a passageway in the semipermeable membrane in a pulsed manner. Further refinements have included modifications to the semipermeable membrane surrounding the active core such as varying the proportions of the components that form the membrane, e.g. U.S. Pat. Nos. 5,178,867, 4,587,117 and 4,522,625 or increasing the number of coatings surrounding the active core, e.g. U.S. Pat. Nos. 5,650,170 and 4,892,739.

[0006] Certain controlled or sustained release formulations that employ antihyperglycemic drugs such as metformin hydrochloride have been limited to the use of an

expanding or gelling agent to control the release of the drug from the dosage form. This limited research is exemplified by the teachings of WO 96/08243 and by the GLUCOPHAGE™ XR product insert which is a controlled release metformin HCl product commercially available from Bristol-Myers Squibb Co.

[0007] Thiazolidinedione derivatives have been described in U.S. Pat. No. 4,687,777. The therapeutic value of these compounds in combination therapy has further been described in U.S. Pat. Nos. 5,859,037; 5,952,356; 5,965,584; 6,150,384 and 6,172,090. However, none of these patents describe a dosage form having the advantages of the subject invention.

[0008] Pharmaceutical dosage forms containing combinations of antihyperglycemic drugs and thiazolidinedione derivatives have been proposed in the art. For example, EPO 0 749 751 (which is incorporated herein by reference) teaches pharmaceutical compositions comprising an insulin sensitivity enhancer, which could be a thiazolidinedione compound, in combination with other antidiabetics. More specifically, EPO 0 749 751 teaches that the preferred insulin sensitivity enhancer is pioglitazone, which can be combined with other antidiabetics such as metformin, phenformin or buformin, and further that these drugs can be associated (mixed and/or coated) with conventional excipients to provide taste masking or sustained release behavior. Another example of a combination of antihyperglycemic drugs and thiazolidinedione derivatives is U.S. Pat. No. 6,011,049, (which is incorporated herein by reference). This patent teaches a single pharmaceutical composition that contains pioglitazone or troglitazone and metformin in slow release forms such as osmotic pumps or skin patches. Other combinations of antihyperglycemic drugs and thiazolidinedione derivatives can be found in U.S. Pat. Nos. 6,524,621; 6,475,521; 6,451,342 and 6,153,632 and PCT patent applications WO 01/3594 and WO 01/3594, which are incorporated herein by reference.

[0009] Also known in the art is WO 99/47125 and U.S. Pat. No. 6,099,862 that disclose a metformin osmotic tablet coated with an immediate release coating containing an antihyperglycemic or an hypoglycemic drug.

[0010] Although the prior art teaches pharmaceutical dosage formulations that contain both an antihyperglycemic compound and thiazolidinedione derivatives, the present invention provides numerous benefits over the prior art teachings as will be described below.

[0011] It is an object of the present invention to provide a dosage form comprising a first active drug, which is formulated to provide a controlled or sustained release delivery. Preferably, the first active drug is an antihyperglycemic compound. The present invention further provides for a second active drug which preferably is a thiazolidinedione derivative. The novel dosage form described herein provides for delivery of first and second active drugs such that the bioavailability of either drug is not decreased by the presence of food.

[0012] It is a further object of the present invention to provide a dosage form, as described above, comprising delivery of a first active drug as a controlled or sustained release formulation for an antihyperglycemic compound, wherein said controlled or sustained release mechanism is

not regulated by an expanding polymer, in combination with delivery of a second active drug by immediate release comprising a thiazolidinedione derivative.

[0013] It is also a further object of the present invention to provide a dosage form as described above, comprising delivery of a first active drug as a controlled or sustained release formulation for an antihyperglycemic compound in combination with delivery of a second active drug by immediate release comprising a thiazolidinedione derivative that can provide continuous and non-pulsating therapeutic levels of said antihyperglycemic drug to an animal or human in need of such treatment over a eight hour to twenty-four hour period.

[0014] It is an additional object of the present invention to provide a dosage form comprising delivery of a first active drug as a controlled or sustained release formulation for an antihyperglycemic compound in combination with delivery of a second active drug by immediate release comprising a thiazolidinedione derivative that obtains peak plasma levels of the antihyperglycemic compound approximately 8-12 hours after administration and peak plasma levels of thiazolidinedione derivative approximately 1-4 hours after dosing.

[0015] It is also an object of the present invention to provide a dosage form comprising a first active drug as a controlled or sustained release pharmaceutical core tablet having only a homogeneous osmotic core wherein the osmotic core component may be made using ordinary tablet compression techniques.

[0016] It is an additional object of the present invention to provide a dosage form comprising delivery of a first active drug as a controlled or sustained release formulation for an antihyperglycemic compound in combination with delivery of a second active drug by immediate release comprising a thiazolidinedione derivative that obtains peak plasma levels of the antihyperglycemic compound approximately 8-12 hours after administration and peak plasma levels of thiazolidinedione derivative approximately 1-4 hours after dosing.

[0017] It is a further object of the present invention to provide a dosage form comprising an antihyperglycemic drug as a controlled or sustained release component and a thiazolidinedione derivative as a immediate release component, wherein not less than 85% of the total amount of the thiazolidinedione derivative is released from the dosage form within 45 minutes or less.

[0018] It is a further additional object of the present invention to provide a shelf stable dosage form comprising an antihyperglycemic drug as a controlled or sustained release component and a thiazolidinedione derivative as a immediate release component, wherein the total amount of thiazolidinedione related compounds or impurities are not more than 0.6% after two years of storage and no individual related compound or impurity is more than 0.2%.

SUMMARY OF THE INVENTION

[0019] The present invention relates to a pharmaceutical dosage form comprising a first active drug, preferably an antihyperglycemic drug, in combination with a second active drug, preferably a thiazolidinedione derivative. More specifically, the present invention relates to an oral dosage

form comprising a first active drug comprising a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof e.g., metformin hydrochloride or the metformin salts, in combination with a second active drug comprising a thiazolidinedione derivative

[0020] The foregoing objectives are met by a dosage form comprising a first and second active drug, wherein the first active drug is formulated as a controlled release core, preferably an osmotic tablet, with or without a gelling or expanding polymer. The second active ingredient may be part of the controlled release core or it may preferably be combined with the controlled release core in a manner that provides for immediate release of the second active ingredient. For example, the second active ingredient can be incorporated into a membrane that is applied to the core or the second active ingredient may be applied to a coated or uncoated controlled release core.

[0021] In one embodiment the second active drug, which may be the thiazolidinedione derivative, is provided as an immediate release formulation in the dosage form whereas the antihyperglycemic component is provided as a controlled release formulation in the dosage form. This immediate release portion of the formulation should provide peak plasma levels (T_{max}) of 1-12 hours preferably, 14 hours of the thiazolidinedione derivative, while the controlled release portion of the formulation may provide peak plasma levels (T_{max}) of 8-12 hours of the antihyperglycemic component.

[0022] Preferably, the dosage form according to the subject invention may be administered once a day, preferably with or after a meal, and most preferably with or after the evening meal. The subject dosage form can provide therapeutic levels of the drug throughout the day with peak plasma levels (T_{max}) of the antihyperglycemic drug being obtained between 8-12 hours after administration.

DETAILED DESCRIPTION OF THE INVENTION

[0023] The subject invention concerns a pharmaceutical formulation or dosage form comprising a first active drug comprising an antihyperglycemic drug in combination with a second active drug comprising a thiazolidinedione derivative. Preferably, the antihyperglycemic drug is a biguanide e.g. metformin or buformin or a pharmaceutically acceptable salt thereof. The antihyperglycemic drug is delivered in a controlled release manner from a tablet core, preferably an osmotic tablet core with or without a gelling or swelling polymer. The tablet core should include the antihyperglycemic drug and at least one pharmaceutically acceptable excipient. In one embodiment of the present invention the tablet core includes the antihyperglycemic drug, a binding agent and an absorption enhancer, and the tablet core is preferably coated with a polymeric coating to form a membrane around the tablet and drilled to create one passageway on each side of the membrane. The second active drug comprises a thiazolidinedione derivative, and is preferably applied to the membrane of the tablet core and provides for either immediate or controlled release of said thiazolidinedione derivative.

[0024] The term, antihyperglycemic drugs as used in this specification, refers to drugs that are useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM). Antihyperglycemic drugs include the biguanides

such as metformin, phenformin or buformin or the like, and pharmaceutically acceptable salts, isomers or derivatives thereof.

[0025] The term thiazolidinedione derivative as used in this specification refers to drugs that are useful for controlling or managing NIDDM. These include, but are not limited to, troglitazone, rosiglitazone, pioglitazone, ciglitazone or the like, and pharmaceutically acceptable salts, isomers or derivatives thereof.

[0026] The term binding agent refers to any conventionally known pharmaceutically acceptable binder such as polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, ethylcellulose, polymethacrylate, polyvinylalcohol, waxes and the like. Mixtures of the aforementioned binding agents may also be used. The preferred binding agents are water soluble materials such as polyvinyl pyrrolidone having a weight average molecular weight of 25,000 to 3,000,000. The binding agent may comprise approximately about 0 to about 40% of the total weight of the core and preferably about 3% to about 15% of the total weight of the core. In one embodiment, the use of a binding agent in the core is optional.

[0027] In a preferred embodiment, the core may optionally comprise an absorption enhancer. The absorption enhancer can be any type of absorption enhancer commonly known in the art such as a fatty acid, a surfactant (anionic, cationic, amphoteric), a chelating agent, a bile salt or mixtures thereof. Examples of some preferred absorption enhancers are lecithin, fatty acids such as capric acid, oleic acid and their monoglycerides, surfactants such as sodium lauryl sulfate, sodium taurocholate and polysorbate 80, chelating agents such as citric acid, phytic acid, ethylenediamine tetraacetic acid (EDTA) and ethylene glycol-bis(β -aminoethyl ether)-N,N,N,N-tetraacetic acid (EGTA). The core may comprise approximately 0 to about 20% of the absorption enhancer based on the total weight of the core and most preferably about 2% to about 10% of the total weight of the core.

[0028] In one embodiment of the present invention, which does not employ a gelling or swelling polymer, the core of the present invention is preferably formed by granulating an antihyperglycemic drug with a binding agent and compressing the granules with the addition of a lubricant and absorption enhancer into a tablet. The core may also be formed by dry granulating the core ingredients by passing them through a roller compactor and compressing the granules with the addition of a lubricant into tablets. Direct compression may also be employed for tableting. Other commonly known granulation procedures are known in the art. Additionally, other excipients such as lubricants, pigments or dyes may also be employed in the formulation of the subject invention.

[0029] The term gelling or swelling polymer refers to polymers that gel, swell or expand in the presence of water or biological fluids. Representative examples of gelling or swelling polymers are high molecular weight hydroxypropyl methylcellulose (such as METHOCEL® K100M, which is commercially available from Dow Chemical) and high molecular weight polyethylene oxides (such as POLYOX WSR 301, WSR 303 or WSR COAGULANT). Other gelling or swelling polymers are described in U.S. Pat. No. 4,522, 625 (which is incorporated herein by reference).

[0030] The core formed as described herein, can be coated with a membrane or sustained release coating. Materials that are useful in forming the membrane or sustained release coating are ethylcellulose, cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate and cellulose acetate butyrate. Other suitable polymers are described in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,008,719; 4,036,228 and 4,612, 008 (which are incorporated herein by reference). The most preferred membrane or sustained release coating material is cellulose acetate comprising an acetyl content of 39.3 to 40.3%, and is commercially available from Eastman Fine Chemicals.

[0031] In an alternative embodiment, the membrane or sustained release coating can include one of the above-described polymers and a flux-enhancing agent. The flux enhancing agent can increase the volume of fluid imbibed into the core to enable the dosage form to dispense substantially all of the antihyperglycemic drug through the passageway and/or the porous membrane. The flux-enhancing agent can be a water-soluble material or an enteric material. Examples of the preferred materials that are useful as flux enhancers are sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycols (PEG), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers, poloxamers (such as LUTROL F68, LUTROL F127, LUTROL F108 which are commercially available from BASF) and mixtures thereof. A preferred flux-enhancer is PEG 400.

[0032] The flux enhancer may also be a drug that is water soluble such as metformin or its pharmaceutically acceptable salts, or the flux enhancer may be a drug that is soluble under intestinal conditions. If the flux enhancer is a drug, the present dosage form has the added advantage of providing an immediate release of the drug, that has been selected as the flux enhancer.

[0033] The flux enhancing agent comprises approximately 0 to about 40% of the total weight of the coating, most preferably about 2% to about 20% of the total weight of the coating. The flux enhancing agent dissolves or leaches from the membrane or sustained release coating to form channels in the membrane or sustained release coating which enables fluid to enter the core and dissolve the active ingredient.

[0034] The membrane or sustained release coating may also be formed using a commonly known excipient such as a plasticizer. Some commonly known plasticizers include adipate, azelate, enzoate, citrate, stearate, isobucate, sebacate, triethyl citrate, tri-n-butyl citrate, acetyl tri-n-butyl citrate, citric acid esters, and those described in the Encyclopedia of Polymer Science and Technology, Vol. 10 (1969), published by John Wiley & Sons. The preferred plasticizers are triacetin, acetylated monoglyceride, grape seed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethylxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate and the like. Depending on the particular plasticizer, amounts from about 0 to about 25%,

and preferably about 2% to about 15% of the plasticizer can be used based upon the total weight of the membrane or sustained release coating.

[0035] Generally, the membrane or sustained release coating around the core will comprise from about 1% to about 10% and preferably about 2% to about 5% based upon the total weight of the core and coating.

[0036] In a preferred embodiment, the membrane or sustained release coating surrounding the core further comprises a passageway that will allow for controlled release of the drug from the core. As used herein the term passageway includes an aperture, orifice, bore, hole, weakened area or an erodible element such as a gelatin plug that erodes to form an osmotic passageway for the release of the antihyperglycemic drug from the dosage form. Passageways used in accordance with the subject invention are well known and are described in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,034,758; 4,077,407; 4,783,337 and 5,071,607.

[0037] Independent of the antihyperglycemic is a second active drug, preferably a thiazolidinedione derivative. This second active drug may be formulated to provide an immediate release of the thiazolidinedione derivative. In one embodiment of the present invention the thiazolidinedione derivative is applied in the form of a layer to a controlled or sustained released core comprising the antihyperglycemic drug as a layer using a binder and other conventional pharmaceutical excipients such as absorption enhancers, surfactants, plasticizers, antifoaming agents and combinations of the foregoing. An absorption enhancer may be present in the thiazolidinedione derivative layer in an amount up to about 30% w/w in comparison to the weight of the thiazolidinedione derivative. A binding agent may be present in an amount up to 150% w/w of the thiazolidinedione derivative. A second active drug immediate release formulation may be incorporated into a single dosage form by coating onto the membrane or sustained release coating of the dosage form by conventional methods. Alternatively, it may be incorporated by any pharmaceutically acceptable method into a single dosage form with the first active drug. The incorporation of the second active drug may be performed by, but would not be limited to, the processes selected from the group consisting of drug layering, lamination, dry compression, deposition and printing.

[0038] When the thiazolidinedione derivative is coated onto a membrane or sustained release coating of an osmotic tablet core, the thiazolidinedione coating should be applied from a coating solution or suspension that employs an aqueous solvent, an organic solvent or a mixture of an aqueous and an organic solvent. Typical organic solvents include acetone, isopropyl alcohol, methanol and ethanol. If a mixture of aqueous and organic solvents is employed, the ratio of water to organic solvent should range from 98:2 to 2:98, preferably 50:50 to 2:98, most preferably 30:70 to 20:80 and ideally about 25:75 to 20:80. If a mixed solvent system is employed, the amount of binder required for coating the thiazolidinedione derivative onto the membrane or sustained release coating may be reduced. For example, successful coatings have been obtained from a mixed solvent system where the ratio of binder to thiazolidinedione derivative is 1:9 to 1:11. Although acceptable coatings can be obtained when the thiazolidinedione coat is applied directly to the membrane or sustained release coating, a

preferred approach is to first coat the membrane or sustained release coating with a seal coat prior to the application of the thiazolidinedione coating. As used herein a seal coat is a coating that does not contain an active pharmaceutical ingredient and that rapidly disperses or dissolves in water.

[0039] The thiazolidinedione coating solution or suspension may also contain a surfactant and a pore forming agent. A pore forming is preferably a water-soluble material such as sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycols (PEG), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers, poloxamers (such as LUTROL F68, LUTROL F127, LUTROL F108 which are commercially available from BASF) and mixtures thereof. In an alternative embodiment, the dosage form of the present invention may also comprise an effective immediate release amount of the antihyperglycemic drug. The effective immediate release amount of antihyperglycemic drug may be coated onto the membrane or sustained release coating of the dosage form or it may be incorporated into the membrane or sustained release coating.

[0040] In addition, various diluents, excipients, lubricants, dyes, pigments, dispersants, etc., which are disclosed in Remington's Pharmaceutical Sciences (1995), may be used to optimize the above listed formulations of the subject invention.

[0041] Biguanides, such as metformin are commonly administered in dosage forms containing 500 mg, 750 mg, 850 mg, and 1000 mg. Thiazolidinedione derivatives, for example pioglitazone, are commonly administered in dosage forms containing 15 mg, 30 mg and 45 mg. The present invention is intended to encompass the above listed therapeutic combinations, without providing a specific example of each possible combination of compounds and their respective dosage amounts.

[0042] A preferred embodiment the dosage form will have the following composition:

FIRST ACTIVE DRUG		
Core:	Amount (% of core)	
drug	50-98%	(75-95% preferred)
binder	0.1-40%	(3-15% preferred)
absorption enhancer	0-20%	(2-10% preferred)
lubricant	0-5%	(0.5-1% preferred)
Coating:	Amount (% of coating)	
polymer	50-99%	(75-95% preferred)
flux enhancer	0-40%	(2-20% preferred)
plasticizer	0-25%	(2-15% preferred)

[0043]

SECOND ACTIVE DRUG		
	Amount (% of total dosage form)	
drug	0.1-20%	(1-10% preferred)
binder	0.1-30%	(1-15% preferred)

-continued

SECOND ACTIVE DRUG	Amount (% of total dosage form)	
surfactant	0-20%	(0.1-15% preferred)
pore former	0-25%	(0.1-15% preferred)
polymer (optional)	0-30%	(0.1-20% preferred)

[0044] The dosage forms prepared according to the present invention exhibit the following dissolution profile when tested in a USP Type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37° C.:

[0045] Release of First Active Drug

Time (hours)	% release	
2	0-25%	(0-15% preferred)
4	10-45%	(20-40% preferred)
8	30-90%	(45-90% preferred)
12	NLT 50%	(NLT 60% preferred)
16	NLT 60%	(NLT 70% preferred)
20	NLT 70%	(NLT 80% preferred)

NLT = NOT LESS THAN

[0046] Release of Second Active Drug

Time (hours)	% release	
0.5	NLT 60%	(NLT 75% preferred)

[0047] It has been discovered that the selection of the excipients for use in the thiazolidinedione component of the dosage form can greatly affect the release characteristics, potency and stability of the thiazolidinedione. Therefore, in an alternate embodiment of the present invention, the composition of the thiazolidinedione component of the present invention should be selected so that not less than 85%, preferably not less than 90% and most preferably not less than 95% of the thiazolidinedione is released from the dosage form within 45 minutes, preferably within 40 minutes and most preferably within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

[0048] Further the excipients for use in the thiazolidinedione component of the dosage form should be selected so that the total thiazolidinedione related compounds or impurities in the final dosage form are not more than 0.6%, preferably not more than 0.5% and most preferably not more than 0.25% and each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.25%, preferably not more than 0.2% and most preferably not more than 0.1%. The thiazolidinedione related compounds or impurities in the final dosage form are determined by High Performance Liquid Chromatography (HPLC) using a YMC-ODS-AQ, 5 μ m, 120 Å, 4.6×250 mm or equivalent column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, about a

40 μ L injection volume, 0.7 mL/min flow rate, 25° C. column temperature and 269 nm wavelength for the UV detector.

EXAMPLES

[0049] The following are provided by way of example only and are in no means intended to be limiting.

Example 1

[0050] A controlled release tablet containing 850 mg of metformin HCl and 15 mg pioglitazone is prepared as follows:

First Active Drug	
I. Core	(% composition of core)
Metformin HCl	90.54%
Povidone K-30 ¹ , USP	4.38%
Sodium Tribasic Phosphate	4.58%
Magnesium stearate	0.5%

¹approximate molecular weight = 50,000; dynamic viscosity (10% w/v solution at 20° C.) = 5.5-8.5 mPa · s.

[0051] (a) Granulation

[0052] The metformin HCl is delumped by passing it through a 40 mesh screen and collecting it in a clean, polyethylene-lined container. The povidone, K-30, and sodium tribasic phosphate are dissolved in purified water. The delumped metformin HCl is then added to a top-spray fluidized bed granulator and granulated by spraying the binding solution of povidone and sodium tribasic phosphate under the following conditions: inlet air temperature of 50-70° C.; atomization air pressure of 1-3 bars and spray rate of 10-100 ml/min.

[0053] Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a conil equipped with the equivalent of an 18 mesh screen.

[0054] (b) Tableting

[0055] The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 1½" round standard concave punches (plain lower punch, upper punch with an approximately 1 mm indentation pin).

[0056] As stated above, the orifice may be formed by any means commonly employed in the pharmaceutical industry.

[0057] (c) Seal Coating (Optional)

[0058] The core tablet can be seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear, in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42° C.; atomization pressure of 28-40 psi and spray rate of 10-15 ml/min. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2-4% is obtained.

II Membrane	(% composition of membrane)
Cellulose Acetate (398-10) ²	85%
Triacetin	5%
PEG 400	10%

²acetyl content 39.3-40.3%

[0059] (a) Membrane Coating Process

[0060] The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The clear membrane coating solution is then sprayed onto the seal coated tablets using a fluidized bed coater employing the following conditions: product temperature of 16-22° C.; atomization pressure of approximately 3 bars and spray rate of 120-150 ml/min. The sealed core tablet is coated until a theoretical coating level of approximately 3% is obtained.

III. Second Active Drug Layering	(% composition of second component)
Pioglitazone HCl	43.5%
Tween 80	2.0%
Hydroxypropyl methylcellulose	54.5%

[0061] Tween 80 and hydroxypropyl methylcellulose are dissolved in purified water. Pioglitazone HCl is then dispersed into this solution. The resulting suspension is then sprayed onto the above-membrane-coated tablets.

Example 2

[0062] A controlled release tablet containing 850 mg of metformin HCl and 15 mg pioglitazone is prepared as follows:

First Active Drug	
I. Core	(% composition of core)
Metformin HCl	88.555%
Povidone K-90 ³ , USP	6.368%
Sodium Lauryl Sulfate	4.577%
Magnesium Stearate	0.5%

³approximate molecular weight = 1,000,000, dynamic viscosity (10% w/v solution) 300-700 mPa · s at 20° C.

[0063] (a) Granulation

[0064] The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90, is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a top-spray fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50-70° C.; atomization air pressure of 1-3 bars and spray rate of 10-100 ml/min.

[0065] Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a conical equipped with the equivalent of an 18 mesh screen.

[0066] (b) Tableting

[0067] The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 1½" round standard concave punches (plain lower punch, upper punch with an approximately 1 mm indentation pin).

[0068] As stated above, the orifice may be formed by any means commonly employed in the pharmaceutical industry.

[0069] (c) Seal Coating (optional)

[0070] The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42° C.; atomization pressure of 2840 psi and spray rate of 10-15 ml/min. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2% is obtained.

II Membrane	(% composition of membrane)
Cellulose Acetate (398-10) ⁴	85%
Triacetin	5%
PEG 400	10%

⁴acetyl content 39.3-40.3%

[0071] (a) Membrane Coating Process

[0072] The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred. The coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22° C.; atomization pressure of approximately 3 bars and spray rate of 120-150 ml/min. The sealed core tablet is coated until a theoretical coating level of approximately 3% is obtained.

III. Second Active Drug Layering	(% composition of second component)
Pioglitazone HCl	43.5%
Tween 80	2.0%
Hydroxypropyl methylcellulose	54.5%

[0073] Tween 80 and hydroxypropyl methylcellulose are dissolved in purified water. Pioglitazone HCl is then dispersed into this solution. The resulting suspension is then sprayed onto the above described tablets.

Example 3

[0074] A controlled release tablet containing 500 mg of metformin HCl and 15 mg pioglitazone is prepared as follows:

[0075] I. First Active Drug

[0076] A 500 mg metformin membrane coated tablet is prepared as described in Example 2 above except that compound cup toolings are used during tableting. The 500 mg metformin membrane coated tablet has the following composition:

<u>CORE</u>	
Metformin HCl	500 mg/tablet
Povidone K-90, USP	35.96 mg/tablet
Sodium lauryl sulfate, NF	25.84 mg/tablet
Magnesium stearate, NF	2.82 mg/tablet
<u>SEAL COATING</u>	
Opadry Clear (YS-1-7006)	23.53 mg/tablet
<u>MEMBRANE COATING</u>	
Cellulose Acetate, 398-10, NF	23.56 mg/tablet
Triacetin, USP	1.39 mg/tablet
Polyethylene Glycol 400, NF	2.77 mg/tablet
Total weight	615.87 mg/tablet

[0077] II. Second Active Drug Layering

[0078] An immediate release amount of pioglitazone HCl is applied to the 500 mg metformin HCl membrane coated tablet prepared in step I. The final tablet has the following composition:

Metformin HCl membrane coated Pioglitazone Coating	615.87 mg/tablet
Pioglitazone HCl	16.53 mg/tablet
Tween 80	2.0 mg/tablet
Polyplasdone XL	15.0 mg/tablet
Opadry Clear (YS-1-7006)	8.47 mg/tablet
<u>Color Coating</u>	
Opadry White Polishing Coat	10.0 mg/tablet
Candelilla Wax Powder	2.0 mg/tablet

[0079] The pioglitazone coating is directly applied to the 500 mg metformin HCl membrane coated tablets. The pioglitazone coating is prepared by dissolving 0.252 kg of Opadry Clear, 0.269 kg of Polyplasdone XL and 0.036 kg of Tween 80 in 9.908 kg of purified water using a homogenizer. Once these ingredients are dissolved, 0.296 kg of pioglitazone HCl is dispersed into the solution and homogenized. The homogenized dispersion is then directly applied to the 500 mg metformin HCl membrane coated tablets using a 24" O'Hara Labcoat III pan coater with the following conditions:

Spray Rate	15-27 mL/min
Exhaust Temperature	42-47° C.
Atomization Air Pressure	25 psi
Pan Speed	5-9 rpm
Inlet Air Flow	300-400 CFM

[0080] Once the pioglitazone coating has been applied to the 500 mg metformin-HCl membrane coated tablet, an aesthetic or color coating of Opadry white is applied to the pioglitazone coated tablet. The color coating is prepared by dispersing 0.179 kg of Opadry White in 1.791 kg of purified water. The Opadry White suspension is applied to the pioglitazone coated tablet using a 24" O'Hara Labcoat III pan coater under the following conditions:

Spray Rate	20-35 mL/min
Exhaust Temperature	35-45° C.
Atomization Air Pressure	25 psi
Pan Speed	9 rpm
Inlet Air Flow	390-500 CFM

[0081] Once the color coating is applied, the tablets are polished using 0.036 kg of Candelilla wax powder.

Example 4

[0082] A controlled release tablet containing 500 mg of metformin HCl and 15 mg pioglitazone is prepared as follows:

[0083] I. First Active Drug

[0084] A 500 mg membrane coated tablet is prepared as described in Example 2 above except that compound cup toolings are used during tableting. The 500 mg membrane coated tablet has the following composition:

<u>CORE</u>	
Metformin HCl	500 mg/tablet
Povidone K-90, USP	35.96 mg/tablet
Sodium Lauryl Sulfate, NF	25.84 mg/tablet
Magnesium Stearate, NF	2.82 mg/tablet
<u>SEAL COATING</u>	
Opadry Clear (YS-1-7006)	23.53 mg/tablet
<u>MEMBRANE COATING</u>	
Cellulose Acetate, 398-10, NF	23.56 mg/tablet
Triacetin, USP	1.39 mg/tablet
Polyethylene Glycol 400, NF	2.77 mg/tablet
Total weight	615.87 mg/tablet

[0085] II. Second Active Drug Layering

[0086] An immediate release amount of pioglitazone HCl is applied to the 500 mg metformin HCl seal coated tablet prepared in Step I. The final tablet has the following composition:

Metformin HCl membrane coated tablet Seal Coat	615.87 mg/tablet
Opadry Clear (YS-1-7006) Pioglitazone Coating	13.8 mg/tablet
Pioglitazone HCl	16.53 mg/tablet
Tween 80	2.0 mg/tablet
Sodium Chloride	4.27 mg/tablet
Opadry Clear (YS-1-7006) Color Coating	2.0 mg/tablet
Opadry White Polishing Coat	8.10 mg/tablet
Candelilla Wax	0.20 mg/tablet

[0087] The seal coating solution is prepared by dissolving 0.258 kg of Opadry Clear in 2.576 kg of purified water and spraying the solution onto approximately 12.088 kg of the 500 mg membrane coated metformin HCl tablet cores using a 24" O'Hara Labcoat III pan coater. The seal coat is applied under the following conditions:

Spray Rate	20-35 mL/min
Exhaust Temperature	35-45° C.
Atomization Air Pressure	25 psi
Pan Speed	9 rpm
Inlet Air Flow	390-500 CFM

[0088] The pioglitazone coating is applied to the seal coated 500 mg metformin HCl membrane coated tablets. The pioglitazone coating is prepared by dissolving 0.040 kg of Opadry Clear, 0.085 kg of sodium chloride and 0.040 kg of Tween 80 in 4.915 kg of purified water using a homogenizer. Once these ingredients are dissolved, 0.328 kg of pioglitazone HCl is dispersed into the solution and homogenized. The homogenized dispersion is then applied to the seal coated 500 mg metformin HCl membrane coated tablets using a 24" O'Hara Labcoat III pan coater with the following conditions:

Spray Rate	10-30 mL/gun/min
Exhaust Temperature	35-45° C.
Atomization Air Pressure	20-40 psi
Pattern Air Pressure	20-40 psi
Pan Speed	8-12 rpm
Inlet Air Flow	250-450 CFM

[0089] Once the pioglitazone coating has been applied to the seal coated 500 mg metformin HCl membrane coated tablets, an aesthetic or color coating of Opadry White is applied to the pioglitazone coated tablet. The color coating is prepared by dispersing 0.159 kg of Opadry White in 1.585 kg of purified water. The Opadry White suspension is applied to the pioglitazone coated tablet using conditions similar to those described above for application of the seal coating. Once the color coating is applied, the tablets are polished using 0.004 kg of Candelilla wax powder.

Example 5

[0090] A controlled release tablet containing 1000 mg of metformin HCl and 30 mg pioglitazone is prepared as follows:

[0091] I. First Active Drug

[0092] A 1000 mg metformin membrane coated tablet is prepared as described in Example 3 above. The 1000 mg membrane coated tablet has the following composition:

<u>CORE</u>	
Metformin HCl	1000 mg/tablet
Povidone K-90, USP	78.0 mg/tablet
Sodium Lauryl Sulfate, NF	51.69 mg/tablet
Magnesium Stearate, NF	5.66 mg/tablet
<u>SEAL COATING</u>	
Opadry Clear (YS-1-7006) MEMBRANE COATING	47.05 mg/tablet
Cellulose Acetate, 398-10, NF	15.77 mg/tablet
Triacetin, USP	0.92 mg/tablet
Polyethylene Glycol 400, NF	1.85 mg/tablet
Total weight	1201.0 mg/tablet

[0093] II. Second Active Drug

[0094] An immediate release amount of pioglitazone HCL is applied to the 1000 mg metformin HCl membrane coated tablets prepared in step I. The final tablet has the following composition:

Metformin HCl membrane coated tablet Seal Coating	1201.0 mg/tablet
Opadry Clear (YS-1-7006) Pioglitazone Coating	16.0 mg/tablet
Pioglitazone HCl	33.06 mg/tablet
Sodium Chloride	4.27 mg/tablet
Opadry Clear (YS-1-7006) Color Coating	3.0 mg/tablet
Opadry II White (Y-22-7719) Polishing Coat	20.27 mg/tablet
Candelilla Wax Powder	0.40 mg/tablet

[0095] The seal coating is prepared by dispersing 0.174 kg of Opadry Clear in 3.478 kg of ethanol and mixing the dispersion for 15 minutes. The dispersion is then sprayed onto approximately 13.174 kg of the 1000 mg metformin HCl membrane coated tablets using a 24" O'Hara Labcoat III pan coater. The seal coat is applied to the 1000 mg metformin HCl membrane coated tablets with the following conditions:

Spray Rate	10-30 mL/gun/min
Exhaust Temperature	25-45° C.
Atomization Air Pressure	20-40 psi
Pan Speed	6-12 rpm

-continued

Pattern Air Pressure	20-40 psi
Inlet Air Flow	250-450 CFM

[0096] The pioglitazone coating then is applied to the seal coated 1000 mg metformin HCl membrane coated tablets. The pioglitazone coating is prepared by dissolving 0.036 kg of Opadry Clear and 0.046 kg of sodium chloride in 5.344 kg of ethanol using a homogenizer. Once the ingredients are dispersed, 0.359 kg of pioglitazone HCl is dispersed into the solution and homogenized. The homogenized dispersion is then applied to the seal coated 1000 mg metformin HCl membrane coated tablets using a 24" O'Hara Labcoat III pan coater with the following conditions:

Spray Rate	10-30 mL/gun/min
Exhaust Temperature	25-45° C.
Atomization Air Pressure	20-40 psi
Pan Speed	6-12 rpm
Pattern Air Pressure	20-40 psi
Inlet Air Flow	250-450 CFM

[0097] Once the pioglitazone coating has been applied, an aesthetic or color coating of Opadry II White is applied to the pioglitazone coated tablets. The color coating is prepared by dispersing 0.220 kg of Opadry II White in 4.407 kg of ethanol. The Opadry II White suspension is then applied to the pioglitazone HCl coated tablets using a 24" O'Hara Labcoat III pan coater using conditions similar to those described above for the seal coating. Once the color coating is applied, the tablets are polished using 0.004 kg of Candellilla wax powder.

Example 6

[0098] A controlled release tablet containing 1000 mg of metformin HCl and 30 mg pioglitazone is prepared as follows:

[0099] I. First Active Drug

[0100] A 1000 mg membrane coated tablet is prepared as described in Example 3 above. The 1000 mg membrane coated tablet has the following composition:

CORE	
Metformin HCl	1000 mg/tablet
Povidone K-90, USP	78.0 mg/tablet
Sodium Lauryl Sulfate, NF	51.69 mg/tablet
Magnesium Stearate, NF	5.65 mg/tablet
SEAL COATING	
Opadry Clear (YS-1-7006)	47.05 mg/tablet
MEMBRANE COATING	
Cellulose Acetate, 398-10, NF	15.77 mg/tablet
Triacetin, USP	0.92 mg/tablet
Polyethylene Glycol 400, NF	1.85 mg/tablet
Total weight	1201.0 mg/tablet

[0101] II. Second Active Drug

[0102] An immediate release amount of pioglitazone HCl is applied to the 1000 mg metformin HCl membrane coated tablets prepared in step I. The final tablet has the following composition:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	21.0 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Sodium Chloride	5.0 mg/tablet
Opadry Clear (YS-1-7006)	3.7 mg/tablet
Color Coating	
Opadry II White (Y-22-7719)	21.54 mg/tablet
Polishing Coat	
Candellilla Wax Powder	0.40 mg/tablet

[0103] The seal coat is applied to the 1000 mg metformin HCl membrane coated tablet. The seal coating is prepared by dispersing 0.229 kg of Opadry Clear in 4.573 kg of alcohol USP and mixing the dispersion for 15 minutes. The dispersion is then sprayed onto approximately 13.08 kg of the 1000 mg metformin HCl tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed and the following conditions:

Spray Rate	25 ± 10 mL/gun/min
Exhaust Temperature	25° C. ± 5° C.
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	200 ± 100 CFM
Pattern Air Pressure	10-40 psi

[0104] The seal coating dispersion is continuously stirred until it is consumed during the coating process.

[0105] The pioglitazone coating then is applied to the seal coated 1000 mg metformin HCl membrane coated tablets. The pioglitazone coating is prepared by mixing 4.434 kg of alcohol USP and 1.250 kg of purified water (approximately a 78:22 alcohol to purified water ratio) and slowly dispersing 0.040 kg of Opadry Clear into the solvent mixture. Once the Opadry Clear is dispersed, it is homogenized for about 10 minutes. Once the Opadry Clear dispersion is homogenized, 0.054 kg of sodium chloride is added to the dispersion and homogenized for about 2 minutes. After the sodium chloride is homogenized, 0.360 kg of pioglitazone HCl is slowly dispersed into the solvent mix and then homogenized for about 10 minutes. Once the pioglitazone HCl is homogenized, the homogenizer is removed from the mixing vessel and replaced with an air mixer and mixed for an additional 15 minutes. The pioglitazone suspension is stirred until the suspension is consumed during the coating process. The pioglitazone HCl suspension is applied to the seal coated 1000 mg metformin HCl membrane coated tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" above the top of the static bed with the following conditions:

Spray Rate	25 ± 10 mL/gun/min
Exhaust Temperature	25 ± 5° C.
Atomization Air Pressure	10–40 psi
Pan Speed	4–9 rpm
Pattern Air Pressure	10–40 psi
Supply Air Flow	200 ± 100 CFM

[0106] Once the pioglitazone coating has been applied to the seal coated 1000 mg metformin HCl membrane coated tablets, an aesthetic coating of Opadry II White is applied to the pioglitazone coated tablet. The aesthetic coating is prepared by dispersing 0.235 kg of Opadry II White (Y-22-7719) in 4.691 kg of alcohol USP and mixing the dispersion for about 1 hour. The Opadry II White dispersion is then sprayed onto the pioglitazone HCl coated tablets using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed and the following conditions:

Spray Rate	25 ± 10 mL/gun/min
Exhaust Temperature	25° C. ± 5° C.
Atomization Air Pressure	10–40 psi
Pan Speed	4–9 rpm
Supply Air Flow	200 ± 100 CFM
Pattern Air Pressure	10–40 psi

[0107] The color coating dispersion is continuously stirred until the dispersion is consumed during the coating process.

[0108] Once the aesthetic coating suspension is consumed, the tablets are dried in the coating pan for about 5 minutes with a pan speed of about 2–8 rpm and an exhaust temperature of 25±5° C. Once the tablets are dried, the exhaust air is turned off and the pan speed is adjusted to about 3–4 rpm and 0.004 kg of Candellia wax powder that had been passed through a 60 mesh screen is sprinkled onto the tablets. After the tablets have rolled in the wax for about 5 minutes the exhaust air is turned on and the tablets are rolled for an additional 10 minutes.

[0109] The finished polished tablet exhibited the following pioglitazone HCl dissolution profile when tested in a USP apparatus type 1 at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution:

Time	% Pioglitazone Released
10 min.	42%
20 min	79%
30 min	95%
45 min	102%

[0110] The finished polished tablet also contained the following pioglitazone related compounds when tested by HPLC using a YMC-ODS-AQ, 5 µm, 120 Å, 4.6×250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40 µL injection volume, 0.7 mL/min flow rate, 25° C. column temperature and 269 nm wavelength for the UV detector.

Name	Relative Retention Time	Amount (%)
RS-1	0.7	N.D.*
Pioglitazone	1.0	
RS-2	1.5	0.03
RS-3	3.4	0.04
RS-4	1.2	0.03
RS-5	2.8	0.04

*N.D. = none detected

[0111] RS-1 is (+/-)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-5-hydroxy-2,4-thiazolidinedione.

[0112] RS-2 is (z)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzylidene]-2,4-thiazolidinedione.

[0113] RS-3 is (+/-)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-3-[2-(5-ethyl-2-pyridyl)ethyl]-2,4-thiazolidinedione.

[0114] RS-4 is (+/-)-ethyl-2-carbamoyltio-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl]-propionate.

[0115] RS-5 is ethyl-3-p-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl-propionate.

[0116] The final polished tablet was packaged in a 100 cc HDPE bottle containing one (1) 2 g SORB-IT® desiccant canister and subjected to accelerated stability conditions of 40° C. and 75% relative humidity for three (3) months. After storage, the final polished tablet was tested and exhibited the following pioglitazone HCl dissolution profile when tested in a USP apparatus type 1 at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution:

Time	% Pioglitazone Released
10 min.	38%
20 min	73%
30 min	92%
45 min	101%

[0117] The stored final polished tablet also contained the following pioglitazone related compounds when tested by HPLC using a YMC-ODS-AQ, 5 µm, 120 Å, 4.6×250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40 µL injection volume, 0.7 mL/min flow rate, 25° C. column temperature and 269 nm wavelength for the UV detector.

Name	Relative Retention Time	Amount (%)
RS-1	0.7	N.D.*
Pioglitazone	1.0	
RS-2	1.5	0.03
RS-3	3.4	0.05
RS-4	1.2	0.02
RS-5	2.8	0.04

*N.D. = none detected

[0118] While certain preferred and alternative embodiments of the invention have been set forth for purposes of

disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

What is claimed is:

1. A pharmaceutical dosage form having a first and second active drug, said dosage form comprising:

(a) a controlled release core comprising an antihyperglycemic drug and at least one pharmaceutically acceptable excipient; and

(b) an immediate release thiazolidinedione derivative containing component wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

2. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

3. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

4. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

5. The pharmaceutical dosage form as defined in claim 1 wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

6. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

7. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

8. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

9. The pharmaceutical dosage form as defined in claim 1 wherein not less than 85%, of the thiazolidinedione is

released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

10. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

11. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

12. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37° C. and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

13. A pharmaceutical dosage form having a first and second active drug, said dosage form comprising:

(a) a controlled release core comprising an antihyperglycemic drug and at least one pharmaceutically acceptable excipient; and

(b) an immediate release thiazolidinedione derivative containing component wherein the total thiazolidinedione related compounds or impurities in the final dosage form are not more than 0.6 as determined by high performance liquid chromatography.

14. The pharmaceutical dosage form as defined in claim 13 wherein the total thiazolidinedione related compounds are not more than 0.5%.

15. The pharmaceutical dosage form as defined in claim 13 wherein the total thiazolidinedione related compounds are not more than 0.5%.

16. The pharmaceutical dosage form as defined in claim 13 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.25%.

17. The pharmaceutical dosage form as defined in claim 16 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.20%.

18. The pharmaceutical dosage form as defined in claim 17 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.10%.

19. The dosage form of claim 1 wherein said controlled release core is an osmotic tablet.

20. The dosage form of claim 19 wherein the osmotic tablet comprises:

(a) a core comprising:

(i) 50-98% of said antihyperglycemic drug;

(ii) 0.1-40% of a binding agent;

(iii) 0-20% of an absorption enhancer; and

(iv) 0-5% of a lubricant;

(b) optionally a seal coat surrounding the core; and

(c) a sustained release membrane comprising:

(i) 50-99% of a polymer;

(ii) 0-40% of a flux enhancer and

(iii) 0-25% of a plasticizer, said membrane having at least one passageway formed therein for release of the antihyperglycemic drug.

21. The dosage form of claim 1 wherein said antihyperglycemic drug is a biguanide.

22. The dosage form of claim 1 wherein said thiazolidinedione derivative is troglitazone, rosiglitazone, pioglitazone, ciglitazone or pharmaceutically acceptable salts, isomers or derivatives thereof.

23. The dosage form of claim 1 wherein said core is substantially free from any gelling or expanding polymer.

24. The dosage form of claim 1 wherein said controlled release of said antihyperglycemic drug provides a Tmax of 8-12 hours.

25. The dosage form of claim 1 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-12 hours.

26. The dosage form of claim 25 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-4 hours.

27. The dosage form of claim 13 wherein said controlled release core is an osmotic tablet.

28. The dosage form of claim 27 wherein the osmotic tablet comprises:

(d) a core comprising;

(i) 50-98% of said antihyperglycemic drug;

(ii) 0.1-40% of a binding agent;

(iii) 0-20% of an absorption enhancer; and

(iv) 0-5% of a lubricant;

(e) optionally a seal coat surrounding the core; and

(f) a sustained release membrane comprising;

(iv) 50-99% of a polymer;

(v) 0-40% of a flux enhancer and

(vi) 0-25% of a plasticizer, said membrane having at least one passageway formed therein for release of the antihyperglycemic drug.

29. The dosage form of claim 13 wherein said antihyperglycemic drug is a biguanide.

30. The dosage form of claim 13 wherein said thiazolidinedione derivative is troglitazone, rosiglitazone, pioglitazone, ciglitazone or pharmaceutically acceptable salts, isomers or derivatives thereof.

31. The dosage form of claim 13 wherein said core is substantially free from any gelling or expanding polymer.

32. The dosage form of claim 13 wherein said controlled release of said antihyperglycemic drug provides a Tmax of 8-12 hours.

33. The dosage form of claim 13 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-12 hours.

34. The dosage form of claim 33 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-4 hours.

* * * * *

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In the new oral, once-daily, extended-release (ER), single-composition osmotic tablet formulation of the biguanide metformin hydrochloride (metformin XT), metformin is released at a controlled rate from a central osmotic tablet core through a semipermeable coating. A decrease in fasting plasma insulin, a marker of insulin resistance, was seen with metformin XT but not with immediate-release (IR) metformin in one well designed trial, but changes were similar in another. The pharmacokinetics of metformin XT reflect its extended-release characteristics. While the bioavailability (in terms of area under the plasma concentration-time curve) of metformin XT taken after the evening meal is similar to that of the IR formulation taken in divided doses, time to peak plasma concentrations is prolonged. Increases in metformin XT dose from 1000mg to 2500mg resulted in predictable and consistent dose-associated increases in metformin exposure. As with other ER metformin formulations, the bioavailability of metformin XT is increased after food, in contrast to the slight decrease seen with the IR formulation. The efficacy of metformin XT 1000, 1500, 2000, or 2500mg once daily with the evening meal was found not inferior to a similar dose range of metformin IR given in divided doses (measured by changes in glycosylated hemoglobin [HbA(1c)]) in a well designed study of 659 evaluable patients with type 2 (non-insulin-dependent) diabetes mellitus previously stabilized on metformin IR. Metformin XT and IR 2000 or 2500 mg/day had clinically similar efficacy (using changes in HbA(1c) and fasting plasma glucose) in another well designed study of 102 evaluable patients with type 2 diabetes. Like the IR formulation, metformin XT is generally well tolerated; gastro-intestinal adverse events are, however, common.

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Metformin (Fortamet®, Glucophage®, Glucophage® XR, ...) Metformin is used alone or with other medications, including insulin, to treat type 2 diabetes (condition in which the body does not use insulin normally and, therefore, cannot control the amount of sugar in the blood)

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(54) Title: NOVEL PHARMACEUTICAL FORMULATION CONTAINING A BIGUANIDE AND A THIAZOLIDINEDIONE
DERIVATIVE

(57) Abstract: A pharmaceutical dosage form comprising a controlled release component comprising an antihyperglycemic drug
in combination with a second component comprising a thiazolidinedione derivative is herein disclosed and described.

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What is claimed is:

1. A pharmaceutical dosage form having a first and second active drug, said dosage form comprising:
 - (a) a controlled release core comprising an antihyperglycemic drug and at least one pharmaceutically acceptable excipient; and
 - (b) an immediate release thiazolidinedione derivative containing component that comprises a thiazolidinedione derivative and a low viscosity water soluble binder;wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
2. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
3. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
4. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
5. The pharmaceutical dosage form as defined in claim 1 wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
6. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 40

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- minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
7. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
8. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
9. The pharmaceutical dosage form as defined in claim 1 wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
10. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
11. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.
12. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

13. A pharmaceutical dosage form having a first and second active drug, said dosage form comprising:
- (a) a controlled release core comprising an antihyperglycemic drug and at least one pharmaceutically acceptable excipient; and
- 5 (b) an immediate release thiazolidinedione derivative containing component that comprises a thiazolidinedione derivative and a low viscosity water soluble binder; wherein the total thiazolidinedione related compounds or impurities in the final dosage form are not more than 0.6 as determined by high performance liquid chromatography.
- 10 14. The pharmaceutical dosage form as defined in claim 13 wherein the total thiazolidinedione related compounds are not more than 0.5%.
- 15 15. The pharmaceutical dosage form as defined in claim 13 wherein the total thiazolidinedione related compounds are not more than 0.5%.
- 16 16. The pharmaceutical dosage form as defined in claim 13 wherein each
- 15 individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.25%.
- 17 17. The pharmaceutical dosage form as defined in claim 16 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.20%.
- 20 18. The pharmaceutical dosage form as defined in claim 17 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.10%.
- 19 19. The dosage form of claim 1 wherein said controlled release core is an osmotic tablet.
- 25 20. The dosage form of claim 19 wherein the osmotic tablet comprises:
- (a) a core comprising:
- (i) 50-98% of said antihyperglycemic drug;
- (ii) 0.1-40% of a binding agent;
- (iii) 0-20% of an absorption enhancer; and
- 30 (iv) 0-5% of a lubricant;
- (b) optionally a seal coat surrounding the core; and
- (c) a sustained release membrane comprising:
- (i) 50-99% of a polymer;
- (ii) 0-40% of a flux enhancer and

- (iii) 0-25% of a plasticizer, said membrane having at least one passageway formed therein for release of the antihyperglycemic drug.
21. The dosage form of claim 1 wherein said antihyperglycemic drug is a biguanide.
- 5 22. The dosage form of claim 1 wherein said thiazolidinedione derivative is troglitazone, rosiglitazone, pioglitazone, ciglitazone or pharmaceutically acceptable salts, isomers or derivatives thereof.
23. The dosage form of claim 1 wherein said core is substantially free from any gelling or expanding polymer.
- 10 24. The dosage form of claim 1 wherein said controlled release of said antihyperglycemic drug provides a Tmax of 6-12 hours.
25. The dosage form of claim 1 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-12 hours.
26. The dosage form of claim 25 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-4 hours.
- 15 27. The dosage form of claim 13 wherein said controlled release core is an osmotic tablet.
28. The dosage form of claim 27 wherein the osmotic tablet comprises:
- (d) a core comprising;
- 20 (i) 50-98% of said antihyperglycemic drug;
- (ii) 0.1-40% of a binding agent;
- (iii) 0-20% of an absorption enhancer; and
- (iv) 0-5% of a lubricant;
- (e) optionally a seal coat surrounding the core; and
- 25 (f) a sustained release membrane comprising;
- (iv) 50-99% of a polymer;
- (v) 0-40% of a flux enhancer and
- (vi) 0-25% of a plasticizer, said membrane having at least one passageway formed therein for release of the antihyperglycemic drug.
- 30 29. The dosage form of claim 13 wherein said antihyperglycemic drug is a biguanide.

30. The dosage form of claim 13 wherein said thiazolidinedione derivative is troglitazone, rosiglitazone, pioglitazone, ciglitazone or pharmaceutically acceptable salts, isomers or derivatives thereof.
31. The dosage form of claim 13 wherein said core is substantially free from any gelling or expanding polymer.
32. The dosage form of claim 13 wherein said controlled release of said antihyperglycemic drug provides a Tmax of 6-12 hours.
33. The dosage form of claim 13 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-12 hours.
34. The dosage form of claim 33 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-4 hours.
35. The dosage form of claim 1 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 50 mPa.S when tested as a 2% aqueous solution at 20°C.
36. The dosage form of claim 35 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 25 mPa.S when tested as a 2% aqueous solution at 20°C.
37. The dosage form of claim 35 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 10 mPa.S when tested as a 2% aqueous solution at 20°C.
38. The dosage form of claim 35 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity between 2 and 6 mPa.S when tested as a 2% aqueous solution at 20°C.
39. The dosage form of claim 37 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component is hydroxypropyl cellulose.
40. The dosage form of claim 38 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component is hydroxypropyl cellulose.
41. The dosage form of claim 13 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 50 mPa.S when tested as a 2% aqueous solution at 20°C.

42. The dosage form of claim 41 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 25 mPa.S when tested as a 2% aqueous solution at 20°C.
- 5 43. The dosage form of claim 41 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 10 mPa.S when tested as a 2% aqueous solution at 20°C.
44. The dosage form of claim 41 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity between 2 and 6 mPa.S when tested as a 2% aqueous solution at 10 20°C.
45. The dosage form of claim 43 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component is hydroxypropyl cellulose.
- 15 46. The dosage form of claim 44 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component is hydroxypropyl cellulose.

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AA 3286 315 70
NOTARIA TERCERA
ENCUENTRO



ESCRITURA NUMERO CUATRO MIL QUINIENTOS -
TREINTA Y NUEVE (No.4.539) -----
En la ciudad de Cali, Capital del Depar-
tamento del Valle del Cauca, República de
Colombia, a los VEINTITRES (23) días -
del mes de OCTUBRE del año DOS MIL UNO --

(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario
T E R C E R O (3o.) del Círculo de Cali, - - - - -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: -----

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y
representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida
mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
junio de 1957, reformada en distintas oportunidades, según consta en el certificado
expedido por la Cámara de Comercio de Cali -----

SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial
pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de
Bogotá, identificado con C.C. # 79.152.473 de Isaquén, abogado en ejercicio, portador
de la T.P 44655 del C.S.de la J., domiciliado en Bogotá, D.C., República de Colombia
con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante
con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad
industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos
represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente
ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo
concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y
oposición a patentes de invención, modelos y dibujos industriales y el registro de
licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad,
medidas cautelares, concesión de licencias y en general los procesos civiles, penales,
administrativos o contencioso-administrativos relacionados con estos derechos u otros de
diferente naturaleza; acciones y procesos que promovamos o se nos promuevan o se nos promuevan

13 AGO 2007
WILLY VALERIO
NOTARIO
BOGOTÁ D.C.

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LUZ MERY CORREA
ELABORACION DE ESCRITURAS
Notaría 3ª de Cali

ESTE PAPEL NO TIENE COSTO ALGUNO PARA EL USUARIO 27 AGO 2008

REPUBLICA DE COLOMBIA
NOTARIO NOVENO
BOGOTÁ, D.C.

que en todos los asuntos arriba determinados, , tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.

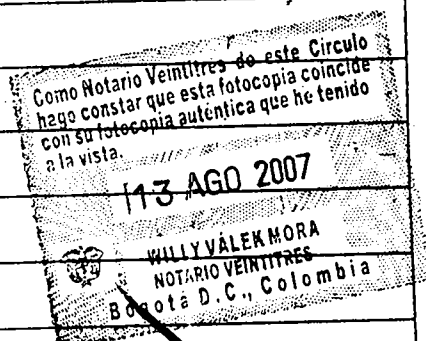
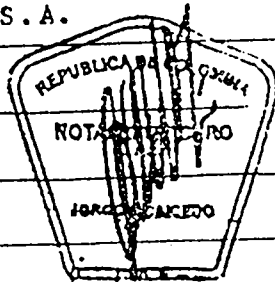
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.

Se agregan comprobantes. Derechos \$30.000.00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

Juan m. Barberi

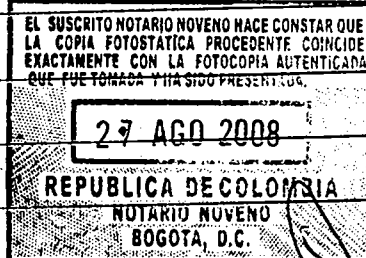
JUAN MANUEL BARBERI OSPINA

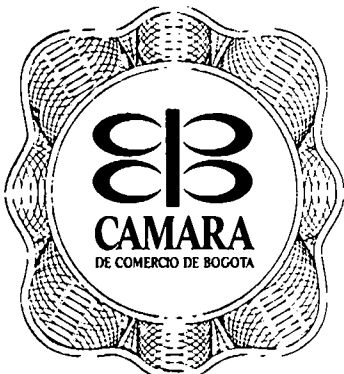
En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO





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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

Hora Certificado 11:48:54

Operacion : 02CP20827018

PAGINA No. 1

null

CERTIFICA:

NOMBRE:TECNOQUIMICAS S.A.

SIGLA : TQ S.A.

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL :---C 23 7 39

DIRECCION NOTIFICACION JUDICIAL:---C 23 7 39

CIUDAD:CALI

MATRICULA MERCANTIL NRO. 7049-4 FECHA MATRICULA : 01 DE JULIO DE 1957

AFILIADO

CERTIFICA:

NIT : 890300466-5

CERTIFICA:

QUE POR ESCRITURA NRO. 2670 DEL 12 DE JUNIO DE 1957 NOTARIA SEGUNDA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 01 DE JULIO DE 1957 BAJO EL NRO. 16627 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA COMPANIAS TECNOQUIMICAS LIMITADA

CERTIFICA:

QUE POR ESCRITURA NRO. 8438 DEL 30 DE DICIEMBRE DE 1970 NOTARIA SEGUNDA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 07 DE ENERO DE 1971 BAJO EL NRO. 42260 DEL LIBRO IX ,LA SOCIEDAD SE TRANSFORMO DE SOCIEDAD LIMITADA EN SOCIEDAD EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA COMANDITA POR ACCIONES (SIC) .

CERTIFICA:

QUE POR ESCRITURA NRO. 2139 DEL 21 DE ABRIL DE 1972 NOTARIA SEGUNDA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 26 DE ABRIL DE 1972 BAJO EL NRO. 794 DEL LIBRO IX , LA SOCIEDAD CAMBIO SU NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA COMANDITA POR ACCIONES (SIC) . POR EL DE TECNOQUIMICAS LIMITADA & CIA S.C. A. .

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827 Hora Certificado 11:48:54

Operacion : 02CP20827018 PAGINA No. 2

CERTIFICA:

QUE POR ESCRITURA NRO. 3255 DEL 30 DE AGOSTO DE 1983 NOTARIA DECIMA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 31 DE AGOSTO DE 1983 BAJO EL NRO. 62343 DEL LIBRO IX ,LA SOCIEDAD SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES EN SOCIEDAD AN?NIMA BAJO EL NOMBRE DE TECNOQUIMICAS S A .

CERTIFICA:

QUE POR ESCRITURA NRO. 5664 DEL 12 DE DICIEMBRE DE 2005 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 19 DE DICIEMBRE DE 2005 BAJO EL NRO. 14102 DEL LIBRO IX ,SE APROBO LA FUSION POR ABSORCION ENTRE (ABSORBENTE) TECNOQUIMICAS S.A. Y (ABSORBIDA (S)) DISTRIBUIDORA FARMACEUTICA CALOX COLOMBIANA S.A. - EN LIQUIDACION-, ORGANIZACION FARMACEUTICA AMERICANA S.A. OFA - EN LIQUIDACION- .

CERTIFICA:

QUE POR ESCRITURA NRO. 1675 DEL 08 DE MAYO DE 2008 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 16 DE MAYO DE 2008 BAJO EL NRO. 5362 DEL LIBRO IX , LA SOCIEDAD CAMBIO SU NOMBRE DE TECNOQUIMICAS S A . POR EL DE TECNOQUIMICAS S.A. . SIGLA: TQ S.A.

CERTIFICA:

REFORMAS DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
INS LIBRO				
E.P. 4075	05/09/1957	NOTARIA SEGUNDA DE CALI	27/09/1957	
16922				
E.P. 5718	28/11/1957	NOTARIA SEGUNDA DE CALI	30/12/1957	
17242				
E.P. 5507	31/12/1957	NOTARIA PRIMERA DE CALI	13/03/1958	
17529				
E.P. 3124	16/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	
18365				
E.P. 3325	29/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	
18366				
E.P. 5726	17/12/1958	NOTARIA PRIMERA DE CALI	12/05/1959	
19258				
E.P. 2374	12/05/1959	NOTARIA PRIMERA DE CALI	03/06/1959	
19368				
E.P. 2793	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961	

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PAGINA No. 3

22616	E.P. 2794	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961
22617	E.P. 6365	30/12/1961	NOTARIA PRIMERA DE CALI	23/01/1962
23489	E.P. 1383	21/03/1962	NOTARIA PRIMERA DE CALI	28/03/1962
23850	E.P. 3396	28/05/1963	NOTARIA PRIMERA DE CALI	11/06/1963
26016	E.P. 8853	30/12/1963	NOTARIA PRIMERA DE CALI	23/01/1964
27107	E.P. 5718	28/11/1957	NOTARIA SEGUNDA DE CALI	10/02/1964
27181	E.P. 2743	29/04/1964	NOTARIA PRIMERA DE CALI	06/05/1964
27681	E.P. 2744	29/04/1964	NOTARIA PRIMERA DE CALI	06/05/1964
27682	E.P. 7057	21/10/1964	NOTARIA PRIMERA DE CALI	22/10/1964
28591	E.P. 1693	26/04/1965	NOTARIA PRIMERA DE CALI	28/04/1965
29569	E.P. 1799	10/05/1966	NOTARIA PRIMERA DE CALI	11/05/1966
31623	E.P. 2498	18/11/1966	NOTARIA CUARTA DE CALI	25/11/1966
32757	E.P. 2792	27/12/1966	NOTARIA CUARTA DE CALI	05/01/1967
33009	E.P. 2209	25/09/1967	NOTARIA CUARTA DE CALI	04/10/1967
34591	E.P. 6933	20/12/1967	NOTARIA SEGUNDA DE CALI	28/12/1967
35082	E.P. 6363	14/11/1968	NOTARIA SEGUNDA DE CALI	26/11/1968
37141	E.P. 7711	31/12/1968	NOTARIA SEGUNDA DE CALI	04/02/1969
37615	E.P. 5597	30/09/1969	NOTARIA SEGUNDA DE CALI	18/10/1969
39341	E.P. 5211	27/08/1970	NOTARIA SEGUNDA DE CALI	04/09/1970
41379	E.P. 6576	07/10/1971	NOTARIA SEGUNDA DE CALI	14/10/1971
44154	E.P. 7286	08/11/1971	NOTARIA SEGUNDA DE CALI	10/11/1971
44367	E.P. 8042	03/12/1971	NOTARIA SEGUNDA DE CALI	21/12/1971
44716	E.P. 6209	05/10/1973	NOTARIA SEGUNDA DE CALI	15/10/1973
5505	IX			
E.P. 8741		31/12/1973	NOTARIA SEGUNDA DE CALI	08/03/1974

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CERTIFICADO NACIONAL

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PAGINA No. 4

7636 IX						
E.P. 9270	31/12/1974	NOTARIA	SEGUNDA	DE	CALI	31/01/1975
11772 IX						
E.P. 9504	31/12/1974	NOTARIA	SEGUNDA	DE	CALI	04/04/1975
12441 IX						
E.P. 7566	05/12/1975	NOTARIA	SEGUNDA	DE	CALI	09/01/1976
15581 IX						
E.P. 2671	09/05/1980	NOTARIA	SEGUNDA	DE	CALI	22/10/1980
41529 IX						
E.P. 779	10/03/1982	NOTARIA	DECIMA	DE	CALI	03/08/1982
54655 IX						
E.P. 4324	10/11/1982	NOTARIA	DECIMA	DE	CALI	30/06/1983
61172 IX						
E.P. 1269	18/03/1986	NOTARIA	DECIMA	DE	CALI	01/04/1986
83730 IX						
E.P. 5089	24/09/1986	NOTARIA	DECIMA	DE	CALI	29/09/1986
87933 IX						
E.P. 7064	04/11/1987	NOTARIA	DECIMA	DE	CALI	19/11/1987
2552 IX						
E.P. 7065	04/11/1987	NOTARIA	DECIMA	DE	CALI	19/11/1987
2553 IX						
E.P. 5929	14/07/1989	NOTARIA	DECIMA	DE	CALI	26/07/1989
20225 IX						
E.P. 8569	29/09/1989	NOTARIA	DECIMA	DE	CALI	02/10/1989
22250 IX						
E.P. 10571	04/12/1992	NOTARIA	DECIMA	DE	CALI	15/12/1992
60929 IX						
E.P. 10249	18/12/1995	NOTARIA	DECIMA	DE	CALI	20/12/1995
10214 IX						
E.P. 2359	22/05/1997	NOTARIA	TERCERA	DE	CALI	27/05/1997
3813 IX						
E.P. 2624	30/06/2000	NOTARIA	TERCERA	DE	CALI	07/07/2000
4740 IX						
E.P. 3814	15/09/2000	NOTARIA	TERCERA	DE	CALI	18/09/2000
6381 IX						
E.P. 3588	30/07/2004	NOTARIA	TERCERA	DE	CALI	04/08/2004
8542 IX						
E.P. 2224	24/05/2006	NOTARIA	TERCERA	DE	CALI	30/05/2006
6565 IX						
E.P. 1675	08/05/2008	NOTARIA	TERCERA	DE	CALI	16/05/2008
5362 IX						

CERTIFICA:

VIGENCIA: 01 DE ENERO DEL AÑO 2057

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CAMARA DE COMERCIO DE CALI

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PAGINA No. 5

CERTIFICA:

OBJETO SOCIAL. LA SOCIEDAD TIENE POR OBJETO: A) LA FABRICACION, EL ENVASADO, LA IMPORTACION, LA EXPORTACION, LA VENTA Y DISTRIBUCION DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS Y ALIMENTOS NATURALES Y/O PRODUCTOS DE CONSUMO POPULAR DE CUALQUIER NATURALEZA Y SERVICIOS EN GENERAL. B) INVERTIR EN SOCIEDADES O EMPRESAS DE CUALQUIER NATURALEZA O ESPECIE DE LA SOCIEDAD MERCANTIL, NACIONAL O EXTRANJERA, QUE TENGAN COMO ACTIVIDAD O NEGOCIO PROPIO DE SU OBJETO LA FABRICACION, DISTRIBUCION Y COMERCIO EN GENERAL DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS, ALIMENTOS NATURALES Y/O PROCESADOS, PRODUCTOS DE CONSUMO POPULAR, SERVICIOS EN GENERAL O LA EXPLOTACION DE ESTABLECIMIENTOS DE COMERCIO DEDICADOS A DICHO GIRO. C) ADQUIRIR ACCIONES, CUOTAS SOCIALES, BONOS CEDULAS, TITULOS U OTROS VALORES EN COMPANIAS DE CUALQUIER NATURALEZA O TIPO LEGAL, DEDICADAS A LA EXPLOTACION DE CUALQUIER ACTIVIDAD ECONOMICA LICITA Y ENAJENARLAS. D) LA EXPLOTACION DEL NEGOCIO DE LA PUBLICIDAD Y EL ESTABLECIMIENTO DE OFICINAS DEDICADAS A ESTE NEGOCIO O A LA CREACION DE ORGANOS DE PUBLICIDAD HABLADOS O ESCRITOS. E) GARANTIZAR LAS OBLIGACIONES PROPIAS DE LOS ACCIONISTAS O DE TERCEROS. F) LA ADQUISICION DE BIENES MUEBLES, INMUEBLES Y DE TODA CLASE DE EQUIPO Y MAQUINARIA PARA SU ARRENDAMIENTO O PARA LA COMERCIALIZACION DE ELLOS. EN DESARROLLO DEL OBJETO SOCIAL PODRA OBTENER PRIVILEGIOS INDUSTRIALES, CONCESIONES, PATENTES DE INVENCION, DE MEJORAS O PROCEDIMIENTOS, MARCAS DE FABRICA O DE COMERCIO, YA SEA EN NOMBRE PROPIO O DE TERCEROS, OTORGAR A TERCEROS, DENTRO O FUERA DEL PAIS CONCESIONES O USOS DE EXPLOTACION SOBRE ESTOS DERECHOS, EJECUTAR TODA CLASE DE CONTRATOS DE COMPRAVENTA, DISTRIBUCION DE MATERIAS PRIMAS, DE PRODUCTOS SEMIELABORADOS O ELABORADOS EN EL MERCADO INTERNO O EN EL EXTERIOR Y EN GENERAL, LA CELEBRACION DE TODO ACTO O CONTRATO SOBRE BIENES MUEBLES O INMUEBLES DE COMERCIO, INDUSTRIALES O DE OTRA INDOLE QUE SE REFIERAN DIRECTAMENTE A LAS ACTIVIDADES QUE PERSIGUE LA SOCIEDAD.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION. PARA LOS FINES DE SU DIRECCION, ADMINISTRACION Y REPRESENTACION, LA SOCIEDAD TIENE LOS SIGUIENTES ORGANOS: A) ASAMBLEA GENERAL DE ACCIONISTAS. B) JUNTA DIRECTIVA. C) PRESIDENTE EJECUTIVO. D) TRES VICEPRESIDENTES EJECUTIVOS. E) VICEPRESIDENCIAS ADMINISTRATIVAS.

LA DIRECCION DE LA SOCIEDAD CORRESPONDE, EN PRIMER TERMINO A LA ASAMBLEA GENERAL DE ACCIONISTAS Y EN SEGUNDO LUGAR, A LA JUNTA DIRECTIVA COMO DELEGADA DE AQUELLA.

LA REPRESENTACION LEGAL DE LA SOCIEDAD Y LA GESTION DE LOS NEGOCIOS SOCIALES, ESTARAN A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 6

EJECUTIVOS.

FUNCIONES DE LA ASAMBLEA DE ACCIONISTAS. ENTRE OTRAS LAS SIGUIENTES: 1) ACORDAR LA FUSI?N DE LA SOCIEDAD, SU TRANSFORMACI?N, LA ENAJENACI?N O EL ARRENDAMIENTO DE LA EMPRESA SOCIAL, LA DISOLUCI?N O LA PRORROGA Y CUALQUIER REFORMA, AMPLIACI?N MODIFICACI?N DEL CONTRATO SOCIAL. 9) AUTORIZAR LA ADQUISICI?N DE ACCIONES PROPIAS, CON SUJECI?N A LOS REQUISITOS ESTABLECIDOS POR LA LEY. 10) ADOPTAR EN GENERAL, TODAS LAS MEDIDAS QUE RECLAMEN EL CUMPLIMIENTO DE LOS ESTATUTOS O EL INTER?S DE LA SOCIEDAD.

LA JUNTA DIRECTIVA SE COMPONE DE SEIS (6) MIEMBROS PRINCIPALES O DIRECTORES, ELEGIDOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS PARA PER?ODOS DE DOS A?OS, SIN PERJUICIO DE QUE PUEDAN SER REMOVIDOS LIBREMENTE POR LA ASAMBLEA O REELEGIDOS INDEFINIDAMENTE. SIMULT?NEAMENTE CON LA ELECCI?N DE LOS PRINCIPALES, LA ASAMBLEA ELEGIR? SEIS (6) SUPLENTE NUM?RICOS LOS CUALES, EN EL ORDEN DE DESIGNACI?N, REEMPLAZAR?N A LOS PRINCIPALES EN SUS FALTAS ABSOLUTAS, ACCIDENTALES O TEMPORALES.

EN LA JUNTA DIRECTIVA SE ENTIENDE DELEGADO EL MAS AMPLIO MANDATO PARA ADMINISTRAR LA SOCIEDAD Y POR CONSIGUIENTE, TENDR? ATRIBUCIONES SUFICIENTES PARA ORDENAR QUE SE EJECUTE O CELEBRE CUALQUIER ACTO O CONTRATO COMPRENDIDO DENTRO DEL OBJETO SOCIAL Y PARA ADOPTAR LAS DETERMINACIONES NECESARIAS EN ORDEN A QUE LA SOCIEDAD CUMPLA SUS FINES Y DE MANERA ESPECIAL, TENDR? LAS SIGUIENTES FUNCIONES ENTRE OTRAS: C) NOMBRAR Y REMOVER LIBREMENTE AL PRESIDENTE EJECUTIVO, A LOS VICEPRESIDENTES EJECUTIVOS Y A LOS VICEPRESIDENTES ADMINISTRATIVOS. E) DISPONER EL ESTABLECIMIENTO O LA CLAUSURA DE SUCURSALES O AGENCIAS, DENTRO O FUERA DEL DOMICILIO SOCIAL. F) FIJAR LAS POL?TICAS DE LA SOCIEDAD EN LOS DIFERENTES ORDENES DE SU ACTIVIDAD, ESPECIALMENTE EN MATERIA FINANCIERA, ECON?MICA Y LABORAL; APROBAR PLANES DE INVERSI?N Y DE PRODUCCI?N; DECIDIR SOBRE NUEVAS LINEAS DE PRODUCCI?N Y VENTA, ESTABLECER NORMAS GENERALES EN MATERIA DE PRECIOS Y DE VENTAS DE LOS PRODUCTOS ELABORADOS POR LA SOCIEDAD O DE LOS MATERIALES Y DEM?S ELEMENTOS EN QUE ELLA NEGOCIE Y DICTAR NORMAS Y REGLAMENTOS PARA LA ORGANIZACI?N Y EL FUNCIONAMIENTO DE TODAS LAS DEPENDENCIAS DE LA SOCIEDAD. G) DETERMINAR LA APLICACI?N QUE DEBA DARSE A LAS UTILIDADES QUE, CON EL CAR?CTER DE RESERVAS DE INVERSI?N, HAYAN SIDO APROPIADAS POR LA ASAMBLEA DE ACCIONISTAS. H) AUTORIZAR PREVIAMENTE LAS OPERACIONES QUE TENGAN POR OBJETO: 1) ADQUIRIR, HIPOTECAR Y EN CUALQUIER OTRA FORMA GRAVAR O LIMITAR EL DOMINIO DE BIENES RA?CES CUYA CUANT?A SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE; 2) CONSTITUIR PRENDA SOBRE BIENES SOCIALES O DARLOS EN ANTICRESIS PARA ACTOS O CONTRATOS CUYA CUANT?A SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE; 3) AUTORIZAR INVERSIONES EN BIENES DE CAPITAL O EFECTUAR REPARACIONES O MEJORAS DE LOS MISMOS, CUANDO UNAS U OTRAS IMPLIQUEN, EN CADA CASO, COSTOS O DESEMBOLSOS EN CUANT?A O SUPERIOR A CIEN MIL D?LARES AMERICANOS (\$US100.000.00). 4) AUTORIZAR LOS CONTRATOS DE MUTUO QUE PUEDAN CELEBRAR LA SOCIEDAD LOS REPRESENTANTES LEGALES CUANDO SU CUANT?A SEA SUPERIOR A \$100.000.000.00 MONEDA LEGAL COLOMBIANA O A US\$300.000.00. L) AUTORIZAR AL REPRESENTANTE LEGAL PARA QUE SOLICITE, LLEGADO EL CASO, QUE SE ADMITA A LA COMPA??A A LA CELEBRACI?N DE CONCORDATO PREVENTIVO CON SUS ACREEDORES. M)

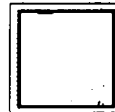
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

Hora Certificado 11:48:54

Operacion : 02CP20827018

PAGINA No. 7

SERVIR DE ?RGANO CONSULTIVO Y ASESOR DE LOS REPRESENTANTES DE LA COMPA??A.

LA ADMINISTRACI?N INMEDIATA DE LA COMPA??A, SU REPRESENTACI?N LEGAL Y LA GESTI?N DE LOS NEGOCIOS SOCIALES ESTAR?N A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES EJECUTIVOS, DESIGNADOS POR LA JUNTA DIRECTIVA PARA PERIODOS DE UN A?O, REELEGIBLES INDEFINIDAMENTE Y REMOVIBLES LIBREMENTE POR ELLA EN CUALQUIER TIEMPO, QUIENES COMO REPRESENTANTES LEGALES PODR?N ACTUAR CONJUNTA O SEPARADAMENTE CON IGUALDAD DE FUNCIONES Y CALIDADES. TODOS LOS EMPLEADOS DE LA COMPA??A CON EXCEPCI?N DE LOS DESIGNADOS POR LA ASAMBLEA DE ACCIONISTAS Y LOS DEPENDIENTES DEL REVISOR FISCAL, SI LOS HUBIERE, ESTAR?N SOMETIDOS EN EL DESEMPE?O DE SUS CARGOS A LOS REPRESENTANTES LEGALES.

LOS REPRESENTANTES LEGALES SON MANDATARIOS CON REPRESENTACI?N INVESTIDOS DE FUNCIONES EJECUTIVAS Y ADMINISTRATIVAS Y COMO TALES TIENEN A SU CARGO LA REPRESENTACI?N LEGAL DE LA COMPA??A, LA GESTI?N COMERCIAL Y FINANCIERA, LA RESPONSABILIDAD DE LA ACCI?N ADMINISTRATIVA, LA COORDINACI?N Y LA SUPERVISI?N GENERAL DE LA EMPRESA, LAS CUALES CUMPLIR?N CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS Y A LAS DISPOSICIONES LEGALES Y CON SUJECI?N A LAS ORDENES E INSTRUCCIONES DE LA JUNTA DIRECTIVA.

COMO REPRESENTANTES LEGALES DE LA COMPA??A EN JUICIO Y FUERA DE JUICIO, LOS REPRESENTANTES TIENEN FACULTADES PARA EJECUTAR O CELEBRAR SIN OTRAS LIMITACIONES QUE LAS ESTABLECIDAS EN LOS ESTATUTOS EN CUANTO SE TRATE DE OPERACIONES QUE DEBAN SER PREVIAMENTE AUTORIZADAS POR LA JUNTA DIRECTIVA O POR LA ASAMBLEA DE ACCIONISTAS, TODOS LOS ACTOS O CONTRATOS COMPRENDIDOS DENTRO DEL OBJETO SOCIAL O QUE TENGAN CAR?CTER SIMPLEMENTE PREPARATORIO, ACCESORIO O COMPLEMENTARIO PARA LA REALIZACI?N DE LOS FINES QUE PERSIGUE LA SOCIEDAD Y LOS QUE SE RELACIONAN DIRECTAMENTE CON LA EXISTENCIA Y EL FUNCIONAMIENTO DE LA MISMA. LOS REPRESENTANTES QUEDAN INVESTIDOS DE PODERES ESPECIALES PARA TRANSIGIR, ARBITRAR Y COMPROMETER LOS NEGOCIOS SOCIALES; PROMOVER O COADYUVAR ACCIONES JUDICIALES, ADMINISTRATIVAS O CONTENCIOSO ADMINISTRATIVAS EN QUE LA COMPA??A TENGA INTER?S E INTERPONER TODOS LOS RECURSOS QUE SEAN PROCEDENTES CONFORME A LA LEY; DESISTIR DE LAS ACCIONES O RECURSOS QUE INTERPONGAN; NOVAR OBLIGACIONES O CR?DITOS; DAR O RECIBIR BIENES EN PAGO; CONSTITUIR APODERADOS JUDICIALES O EXTRAJUDICIALES, DELEGARLES FACULTADES REVOCAR MANDATOS Y SUSTITUCIONES.

PAR?GRAFO: LOS REPRESENTANTES LEGALES DE LA SOCIEDAD TIENEN AMPLIAS FACULTADES, SIN NINGUNA LIMITACI?N Y SIN REQUERIR AUTORIZACI?N PREVIA DE LA JUNTA DIRECTIVA, PARA ACTUAR EN NOMBRE DE LA SOCIEDAD EN LICITACIONES PUBLICAS, PRIVADAS O CUALQUIER OTRA MODALIDAD DE CONTRATACI?N, PRESENTAR PROPUESTAS, ACEPTAR ADJUDICACIONES Y CONTRATAR SIN LIMITACI?N DE CUANT?A ALGUNA ANTE LAS ENTIDADES PUBLICAS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOM?A MIXTA, BIEN SEAN ELLAS DEL ORDEN NACIONAL, DISTRITAL, DEPARTAMENTAL O MUNICIPAL.

CERTIFICA:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

Hora Certificado 11:48:54

Operacion : 02CP20827018

PAGINA No. 8

DOCUMENTO: ACTA No. 393 DEL 20 DE ENERO DE 1993

ORIGEN: JUNTA DIRECTIVA

INSCRIPCION: 26 DE ENERO DE 1993 No. 62203 DEL LIBRO IX

FUE(ON) NOMBRADO(S) :

PRESIDENTE EJECUTIVO

FRANCISCO JOSE BARBERI OSPINA

C.C.14445880

VICEPRESIDENTE EJECUTIVO

JUAN MANUEL BARBERI OSPINA

C.C.14949561

VICEPRESIDENTE EJECUTIVO

JUAN BAUTISTA DE LOS RIOS GUTIERREZ ,

C.C.17108621

VICEPRESIDENTE EJECUTIVO

EMILIO SARDI APARICIO

C.C.14434582

CERTIFICA:

DOCUMENTO: ACTA No. 67 DEL 28 DE MARZO DE 2008

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 16 DE MAYO DE 2008 No. 5363 DEL LIBRO IX

FUE(ON) _NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

FRANCISCO JOSE BARBERI OSPINA

C.C.14445880

SEGUNDO RENGLON

JUAN MANUEL BARBERI OSPINA

C.C.14949561

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

Hora Certificado 11:48:54

Operacion : 02CP20827018

PAGINA No. 9

TERCER RENGLON

EMILIO SARDI APARICIO

C.C.14434582

CUARTO RENGLON

ANTONIO JAIRO RAMIREZ ECHAVE

C.C.16741040

QUINTO RENGLON

DIEGO HUMBERTO QUIJANO REISSNER

C.C.16615708

SEXTO RENGLON

ALONSO BOTERO PARDO

C.C.16830282

SUPLENTES

PRIMER RENGLON

VICTOR RICARDO ROSA GARCIA

C.C.6811102

SEGUNDO RENGLON

ERNESTO TRUJILLO PEREZ

C.C.14984104

TERCER RENGLON

ANA MARIA ALVAREZ ROBLEDO

C.C.31170896

CUARTO RENGLON

GUSTAVO ADOLFO SANCHEZ LESMES

C.C.16625960

QUINTO RENGLON

JORGE ENRIQUE ARIZA BERNAL

C.C.19494493

SEXTO RENGLON

MARTHA LUZ GONZALEZ TORRES

C.C.31854671

CERTIFICA:

DOCUMENTO: ACTA No. 59 DEL 31 DE MARZO DE 2003

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

Hora Certificado 11:48:54

Operacion : 02CP20827018

PAGINA No. 10

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 23 DE ABRIL DE 2003 No. 2845 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

REVISOR FISCAL

DELOITTE & TOUCHE LTDA D & T LTDA

NIT.860005813-4

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 26 DE AGOSTO DE 2004

ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA

INSCRIPCION: 30 DE AGOSTO DE 2004 No. 9417 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL

LUIS FERNANDO QUICENO BENAVIDES

C.C.6106227

REVISOR FISCAL SUPLENTE

JESUS DARIO LOPEZ CASELLA

C.C.16789097

CERTIFICA:

QUE POR ESCRITURA NRO. 5235 DEL 19 DE JULIO DE 1996 NOTARIA DECIMA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 25 DE JULIO DE 1996 BAJO EL NRO. 144 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A CARLOS ALBERTO QUINTERO, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO.

14.440.778 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA, EL REPRESENTANTE EN LOS SIGUIENTES ACTOS: A) PRESENTAR EN LA ADMINISTRACION DE IMPUESTOS Y ADUANAS NACIONALES O DEL ORGANISMO QUE HAGA SUS VECES Y FIRMAR EN REPRESENTACION DE LA SOCIEDAD, LAS DECLARACIONES DEL IMPUESTO SOBRE LA RENTA Y COMPLEMENTARIOS QUE CORRESPONDA A LA SOCIEDAD, Y TODAS LAS DEMAS DECLARACIONES QUE LA SOCIEDAD DEBA PRESENTAR ANTE DICHA ENTIDAD, TALES COMO LA DE VENTAS, RETENCION EN LA FUENTE, TIMBRE Y CUALESQUIER OTRA DECLARACION QUE POR LEY LA SOCIEDAD ESTE OBLIGADA A PRESENTAR.

B) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A

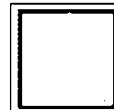
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

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Operacion : 02CP20827018

PAGINA No. 11

TECNOQUIMICAS S.A., COMO DECLARANTE DEL IMPUESTO DE INDUSTRIA Y COMERCIO Y EL COMPLEMENTARIO DE AVISOS Y TABLEROS EN LOS MUNICIPIOS EN QUE LA SOCIEDAD ESTE OBLIGADA AL PAGO DE LOS CITADOS IMPUESTOS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE LOS MENCIONADOS TRIBUTOS. C) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A TECNOQUIMICAS S.A. COMO DECLARANTE DEL IMPUESTO PREDIAL Y COMPLEMENTARIOS EN LOS MUNICIPIOS DONDE TENGA BIENES INMUEBLES, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DEL CITADO IMPUESTO. D) PARA DAR RESPUESTA A LOS REQUERIMIENTOS ORDINARIOS Y A LAS SOLICITUDES DE INFORMACION EN RELACION CON LOS IMPUESTOS ADMINISTRADOS POR LA DIRECCION DE IMPUESTOS Y ADUANAS NACIONALES Y POR LAS DEPENDENCIAS MUNICIPALES QUE ADMINISTREN LOS IMPUESTOS DE CARACTER TERRITORIAL. E) Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO LA SOCIEDAD QUEDE SIN REPRESENTACION EN LOS ASUNTOS RELACIONADOS CON LAS FACULTADES OTORGADAS.

CERTIFICA:

QUE POR ESCRITURA NRO. 307 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 298 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A JORGE ROBERTO OBANDO RODRIGUEZ, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 14.960.183 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA: 1o.) PROMUEVA O DESISTA DE ACCIONES ANTE CORPORACIONES, ENTIDADES O FUNCIONARIOS DEL ORDEN JUDICIAL O GUBERNATIVO, YA SEA EN PROCESOS, ACTUACIONES O ACTOS SIMPLES, DILIGENCIAS O GESTIONES EN QUE TECNOQUIMICAS S.A. TENGA INTERES COMO ACTOR, DEMANDANDO O TERCERO INTERVINIENTE EN RELACION CON LOS ASUNTOS DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA, EN QUE LA EMPRESA SEA PARTE ACTIVA O PASIVA, CON CAPACIDAD PARA NOTIFICARSE Y CONTESTAR Y HACERSE PARTE DE ELLOS EN NOMBRE DE TECNOQUIMICAS S.A. 2o.) SUSCRIBA Y DE POR TERMINADO LOS CONTRATOS DE TRABAJO DEL PERSONAL VINCULADO A LA EMPRESA. 3o.) CONSTITUYA APODERADOS EN DESARROLLO DE ESTA REPRESENTACION LABORAL, REVOQUE Y SUSTITUYA DICHOS PODERES CUANDO LO ESTIME PROCEDENTE. 4o.) TRANSIGA, CONCILIE, DESISTA Y COMPROMETA A LA EMPRESA EN TODOS LOS TRAMITES ADMINISTRATIVOS Y PROCESOS JUDICIALES, DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA EN LOS QUE LA EMPRESA SEA PARTE DEMANDANTE, DEMANDADA O TERCERO INTERVINIENTE. PARAGRAFO. LA FACULTAD PARA TRANSIGIR O CONCILIAR SE LIMITA A LA SUMA DE QUINIENTOS (500) SALARIOS LEGALES MENSUALES. 5o.) OTORQUE PODERES Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES JUDICIALES DE CARACTER CIVIL, COMERCIAL Y PENAL TENDIENTES A LA RECUPERACION DE LOS CREDITOS A FAVOR DE LA SOCIEDAD, BIEN SEA REPRESENTADOS EN FACTURAS, CHEQUES, TITULOS VALORES O CUALQUIER OTRO DOCUMENTO REPRESENTATIVO DE CREDITO, HASTA POR SUMA EQUIVALENTE A QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE TECNOQUIMICAS S.A. A LAS AUDIENCIAS DE CONCILIACION QUE PROGRAMEN LOS JUZGADOS CIVILES MUNICIPALES Y DEL CIRCUITO, CON AUTORIZACION PARA TRANSIGIR, DESISTIR

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

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Operacion : 02CP20827018

PAGINA No. 12

 CONCILIAR O COMPROMETER A LA SOCIEDAD HASTA POR LA CUANTIA INDICADA. 6o. REPRESENTA A TECNOQUIMICAS S.A. DENTRO DE LOS TRAMITES DE CONCORDATOS, PROCESOS DE REESTRUCTURACION ECONOMICA PREVISTO EN LA LEY 550 DE 1999 Y LAS NORMAS QUE LA ADICIONEN O MODIFIQUEN Y LIQUIDACIONES OBLIGATORIAS QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE ACREEDORES O ANTE LOS JUZGADOS CIVILES, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER, NOMBRAR APODERADOS, PRESENTAR LOS CREDITOS, APORTAR LAS PRUEBAS QUE ESTIME NECESARIAS, ASISTIR A LAS AUDIENCIAS PRELIMINARES Y DEFINITIVAS, ACORDAR FORMULAS DE PAGO, RECIBIR Y EN GENERAL PARA EJERCER TODAS AQUELLAS GESTIONES NECESARIAS PARA OBTENER EL RECONOCIMIENTO Y PAGO DE LOS CREDITOS PRESENTADOS. LAS FACULTADES AQUI ESTABLECIDAS ESTAN LIMITADAS PARA LOS CREDITOS HASTA POR CUANTIA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. PARAGRAFO. IGUALMENTE QUEDA FACULTADO PARA ACEPTAR Y REPRESENTAR A TECNOQUIMICAS CUANDO LA EMPRESA SEA NOMBRADA EN JUNTA DE ACREEDORES O EN ORGANOS EQUIVALENTES O SIMILARES, EN LOS PROCESOS QUE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES. 7o.) REPRESENTA A TECNOQUIMICAS S.A. EN LOS PROCEDIMIENTOS DE CONCILIACION QUE LOS DEUDORES DE LA SOCIEDAD CONVOQUEN ANTE LAS ENTIDADES FACULTADAS PARA ELLO CON EL FIN OBTENER UN ACUERDO EN EL PAGO DE LAS ACREENCIAS, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER Y RECIBIR, FACULTADES QUE SE LIMITAN HASTA POR LA SUMA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. 8o.) REVISE LOS EXPEDIENTES DE LOS PROCESOS JUDICIALES DE CARACTER EJECUTIVO EN QUE LA SOCIEDAD SEA PARTE DEMANDANTE, EN TODO EL TERRITORIO NACIONAL, PARA LA RECUPERACION DE SUS ACREENCIAS. 9o.) APRUEBE Y SUSCRIBA ACUERDOS PRIVADOS DE PAGO Y CONCILIACIONES DE OBLIGACIONES A FAVOR DE TECNOQUIMICAS POR LA VENTA DE SUS PRODUCTOS HASTA POR LA SUMA DE (500) SALARIOS MINIMOS LEGALES MENSUALES.

CERTIFICA:

QUE POR ESCRITURA NRO. 4.202 DEL 31 DE MAYO DE 1995 NOTARIA DECIMA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 24 DE SEPTIEMBRE DE 2003 BAJO EL NRO. 134 DEL LIBRO V SE CONFIERE PODER ESPECIAL A ANTONIO JAIRO RAMIREZ ECHAVE, ABOGADO TITULADO Y EN EJERCICIO, CON TARJETA PROFESIONAL No. 58.401 DEL MINISTERIO DE JUSTICIA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 16.741.040 DE CALI PARA QUE REPRESENTA A TECNOQUIMICAS S.A., EN LOS SIGUIENTES ACTOS: A) SOLICITAR Y ADELANTAR ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO TODOS LOS TRAMITES ATINENTES A LA OBTENCION DE LICENCIAS DE VENTA Y LICENCIAS DE FUNCIONAMIENTO, RENOVACIONES, CERTIFICACIONES, AMPLIACIONES, INSCRIPCIONES Y MODIFICACIONES EN GENERAL; B) TODOS LOS TRAMITES ANTE EL INVIMA ATINENTES A LA OBTENCION DE REGISTRO SANITARIO, RENOVACION DEL MISMO, REFORMULACIONES, ADICIONES DE NUESTRA LINEA DE PRODUCTOS, CAMBIOS DE TITULAR Y DE FABRICANTE, CESIONES, CERTIFICACIONES DE FORMULA Y EXCLUSIVIDAD, MODIFICACIONES DE FABRICAR Y VENDER A IMPORTAR Y VENDER Y VICEVERSA, E IGUALMENTE CERTIFICACIONES SOBRE LA LINEA COMPLETA DE NUESTROS PRODUCTOS, A CUYO OBJETO LO FACULTO PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS PASOS NECESARIOS,

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 13

PRESENTAR SOLICITUDES, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPLOTACIONES, SOLICITAR TESTIMONIOS, RECIBIR DOCUMENTOS, FORMULAR APELACIONES Y RECLAMOS, DESISTIR Y PERCIBIR. ASI MISMO DICHO APODERADO ESTA AUTORIZADO PARA HACER CUANTO FUERE NECESARIO ANTE LAS AUTORIDADES ADMINISTRATIVAS PARA LOS FINES ARRIBA INDICADOS CON TODAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE FUEREN NECESARIAS INCLUIDAS LAS DE SUSTITUIR Y DELEGAR EL PRESENTE PODER SI LO ESTIMARE CONVENIENTE Y EN CASO NECESARIO REVOCAR DICHAS SUSTITUCIONES. PUDIENDO ATENDER ASI MISMO LAS NOTIFICACIONES QUE DIRECTA O INDIRECTAMENTE SE GENERE DE LOS ACTOS, ACTUACIONES, DILIGENCIAS O GESTIONES QUE TENGAN RELACION DE CAUSALIDAD POR LOS SUSODICHOS TRAMITES Y 3) EN GENERAL PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. ANTONIO JAIRO RAMIREZ ECHAVE SE CENIRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O SU REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA:

QUE POR ESCRITURA NRO. 6224 DEL 15 DE DICIEMBRE DE 2004 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 17 DE ENERO DE 2005 BAJO EL NRO. 3 DEL LIBRO V MEDIANTE LA CUAL CONCEDE PODER ESPECIAL PERO AMPLIO Y SUFICIENTE A DIEGO PEREZ MENDOZA MAYOR DE EDAD, VECINO DE BOGOTA, IDENTIFICADO CON CEDULA DE CIUDADANIA NUMERO 16.820.530 DE CALI, COMO SU REPRESENTANTE CON PODER ESPECIAL, AMPLIO Y SUFICIENTE, PARA REALIZAR TODOS LOS TRAMITES RELACIONADOS CON EL PROCEDIMIENTO DE OTORGAMIENTO DE LICENCIA DE VENTA DE LOS PRODUCTOS AGRICOLAS DE LA SOCIEDAD, CON FACULTAD PARA FIRMAR TODO TIPO DE DOCUMENTOS, SOLICITUDES, REQUERIMIENTOS, MEMORIALES RESPUESTAS, ACLARACIONES BIEN SEA ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO ICA, MINISTERIO DEL MEDIO AMBIENTE, MINISTERIO DE PROTECCION SOCIAL O ANTE LAS AUTORIDADES GUBERNAMENTALES COMPETENTES EN LO RELACIONADO CON LOS TRAMITES QUE PERMITAN LA COMERCIALIZACION DE ESE TIPO DE PRODUCTOS. LA FACULTAD TAMBIEN COMPRENDERA LA DE NOTIFICARSE, RESPONDER E INTERPONER RECURSOS DE TODO TIPO DE ACTO ADMINISTRATIVO. EL APODERADO SUSCRIBIRA TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A LA SOCIEDAD ANTE LAS AUTORIDADES MENCIONADAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA A NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. EL APODERADO SE CE?IRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

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PAGINA No. 14

CERTIFICA:

QUE POR ESCRITURA NRO. 4265 DEL 16 DE SEPTIEMBRE DE 2005 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE OCTUBRE DE 2005 BAJO EL NRO. 168 DEL LIBRO V EL SE?OR JUAN BAUTISTA DE LOS RIOS GUTIERREZ MAYOR DE EDAD, DOMICILIADO EN CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 17108621 DE BOGOTA, QUIEN ACTUA EN SU CALIDAD DE REPRESENTANTE LEGAL DE TECNOQUIMICAS S. A. SOCIEDAD COMERCIAL ORGANIZADA Y EXISTENTE CONFORME A LAS LEYES COLOMBIANAS, CON DOMICILIO Y SEDE PRINCIPAL EN CALI. EN DICHA CONDICION CONFIERE PODER AMPLIO Y SUFICIENTE A LAS SIGUIENTES PERSONAS: CLAUDETTE VERNOT HERNANDEZ ABOGADA TITULADA Y EN EJERCICIO, IDENTIFICADA CON LA CEDULA DE CIUDADANIA No. 51722517 DE BOGOTA, PORTADORA DE LA TARJETA PROFESIONAL DE ABOGADO No. 57111 DEL C.S. DE LA J., ANDRES FELIPE ZAPATA OCAMPO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79598546 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 107240 DEL C.S. DE LA J. Y JUAN MANUEL SERRANO CASTILLO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79875670 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 124953 DE C.S. DE LA J., TODOS CON DOMICILIO EN LA CIUDAD DE BOGOTA, D.C., PARA QUE EN NOMBRE DE MI REPRESENTADA ACTUEN EN TODOS LOS ASUNTOS DE PROPIEDAD INTELECTUAL Y LOS DERIVADOS DE ELLA, CON FACULTAD PARA RECIBIR NOTIFICACIONES, NOMBRAR APODERADOS JUDICIALES O EXTRAJUDICIALES EN ESTOS ASUNTOS.

EL PRESENTE PODER SE CONFIERE PARA QUE LOS APODERADOS ACTUEN ANTE CUALQUIER PERSONA O AUTORIDAD ADMINISTRATIVA DEL ORDEN NACIONAL, DEPARTAMENTAL, DISTRITAL Y LOCAL; ANTE LAS AUTORIDADES CONTENCIOSO ADMINISTRATIVAS Y JUDICIALES, PARA OBTENER LA PROTECCION DE NUESTRA PROPIEDAD INTELECTUAL Y CONTRA LAS PRACTICAS RESTRICTIVAS DE LA COMPETENCIA Y LOS ASUNTOS DE COMPETENCIA DESLEAL, A CUYO EFECTO LA AUTORIZO, EN TODO LO CONCERNIENTE A LOS SIGUIENTES ASUNTOS: A) OBTENCION DE PATENTES DE INVENCION, DE MODELO DE UTILIDAD, ESQUEMAS DE TRAZADOS DE CIRCUITOS INTEGRADOS, DISE?OS INDUSTRIALES, EL REGISTRO DE MARCAS DE PRODUCTOS O SERVICIOS; LEMAS COMERCIALES; DEPOSITO DE NOMBRES Y ENSE?AS COMERCIALES, INDICACIONES GEOGRAFICAS; RENOVACION DE SIGNOS DISTINTIVOS, RENOVACIONES, AFECTACIONES AL REGISTRO, INSCRIPCION DE CONTRATOS, SOLICITUD Y RENOVACION DE NOMBRES DE DOMINIO; B) PRESENTACION DE OPOSICIONES AL REGISTRO DE MARCAS DE TERCERO, PRESENTACION DE ALEGATOS EN DEFENSA DE OPOSICIONES AL REGISTRO, ACCION DE CANCELACION, ACCION POR INFRACCION DE DERECHOS, REVOCATORIA DIRECTA, ACCION DE NULIDAD, ACCION DE NULIDAD Y RESTABLECIMIENTO DEL DERECHO, ACCION REIVINDICATORIA, ACCIONES DE TUTELA, POPULARES, DE GRUPO, DE CLASE; ACCIONES Y PROCESOS QUE PROMOVAMOS O SE NOS PROMUEVAN; C) AGOTAMIENTO DE LA VIA GUBERNATIVA, EJERCICIO DEL DERECHO DE PETICION ANTE CUALQUIER PERSONA O AUTORIDAD; D) SOLICITUD DE MEDIDAS CAUTELARES, PRESENTACION DE ACCIONES MEDIANTE PROCESOS CIVILES, PENALES, ADMINISTRATIVOS O CONTENCIOSO ADMINISTRATIVOS RELACIONADOS CON ESTOS DERECHOS U OTROS DE DIFERENTE NATURALEZA, MEDIDAS EN FRONTERA, ACCIONES Y PROCESOS QUE PROMOVAMOS O SE NOS PROMUEVAN; E) OBTENER Y TRAMITAR TODO LO RELACIONADO CON EL RECONOCIMIENTO DE DERECHOS DE AUTOR, DERECHOS CONEXOS Y NUEVAS TECNOLOGIAS Y SU PROTECCION LEGAL; F) SOLICITUD DE REGISTRO Y RENOVACION DE CONTRATOS DE TRANSFERENCIA DE TECNOLOGIA; G) OBTENER Y TRAMITAR TODO LO RELACIONADO CON

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LICENCIAS DE FUNCIONAMIENTO, REGISTROS SANITARIOS, AUTORIZACION DE CERTIFICADOS DE LIBRE VENTA, AUTORIZACION DE PUBLICIDAD ANTE EL MINISTERIO DE PROTECCION SOCIAL O EL INVIMA O ANTE CUALQUIER AUTORIDAD SANITARIA; H) OBTENCION DE CERTIFICADOS DE CARENCIA DE INFORMES POR TRAFICO DE ESTUPEFACIENTES. RENOVACIONES, AUTORIZACIONES EXTRAORDINARIAS ANTE LA DIRECCION NACIONAL DE ESTUPEFACIENTES O EL CONSEJO NACIONAL DE ESTUPEFACIENTES; I) SOLICITUD DE AUTORIZACIONES PARA PROMOCIONES, RIFAS Y JUEGOS ANTE ETESA O ANTE LAS AUTORIDADES COMPETENTES DEL ORDEN LOCAL, DISTRITAL O DEPARTAMENTAL; Y EN GENERAL CUALQUIERA OTRA PETICION ANTE LAS AUTORIDADES ADMINISTRATIVA, ASI COMO PARA NOTIFICARSE DE CUALQUIER PROVIDENCIA Y RENUNCIAR A TERMINOS. EN TODOS LOS ASUNTOS ARRIBA DETERMINADOS LA APODERADA QUEDA FACULTADA PARA SUSTITUIR TOTAL O PARCIALMENTE ESTE MANDATO, TRANSIGIR, CONCILIAR EXTRAJUDICIAL O JUDICIALMENTE, ADMITIR LOS HECHOS DEL PROCESO PERO NO PARA CONFESAR, DESISTIR, CANCELAR, RECIBIR, RENUNCIAR Y RATIFICAR LOS ACTOS DE AGENTES OFICIOSOS.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 22 DE MAYO DE 2008 DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE JUNIO DE 2008 BAJO EL NRO. 90 DEL LIBRO V Y MODIFICADO POR DOCUMENTO PRIVADO DE FECHA 18 DE JULIO DE 2008, INSCRITA EN LA CAMARA DE COMERCIO EL 08 DE AGOSTO DE 2008 BAJO EL NRO. 151 DEL LIBRO V, SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A LOS SIGUIENTES FUNCIONARIOS DE LA EMPRESA:

1. ANA MAR?A ?LVAREZ R., CON C.C. 31.170.896 DE CALI Y JORGE ENRIQUE GIRALDO, CON C.C. 16.784.794 DE CALI, OBRARAN COMO APODERADOS ESPECIALES PARA EL DESARROLLO DE LAS SIGUIENTES FACULTADES:

A. SUSCRIBIR LOS CONTRATOS DE TRABAJO, SUS MODIFICACIONES Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE A TECNOQU?MICAS S.A.

B. SUSCRIBIR CONTRATOS DE APRENDIZAJE Y PASANTIAS ASI COMO SUS MODIFICACIONES Y ADICIONES.

C. SUSCRIBIR ACUERDOS CON LOS EMPLEADOS DE LA SOCIEDAD.

D. COMPARECER DIRECTAMENTE U OTORGAR PODER PARA ATENDER RECLAMACIONES Y PROCESOS DE ORDEN LABORAL BIEN SEA DE CAR?CTER ADMINISTRATIVO O JUDICIAL ANTE LAS OFICINAS REGIONALES DE TRABAJO, MINISTERIO DE LA PROTECCI?N SOCIAL Y ANTE CUALQUIER OTRA AUTORIDAD O ENTIDAD ANTE LA QUE SE INICIE Y TRAMITE PROCEDIMIENTOS DE CAR?CTER LABORAL O RELACIONADOS CON TEMAS DE LA SEGURIDAD SOCIAL.

E. FIRMAR TODOS LOS DOCUMENTOS Y ATENDER TODOS LOS TR?MITES ANTE LAS CAJAS DE COMPENSACI?N FAMILIAR, EMPRESAS PRESTADORAS DE SERVICIOS DE SALUD (EPS), FONDOS DE PENSIONES Y CESANT?AS, ADMINISTRADORA DE RIESGOS PROFESIONALES (ARP), INSTITUTO DE LOS SEGUROS SOCIALES (ISS). ESTA FACULTAD TAMBI?N COMPRENDE

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LA DESIGNACION DE APODERADOS.

F. ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, DECLARACIONES DE PARTE Y RENDICION DE TESTIMONIOS DENTRO DE LOS PROCESOS DE LA JURISDICCION LABORAL Y TRAMITES ADMINISTRATIVOS, CUANDO ELLO SEA REQUERIDO.

G. RESPONDER LAS DEMANDAS DE TUTELA DIRECTAMENTE O A TRAVES DE APODERADO ESPECIAL.

H. SUSCRIBIR LOS CONTRATOS DE TODO TIPO CON ENTIDADES EDUCATIVAS DE TODO ORDEN, SIN LIMITACION DE CUANTIA.

I. SUSCRIBIR LOS DOCUMENTOS Y ESCRITURAS DE DONACION QUE SEAN AUTORIZADAS POR LA JUNTA DIRECTIVA, SIN LIMITACION ALGUNA.

J. SUSCRIBIR TODOS LOS CONTRATOS DE CONSTRUCCION, INSTALACION, SERVICIOS, REPARACIONES Y ADECUACIONES QUE SE REALICEN Y PRESTEN EN LA PLANTA Y SEDE ADMINISTRATIVA DE TECNOQUIMICAS S.A. LOCALIZADAS EN CALI, HASTA POR LA SUMA EQUIVALENTE A TRESCIENTOS (300) SALARIOS MINIMOS LEGALES MENSUALES, DARLOS POR TERMINADO POR CUALQUIER CAUSA, PRESENTAR RECLAMOS ANTE LAS COMPAÑIAS ASEGURADORAS, EXIGIR EL PAGO DE MULTAS E INDEMNIZACIONES DE CUALQUIER TIPO QUE ESTEN PACTADAS EN LOS RESPECTIVOS CONTRATOS Y EL CUMPLIMIENTO DE ELLOS.

K. ANTE EL MINISTERIO DEL MEDIO AMBIENTE Y ORGANISMOS DE CONTROL AMBIENTAL DEL ORDEN NACIONAL, DEPARTAMENTAL Y MUNICIPAL O DISTRITAL: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TRAMITES QUE LA SOCIEDAD TECNOQUIMICAS S.A. REQUIERA ADELANTAR ANTE LA ENTIDAD, ASÍ COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CARACTER JUDICIAL O GUBERNATIVO.

L. SUSCRIBIR LOS CONTRATOS DE PRENDA SOBRE VEHICULOS DE PROPIEDAD DE TERCEROS PARA RESPALDAR LOS PRESTAMOS QUE LA EMPRESA OTORQUE Y TODO LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA SU FORMALIZACION ANTE LAS SECRETARIAS DE TRANSITO Y/O MOVILIDAD DE LOS RESPECTIVOS MUNICIPIOS. ESTE PODER TAMBIEN COMPRENDE LA CANCELACION DE LAS PRENDAS Y LA FIRMA DE TODOS LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA TAL FIN.

M. FORMULAR PETICIONES RELACIONADAS CON LAS FACULTADES OTORGADAS ANTE CUALQUIER AUTORIDAD.

PARAGRAFO I. EN LA ATENCION DE TODOS LOS ASUNTOS MENCIONADOS TENDRA LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARACTER JUDICIAL, GUBERNATIVO, TRIBUNALES DE ARBITRAMIENTO Y RECLAMOS ANTE LAS COMPAÑIAS ASEGURADORAS.

PARAGRAFO II. LOS APODERADOS EJERCERAN SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACION.

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2. JORGE ENRIQUE ARIZA BERNAL, IDENTIFICADO CON LA C?DULA DE CIUDADAN?A NO. 19.494.493 DE BOGOT?, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES:

A. ANTE EL MINISTERIO DEL MEDIO AMBIENTE: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TR?MITES QUE LA SOCIEDAD TECNOQU?MICAS S.A. REQUIERA ADELANTAR ANTE LA ENTIDAD, AS? COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CAR?CTER JUDICIAL O GUBERNATIVO.

B. ANTE LA SUPERINTENDENCIA DE VIGILANCIA: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, OTORGAR PODERES, RENDIR DECLARACIONES, ATENDER VISITAS, FIRMAR LAS ACTAS CORRESPONDIENTES Y NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TR?MITES QUE LA SOCIEDAD TECNOQU?MICAS S.A. REQUIERA ADELANTAR ANTE LA ENTIDAD, AS? COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CAR?CTER JUDICIAL O GUBERNATIVO.

C. ANTE EL FONDO NACIONAL DE ESTUPEFACIENTES Y DIRECCI?N NACIONAL DE ESTUPEFACIENTES FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TR?MITES QUE LA SOCIEDAD TECNOQU?MICAS S.A. REQUIERA ADELANTAR ANTE LAS CITADAS ENTIDADES, SUSCRIBIR LAS ACTAS DE VISITA, Y DESIGNAR APODERADOS PARA NOTIFICARSE DE ACTOS ADMINISTRATIVOS, INICIAR O RESPONDER PROCESOS DE CAR?CTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

D. EN TODO LO RELACIONADO CON LOS TR?MITES DE IMPORTACIONES Y EXPORTACIONES, SEG?N SE INDICA:

I. OTORGAR PODERES Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS ADMINISTRACIONES DE ADUANAS DE LA DIRECCI?N DE IMPUESTOS Y ADUANAS - DIAN - AS? COMO RENDIR DECLARACIONES, ATENDER VISITAS E INSPECCIONES Y FIRMAS LAS CORRESPONDIENTES ACTAS ATENDER DIRECTAMENTE, CUANDO ELLO SEA REQUERIDO Y EN GENERAL OBRAR COMO APODERADO ESPECIAL ANTE LAS AUTORIDADES ADUANERAS EN TODAS LAS OPERACIONES RELACIONADAS CON EL COMERCIO EXTERIOR.

II. OTORGAR PODERES Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS SOCIEDADES PORTUARIAS DE BUENAVENTURA, CARTAGENA Y BARRANQUILLA, AS? COMO RESPONDER Y ATENDER LOS TR?MITES DIRECTAMENTE O A TRAV?S DE APODERADOS.

III- OTORGAR PODERES ESPECIALES Y GENERALES, OTORGAR GARANT?AS Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS NAVIERAS Y EMPRESAS ADMINISTRADORAS DE CONTENEDORES PARA EL MANEJO Y RETIRO DE ELLOS.

IV. OTORGAR PODERES ESPECIALES Y GENERALES A LAS SOCIEDADES DE INTERMEDIACI?N ADUANERA - SIA- Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN

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DE ACUERDA CON LA NORMATIVIDAD LEGAL SOBRE LA MATERIA.

V. SUSCRIBIR LAS CARTAS DE ANTINARCOTICOS QUE SE PRESENTAN ANTE LA POLICIA AEROPORTUARIA BIEN DIRECTAMENTE O AUTORIZANDO A LOS JEFES DE BODEGA DE YUMBO Y JAMUND? PARA ESE TRAMITE DOCUMENTOS DENTRO DE LOS TRAMITES DE EXPORTACIONES O REEMBARQUES DE MERCANCAS, Y EN GENERAL ATENDER TODAS LAS DILIGENCIAS DIRECTAMENTE U OTORGAR PODER AUN TERCERO.

D. SUSCRIBIR CONTRATOS DE CONSTRUCCION Y DE OBRA QUE SE REALICEN Y PRESTEN EN LAS PLANTAS DE TECNOQUIMICAS S.A. LOCALIZADAS EN JAMUND?, YUMBO Y VILLA RICA (DEPARTAMENTO DEL CAUCA EN EL CONJUNTO INDUSTRIAL PARQUESUR) HASTA POR LA SUMA EQUIVALENTE A TRESCIENTOS (300) SALARIOS MINIMOS LEGALES MENSUALES.

E. SUSCRIBIR CONTRATOS, SIN LIMITACION DE CUANTIA QUE TENGA QUE VER CON LA ADQUISICION DE EQUIPO Y MAQUINARIA, REPARACION, ADECUACION, INSTALACION, SERVICIOS TECNICOS Y DE ASESORIA.

E. SUSCRIBIR CONTRATOS DE FABRICACION CON TERCEROS BIEN SEA QUE TECNOQUIMICAS OBRE COMO FABRICANTE O COMO PROPIETARIO.

PARAGRAFO. EN LA ATENCION DE TODOS LOS ASUNTOS MENCIONADOS TENDRA LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARACTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

3. MARA TERESA CAON DE GUZMAN, IDENTIFICADA CON LA Cedula DE CIUDADANA NO. 31.238.104 DE CALI, CARLOS ARTURO PEÑA NIETO IDENTIFICADO CON LA Cedula DE CIUDADANA NO. 19.483.439 DE BOGOT? Y ANGELA MARA CORREA CARDONA IDENTIFICADA CON LA Cedula DE CIUDADANA NO. 66.835.555 DE CALI, LA PRIMERA COMO PRINCIPAL, EL SEGUNDO COMO PRIMER SUPLENTE Y LA TERCERA COMO SEGUNDA SUPLENTE, PARA QUE REPRESENTEN A TECNOQUIMICAS S.A. EN:

A. EN TODOS LOS ASUNTOS CAMBIARIOS, CON FACULTAD PARA FIRMAR DECLARACIONES DE CAMBIOS SEA POR CREDITOS EN MONEDA EXTRANJERA, POR MOVIMIENTOS DE LA CUENTAS CORRIENTES DE COMPENSACION, IMPORTACIONES DE BIENES Y SERVICIOS, TRANSFERENCIAS Y OTROS CONCEPTOS, REGISTRO DE PRSTAMOS EN MONEDA EXTRANJERA OTORGADOS A LA EMPRESA EN SU CONDICION DE RESIDENTE Y TODOS AQUELLOS DOCUMENTOS, DECLARACIONES O RESPUESTAS A REQUERIMIENTOS QUE DEBAN HACERSE ANTE EL BANCO DE LA REPUBLICA U OTRAS ENTIDADES GUBERNAMENTALES RESPECTO DE OPERACIONES EN EL MERCADO CAMBIARIO.

LOS APODERADOS SUSCRIBIRAN TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A LA SOCIEDAD ANTE LAS AUTORIDADES CAMBIARIAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL, PARA QUE ASUMAN LA PERSONERA A NOMBRE DE TECNOQUIMICAS S.A., BIEN SEA DIRECTAMENTE O A TRAVES DE APODERADO, SIEMPRE QUE LO ESTIMEN CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS

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DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES DE CAR?CTER CAMBIARIO Y EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER.

B. EN RELACI?N CON SECTOR FINANCIERO:

I. SUSCRIBIR LOS CONTRATOS DE CR?DITO Y LEASING CON LOS BANCOS, ENTIDADES FINANCIERAS, COMPA??AS DE FINANCIAMIENTO COMERCIAL, DE ACUERDO CON LOS CUPOS FIJADOS POR LA JUNTA DIRECTIVA, AS? COMO LOS PAGAR?S, LOS CONTRATOS DE GARANT?A PRENDAR?A E HIPOTECARIA, LA CONFIRMACI?N DE FORWARDS Y TODOS LOS DEM?S DOCUMENTOS QUE SEAN REQUERIDOS PARA LA CULMINACI?N Y FORMALIZACI?N DE ESTOS TR?MITES.

ESTAS FACULTADES IGUALMENTE APLICAN PARA TODOS LOS CR?DITOS QUE OTORQUE EL BANCO DE COMERCIO EXTERIOR DE COLOMBIA - BANCOLDEX.

II. SUSCRIBIR LOS FORMATOS Y CONTRATOS DE APERTURAS DE CUENTAS CORRIENTES, AHORROS, SERVICIOS DE BANCA VIRTUAL, LOS FORMATOS DE PROVEEDORES PARA PAGOS POR TRANSFERENCIA ELECTR?NICA Y LOS FORMULADOS ?NICOS DE CONOCIMIENTO DE PERSONA JUR?DICA QUE EXIGE EL SECTOR FINANCIERO.

III. SUSCRIBIR LAS LETRAS DE COBRANZA Y LAS CARTAS DE CR?DITO.

C. SOLICITAR TIDIS Y FIRMAR TODOS LOS DOCUMENTOS RELACIONADOS CON ESTE TR?MITE.

D. EN RELACI?N CON LA COMPA??AS ASEGURADORAS:

I. SUSCRIBIR DOCUMENTOS DE RECLAMACI?N Y OTORGAR PODERES PARA QUE COMPAREZCAN A LAS AUDIENCIAS DE RECLAMACIONES, AS? COMO LOS DOCUMENTOS DE TRANSACCI?N. ESTAS FACULTADES SE OTORGAN SIN LIMITACI?N DE CUANT?A.

II. SUSCRIBIR LAS CARTAS DE NO RECLAMACI?N A LAS COMPA??AS ASEGURADORAS POR OCURRENCIA DE SINIESTROS Y LAS RESPECTIVAS CONSTANCIAS.

III. SUSCRIBIR LOS DOCUMENTOS REQUERIDOS POR EL SISTEMA DE INFORMACI?N PARA LA PREVENCI?N DE LAVADO DE ACTIVOS (SIPLA).

E. FORMULAR PETICIONES RELACIONADAS CON LAS FACULTADES OTORGADAS.

PAR?GRAFO 1. EN LA ATENCI?N DE TODOS LOS ASUNTOS MENCIONADOS TENDR? LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CAR?CTER JUDICIAL O GUBERNATIVO.

PAR?GRAFO II. LOS APODERADOS EJERCER?N SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACI?N.

4. ADRIANA JIM?NEZ MERA, IDENTIFICADA CON LA C.C. 31.174.077 DE PALMIRA, PARA EL DESARROLLO DE LAS SIGUIENTES FUNCIONES:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

Hora Certificado 11:48:54

Operacion : 02CP20827018

PAGINA No. 20

A. OTORGAR PODER Y CONSTITUIR MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON LAS DEUDAS A FAVOR DE TECNOQUIMICAS S. A.

B. SUSCRIBIR LOS CONTRATOS DE ARRENDAMIENTO DE INMUEBLES, SU MODIFICACION Y O TERMINACION, INVENTARIOS Y ANEXOS PERTINENTES, BIEN SEA QUE LA SOCIEDAD OBRE COMO ARRENDADOR O ARRENDATARIO, SIN LIMITACION DE CUANTIA. ESTA FUNCION LA PODRA EJERCER DIRECTAMENTE O MEDIANTE LA DESIGNACION DE APODERADOS.

C. SUSCRIBIR LOS FORMATOS DE AUTORIZACION DE CREACION DE CLIENTES Y PROVEEDORES DE LA EMPRESA.

D. EN RELACION CON LOS VEHICULOS DE TODO TIPO QUE FIGUREN A NOMBRE DE TECNOQUIMICAS, TIENE LA FACULTAD DE SUSCRIBIR LOS FORMULARIOS OFICIALES PARA TODO TIPO DE TRAMITE, ENTRE ELLOS EL TRASPASO, QUE SE REQUIERA REALIZAR, ANTE LAS SECRETARIAS DE TRANSITO Y ANTE LAS AUTORIDADES DE TRANSITO Y TRANSPORTE DE CUALQUIER ORDEN, ASÍ COMO FIRMAR TODO TIPO DE CONTRATOS RELACIONADOS CON LOS VEHICULOS.

PARAGRAFO. EN LA ATENCION DE TODOS LOS ASUNTOS MENCIONADOS TENDRA LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARACTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

ESTOS PODERES ESTARAN VIGENTES HASTA TANTO SEAN REVOCADOS O MODIFICADOS
EXPRESAMENTE POR DOCUMENTO PRIVADO.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 10 DE JULIO DE 2008 DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 29 DE JULIO DE 2008 BAJO EL NRO. 141 DEL LIBRO V, SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A LOS SIGUIENTES FUNCIONARIOS DE LA EMPRESA:

- GERMAN ALBERTO SUAREZ HINCAPIE, C.C. 16.722.521 DE CALI, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL CENTRO PACIFICO DE LA SOCIEDAD, CON SEDE EN CALI.

- MARIA VICTORIA VARGAS PORRAS, C.C. 39.638.185 DE BOGOTA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA D.C.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

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PAGINA No. 21

- ESPERANZA GRANADOS JAIMES, C.C. 63.392.189 DE MALAGA (SANTANDER), SUBGERENTE ADMINISTRATIVO DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA D.C.

- DIEGO FERNANDO MUÑOZ QUINTERO, C.C. 94.282.452 DE CALI, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ANTIOQUIA DE LA SOCIEDAD, CON SEDE EN MEDELLIN.

- CARLOS ORLANDO MUTIS PICON, C.C. 91.200.418 DE BUCARAMANGA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ORIENTE DE LA SOCIEDAD, CON SEDE EN BUCARAMANGA.

- DANIEL AMEZQUITA LIZARAZO, C.C. 8.681.962 DE BARRANQUILLA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ATLANTICO DE LA SOCIEDAD, CON SEDE EN BARRANQUILLA.

LOS MENCIONADOS FUNCIONARIOS EJERCERAN, EN SUS RESPECTIVAS REGIONALES, LAS SIGUIENTES FACULTADES:

1. PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A., Y EN ASUNTOS QUE TENGA QUE VER CON SUS RESPECTIVOS DISTRITOS DE VENTAS SE NOTIFIQUEN Y PROMUEVAN ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES, DISTRITALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE.

PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES.

2. PARA QUE OTORGUEN PODERES Y CONSTITUYAN MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION E INTERROGATORIOS DE PARTE, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVOS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO, CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR.

3. PARA QUE OTORQUE PODERES Y CONSTITUYAN MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

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PAGINA No. 22

EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LOS INTERROGATORIOS DE PARTE, A LAS DIVERSAS AUDIENCIAS, ENTRE ELLAS LAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES, JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO.

4. PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO Y EXPEDIR CERTIFICACIONES LABORALES.

5. PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A., EN NINGUN CASO, QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES Y A ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DILIGENCIAS DE INTERROGATORIOS DE PARTE.

6. SUSCRIBIR LOS CONTRATOS DE PRENDA SOBRE VEHICULOS DE PROPIEDAD DE TERCEROS PARA RESPALDAR LOS PRESTAMOS QUE LA EMPRESA OTORGUE Y TODO LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA SU FORMALIZACION ANTE LAS SECRETARIAS DE TRANSITO Y/O MOVILIDAD DE LOS RESPECTIVOS MUNICIPIOS. ESTE PODER TAMBIEN COMPRENDE LA CANCELACION DE LAS PRENDAS Y LA FIRMA DE TODOS LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA TAL FIN.

7. PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO ADQUIERA Y ENAJENE TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD.

ESTOS PODERES ESTARAN VIGENTES HASTA TANTO SEAN REVOCADOS O MODIFICADOS
EXPRESAMENTE POR DOCUMENTO PRIVADO.

CERTIFICA:

CAPITAL AUTORIZADO: \$27,200,000,000
NUMERO DE ACCIONES: 54,400,000
VALOR NOMINAL: \$500
CAPITAL SUSCRITO: \$27,123,804,000
NUMERO DE ACCIONES: 54,247,608
VALOR NOMINAL: \$500
CAPITAL PAGADO: \$27,123,804,000
NUMERO DE ACCIONES: 54,247,608
VALOR NOMINAL: \$500

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Operacion : 02CP20827018 PAGINA No. 23

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

Hora Certificado 11:48:54

Operacion : 02CP20827018

PAGINA No. 24

UNIDAD DE PROPOSITO Y DIRECCION YA QUE LOS PLANES Y OBJETIVOS DE ESTA ULTIMA
ESTAN DETERMINADAS POR LA PRIMERA.

DE IGUAL MANERA SE CONCRETA EL CONTROL ADMINISTRATIVO SOBRE LA FILIAL A TRAVES
DE LA GERENCIA Y LA JUNTA DIRECTIVA CUYOS MIEMBROS PRINCIPALES HACEN PARTE
IGUALMENTE DE LA JUNTA Y ADMINISTRACION DE LA MATRIZ.

CERTIFICA:

QUE EL 27 DE MARZO DE 2001 BAJO EL NRO.1979 DEL LIBRO IX, SE INSCRIBIO EN LA
CAMARA DE COMERCIO UN DOCUMENTO PRIVADO DE FECHA MARZO 21 DE 2001, EN LA CUAL
CONSTA LA SITUACION DE CONTROL EJERCIDA POR LA SOCIEDAD TECNOQUIMICAS S.A.

MATRIZ: TECNOQUIMICAS S.A.

DOMICILIO: SANTIAGO DE CALI.

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE TECNOQUIMICAS CORRESPONDEN A LA PRODUCCION Y
COMERCIALIZACION DE PRODUCTOS BIOLOGICOS, QUIMICOS, MEDICAMENTOS Y PRODUCTOS
FARMACEUTICOS, PANALES, PRODUCTOS VETERINARIO Y AGRICOLAS, ALIMENTOS,
COSMETICOS Y DE TOCADOR Y PRODUCTOS DE ASEO PARA EL HOGAR.

SUBORDINADA: ADHESIVOS INTERNACIONALES S.A.- ADHINTER S.A. DOMICILIO: CALI
VALLE DEL CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE ADHINTER S.A. SE DESARROLLAN EXCLUSIVAMENTE EN
LA ZONA FRANCA DEL PACIFICO CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION EN
EL MERCADO NACIONAL E INTERNACIONAL DE ADHESIVOS MEDICINALES TALES COMO CURAS,
VENDITAS, ESPARADRAPOS, PARCHES, VENDAS; ADHESIVOS PARA USO EN OFICINA TALES
COMO CINTAS, PEGANTES, PAPELES ADHESIVOS Y CINTAS ADHESIVAS PARA USO
INDUSTRIAL.

PRESUPUESTO DE CONTROL: TECNOQUIMICAS S.A., TIENE SUSCRITAS EN LA SOCIEDAD
ADHESIVOS INTERNACIONALES S.A. ADHINTER S.A., LA CANTIDAD DE DOS MILLONES
CUATROCIENTOS TREINTA MIL (2.430.000) ACCIONES ORDINARIAS DE VALOR NOMINAL DE
CIEN PESOS (\$100.00) SOBRE UN TOTAL DE TRES MILLONES (3.000.000) DE ACCIONES
ORDINARIAS SUSCRITAS QUE REPRESENTA UNA PARTICIPACION DIRECTA DEL 81% SOBRE EL
TOTAL DEL CAPITAL SUSCRITO Y PAGADO DE LA SOCIEDAD.

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.7050-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: ---C 23 7 39 DE CALI
RENOVO : POR EL AÑO 2008

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827 Hora Certificado 11:48:54

Operacion : 02CP20827018 PAGINA No. 25

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.311234-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: -K 7 22 122 DE CALI
FECHA MATRICULA : 22 DE ABRIL DE 1992
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.311235-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: -C 23 4 66 DE CALI
FECHA MATRICULA : 22 DE ABRIL DE 1992
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.606730-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A JAMUNDI
UBICADO EN: --CARRETERA JAMUNDI KM. 23 DE JAMUNDI
FECHA MATRICULA : 14 DE ABRIL DE 2003
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.606736-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A YUMBO
UBICADO EN: --CL. 15 NRO. 30 98 AUTOPISTA CALI-YUMBO KILOMETRO 4 DE YUMBO
FECHA MATRICULA : 14 DE ABRIL DE 2003
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 29 DE
MARZO DE 2008 .

CERTIFICA:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

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PAGINA No. 26

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL PRESENTE CERTIFICADO.

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 27 DIAS DEL MES DE AGOSTO DEL AÑO 2008 HORA: 11:48:11



Diego Fernando Campo Sarcia

84
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176099-2

RECIBO OFICIAL DE CAJA : 09 - 68.471
FECHA : AGOSTO 28 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-096487- -00006-0000

Fecha: 2008-08-28 08:41:22 Dep. 2020 NULCRACIONI
Tra. 11 PATENTE:YII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 85

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754327	4276344	27/08/2008	1,023,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	266,000.00
		TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 990176089-2

RECIBO OFICIAL DE CAJA : 08 - 68,476
FECHA : AGOSTO 28 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-096487- -00006-0000

Fecha: 2008-08-28 08:41:22 Dep 2020 NULCRLACIONI
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act. 400 OPOSIOBSERVIER Folios: 85

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754327	4276344	27/08/2008	1,023,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	75,000.00
		TOTAL :	\$ 75,000.00

SON: SETENTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.