

Castillo Grau & Asociados

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Señores

DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá, D.C.

Re.: Código 02-01-444
Expediente No. 01046749
Solicitud de Patente
SMITHKLINE BEECHAM p.l.c.

En relación con el expediente de la referencia y dando cumplimiento a la última providencia recaída sobre este asunto por medio del presente escrito me permito manifestarles lo siguiente:

1. Adjunto a este memorial un nuevo capítulo reivindicatorio del cual se han eliminado las Reivindicaciones originales 1 a12. Las reivindicaciones 13 a 22 han sido reenumeradas como reivindicaciones 1 a 10. La reivindicación 1 ahora se refiere a una composición farmacéutica que comprende de 2 a 8 mg de Compuesto (I) o una forma farmacéuticamente aceptable de la misma y hasta 3000 mg de metformin o clorhidrato de metformin y un vehículo farmacéuticamente aceptable para el mismo.
2. El Despacho ha hecho una objeción de falta de novedad basada en los antecedentes D1 a D4. No obstante, sólo D2 es citable contra la presente solicitud. Las reivindicaciones que han sido modificadas son novedosas con respecto a D2.

lo menos una sustancia seleccionada de entre un inhibidor de la alfa-glucosidasa, un inhibidor de la reductasa de aldosa, una biguanida, una estatina, o un inhibidor de la síntesis del escualeno. Afirma que D2 contempla combinar un sensibilizador a la insulina, como la pioglitazona, y una biguanida, como el metformin.

4. D2 revela una composición farmacéutica que comprende un sensibilizador a la insulina y un agente hipoglucemiante biguanida. El compuesto (I) y el metformin se revelan como ejemplos de cada una de estas clases del agente en D2. Sin embargo, D2 no revela nada sobre la combinación específica del Compuesto (I) y metformin. Ciertamente no se hace mención de las dosificaciones específicas de 2 a 8 mg del Compuesto (I) y hasta 3000 mg de metformin. La combinación que comprende de 2 a 8 mg del Compuesto (I) y hasta 3000 mg de metformin o clorhidrato de metformin, según se define en las reivindicaciones modificadas 1 a 12, es por tanto novedosa con respecto a D2.
5. Por las mismas razones, las reivindicaciones 1 a 12 dirigidas a una composición farmacéutica que comprende de 2 a 8 mg del Compuesto (I) y hasta 3000 mg de metformin o clorhidrato de metformin son novedosas con respecto al antecedente mencionado.

6. Datos clínicos

La compañía solicitante tiene dos piezas de datos experimentales disponibles,

de las solicitudes de contraparte en otros lugares. Claramente no constituye un requisito proporcionar estas evidencias en respuesta al presente Concepto Técnico, porque no se ha suscitado una objeción contra el nivel inventivo. Sin embargo, nos gustaría que la Oficina Colombiana de Patentes tuviese en cuenta estos datos para el examen. Los dos conjuntos de datos se examinan a continuación. Sírvanse presentárselos a la Oficina Colombiana de Patentes.

7. Datos clínicos extraídos de la Solicitud de Licencia de Mercadeo para la rosiglitazona (compuesto I)

Los datos clínicos que se presentan en las figuras 1 a 4 del anexo se extraen de la Solicitud de Licencia de Mercadeo (SLM) para la rosiglitazona (compuesto I). La naturaleza inventiva de la opción específica de 2 a 8 mg del Compuesto (I) está sustentada por estos resultados experimentales. Los datos clínicos se pueden resumir de la siguiente forma:

Figura 1

Los datos se derivan de un estudio multicéntrico, doble-ciego, controlado con placebo, de grupos paralelos, de doce semanas de duración en que se valoraron seguridad, tolerabilidad y eficacia del Compuesto (I) en dosis diarias de 0,1, 0,5, 2 y 4 mg.

La Figura 1 muestra que hubo una disminución estadísticamente significativa

Los datos obtenidos de los estudios clínicos que se examinaron arriba y se ilustran en las figuras que se acompañan, respaldan en particular el intervalo de dosificación de 2 a 8 mg y las dosis individuales de 2, 4 y 8 mg de Compuesto (I). La dosificación umbral mínima para obtener el efecto beneficioso sobre el control de la glucemia es de 2 mg. Además, no se observó una mejora del control de la glucemia al aumentar la dosis diaria del Compuesto (I) de 8 a 12 mg. También se observó que los pacientes pueden tener un mayor riesgo de efectos secundarios relacionados con los fluidos cuando la dosis se aumenta más allá de los 8 mg al día.

La observación de aumento de la eficacia del control de la glucemia se ve complementada por la observación de que no sobrevinieron efectos secundarios adversos con el mismo intervalo de dosificación. Por ello, el intervalo de dosificación ofrece un perfil farmacológico aceptable de efectos secundarios. Por estas razones, las combinaciones de la presente invención permiten una administración segura y eficaz del Compuesto(I).

"Rosiglitazona" by Julia A Barman Balfour y Greg L Plosker Introducción

El artículo que se anexa, "Rosiglitazona", Drugs 1999 Jun; 57(6): 921-930, ofrece datos clínicos que ilustran el efecto provechoso de la combinación reivindicada sobre el control de la glucemia (La rosiglitazona es el presente Compuesto (I)).

los datos se obtuvieron en pacientes que tenían diabetes grave (glucemia plasmática en ayuno basal superior a 210mg/dL). El restablecimiento del control de la glucemia en estos pacientes no era predecible de ninguna manera. La adición de un segundo agente antidiabético (p.ej., 4 u 8mg de Compuesto (I)) a un primer agente (metformin) no fue garantía de éxito en el efecto y el tratamiento. Que un efecto tan pronunciado sobre el control de la glucemia se demostrase en este estudio fue sorprendente. Según esto, la combinación reivindicada de 2 a 8 mg de Compuesto (I) y hasta 3000 mg de metformin tiene nivel inventivo.

8. Respecto a D3 (EP 0861666) se divide de D2. La revelación de D3 es prácticamente idéntica a la de D2. Es cierto que no se hacen otras revelaciones relevantes a la novedad de las presentes reivindicaciones en D3 distintas de la revelación de D2. Según esto, los comentarios que se aplican a D2 también se aplican a D3.
9. La anterioridad D4 es una cartelera de resultados experimentales publicada en 1999. Hoy sabemos que esta revelación constituye parte del estado de la técnica previo a la presente solicitud. Por tanto, hemos hecho las modificaciones a las reivindicaciones que ahora anexamos con el fin de dar consideración a esta situación. D4 enseña la administración de rosiglitazona y metformin con miras a reducir la hiperglucemia en pacientes con diabetes tipo 2. No obstante, los dos agentes se dan por separado. D4 no hace mención específica de una composición farmacéutica unitaria compuesta por de 2 a 8

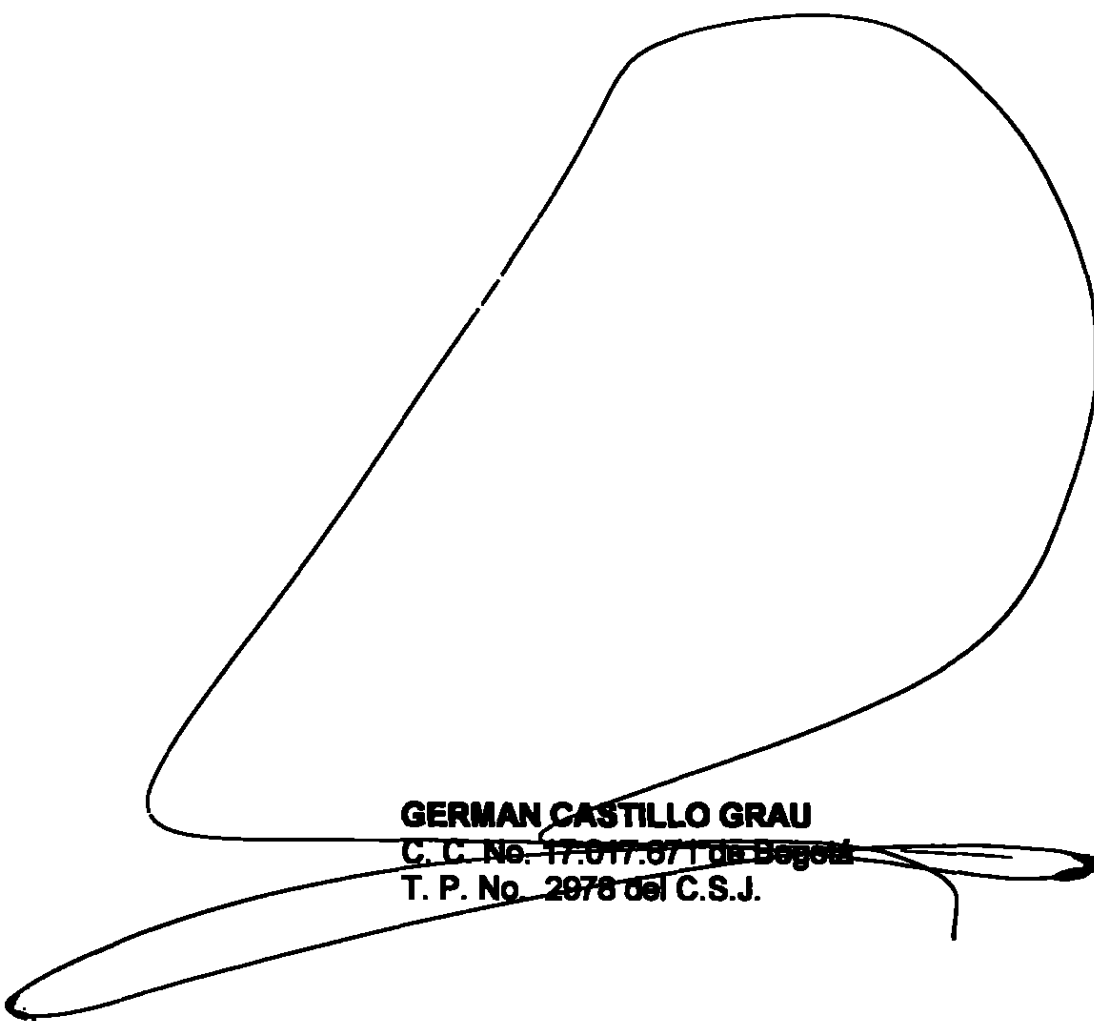
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ABOGADOS

la nueva reivindicación 1. Según esto, las reivindicaciones 1 a 10 modificadas son novedosas con respecto a D4.

Acompaño el comprobante de pago por concepto de modificación de la solicitud recibo No. 07-5,246

Renuncio al término faltante de traslado, y les solicito ordenar la publicación del extracto.

De Ustedes Atentamente,



GERMAN CASTILLO GRAU
C. C. No. 17.017.071 de Bogotá
T. P. No. 2078 del C.S.J.

REIVINDICACIONES

1. Una composición farmacéutica que comprende de 2 a 8 mg de 5-[4-[(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidine-2,4-diona (Compuesto (I)) o una forma farmacéuticamente aceptable de la misma, hasta 3000 mg de metformin o clorhidrato de metformin, y un vehículo farmacéuticamente aceptable de la misma.
2. Una composición conforme a la reivindicación 1, que comprende de 2 a 4, o de 4 a 8 mg del Compuesto (I) o una forma farmacéuticamente aceptable de la misma.
3. Una composición conforme a la reivindicación 1 o a la reivindicación 2, que comprende de 2 a 4 mg del Compuesto (I) o una forma farmacéuticamente aceptable de la misma.
4. Una composición conforme a la reivindicación 1 o a la reivindicación 2, que comprende de 4 a 8 mg del Compuesto (I) o una forma farmacéuticamente aceptable de la misma.
5. Una composición conforme cualquiera de las reivindicaciones 1 a 3, que comprende 2 mg del Compuesto (I) o una forma farmacéuticamente aceptable de la misma.
6. Una composición conforme cualquiera de las reivindicaciones 1 a 4, que comprende 4 mg del Compuesto (I) o una forma farmacéuticamente aceptable de la misma.
7. Una composición conforme cualquiera de las reivindicaciones 1, 2 y 4, que comprende 8 mg del Compuesto (I) o una forma farmacéuticamente aceptable de la misma.
8. Una composición conforme cualquiera de las reivindicaciones 1 a 7, que comprende 500 mg u 850 mg de metformin o clorhidrato de metformin.
9. Una composición conforme cualquiera de las reivindicaciones 1 a 8, en la cual el compuesto (I) se encuentra en la forma de la sal maleato.
10. Una composición conforme cualquiera de las reivindicaciones 1 a 9 para usar en el tratamiento de la diabetes mellitus o un padecimiento asociado con la diabetes mellitus.

TRATAMIENTO DE LA DIABETES CON TIAZOLIDINEDIONA Y METFORMIN

La presente invención se relaciona con el tratamiento de la diabetes mellitus, principalmente la diabetes no insulino dependiente (NIDM) o diabetes tipo 2 y los padecimientos que se asocian con la diabetes mellitus.

Los biguanida agentes antihiper glucémicos se usan comúnmente en el tratamiento de la NIDM (o diabetes tipo 2). La 1,1- Dimetilbiguanidina (o Metformin) es un ejemplo de un agente antihiper glucémico del tipo biguanida.

La solicitud de patente europea número 0,306,228 se relaciona con ciertos derivados de las tiazolidinedionas de los que se ha revelado que tienen actividad antihiper glucémica e hipolipemiante. Una tiazolidinediona particular revelada en EP 0306228 es la 5-[4-[2(N-metil-1-N-(piridil)amino)etoxi]benzil]tiazolidine-2,4-diona (en lo sucesivo 'Compuesto (I)'). WO94/05659 revela ciertas sales del Compuesto (I) incluido el maleato en su ejemplo 1.

El Compuesto (I) constituye un ejemplo de una clase de agentes antihiper glucémicos conocidos como "Sensibilizadores a la insulina". En particular, el Compuesto (I) es una tiazolidinediona sensibilizadora a la insulina.

Las solicitudes de patente europea, con números de publicación: 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; La solicitud internacional de patente, Números de publicación 92/18501, 93/02079, 93/22445 y las patentes estadounidenses números 5104888 y 5478852, también revelan ciertos sensibilizadores a la insulina del tipo tiazolidinediona.

Otra serie de compuestos generalmente reconocidos como dotados de actividad sensibilizadora a la insulina son los tipificados por los compuestos revelados en las solicitudes internacionales de patente, números de publicación WO93/21166 y WO94/01420. Estos compuestos se mencionan aquí como sensibilizadores acíclicos de la insulina. Otros ejemplos de sensibilizadores acíclicos a la insulina son los revelados en la patente estadounidense número 5232945 y en las solicitudes internacionales de patente, números de publicación WO92/03425 y WO91/19702.

Algunos ejemplos de otros sensibilizadores a la insulina son los revelados en la solicitud europea de patente, número de publicación 0533933, la solicitud japonesa de patente, número de publicación 05271204 y la patente estadounidense número 5264451.

Las publicaciones arriba mencionadas se incorporan a la presente mediante referencia.

Hoy queda indicado de forma sorprendente que el Compuesto (I) en combinación con un agente antihiper glucémico de tipo biguanida proporciona un efecto especialmente beneficioso sobre el control de la glucemia sin efectos adversos observados; dicha combinación por tanto reviste especial utilidad para el tratamiento de la diabetes mellitus, especialmente la diabetes tipo 2 y los padecimientos asociados con la diabetes mellitus. Según esto, la presente invención ofrece una combinación que comprende de 2 a 8 mg de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidine-2,4-diona (Compuesto (I)) o una forma farmacéuticamente aceptable del mismo, y hasta 3000 mg de metformin o clorhidrato de metformin.

En un aspecto, la combinación comprende de 2 a 4 ó de 4 a 8 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

Típicamente, la combinación comprende de 2 a 4 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

Típicamente, la combinación comprende de 4 a 8 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

De preferencia, la combinación comprende 2 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

De preferencia, la combinación comprende 4 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

De preferencia, la combinación comprende 8 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

De preferencia, la combinación comprende 500 mg o 850 mg de metformin o clorhidrato de metformin.

De preferencia, la composición de la presente invención comprende 500 mg o 850 mg de metformin o clorhidrato de metformin.

De preferencia, la combinación es aquella en la cual el Compuesto (I) o una forma farmacéuticamente aceptable del mismo y hasta 3000 mg metformin o clorhidrato de metformin se formulan como una composición farmacéutica única.

De preferencia, la combinación es aquella en la cual el Compuesto (I) o una forma farmacéuticamente aceptable del mismo y hasta 3000 mg metformin o clorhidrato de metformin se formulan como composiciones farmacéuticas separadas.

El método de administración de la combinación de la presente invención comprende ya sea la co-administración de Compuesto (I) o una forma farmacéuticamente aceptable del mismo, y metformin o clorhidrato de metformin o la administración secuencial de los mismos.

La co-administración incluye la administración de una formulación que comprende tanto compuesto (I) o una forma farmacéuticamente aceptable del mismo, como metformin o clorhidrato de metformin, o la administración esencialmente simultánea de formulaciones separadas de cada agente.

De preferencia, la presente invención proporciona dicha combinación para usar en el tratamiento de la diabetes mellitus o un padecimiento asociado con la diabetes mellitus.

Se entenderá que el Compuesto (I) se administra en una forma farmacéuticamente aceptable, incluidos derivados farmacéuticamente aceptables como sales farmacéuticamente aceptables, ésteres y solvatos de los mismos, según sea el caso. Se entenderá que todas las formas farmacéuticamente aceptables de los agentes activos por sí mismas se encuentra cubiertas por la presente invención.

Las formas farmacéuticamente aceptables del Compuesto (I) adecuadas incluyen las descritas en EP 0306228 y WO94/05659, en especial las formas de sales farmacéuticamente aceptables. Una sal farmacéuticamente aceptable es el maleato.

Las formas farmacéuticamente aceptables de Compuesto (I) adecuadas incluyen las descritas EP 0306228 y WO94/05659, en particular los hidratos.

El Compuesto (I), o una sal farmacéuticamente aceptable del mismo, o un solvato farmacéuticamente aceptable del mismo, se puede preparar usando métodos conocidos como, por ejemplo, los revelados en EP 0306228 y WO94/05659. Las revelaciones de EP 0306228 y WO94/05659 se incorporan a la presente mediante referencia.

El Compuesto (I) puede existir en una de varias formas tautoméricas, todas las cuales quedan cubiertas por el término Compuesto (I) como formas tautoméricas individuales o como mezclas de las mismas. El Compuesto (I) contiene un átomo de carbono quiral, y por ende puede existir en hasta dos formas estereoisoméricas, el término Compuesto (I) abarca todas estas formas isoméricas ya sea como isómeros individuales o como mezclas de isómeros, incluidos los racematos.

El Compuesto (I), las formas farmacéuticamente aceptables del mismo, el metformin y el clorhidrato de metformin se preparan conforme a métodos conocidos, los cuales métodos se encuentran o se hace referencia a ellos en los textos de consulta normales, como las Farmacopeas británica y estadounidense, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (Londres, The Pharmaceutical Press) (por ejemplo, ver la XXXI Edición en la página 341 y las páginas allí citadas) o según se describe en las publicaciones arriba mencionadas.

Cuando se usa en este contexto, el término 'padecimientos asociados con la diabetes' incluye aquellas afecciones que se asocian con el estado pre-diabético, los

padecimientos asociados con la diabetes mellitus misma y las complicaciones asociadas con la diabetes mellitus.

Cuando se usa en este contexto, el término 'padecimientos asociados con el estado pre-diabético' incluye afecciones como resistencia a la insulina, incluida la resistencia hereditaria a la insulina, deterioro de la tolerancia a la glucosa e hiperinsulinemia.

Los 'padecimientos asociados con la diabetes mellitus' misma incluyen hiperglucemia, resistencia a la insulina, incluida la resistencia adquirida a la insulina y obesidad. Otros padecimientos asociados con la diabetes mellitus misma incluyen hipertensión y enfermedad cardiovascular, en especial aterosclerosis y afecciones asociadas con resistencia a la insulina. Los padecimientos asociados con resistencia a la insulina incluyen síndrome de ovario poliquístico, resistencia a la insulina inducida por esteroides y diabetes gestacional.

Las 'complicaciones asociadas con la diabetes mellitus' incluyen enfermedad renal, en especial la enfermedad renal asociada con la diabetes tipo 2, neuropatía y retinopatía.

Las enfermedades renales asociadas con la diabetes tipo 2 incluyen nefropatía, glomerulonefritis, esclerosis glomerular, síndrome nefrótico, nefrosclerosis hipertensiva y enfermedad renal en etapa terminal.

Tal como se usa en este contexto, el término 'farmacéuticamente aceptable' abarca tanto el uso humano como el veterinario: por ejemplo el término 'farmacéuticamente aceptable' abarca un compuesto aceptable para uso veterinario.

Para evitar dudas, cuando en este contexto se hace referencia a cantidades a escala, incluidas cantidades en mg, del Compuesto (I) en una forma farmacéuticamente aceptable, la cantidad a escala a que se hace referencia es con respecto al Compuesto (I) por se: Por ejemplo 2 mg de Compuesto (I) en la forma de la sal maleato es esa cantidad de la sal maleato que contiene 2 mg de Compuesto (I).

Cuando se habla de diabetes mellitus, de preferencia es diabetes tipo 2.

El efecto especialmente beneficioso sobre el control de la glucemia proporcionado por el tratamiento de la invención está indicado por un efecto sinérgico relativo al control esperado de la suma de los efectos de los agentes activos individuales.

El control de la glucemia se puede caracterizar usando métodos convencionales como, por ejemplo, mediante la medición de un índice bastante usado de control de la glucemia como la glucosa plasmática en ayuno o la hemoglobina glucosilada (Hb A1c). Dichos índices se determinan usando metodología estándar como, por ejemplo, la descrita en: Tiescher A, Richterich, P., Schweiz. med. Wschr. 101 (1971), 345 y 390 y Frank P., "Monitoring the Diabetic Patient with Glycosylated Hemoglobin Measurements", Clinical Products 1988.

En un aspecto preferido, el nivel de dosificación de cada uno de los agentes activos cuando se usa de conformidad con el tratamiento de la invención será de menos de lo que se habría requerido de un efecto puramente aditivo sobre el control de la glucemia.

También existen indicios de que el tratamiento de la invención efectuará una mejoría con respecto a los agentes individuales, en los niveles de productos finales de la glucosilación avanzada (AGEs), leptina y lípidos séricos, incluidos el colesterol total, el colesterol de las HDL, el colesterol de las LDL incluyendo mejoras en las proporciones entre ellos, en particular una mejora de los lípidos séricos incluido el colesterol total, el colesterol de las HDL, el colesterol de las LDL incluidas mejoras de las proporciones entre los mismos.

Los medicamentos activos se administran en la forma de la composición farmacéutica. Como quedó indicado, dichas composiciones pueden incluir ambos medicamentos o sólo uno de ellos.

Según esto, en un aspecto de la invención se proporciona una composición farmacéutica que comprende de 2 a 8 mg de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidine-2,4-diona (Compuesto (I)) o una forma farmacéuticamente aceptable del mismo, hasta 3000 mg de metformin o clorhidrato de metformin y un vehículo farmacéuticamente aceptable para ellos.

Dichas composiciones se pueden preparar mezclando de 2 a 8 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo, metformin o clorhidrato de metformin y un vehículo farmacéuticamente aceptable para ellos.

En un aspecto, la composición comprende de 2 a 4 ó de 4 a 8 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

Típicamente, la composición comprende de 2 a 4 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

Típicamente, la composición comprende de 4 a 8 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

De preferencia, la composición comprende 2 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

De preferencia, la composición comprende 4 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

De preferencia, la composición comprende 8 mg de Compuesto (I) o una forma farmacéuticamente aceptable del mismo.

De preferencia, la composición de la presente invención comprende 500 mg o 850 mg de metformin o clorhidrato de metformin.

De preferencia, la presente invención proporciona dicha combinación para usar en el tratamiento de la diabetes mellitus o un padecimiento asociado con la diabetes mellitus.

Por lo general las composiciones se adaptan para administración oral. Sin embargo, se pueden adaptar para otros modos de administración como, por ejemplo, parenteral, sublingual o transdérmica.

Las composiciones pueden estar en la forma de tabletas, cápsulas, polvo, gránulos, grageas, supositorios, polvo para reconstituir, o preparaciones líquidas, como soluciones o suspensiones orales o parenterales estériles.

Con el fin de lograr la coherencia en la administración se prefiere que la composición de la invención se presente en forma de dosis unitaria.

Las formas de presentación en dosis unitaria para la administración oral pueden ser tabletas y cápsulas y pueden contener excipientes convencionales como ligantes como, por ejemplo, jarabe, acacia, gelatina, sorbitol, tragacanto, o polivinilpirrolidona; rellenos como, por ejemplo, lactosa, azúcar, almidón de maíz, fosfato de calcio, sorbitol o glicina; lubricantes para tableteado como, por ejemplo estearato de magnesio; desintegradores como, por ejemplo almidón, polivinilpirrolidona, almidón glucolato de sodio o celulosa microcristalina; o agentes humidificantes farmacéuticamente aceptables como lauril sulfato de sodio.

Las composiciones vienen de preferencia en una forma de dosis unitaria en una cantidad apropiada para la dosificación diaria pertinente.

Las dosis unitarias idóneas del Compuesto de fórmula (I) comprenden 2, 3, 4, 5, 6, 7 u 8 mg de Compuesto (I).

La composición de la invención se puede administrar de 1 a 6 veces al día, pero más de preferencia 1 ó 2 veces al día.

Las dosificaciones particulares del Compuesto (I) son 2 mg/día, 4 mg/día, incluidos 2 mg dos veces al día, y 8 mg/día, incluidos 4 mg dos veces al día.

Las dosificaciones idóneas de metformin o clorhidrato de metformin incluyen hasta 3000 mg por día, en dosis unitarias de 500 mg (por ejemplo dos o tres veces al día) u 850 mg (por ejemplo, dos veces al día), un ejemplo de una dosificación del metformin es 500 mg de una a cinco veces al día.

Así las cosas, un ejemplo de administración de la combinación de la presente invención es 4 u 8 mg de Compuesto (I) (2 mg dos veces al día o 4 mg dos veces al día, respectivamente) y 1000 mg ó 2500 mg de metformin (500 mg dos veces al día ó 500 mg cinco veces al día, respectivamente).

Las composiciones orales sólidas se pueden preparar mediante métodos convencional de mezclado, relleno o tableteado. Las operaciones de mezclado repetido se

pueden usar para distribuir el agente activo a través de esas composiciones empleando grandes cantidades de relleno. Dichas operaciones son por supuesto convencionales del estado de la técnica. Las tabletas se pueden recubrir siguiendo métodos bien conocidos de la práctica farmacéutica normal, en particular con cubierta entérica.

Las preparaciones orales líquidas pueden estar en la forma de, por ejemplo, emulsiones, jarabes o elixires, o se pueden presentar como producto seco para reconstitución con agua u otro vehículo adecuado antes del uso. Dichas preparaciones líquidas pueden contener aditivos convencionales como agentes de suspensión como, por ejemplo sorbitol, jarabe, metil celulosa, gelatina, hidroxietilcelulosa, carboximetilcelulosa, estearato de aluminio en gel, grasas hidrogenadas comestibles; agentes emulsionantes como, por ejemplo, lecitina, monooleato de sorbitán, o acacia; vehículos no acuosos (que pueden incluir aceites comestibles) como, por ejemplo, aceite de almendra, aceite de coco fraccionado, ésteres aceitosos como ésteres de glicerina, propileno glicol, o alcohol etílico; preservantes como, por ejemplo metil o p-hidroxibenzoato de propilo o ácido sórbico; y si se desea, agentes saborizantes o colorantes convencionales.

Para la administración parenteral, las formas fluidas de dosis unitarias se preparan utilizando el compuesto y un vehículo estéril y, dependiendo de la concentración utilizada, se puede o bien suspender o disolver en el vehículo. En la preparación de las soluciones el compuesto se puede disolver en agua para inyección y esterilizarlo por filtrado antes de llenar y sellar el vial o ampolla adecuados. Como ventaja, en el vehículo se pueden disolver adyuvantes como un anestésico local, un preservante y agentes amortiguadores. Para mejorar la estabilidad, la composición se puede congelar después del llenado del vial y eliminar el agua al vacío. Las suspensiones parenterales se preparan sustancialmente de la misma forma, excepto que el Compuesto (I) va suspendido en el vehículo en lugar de disuelto, y la esterilización no se puede lograr mediante filtración. El compuesto se puede esterilizar mediante exposición a óxido de etileno antes de suspenderlo en el vehículo estéril. Como ventaja, se incluye un surfactante o agente humedecedor en la composición para facilitar la distribución uniforme del compuesto.

Las composiciones pueden contener de 0,1% a 99% en peso, de preferencia de 10-60% en peso, del material activo, dependiendo del método de administración.

Si se desea, las composiciones pueden estar en la forma de un empaque acompañado de instrucciones de uso escritas o impresas.

Las composiciones se formulan siguiendo métodos convencionales, como los revelados en los textos de consulta estándar como, por ejemplo, las farmacopeas británica y estadounidense, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (Londres, The Pharmaceutical Press) (por ejemplo, ver la XXXI

Edición, página 341 y las páginas allí citadas) y Harry's Cosmeticology (Leonard Hill Books).

Un intervalo de 2 a 4 mg incluye un intervalo de 2,1 a 4 mg, 2,2 a 4 mg, 2,3 a 4 mg, 2,4 a 4 mg, 2,5 a 4 mg, 2,6 a 4 mg, 2,7 a 4 mg, 2,8 a 4 mg, 2,9 a 4 ó 3 a 4 mg.

Un intervalo de 4 a 8mg incluye un intervalo de 4,1 a 8 mg, 4,2 a 8 mg, 4,3 a 8 mg, 4,4 a 8 mg, 4,5 a 8 mg, 4,6 a 8 mg, 4,7 a 8 mg, 4,8 a 8 mg, 4,9 a 8 mg, 5 a 8 mg, 6 a 8 ó 7 a 8mg.

No se han establecido efectos toxicológicos adversos para las composiciones o métodos de la invención en los intervalos de dosificación arriba mencionados.

El siguiente ejemplo ilustra la invención pero no la limita en manera alguna.

Ejemplo

Este estudio evaluó la farmacocinética (PK) del Compuesto (I) y el metformin (M) administrados solos y en combinación. Dieciséis voluntarios de sexo masculino, con edades de 22 a 55 años, recibieron por vía oral Compuesto (I) (2 mg Q12h), M (500 mg Q12h), o la combinación, cada uno durante 4 días. El plasma recogido el 4 de cada régimen se analizó para determinar las concentraciones de Compuesto (I) y M. Las dosis orales del Compuesto (I) y M fueron seguras y bien toleradas solas o en combinación. No hubo episodios de hipoglucemia y la co-administración no redundó en un aumento de la concentración de ácido láctico.

Parámetro	M		Compuesto (I)	
[unidades]	Solo	Combinado	Solo	Combinado
ABC(0-12)	626	629	6508	6575
[ng·h/mL]	(494-866)	(418-912)	(4694-8705)	(4773-9230)
C _{máx.}	105	104	901	918
[ng/mL]	(78,9-150,2)	(76,5-139,2)	(620-1251)	(635-1344)
T _{máx.}	3,0	3,5	3,0	3,5
[horas]	(2,0-4,0)	(1,5-4,0)	(1,0-6,0)	(1,5-6,0)
T ½ [horas]	3,22	3,21	3,24	3,41
	(2,45-5,01)	(2,36-4,64)	(2,56-4,19)	(2,64-4,58)

Combinado = co-administración de compuesto (I) + M

La co-administración de Compuesto (I) y M no afectó la farmacocinética del estado de equilibrio (ABC(0-12), C_{máx.}, T_{máx.}, o T½) de ninguno de los fármacos. Dado que las concentraciones plasmáticas de M no se vieron afectadas, la co-administración con el Compuesto (I) no acentuará las toxicidades de M dependientes de la concentración.

COMPOSICIONES DEL COMPUESTO (I)

A. Preparación del concentrado

Aproximadamente dos tercios de la lactosa monohidratada se pasa por un tamiz adecuado y se mezcla con el maleato de Compuesto (I) molido. Se pasan almidón glicolato de sodio, hidroxipropilmetilcelulosa, celulosa microcristalina y el resto de la lactosa a través de un tamiz adecuado y se añaden a la mezcla. El mezclado continúa. La mezcla resultante se granula en mojado con agua purificada. Los gránulos húmedos se tamizan, se secan en el secador de lecho fluido y se pasan por otro tamiz y por último se homogenizan.

% COMPOSICIÓN DEL CONCENTRADO GRANULADO

Ingrediente	Cantidad (%)
Compuesto molido (I) como maleato	13,5 (maleato puro)
Almidón glicolato de sodio	5,00
Hidroxipropilmetilcelulosa 2910	5,00
Celulosa microcristalina	20,0
Lactosa Monohidrato, grado regular	hasta 100
Agua purificada	*
* Eliminada durante el procesamiento	

B. Formulación del concentrado en tabletas.

Los gránulos de arriba se ponen en una mezcladora de vuelco. Aproximadamente dos tercios de la lactosa se tamizan y se añaden a la mezcladora. La celulosa microcristalina, el almidón glicolato de sodio, el estearato de magnesio y el resto de la lactosa se tamizan y se añaden a la mezcladora y se incorporan a la mezcla. La mezcla resultante se comprime en una prensa tableteadora giratoria hasta un peso deseado de 150 mg para las tabletas de 1, 2 y 4 mg y hasta un peso deseado de 300 mg para las tabletas de 8 mg.

Los núcleos de las tabletas se transfieren entonces a una máquina recubridora de tabletas, precalentada con aire caliente (aproximadamente a 65°C) y se le aplica la película de recubrimiento hasta que el peso de la tableta ha aumentado en 2,0% a 3,5%.

Potencia de la tableta	Cantidad (mg por Tableta)			
	1,0mg	2,0 mg	4,0 mg	8,0 mg
Ingrediente activo				
Compuesto (I) maleato gránulos de concentrado	10,00	20,00	40,00	80,00
Otros ingredientes:				
Almidón glicolato de sodio	6,96	6,46	5,46	1052
Celulosa microcristalina	27,85	25,85	21,85	43,70

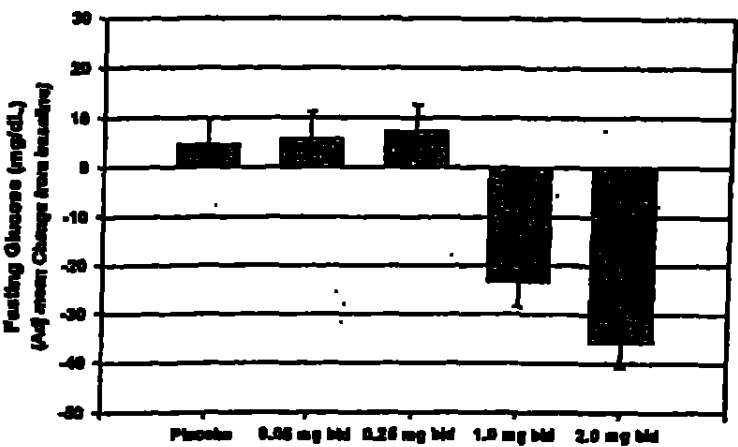
20
98

Lactosa monohidratada	104,44	96,94	81,94	163,88
Estearato de magnesio	0,75	0,75	0,75	1,50
Peso total del núcleo de la tableta	150,0	150,0	150,0	300,0
Material de la película acuosa de recubrimiento	4,5	4,5	4,5	9,0
Peso total de la tableta recubierta con película	154,5	154,5	154,5	309,0

ANNEX I

The following clinical data has been extracted from the Marketing Authorisation Application (MAA) submitted by SmithKline Pharmaceuticals regarding rosiglitazone. This document is publicly available and the data and conclusions therein have been accepted by the relevant authorities.

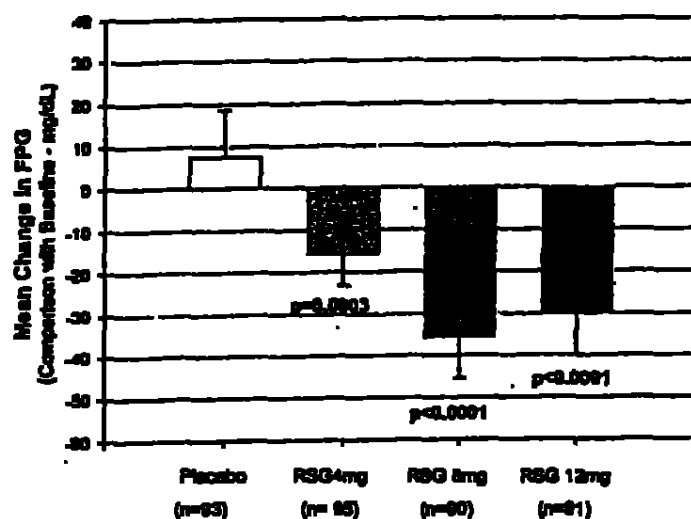
**Figure 1: Change in Fasting Glucose compared to Baseline at Week 12 (mean + SE)
(Intent-to-Treat)**



(ROSIGLITAZONE/006 – ITT Population) (Error Bars = 95%)

22
100

**Figure 2: Change in Fasting Plasma Glucose at Study Endpoint (Week 8)
Compared to Baseline (95 % CI)**



(BRL49653/98 -ITT Population)

(Error Bars = 95% CI)

P value: comparison with placebo using Williams test for dose response models.

MAA Part 1, Vol 8, page 100, Section 3.9.2.

Figure 3: Mean Change In Haemoglobin (Hb) at Week 8 Compared to Baseline

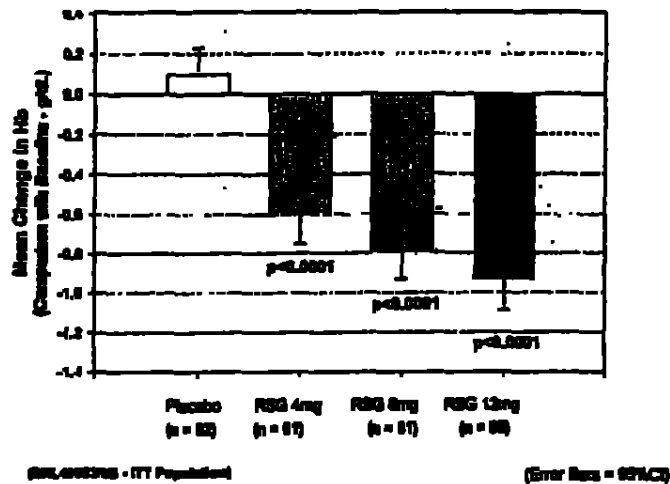
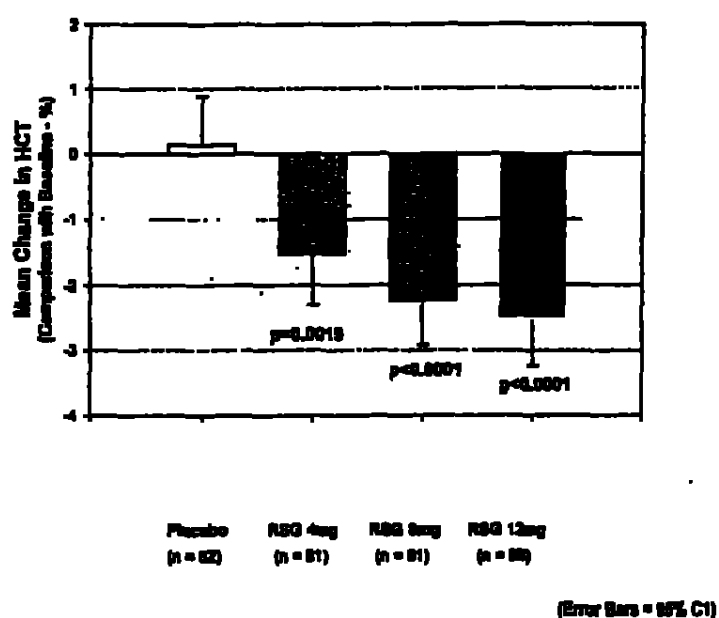


Figure 4: Mean Change In Haematocrit (HCT) at Week 8 Compared to Baseline



NOTE: p value represents comparison to placebo

Rosiglitazone

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Abstract

- ▲ Rosiglitazone, a thiazolidinedione antidiabetic agent, improves insulin resistance, a key underlying metabolic abnormality in most patients with type 2 (non-insulin-dependent) diabetes mellitus.
- ▲ In animal models of insulin resistance, rosiglitazone decreased plasma glucose, insulin and tri-glyceride levels and also attenuated or prevented diabetic nephropathy and pancreatic islet cell degeneration.
- ▲ In contrast with troglitazone, rosiglitazone does not induce cytochrome P450A4 metabolism. It does not interact significantly with nifedipine, oral contraceptives, metformin, digoxin, ranitidine or acarbose.
- ▲ In clinical trials in patients with type 2 diabetes mellitus, rosiglitazone 2 to 12 mg/day (as a single daily dose or 2 divided daily doses) improved glycaemic control, as shown by decreases in fasting plasma glucose and glycosylated haemoglobin (HbA_{1c}).
- ▲ Addition of rosiglitazone 2 to 8 mg/day to existing sulphonylurea, metformin or insulin therapy achieved further reductions in fasting plasma glucose and HbA_{1c}. Oral combinations improved insulin sensitivity and β -cell function according to a homeostasis model assessment.
- ▲ Consistent with its mechanism of action, rosiglitazone appears to be associated with a low risk of hypoglycaemia (<2% of patients receiving monotherapy). There is no evidence to date that rosiglitazone shares the hepatotoxicity of troglitazone.

Features and properties of rosiglitazone (ORL 1050)	
Management of type 2 diabetes mellitus	
Thiazolidinedione antidiabetic agent	Insulin sensitizer; peroxisome proliferator-activated receptor- γ agonist
Usual dosage in clinical trials	2-8 mg/day
Route of administration	Oral
Frequency of administration	Once or twice daily
Peak plasma concentration	182 versus 121 μ g/L
Time to peak plasma concentration	1.3 versus 3.5 h
Area under the plasma concentration-time curve	893 versus 805 μ g/L $\cdot$ h
Elimination half-life	3.84 versus 3.78 h
Most frequent adverse effect	Upper respiratory tract infection
No clinically significant interaction with rosiglitazone	Nifedipine, norethindrone, ethinylestradiol, digoxin, metformin, ranitidine, acarbose

nephromegaly and signs of chronic nephropathy seen in control animals were attenuated or prevented in the prevention group and attenuated in the intervention group. Similarly, pancreatic islet hyperplasia and other pancreatic abnormalities were prevented or attenuated.^[25]

- Rosiglitazone (30 $\mu\text{mol/kg}$ of diet for 10 days) significantly increased the area, number and insulin content of pancreatic islets in *db/db* mice, possibly reflecting reduced secretory pressure on the β -cell after normalisation of hyperglycaemia. Insulin and amylin gene expression were unchanged in this model.^[22] However, in another study hyperexpression of these genes in Zucker fatty rats was reduced ($\sim 50\%$) by rosiglitazone administration (3 $\mu\text{mol/kg/day}$ for 21 days).^[33]

- Rosiglitazone (50 $\mu\text{mol/kg}$ of diet) protected against impaired endothelial function when given to young Zucker rats for 9 to 12 weeks. Vasorelaxant responses of isolated mesenteric resistance vessels to insulin and acetylcholine were partially preserved.^[24]

2. Pharmacokinetics and Drug Interactions

- Administration of rosiglitazone with food reduced the rate, but not the extent, of absorption of the drug. A crossover study in 12 healthy volunteers found that area under the concentration-time curve extrapolated to infinity ($\text{AUC}_{0-\infty}$) after administration of rosiglitazone 2mg was similar in the fasted and fed state (860 versus 805 $\mu\text{g/L} \cdot \text{h}$), but mean maximum plasma concentration (C_{max}) was reduced by 20% (from 152 to 121 $\mu\text{g/L}$) and time to C_{max} (t_{max}) was delayed by 2.2 hours (1.3 vs 3.5 hours), by food intake. Elimination half-life ($t_{1/2}$) was 3.64 versus 3.78 hours.^[34]

- Comparison of pharmacokinetics in young (aged 18 to 45 years) and elderly (aged ≥ 65 years) healthy volunteers after a single 4mg dose of rosiglitazone showed that $\text{AUC}_{0-\infty}$ and C_{max} were 36 and 38% lower in the older group. However, $t_{1/2}$ and t_{max} were similar in the 2 age groups.^[35]

- The pharmacokinetics of rosiglitazone were unaltered by mild to moderate renal impairment^[36] or end-stage renal failure with haemodialysis.^[37] The unbound drug fraction was almost 40% higher in patients with severe renal impairment;^[36] nevertheless, adjustment of rosiglitazone dosage is not necessary on the basis of impaired renal function.^[36,37]

- However, dosage reduction is required in patients with impaired hepatic function: total and unbound AUC were increased by approximately one-third and 3-fold, respectively and $t_{1/2}$ by approximately 1.5-fold (6.0 vs 3.8 hours) compared with healthy volunteers.^[38]

- In contrast with troglitazone,^[39] rosiglitazone does not appear to induce cytochrome P450 (CYP) 3A4 metabolism. Concomitant administration of rosiglitazone (8 mg/day for 14 days) did not affect the pharmacokinetics of the CYP3A4 substrates nifedipine^[40] or ethinylestradiol or norethindrone (in a combined oral contraceptive formulation).^[41]

- Similarly, rosiglitazone did not interact with ranitidine,^[42] metformin^[43] or digoxin.^[44]

- Administration of acarbose (100mg 3-times daily for 7 days) slightly reduced absorption (AUC ; 12%) of a single 8mg dose of rosiglitazone and prolonged $t_{1/2}$ by approximately 1 hour. However, this was not considered clinically relevant.^[45]

3. Therapeutic Trials

Rosiglitazone has been evaluated in clinical trials in patients with type 2 diabetes. Generally, patients had previously been managed with diet or other antidiabetic agents and treatment with rosiglitazone was preceded by a placebo or no-treatment run-in period of 3 to 8 weeks. Mean baseline fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA_{1c}) were $>10.2 \text{ mmol/L}$ and $>8\%$, respectively, in all studies. Changes in HbA_{1c} are expressed as absolute reductions or increases from baseline or placebo.

Dose-Ranging Studies

- A 12-week double-blind multicentre study compared rosiglitazone 0.05, 0.25, 1 or 2mg twice daily

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Changes in HbA_{1c} were made from baseline (mmol/L)

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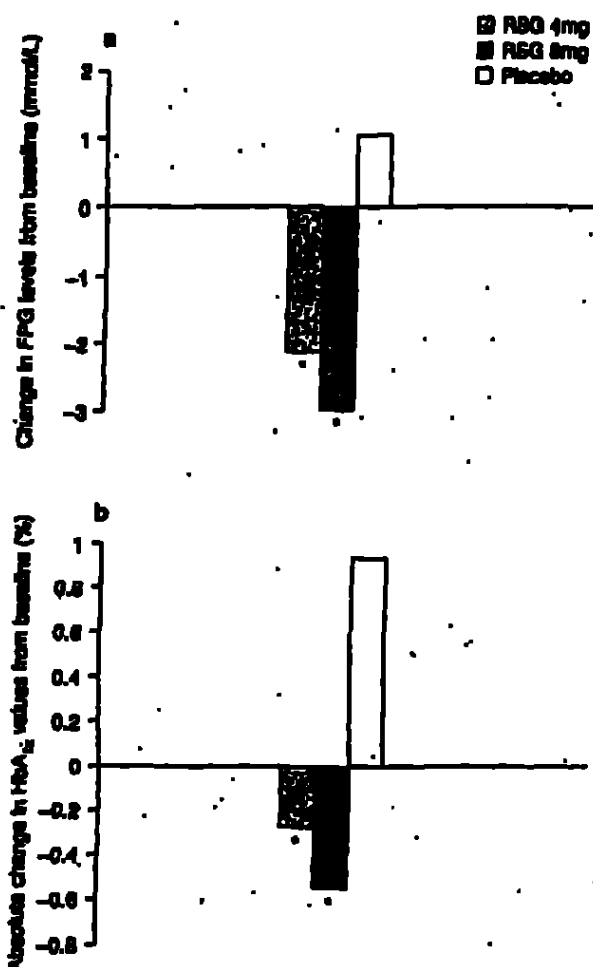


Fig. 2. Antihyperglycaemic efficacy of twice-daily rosiglitazone (RSG). Fasting plasma glucose (FPG) levels (a) and glycosylated haemoglobin (HbA_{1c}) (b) after receiving RSG 2 or 4 mg twice daily or placebo in a metformin 26-week study in 493 patients with type 2 diabetes mellitus. $p < 0.0001$.

Use in Combination with Other Agents

Studies evaluating rosiglitazone as combination treatment with sulphonylureas, metformin or insulin were all randomised and placebo-controlled.

- Addition of rosiglitazone 2 or 4 mg/day (in 2 divided daily doses) to existing sulphonylurea therapy (gliclazide, glibenclamide, glipizide) for 6 months produced additional reductions in HbA_{1c} (0.6 and 1.0%; $p < 0.0001$) and FPG (1.3 and 2.4 mmol/L; 24.3 and 43.9 mg/dl). Worsening of these parameters occurred in placebo recipients. 574 pa-

tients participated in this double-blind study. Over half of patients treated with the higher dosage of rosiglitazone achieved a reduction of $\geq 0.7\%$ in HbA_{1c} and ≥ 1.7 mmol/L (30 mg/dl) in FPG. Free fatty acids decreased by approximately 15% and HDL- and LDL-cholesterol increased by 10 and 5%, respectively, in this treatment group.^[33]

- In patients ($n = 348$) poorly controlled by maximal metformin therapy (2.5 g/day), addition of rosiglitazone 4 or 8 mg/day (once daily) for 26 weeks improved glycaemic control without changing serum insulin levels. FPG decreased by 2.2 and 2.9 mmol/L (39.8 and 52.9 mg/dl) and HbA_{1c} by 0.97 and 1.18%, respectively ($p < 0.0001$ all comparisons). FPG levels < 7.8 mmol/L (140 mg/dl) were achieved in 22 and 30% of patients, respectively, despite mean baseline levels of > 11.7 mmol/L (210 mg/dl).^[34]

- In patients ($n = 319$) poorly controlled on twice daily insulin, addition of rosiglitazone 2 or 4 mg twice daily significantly improved glycaemic control and lowered insulin requirements (by 4.8 and 9.4 U/day, respectively; $p < 0.006$ both comparisons) [fig. 3]. Over the 26-week study period, FPG was reduced by 2.3 and 2.5 mmol/L (41.5 and 44.4 mg/dl) from baseline with rosiglitazone 4 and 8 mg/day, respectively, but increased by 0.6 mmol/L (10.3 mg/dl) in placebo recipients. HbA_{1c} was decreased by 0.6 and 1.2% compared with an increase of 0.1% in the placebo group. Over half of patients receiving the higher dose of rosiglitazone had a decrease of $\geq 1\%$ in HbA_{1c}.^[35]

Homeostasis Model Assessment

- Treatment with rosiglitazone 2 to 8 mg/day with or without sulphonylureas or metformin for 26 weeks decreased insulin resistance (≈ 3 to 25%) and improved β -cell function ($\leq 94\%$), according to a homeostasis model assessment (HOMA).^[36] Insulin resistance increased in those who received placebo or sulphonylurea monotherapy and did not improve in those treated with metformin (fig. 4).^[37,38]

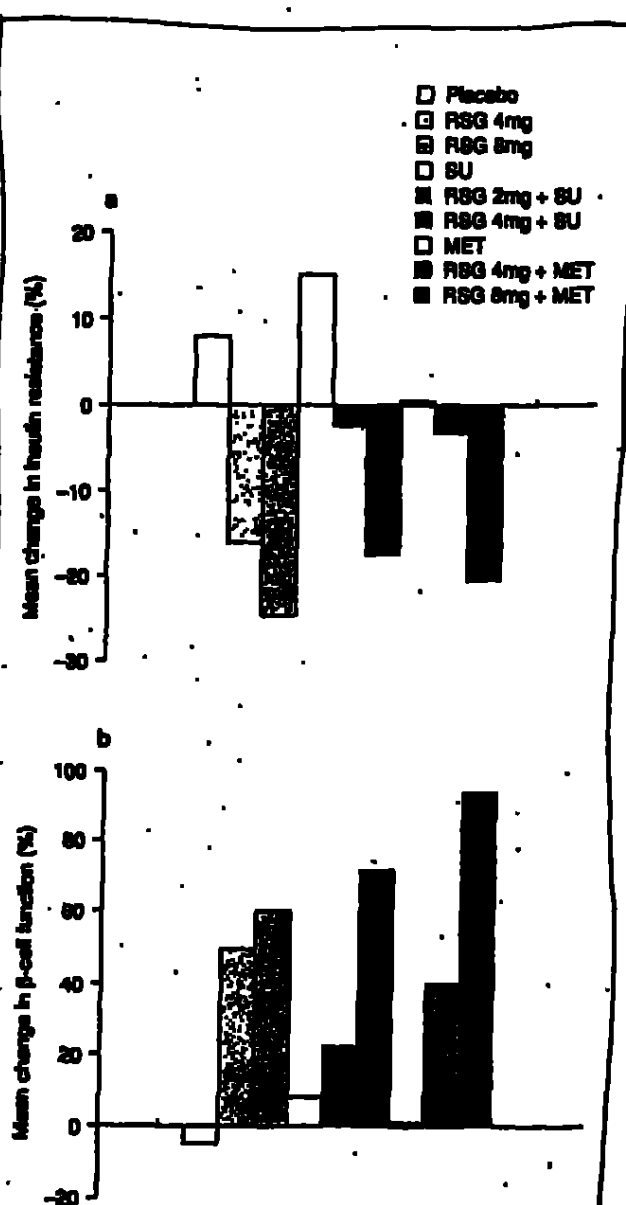
27
105

Fig. 4. Effects of rosiglitazone (RSG) and other antidiabetic agents on insulin resistance (a) and beta-cell function (b) in a homeostatic model assessment. Patients participating in 3 clinical trials received placebo (n = 150), RSG 2mg twice daily (n = 100), RSG 4mg twice daily (n = 100), sulphonylurea therapy (SU; n = 100), RSG 2mg twice daily + SU (n = 100), RSG 2mg twice daily + SU (n = 100), metformin (MET; n = 110), RSG 4mg once daily + MET (n = 110), RSG 8mg once daily + MET (n = 110) for 28 weeks.^[62]

trials or open-label treatment), levels either improved, normalised or did not worsen during continued therapy (follow-up data were not available for 2 patients).^[61]

• These data are supported by the results of a study in rat hepatocytes. In contrast to troglitazone, which was toxic to these cells at a concentration of 20 $\mu\text{mol/L}$, rosiglitazone showed no cytotoxicity at concentrations $\leq 100 \mu\text{mol/L}$.^[62]

Effects on the Cardiovascular System

• As with other thiazolidinediones, rosiglitazone has been associated with small and/or clinically insignificant decreases in haematocrit and haemoglobin in patients with type 2 diabetes.^[44,49] Rosiglitazone 4 or 8 mg/day for 8 weeks did not affect indices of erythropoiesis or red blood cell destruction in healthy volunteers (n = 30). Haemoglobin and haematocrit were reduced slightly (0.6 g/L and 2%, respectively) in the 8mg dosage group, presumably as a result of increased plasma volume.^[63]

• Cardiac hypertrophy has been noted in rodents given high doses of thiazolidinediones. However, treatment of 104 patients with rosiglitazone 4mg twice daily for up to 52 weeks did not result in any adverse changes in cardiac structure or function, on the basis of echocardiographic studies. Only small and clinically unimportant changes were seen in left ventricular mass index and left ventricular end diastolic volume. Ejection fraction was unchanged. Similar results were seen in patients treated with glibenclamide (mean 10.5 mg/day) over the same time period. Diastolic blood pressure was lowered by 2.3mm Hg (p = 0.0016) in rosiglitazone recipients, as assessed by 24-hour ambulatory monitoring.^[64]

• Similarly, no changes in left ventricular mass were detected on echocardiography in 380 patients treated with rosiglitazone 0.1 to 4 mg/day or placebo for up to 12 weeks.^[65]

• Thiazolidinediones can cause oedema and haemodilution, and animal studies have shown that troglitazone has a vasodilatory effect which might lead to fluid retention. However, an *in vitro* study in human resistance vessels showed that rosiglitazone did not have the direct vasorelaxant effect noted with troglitazone. Troglitazone also had a similar vasodilatory effect in Wistar rat arteries that was not abolished by N^G -nitro-L-arginine methyl ester.

Rosiglitazone

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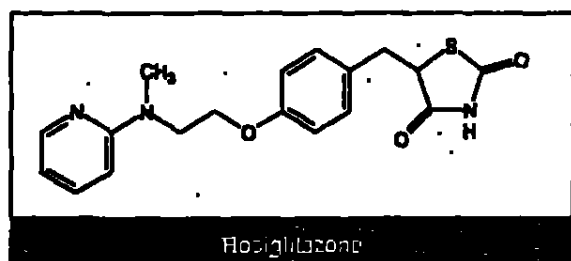
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- ▲ In clinical trials in patients with type 2 diabetes mellitus, rosiglitazone 2 to 12 mg/day (as a single daily dose or 2 divided daily doses) improved glycaemic control, as shown by decreases in fasting plasma glucose and glycosylated haemoglobin (HbA_{1c}).
- ▲ Addition of rosiglitazone 2 to 8 mg/day to existing sulphonylurea, metformin or insulin therapy achieved further reductions in fasting plasma glucose and HbA_{1c}. Oral combinations improved insulin sensitivity and β -cell function according to a homeostasis model assessment.
- ▲ Consistent with its mechanism of action, rosiglitazone appears to be associated with a low risk of hypoglycaemia (<2% of patients receiving monotherapy). There is no evidence to date that rosiglitazone shares the hepatotoxicity of troglitazone.

Features and properties of rosiglitazone (BRL 49573)

Management of type 2 diabetes mellitus	
Thiazolidinedione antidiabetic agent	Insulin sensitizer; peroxisome proliferator-activated receptor- γ agonist
Usual dosage in clinical trials	2-8 mg/day
Route of administration	Oral
Frequency of administration	Once or twice daily
Peak plasma concentration	162 versus 121 pg/L
Time to peak plasma concentration	1.3 versus 3.5 h
Area under the plasma concentration-time curve	890 versus 806 pg/L $\cdot$ h
Elimination half-life	3.84 versus 3.78 h
Most frequent adverse effect	Upper respiratory tract infection
No clinically significant interaction with rosiglitazone	Nifedipine, norethandrone, ethinylestradiol, digoxin, metformin, ranitidine, acarbose



Rosiglitazone is a thiazolidinedione, a relatively new class of antidiabetic agents which enhance sensitivity to insulin in the liver, adipose tissue and muscle, resulting in improved insulin-mediated glucose disposal.^[1] Insulin resistance is a pivotal underlying metabolic abnormality in most patients with type 2 (non-insulin-dependent) diabetes mellitus. Hypersecretion of insulin occurs until the pancreas can no longer compensate for the reduced sensitivity of the tissues to insulin and then overt type 2 diabetes results (reviewed by Henry^[2] and Bloomgarden^[3]).

In all animal and human studies discussed in this article, drugs were given orally unless specified otherwise. In animal studies, dosages are expressed per kg bodyweight unless specified otherwise.

1. Pharmacodynamic Profile

Mechanism of Action

The mechanism of action of rosiglitazone and other members of its class is yet to be clarified. Available data suggest that these agents can modulate several processes to increase sensitivity to insulin. These include effects on insulin receptor kinase activity, insulin receptor phosphorylation, numbers of insulin receptors and hepatic glucose metabolism.^[4] However, it has been suggested that many of the glucoregulatory effects of thiazolidinediones are mediated via reduced systemic and tissue lipid availability.^[5]

One key action of thiazolidinediones is to activate the nuclear receptor peroxisome proliferator-activated receptor- γ (PPAR- γ).^[6-8] This receptor, which is expressed at high levels in mammalian adipose tissue, regulates the transcription of several genes involved in preadipocyte differentiation

and insulin-mediated glucose uptake in peripheral tissues. Thiazolidinediones promote adipose cell differentiation by activating PPAR- γ . They reduce expression of leptin (a signalling factor expressed by the *ob* gene which regulates appetite, body-weight and energy balance) and tumour necrosis factor- α (TNF α), while increasing expression of lipoprotein lipase, adipocyte lipid-binding protein (aP2) and GLUT-4 (which plays a key role in the facilitated transport of glucose into adipocytes and skeletal muscle).^[9]

- Rosiglitazone binds to PPAR- γ with high affinity [dissociation constant (K_d) approximately 40 nmol/L].^[6] It has a higher affinity for PPAR- γ in intact human adipocytes (IC_{50} 10 nmol/L) than pioglitazone (360 nmol/L) or troglitazone (1050 nmol/L).^[9]

- Exposure of pluripotent C3H10T1/2 stem cells^[10] or human preadipocytes^[10] to rosiglitazone at concentrations as low as 100 nmol/L *in vitro* promoted their differentiation to adipocytes.^[6] PPAR- γ expression in C3H10T1/2 cells was increased 3-fold.^[6]

- Rosiglitazone inhibited leptin gene expression in rat 3T3-L1 adipocytes *in vitro*,^[11,12] with an ED_{50} (concentration causing 50% inhibition) of 5 to 50 nmol/L, similar to its K_d for binding to PPAR- γ (40 nmol/L) and identical to its ED_{50} for inducing adipocyte differentiation (5 to 50 nmol/L).^[12]

- In *in vivo* studies in obese or high-fat-diet-fed rats, rosiglitazone reduced *ob* mRNA levels in epididymal fat pads (by 40% at 5 mg/kg/day)^[11] and reduced plasma leptin levels ($\sim 40\%$; $p < 0.05$).^[13,14] Expression of PPAR- γ and aP2 mRNA were significantly increased ($p < 0.01$).^[13]

- Lipoprotein lipase mRNA and activity in epididymal adipose tissue increased by more than 2-fold after administration of rosiglitazone 5 or 10 mg/kg for 7 days to normal rats. A similar increase in mRNA levels was seen when the drug (10 μ mol/L) was added to adipocytes *in vitro*.^[15]

- Rosiglitazone enhanced expression of uncoupling proteins 1^[16,17] and 3^[17] (UCP-1 and UCP-3) (by 5- and 3-fold, respectively, at a concentration of 1 μ mol/L^[17]) in rat or human adipocytes *in vitro*.

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Synergistic effects on UCP-3 were noted between rosiglitazone and the PPAR- α agonist Wy 14643,^[17] which antagonised the effects of rosiglitazone on UCP-1.^[18] Rosiglitazone also increased expression of UCP-2 in adipocytes.^[19]

- Insulin binding to white adipocytes from obese mice was significantly ($p < 0.001$) increased by pretreatment with rosiglitazone (30 $\mu\text{mol/kg}$ of diet for 14 days). The drug appeared to increase the number of insulin receptors rather than change receptor affinity and increased the total tissue content of GLUT-4 by 2.5-fold.^[20]

Effects on Glucose and Lipid Metabolism

- In genetic and dietary animal models of obesity and insulin resistance, including the obese hyperglycaemic *db/db* mouse,^[7,21,22] *ob/ob* mouse,^[20,21] Zucker fatty (*fa/fa*) rat^[23-27] and overfed Wistar rat,^[2,14] rosiglitazone significantly reduces plasma levels of glucose, insulin and/or triglycerides. Rosiglitazone also lowered plasma levels of non-esterified fatty acids^[2,23,28] and ketone bodies.^[2]

- As with other thiazolidinediones,^[8] the *in vivo* antidiabetic potency of rosiglitazone was correlated with its binding affinity for PPAR- γ .^[7]

- Rosiglitazone had a greater effect on plasma triglycerides than on plasma glucose in Zucker fatty rats, improving dyslipidaemia at a dosage (10 to 30 mg/kg/day) which did not significantly lower plasma glucose levels.^[27] In normal rats, rosiglitazone decreased serum triglycerides without affecting plasma glucose levels.^[15]

- As with other thiazolidinediones,^[8] rosiglitazone frequently increases food intake and promotes bodyweight gain and/or fat deposition in rodents.^[11,14,15,23,29] However, no significant effect of thiazolidinediones on body fat mass has been reported in humans to date.^[14] Specifically, thiazolidinediones increase the amount of brown adipose tissue (which dissipates energy via oxidation of fatty acids),^[8] which might contribute to the effects of these drugs on insulin resistance.^[14] Rosiglitazone enhanced rat interscapular brown adipose tissue mass.^[30]

- Glucose tolerance in *ob/ob* mice was improved by rosiglitazone; at 100 $\mu\text{mol/kg}$ of diet, the rise in blood glucose levels following an oral glucose load was completely abolished.^[20] When given to young Zucker fatty rats (aged 6 weeks), rosiglitazone ($\approx 10 \mu\text{mol/kg}$) prevented development of hyperglycaemia, maintaining blood glucose levels similar to those in lean rats.^[31]

- Under euglycaemic clamp conditions, rosiglitazone (10 $\mu\text{mol/kg/day}$ for 4 days) increased glucose uptake, insulin suppressibility of hepatic glucose production and muscle glucose uptake; however, these effects were seen only in insulin-resistant rats.^[32]

- Prior administration of rosiglitazone 3 mg/kg/day for 7 days to obese Zucker rats restored basal glucose uptake in the isolated perfused heart (from 42 to 15% lower than in lean control hearts).^[23]

- Prior administration of rosiglitazone 3 $\mu\text{mol/kg/day}$ to obese Zucker rats decreased the insulin resistance of perfused hindlimbs, as shown by increased responsiveness to insulin. However, no further details of results were provided.^[32]

Effects on Diabetic Complications

- Administration of rosiglitazone (50 $\mu\text{mol/kg}$ of diet) to Zucker rats protected against development and progression of renal injury and adaptive changes to pancreatic islet morphology which result from sustained hyperinsulinaemia. When given as a preventative strategy to young rats (aged 6 to 7 weeks) for 9 months, rosiglitazone delayed the onset (from 3 to 6 months), and markedly reduced subsequent progression, of proteinuria compared with untreated rats. Delayed progression of proteinuria was also noted when rosiglitazone was administered to older rats (age 24 to 25 weeks) with established proteinuria (intervention group). Normalisation of urinary *N*-acetyl- β -D-glucosaminidase activity (a marker for renal proximal tubular damage) and attenuation of the rise in systolic blood pressure that accompanied the development of proteinuria was noted in both groups of rats. Postmortem, histological and ultrastructural examination confirmed the renal protective effect of the drug:

nephromegaly and signs of chronic nephropathy seen in control animals were attenuated or prevented in the prevention group and attenuated in the intervention group. Similarly, pancreatic islet hyperplasia and other pancreatic abnormalities were prevented or attenuated.^[125]

- Rosiglitazone (30 $\mu\text{mol/kg}$ of diet for 10 days) significantly increased the area, number and insulin content of pancreatic islets in *db/db* mice, possibly reflecting reduced secretory pressure on the β -cell after normalisation of hyperglycaemia. Insulin and amylin gene expression were unchanged in this model.^[122] However, in another study hyperexpression of these genes in Zucker fatty rats was reduced ($\sim 50\%$) by rosiglitazone administration (3 $\mu\text{mol/kg/day}$ for 21 days).^[121]

- Rosiglitazone (50 $\mu\text{mol/kg}$ of diet) protected against impaired endothelial function when given to young Zucker rats for 9 to 12 weeks. Vasorelaxant responses of isolated mesenteric resistance vessels to insulin and acetylcholine were partially preserved.^[124]

2. Pharmacokinetics and Drug Interactions

- Administration of rosiglitazone with food reduced the rate, but not the extent, of absorption of the drug. A crossover study in 12 healthy volunteers found that area under the concentration-time curve extrapolated to infinity ($\text{AUC}_{0-\infty}$) after administration of rosiglitazone 2mg was similar in the fasted and fed state (860 versus 805 $\mu\text{g/L} \cdot \text{h}$), but mean maximum plasma concentration (C_{max}) was reduced by 20% (from 152 to 121 $\mu\text{g/L}$) and time to C_{max} (t_{max}) was delayed by 2.2 hours (1.3 vs 3.5 hours), by food intake. Elimination half-life ($t_{1/2}$) was 3.64 versus 3.78 hours.^[124]

- Comparison of pharmacokinetics in young (aged 18 to 45 years) and elderly (aged ≥ 65 years) healthy volunteers after a single 4mg dose of rosiglitazone showed that $\text{AUC}_{0-\infty}$ and C_{max} were 36 and 38% lower in the older group. However, $t_{1/2}$ and t_{max} were similar in the 2 age groups.^[124]

- The pharmacokinetics of rosiglitazone were unaltered by mild to moderate renal impairment^[126] or end-stage renal failure with haemodialysis.^[127] The unbound drug fraction was almost 40% higher in patients with severe renal impairment;^[124] nevertheless, adjustment of rosiglitazone dosage is not necessary on the basis of impaired renal function.^[124,127]

- However, dosage reduction is required in patients with impaired hepatic function: total and unbound AUC were increased by approximately one-third and 3-fold, respectively and $t_{1/2}$ by approximately 1.5-fold (6.0 vs 3.8 hours) compared with healthy volunteers.^[126]

- In contrast with troglitazone,^[128] rosiglitazone does not appear to induce cytochrome P450 (CYP) 3A4 metabolism. Concomitant administration of rosiglitazone (8 mg/day for 14 days) did not affect the pharmacokinetics of the CYP3A4 substrates nifedipine^[129] or ethinylestradiol or norethindrone (in a combined oral contraceptive formulation).^[131]

- Similarly, rosiglitazone did not interact with ranitidine,^[122] metformin^[129] or digoxin.^[140]

- Administration of acarbose (100mg 3-times daily for 7 days) slightly reduced absorption (AUC ; 12%) of a single 8mg dose of rosiglitazone and prolonged $t_{1/2}$ by approximately 1 hour. However, this was not considered clinically relevant.^[129]

3. Therapeutic Trials

Rosiglitazone has been evaluated in clinical trials in patients with type 2 diabetes. Generally, patients had previously been managed with diet or other antidiabetic agents and treatment with rosiglitazone was preceded by a placebo or no-treatment run-in period of 3 to 8 weeks. Mean baseline fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA_{1c}) were $>10.2 \text{ mmol/L}$ and $>8\%$, respectively, in all studies. Changes in HbA_{1c} are expressed as absolute reductions or increases from baseline or placebo.

Dose-Ranging Studies

- A 12-week double-blind multicentre study compared rosiglitazone 0.05, 0.25, 1 or 2mg twice daily

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- On 12 mg by 0.6 mg/dl increase recipient 369 mg/dl fact of placebo (F)

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Change in FPG levels from baseline (mmol/L)

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with placebo in 380 patients. The 1 and 2mg twice daily dosages were effective in reducing FPG; ($p = 0.001$) and fructosamine ($p = 0.003$ for 2mg twice daily group) from baseline; but HbA_{1c} was not significantly reduced in any of the treatment groups. The higher dosage also reduced plasma insulin (by 2.7 mIU/L; $p = 0.0044$) and free fatty acid ($p = 0.0014$) levels and increased total, high density lipoprotein (HDL)- and low density lipoprotein (LDL)-cholesterol ($p < 0.001$).^[46]

- Once daily treatment with rosiglitazone 4, 8 or 12 mg/day for 8 weeks significantly reduced FPG, by 0.8, 2.0 and 1.7 mmol/L (15.8, 35.7 and 30.2 mg/dl), respectively ($p < 0.0001$ for all doses). FPG increased by 0.4 mmol/L (7.4 mg/dl) in placebo recipients in this randomised double-blind study in 369 patients. 8 mg/day was more effective than 4 mg/day, but no additional antihyperglycaemic effect was seen with 12 mg/day (fig. 1). Over 50% of patients treated with the 2 highest dosages had an FPG reduction of >1.7 mmol/L (>30 mg/dl).^[47]

- A randomised placebo-controlled study compared rosiglitazone 4 and 8 mg/day, given as a single daily dose or in 2 divided daily doses, in 959 patients (treatment duration not stated). HbA_{1c} and FPG decreased significantly without any increase

in serum insulin levels in all active treatment groups. Compared with placebo, HbA_{1c} decreased by 0.8, 0.9, 1.1 and 1.5% in the rosiglitazone 4mg once daily, 2mg twice daily, 8mg once daily and 4 mg twice daily treatment groups ($p < 0.0001$ all comparisons).^[48]

- In a multicentre, placebo-controlled 26-week study in 493 patients, rosiglitazone 2 or 4mg twice daily reduced FPG and HbA_{1c} by 2.1 and 3 mmol/L (38.4 and 54.0 mg/dl) and 0.28 and 0.56%, respectively, from baseline ($p < 0.0001$ vs placebo). These parameters increased by 1.0 mmol/L (18.9 mg/dl) and 0.92% in placebo recipients (fig. 2). Serum fructosamine was also significantly reduced by both dosages of rosiglitazone ($p < 0.0001$ vs placebo).^[49]

- In a study in 99 patients, treatment with rosiglitazone 2, 4 or 6mg twice daily for 8 weeks significantly decreased the postprandial plasma glucose AUC (by 144.4, 177.1 and 175.0 mg/dl · h, respectively) and plasma insulin AUC (by 34.0, 77.8 and 139.9 pmol/L · h, respectively) [$p < 0.0004$ vs baseline and placebo for all treatment groups].^[50]

- Rosiglitazone appeared to be equally effective in older (aged ≥ 65 years) and younger (< 65 years) patients. In two 26-week placebo-controlled studies, rosiglitazone 4 and 8 mg/day achieved similar reductions in FPG and HbA_{1c} in the 2 age groups.^[51]

Comparison with Glibenclamide

- Rosiglitazone 4mg twice daily was more effective ($p = 0.033$), and rosiglitazone 2mg twice daily was slightly less effective, than optimally titrated glibenclamide (glyburide) in producing sustained reductions in FPG over a 12-month period. 587 patients participated in this randomised, double-blind study. FPG was reduced by 1.4, 2.3 and 1.7 mmol/L (25, 41 and 30 mg/dl) with rosiglitazone 4 mg/day, rosiglitazone 8 mg/day and glibenclamide, respectively, and 36, 51 and 37% of patients had levels <7.8 mmol/L (140 mg/dl) after treatment. Rosiglitazone 8 mg/day was slightly, but not significantly, less effective than glibenclamide in reducing HbA_{1c} (by 0.53 vs 0.72%).^[52]

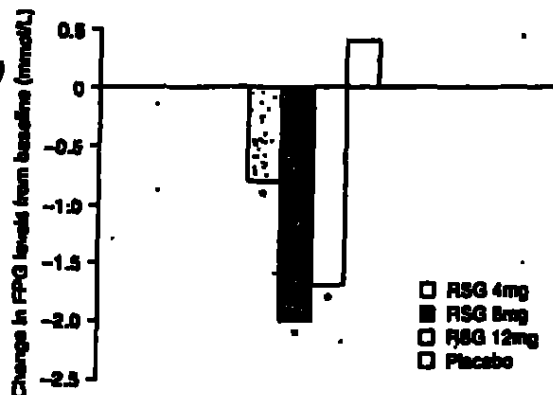


Fig. 1. Antihyperglycaemic efficacy of once daily rosiglitazone (RSG). Fasting plasma glucose (FPG) levels after receiving RSG 4, 8 or 12mg once daily or placebo for 8 weeks in a randomised double-blind study in 369 patients with type 2 diabetes mellitus.^[47] $p < 0.0001$.

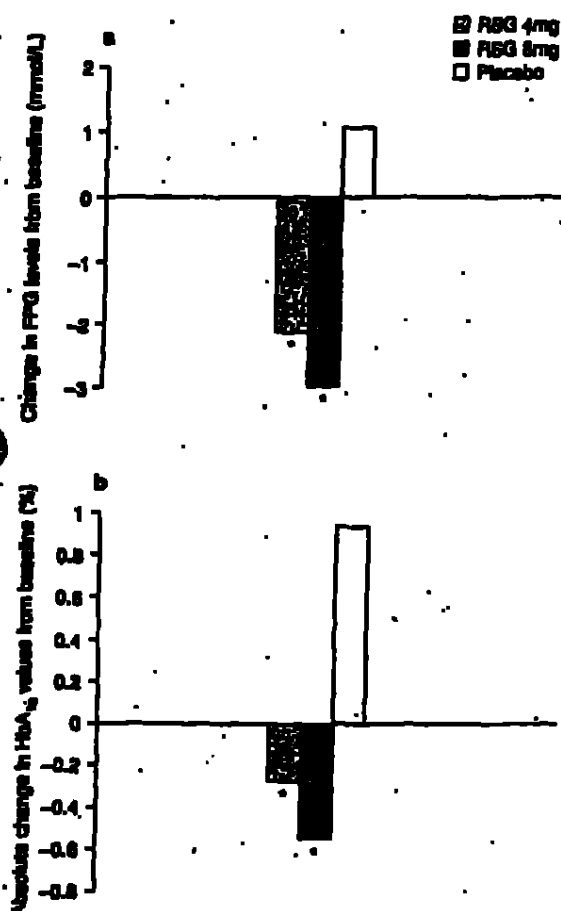


Fig. 2 Antihyperglycaemic efficacy of twice daily rosiglitazone (RSG). Fasting plasma glucose (FPG) levels (a) and glycosylated haemoglobin (HbA_{1c}) (b) after receiving RSG 8 or 4 mg twice daily or placebo in a randomised 26-week study in 400 patients with type 2 diabetes mellitus. $p < 0.0001$.

Use in Combination with Other Agents

Studies evaluating rosiglitazone as combination treatment with sulphonylureas, metformin or insulin were all randomised and placebo-controlled.

- Addition of rosiglitazone 2 or 4 mg/day (in 2 divided daily doses) to existing sulphonylurea therapy (gliclazide, glibenclamide, glipizide) for 6 months produced additional reductions in HbA_{1c} (0.6 and 1.0%; $p < 0.0001$) and FPG (1.3 and 2.4 mmol/L; 24.3 and 43.9 mg/dl). Worsening of these parameters occurred in placebo recipients. 574 pa-

tients participated in this double-blind study. Over half of patients treated with the higher dosage of rosiglitazone achieved a reduction of $\geq 0.7\%$ in HbA_{1c} and ≥ 1.7 mmol/L (30 mg/dl) in FPG. Free fatty acids decreased by approximately 15% and HDL- and LDL-cholesterol increased by 10 and 5%, respectively, in this treatment group.^[33]

- In patients ($n = 348$) poorly controlled by maximal metformin therapy (2.5 g/day), addition of rosiglitazone 4 or 8 mg/day (once daily) for 26 weeks improved glycaemic control without changing serum insulin levels. FPG decreased by 2.2 and 2.9 mmol/L (39.8 and 52.9 mg/dl) and HbA_{1c} by 0.97 and 1.18%, respectively ($p < 0.0001$ all comparisons). FPG levels < 7.8 mmol/L (140 mg/dl) were achieved in 22 and 30% of patients, respectively, despite mean baseline levels of > 11.7 mmol/L (210 mg/dl).^[34]

- In patients ($n = 319$) poorly controlled on twice daily insulin, addition of rosiglitazone 2 or 4 mg twice daily significantly improved glycaemic control and lowered insulin requirements (by 4.8 and 9.4 U/day, respectively; $p < 0.006$ both comparisons) (fig. 3). Over the 26-week study period, FPG was reduced by 2.3 and 2.5 mmol/L (41.5 and 44.4 mg/dl) from baseline with rosiglitazone 4 and 8 mg/day, respectively, but increased by 0.6 mmol/L (10.3 mg/dl) in placebo recipients. HbA_{1c} was decreased by 0.6 and 1.2% compared with an increase of 0.1% in the placebo group. Over half of patients receiving the higher dose of rosiglitazone had a decrease of $\geq 1\%$ in HbA_{1c}.^[35]

Homeostasis Model Assessment

- Treatment with rosiglitazone 2 to 8 mg/day with or without sulphonylureas or metformin for 26 weeks decreased insulin resistance (-3 to 25%) and improved β -cell function ($\leq 94\%$), according to a homeostasis model assessment (HOMA).^[36] Insulin resistance increased in those who received placebo or sulphonylurea monotherapy and did not improve in those treated with metformin (fig. 4).^[37,38]

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4. Tolerability

• Analysis of pooled data from 4327 patients treated with rosiglitazone, alone or in combination with metformin or sulphonylureas, showed that the only adverse events reported in $\geq 5\%$ of patients receiving rosiglitazone were upper respiratory tract infection (13.1% of monotherapy recipients), injury (8.9%) and headache (6.7%). The relationship of these events to treatment was not stated. Adverse events related to the cardiovascular system, elevated serum lipids, anaemia or oedema were at least as common with placebo as with rosiglitazone.^[39] Overall, fewer rosiglitazone than placebo recipients withdrew from clinical trials because of adverse events (56.2 to 7.8% vs 10.8%).^[42,39]

• According to an analysis of 2526 rosiglitazone-treated patients, the proportions of patients with at least 1 adverse event did not differ between elderly (aged ≥ 65 years) and younger patients. As with younger patients, the most common events in the elderly were upper respiratory tract infection, injury and headache and these were equally common in the 2 age groups. However, oedema and anaemia appeared to be more common in the elderly (7.5 vs 3.5% and 2.5 vs 1.7%).^[51]

• Coadministration of rosiglitazone did not increase the frequency of hypoglycaemia associated with sulphonylureas or increased plasma lactate

levels or gastrointestinal events associated with metformin.^[39]

Hypoglycaemia

• Hypoglycaemia occurred in $<1\%$ of 2526 patients receiving rosiglitazone (dosage not stated), in clinical trials.^[51] In a comparative study, hypoglycaemia was more common with glibenclamide (optimally titrated; 12% of 203 patients) than with rosiglitazone 4 or 8 mg/day ($<2\%$ of 384 patients).^[52]

• Rosiglitazone did not appear to increase the risk of hypoglycaemia associated with moderate alcohol intake (0.6 g/kg) with a meal. Concomitant intake of alcohol did not produce any clinically meaningful changes in plasma glucose or overnight urinary cortisol : creatinine ratios in patients who received rosiglitazone 8 mg/day ($n = 11$) or placebo ($n = 12$) for 8 weeks. Hypoglycaemia did not occur.^[60]

Effects on the Liver

Troglitazone has been found to cause significant hepatic toxicity, which has resulted in death or the need for liver transplantation in a small number of patients.^[39] Thus, concern has been raised as to whether this is a class effect of thiazolidinediones. To date, there is no evidence that rosiglitazone is hepatotoxic.

• Pooled data are available from >4500 patients treated with rosiglitazone for ≥ 6 months in double-blind or open-label studies. Of 3455 patients who had frequent liver function tests (every 4 weeks for the first 3 months, every 6 weeks for the next 3 months and quarterly thereafter) in double-blind controlled studies, the proportion of patients with serum ALT levels >3 times the upper limit of normal ($>3 \times \text{ULN}$; 0.17%; $n = 6$) was similar to that in patients receiving placebo (0.18%; $n = 1$ of 561) or sulphonylureas or metformin (0.48%; 4/828). [Patients with baseline ALT or AST values $\leq 2.5 \times \text{ULN}$ were allowed to enter the studies.] Of 13 patients who developed ALT levels $>3 \times \text{ULN}$ during rosiglitazone treatment (during controlled clinical

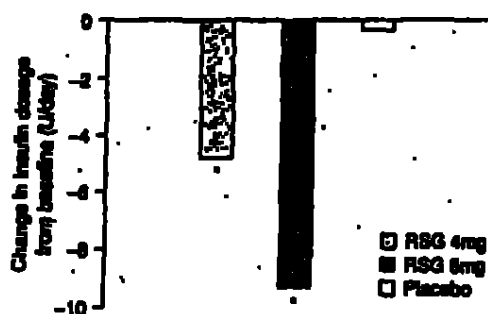


Fig. 2. Efficacy of rosiglitazone (RSG) in combination with insulin. Effects on insulin requirements of adding RSG 2 or 4 mg twice daily or placebo to existing twice daily insulin therapy in patients ($n = 319$) with poorly controlled type 2 diabetes mellitus who participated in a randomised study. $p < 0.005$.

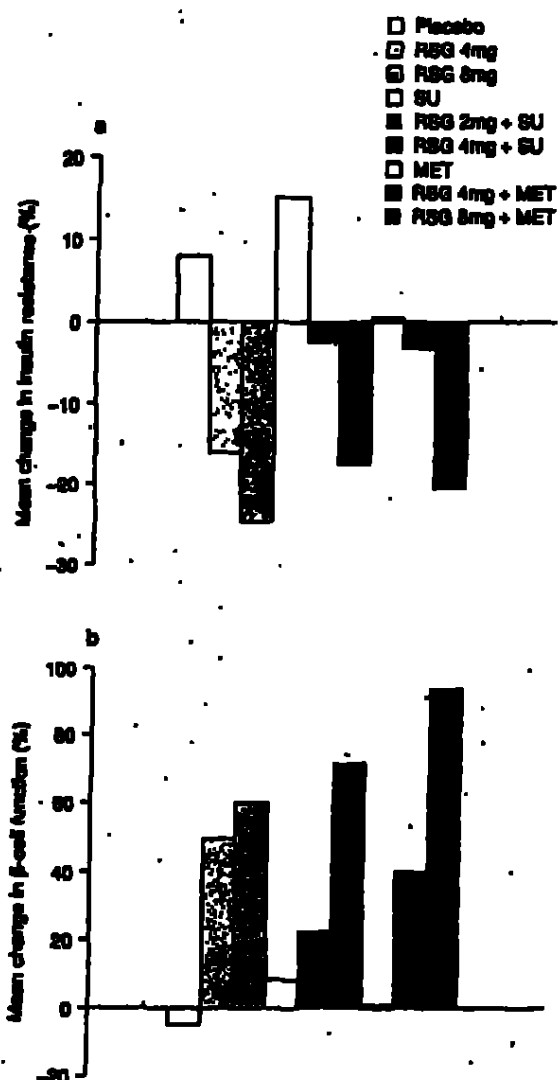


Fig. 4. Effects of rosiglitazone (RSG) and other antidiabetic agents on insulin resistance (a) and beta-cell function (b) in a nonobese model population. Patients participating in 3 clinical trials received placebo ($n = 155$), RSG 2mg twice daily ($n = 166$), RSG 4mg twice daily ($n = 166$), sulphonylurea therapy (SU; $n = 166$), RSG 1mg twice daily + SU ($n = 166$), RSG 2mg twice daily + SU ($n = 166$), metformin (MET; $n = 113$), RSG 4mg once daily + MET ($n = 113$), RSG 8mg once daily + MET ($n = 110$) for 28 weeks.^[62]

trials or open-label treatment), levels either improved, normalised or did not worsen during continued therapy (follow-up data were not available for 2 patients).^[61]

• These data are supported by the results of a study in rat hepatocytes. In contrast to troglitazone, which was toxic to these cells at a concentration of 20 $\mu\text{mol/L}$, rosiglitazone showed no cytotoxicity at concentrations $\leq 100 \mu\text{mol/L}$.^[62]

Effects on the Cardiovascular System

• As with other thiazolidinediones, rosiglitazone has been associated with small and/or clinically insignificant decreases in haematocrit and haemoglobin in patients with type 2 diabetes.^[44,49] Rosiglitazone 4 or 8 mg/day for 8 weeks did not affect indices of erythropoiesis or red blood cell destruction in healthy volunteers ($n = 30$). Haemoglobin and haematocrit were reduced slightly (0.6 g/L and 2%, respectively) in the 8mg dosage group, presumably as a result of increased plasma volume.^[63]

• Cardiac hypertrophy has been noted in rodents given high doses of thiazolidinediones. However, treatment of 104 patients with rosiglitazone 4mg twice daily for up to 52 weeks did not result in any adverse changes in cardiac structure or function, on the basis of echocardiographic studies. Only small and clinically unimportant changes were seen in left ventricular mass index and left ventricular end diastolic volume. Ejection fraction was unchanged. Similar results were seen in patients treated with glibenclamide (mean 10.5 mg/day) over the same time period. Diastolic blood pressure was lowered by 2.3mm Hg ($p = 0.0016$) in rosiglitazone recipients, as assessed by 24-hour ambulatory monitoring.^[64]

• Similarly, no changes in left ventricular mass were detected on echocardiography in 380 patients treated with rosiglitazone 0.1 to 4 mg/day or placebo for up to 12 weeks.^[65]

• Thiazolidinediones can cause oedema and haemodilution, and animal studies have shown that troglitazone has a vasodilatory effect which might lead to fluid retention. However, an *in vitro* study in human resistance vessels showed that rosiglitazone did not have the direct vasorelaxant effect noted with troglitazone. Troglitazone also had a similar vasodilatory effect in Wistar rat arteries that was not abolished by NO -nitro-L-arginine methyl ester.

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Further studies are required to determine whether these differences are apparent *in vivo*.^[64]

5. Rosiglitazone: Current Status

Rosiglitazone is a thiazolidinedione insulin sensitiser that has been filed for approval for the management of type 2 diabetes mellitus.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Feb 2007-01-19 15:57:53 Dep 2020 NUESTRACIONES
1ra 2 PATENTES
EXE 1 REGDEPOSITO

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CASTILLO GRAU ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	17246400	17/01/2007	77,000.00
CASTILLO GRAU ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	17246409	17/01/2007	427,000.00

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

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	
	12 MARCAS Y LEHAS COMERCIALES	99,000.00
	TOTAL :	\$ 99,000.00

SOM: NOVENTA Y NUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

EXAMEN TÉCNICO DE FONDO			
Nº Radicación	01-46749	Fecha de presentación	12/06/2001
Nº Prioridad		Fecha de Prioridad	

Palabras clave	Biguanidinas	Combinación farmacológica	Rosiglitazona
Troglitazona	Ciglitazona	Pioglitazona	Metformina

CLASIFICACIONES INTERNACIONALES DE BUSQUEDA
A61K31/425

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES	
Patente Original	GB2335597

BASES DE DATOS CONSULTADAS	
ESPACENET	EPOLINE

INFORMES DE EXAMEN EN OTRAS OFICINAS DE PI		
Oficina	Fecha	Reivindicaciones
EPO		

ANTERIORIDADES CONSIDERADAS		
Documento	Relevancia	Reivindicaciones afectadas
WO9857634	Novedad	1 a 14
EP0749751	Novedad	1 a 14
EP0861888	Novedad	1 a 14
Artículo 1	Novedad	1 a 14

LITERATURA NO PATENTES		
Documento no Patentes	Relevancia	Reiv. Afectadas

Observaciones

Fecha del examen	01/09/2006