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COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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P-987

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E.

S.

D.

Re: Expediente No. 07.096.487

Solicitud de patente a nombre de **WATSON PHARMACEUTICALS, INC & TAKEDA PHARMACEUTICAL COMPANY LIMITED**

Yo, DILIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como apoderada de las sociedades **WATSON PHARMACEUTICALS, INC & TAKEDA PHARMACEUTICAL COMPANY LIMITED**, domiciliadas en California, Estados Unidos, solicitantes de la patente de la referencia, en respuesta al oficio No. 17934 notificado por fijación en lista el 18 de noviembre de 2011, me permito manifestar:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial un nuevo capítulo reivindicatorio, el cual consta de 1 a 14 reivindicaciones y reemplaza en su totalidad el capítulo reivindicatorio presentado anteriormente.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones a la claridad, planteadas por el examinador en su concepto técnico.

2. Claridad de la Solicitud

El examinador objeta la claridad del capítulo reivindicatorio, con el fin de subsanar la totalidad de dichas objeciones el solicitante presenta un nuevo capítulo reivindicatorio que reemplaza la totalidad del presentado anteriormente.

El solicitante declara que el nuevo capítulo reivindicatorio se encuentra debidamente sustentado por la descripción y no incluye materia nueva.

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3. Novedad

El examinador objeta la novedad de la presente solicitud a la luz de lo divulgado por la anterioridad US 2004/0161462 (en adelante D1). De acuerdo con el examinador, todas las características esenciales de la invención se encuentran comprendidas en D1, por lo que la reivindicación 1 no es nueva.

Al respecto, el solicitante quisiera anotar que las nuevas reivindicaciones adjuntas se relacionan con una modalidad de la invención la cual consiste en una tableta farmacéutica que proporciona niveles terapéuticos de clorhidrato de metformina y clorhidrato de pioglitazona a un paciente mediante administración oral. Como se explica en la descripción, durante el desarrollo de la tableta reclamada fue necesario superar una serie de problemas sustanciales. Específicamente, el solicitante necesitó desarrollar una tableta que permitiera al clorhidrato de pioglitazona adherirse lo suficiente a la superficie externa de una membrana de liberación sostenida permitiendo así el procesamiento adicional, tal como el empaque y el transporte. La adherencia también debía permitir una liberación rápida de la pioglitazona después de la administración (la cual se establece en las reivindicaciones adjuntas como no menor a 90% en 30 minutos). Los problemas de adhesión/liberación se complicaron aún más debido a la estabilidad de la pioglitazona, la cual tendía a degradarse. El solicitante encontró una solución para el problema de adhesión/liberación/estabilidad, el cual se establece en las reivindicaciones propuestas.

Uno de los excipientes empleados para resolver el problema de adhesión/liberación/estabilidad fue un aglutinante soluble en agua de baja viscosidad, y específicamente hidroxipropil celulosa (HPC). Adicionalmente, el solicitante encontró que un grado preferido de hidroxipropil celulosa “exhibía” una viscosidad entre 2 y 6 mPa.s cuando se probaba como una solución acuosa al 2% y 20°C.

El solicitante también adjunta la declaración del señor Okochi, la cual también fue presentada en la solicitud de Estados Unidos para sustentar la patentabilidad de las reivindicaciones propuestas. En su declaración, Okochi demuestra la importancia de la selección del excipiente para su uso en la capa de liberación inmediata de pioglitazona. El señor Okochi asegura en su declaración que el revisó los datos relacionados con las composiciones preparadas de acuerdo con el ejemplo 7 (Formulación A) y el Ejemplo 8 (Formulación B) de la solicitud de patente US 11/093,742 (la cual equivale a la solicitud en estudio). Se notó que el recubrimiento de color aplicado en el ejemplo 8 difiere levemente del recubrimiento de color empleado en la formulación B en los datos adjuntos.

La declaración de Okochi describe además una formulación de

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metformina/pioglitazona (Formulación C), en donde los excipientes en la capa de liberación inmediata difieren de los excipientes empleados en los ejemplos 7 y 8 de la presente solicitud. Específicamente, la única diferencia entre la Formulación B (Ejemplo 8) y la Formulación C es la selección de los excipientes de la capa de liberación inmediata de la pioglitazona. Las Formulaciones A y C difieren en la composición de la capa de liberación inmediata y la adición de una capa de color. Las tres formulaciones contienen el mismo núcleo de metformina rodeado de una membrana de liberación controlada. Más específicamente, en la Formulación C, la providona ha sido reemplazada por hidroxipropil celulosa (3 mg/tableta contra 9 mg/tableta), el monohidrato de lactosa ha sido incrementado de 30 mg/ tableta a 90 mg/tableta, se han empleado un almidón de sodio (un desintegrante) y poloxamer (un surfactante), y se han removido el polietilen glicol (un mejorador de flujo) y dióxido de titano (un agente colorante). Estas mismas diferencias aplican a la comparación de las Formulaciones A y C, con la adición de que a la Formulación A no se le aplicó una capa de color.

La declaración de Okochi describe pruebas de estabilidad a largo plazo de la pioglitazona en las tabletas de metformina/pioglitazona descritas arriba, en donde las tabletas de metformina/pioglitazona fueron expuestas a condiciones de 40°C y 75% de humedad relativa por 0,5 meses, 1 mes, 2 meses y 3 meses. Las pruebas descritas en la declaración de Okochi demuestran que alterar la composición de la capa de liberación inmediata de pioglitazona, o sea cambiar el aglutinante o incluir un excipiente tal como un surfactante, ocasiona que la pioglitazona se degrade e incrementa las impurezas relacionadas. Más específicamente, las impurezas relacionadas con la pioglitazona se incrementaron del 0,16% (Formulación A) y el 0,18% (Formulación B) al 0,75 (Formulación C) después de 3 meses de almacenamiento a 40°C y 75% de humedad relativa. Esto resultó en niveles de impurezas superiores al 0,6%, lo cual es por fuera de los rangos mencionados en las nuevas reivindicaciones.

Los resultados de las pruebas claramente demuestran la importancia de los excipientes empelados en la capa de liberación inmediata de pioglitazona.

Específicamente en relación con la objeción de novedad, el solicitante afirma que D1 no divulga:

- 1) Una dosis farmacéutica que comprende una capa de liberación inmediata de pioglitazona que comprende hidroxipropil celulosa;
- 2) Donde la dosis farmacéutica libera no menos del 90% de la pioglitazona de la dosis dentro de 30 minutos cuando se prueba de acuerdo con la Farmacopea 26 de Estados Unidos, con el aparato 1 a 100 rpm, 37°C y 900 ml de solución tampón de KCl-HCl 0,3M, pH 2; y
- 3) Que proporciona el siguiente perfil de impurezas de ioglitazona:
 - a. la cantidad de impurezas totales de pioglitazona seleccionadas de

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entre:

- i. (+/-)-5-[p-[2-(5-etil-2-piridil)etoxi]benzil]-5-hidroxi-2,4-tiazolidinediona;
- ii. (z)-5-[p-[2-(5-etil-2-piridil)etoxi]benziliden]-2,4-tiazolidinediona;
- iii. (+/-)-5-[p-[2-(5-etil-2-piridil)etoxi]benzil]-3-[2-(5-etil-2-piridil)etil]-2,4-tiazolidinediona;
- iv. (+/-)-etil-2-carbamioiltio-3-[4-[2-(5-etil-2-piridil)etoxi]fenil]propionato; y
- v. Etil-3-p-[2-(5-etil-2-piridil)etoxi]fenil-propionato

las cuales están presentes en la forma de dosis en no más del 0,6% como se determina mediante cromatografía líquida de alto desempeño.

El solicitante nota que D1 menciona de manera general la “hidroxipropil celulosa”, sin embargo, notamos que la descripción de D1 no proporciona ninguna información sobre los grados disponibles o las características de los diferentes grados de hidroxipropil celulosa. A manera informativa, el solicitante adjunta copia de una monografía sobre la hidroxipropil celulosa elaborada por Rowe y colaboradores, incluida en el *Manual de excipientes farmacéuticos*. Cabe anotar que en dicha monografía, los rangos de viscosidad para los diferentes grados de hidroxipropil celulosa se dan de la siguiente forma: “soluciones acuosas de Klucel (Aqualon) a 25°C”, empleando soluciones del 1% al 5%, varían de 75-150 mPa.s a 4000-6500 mPa.s. El solicitante declara que, basándose en la divulgación del Manual la divulgación de D1 no puede anticipar las reivindicaciones adjuntas, sin conocer de antemano el porcentaje en solución y la viscosidad divulgados en la presente descripción y reclamados en el nuevo capítulo reivindicatorio.

Como se divulgó anteriormente, las nuevas reivindicaciones adjuntas están dirigidas específicamente a “un aglutinante soluble en agua de **baja** viscosidad que exhibe una viscosidad entre 2 y 6mPa.s cuando se prueba como una solución acuosa al 2% y 20°C” (resaltado fuera del texto). El Manual claramente divulga que la hidroxipropil celulosa puede exhibir un amplio rango de viscosidades. Por lo tanto, el solicitante declara que el experto medio en la materia no podría derivar de D1 el uso específico de “un aglutinante soluble en agua de **baja** viscosidad que exhibe una viscosidad entre 2 y 6mPa.s cuando se prueba como una solución acuosa al 2% y 20°C”, para lograr la adhesión y liberación adecuadas características proporcionadas por la presente invención.

El solicitante anota que la única información sobre impurezas proporcionada por los ejemplos específicos de D1 se basan en una formulación que no contiene hidroxipropil celulosa en la capa de liberación inmediata de pioglitazona. Las formulaciones de los ejemplos de D1 contienen hidroxipropil metilcelulosa

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(HPMC también conocida como hipromelosa) o OPADRY® Clear en la capa de liberación inmediata de pioglitazona. El solicitante anota que la HPMC también se encuentra disponible en diferentes grados y posee diferentes viscosidades. OPADRY® Clear es una formulación privada, sin embargo, de acuerdo a lo que se conoce públicamente, es de nuestro entender que comprende HPMC y polietilén glicol 400. Por lo tanto, el solicitante establece que D1 no le enseñaría al experto medio en la materia emplear un aglutinante específico de baja viscosidad con el rango de viscosidad establecido en las reivindicaciones adjuntas.

En resumen, me permito decir que gracias a los argumentos anteriormente mencionados, la presente solicitud cumple cabalmente con los requisitos de claridad y novedad respecto la composición expuesta en la presente solicitud. Por lo tanto, solicito comedidamente a ese despacho se sirva reconocer estos requisitos y conceder el privilegio de patente de invención a la solicitud en estudio.

En consecuencia, solicitamos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional. De igual forma, si el examinador considera que subsisten razones para objetar la presente invención ruego expedir otro examen de fondo con los debidos motivos y razones que sustenten su objeción con el fin de que mi mandante tenga la posibilidad de exponer sus argumentos con base en la interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: *"habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares"* y *"(.) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso"*, respectivamente (el subrayado es nuestro).

Señor Superintendente,



DILIA RODRIGUEZ D'ALEMAN

CC. 41.654.882 de Bogotá

TP 20824

Cód. 008

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REIVINDICACIONES

1. Una forma de dosis farmacéutica que comprende:
 - a. Una tableta osmótica que comprende:
 - i. Un núcleo de tableta comprimido que comprende al menos un excipiente farmacéuticamente aceptable y solo una droga activa que consiste de clorhidrato de metformina; y
 - ii. Una membrana de liberación sostenida que rodea el núcleo de tableta comprimido en donde el clorhidrato de metformina es liberado de la tableta osmótica tal que el pico de metformina en plasma se obtiene de 6 – 12 horas después de la administración de la forma de dosis después de la comida; y
 - b. una capa de liberación inmediata que rodea la membrana de liberación controlada de la tableta osmótica , que comprende clorhidrato de pioglitazona y un aglutinante soluble en agua de baja viscosidad que exhibe una viscosidad entre 2 mPa.s y 6 mPa.s cuando se prueba como una solución acuosa al 2% y 20°C, y en donde dicho aglutinante soluble en agua de baja viscosidad es hidroxipropil celulosa;

en donde no menos del 90% de la pioglitazona es liberada de la forma de dosis dentro de 30 minutos cuando se prueba de acuerdo con la Farmacopea 26 de Estados Unidos , con el aparato 1 a 100 rpm, 37°C y 900 ml de solución tapón de KCl-HCl 0,3M, pH 2,0, y la cantidad total de impurezas de pioglitazona se seleccionan del grupo que consiste de:

 - i. (+/-)-5-[p-[2-(5-etil-2-piridil)etoxi]benzil]-5-hidroxi-2,4-tiazolidinediona;
 - ii. (z)-5-[p-[2-(5-etil-2-piridil)etoxi]benziliden]-2,4-tiazolidinediona;
 - iii. (+/-)-5-[p-[2-(5-etil-2-piridil)etoxi]benzil]-3-[2-(5-etil-2-piridil)etil]-2,4-tiazolidinediona;
 - iv. (+/-)-etil-2-carbamioiltio-3-[4-[2-(5-etil-2-piridil)etoxi]fenil]propionato; y
 - v. Etil-3-p-[2-(5-etil-2-piridil)etoxi]fenil-propionato

las cuales están presentes en la forma de dosis en no más del 0,6% como se determina mediante una cromatografía líquida de alto desempeño.
2. La forma de dosis farmacéutica como se define en la reivindicación 1, en donde no menos del 95% de la pioglitazona es liberada de la forma de dosis dentro de 30 minutos cuando se prueba de acuerdo con la Farmacopea 26 de Estados Unidos , con el aparato 1 a 100 rpm, 37°C y 900 ml de solución tapón de KCl-HCl 0,3M, pH 2,0.
3. La forma de dosis farmacéutica como se define en la reivindicación 1, en donde no menos del 100% de la pioglitazona es liberada de la forma de dosis dentro de 30 minutos cuando se prueba de acuerdo con la Farmacopea 26 de Estados Unidos , con el aparato 1 a 100 rpm, 37°C y 900 ml de solución tapón de KCl-HCl 0,3M, pH 2,0.

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4. La forma de dosis farmacéutica como se define en la reivindicación 1, en donde las impurezas de pioglitazona totales no son más del 0,5%.
5. La forma de dosis farmacéutica como se define en la reivindicación 1, en donde cada impureza de pioglitazona individual en la forma de dosis final no es más del 0,25%.
6. La forma de dosis farmacéutica como se define en la reivindicación 1, en donde cada impureza de pioglitazona individual en la forma de dosis final no es más del 0,20%.
7. La forma de dosis farmacéutica como se define en la reivindicación 1, en donde cada impureza de pioglitazona individual en la forma de dosis final no es más del 0,10%.
8. La dosis farmacéutica de la reivindicación 1, en donde la tableta osmótica comprende:
 - a. un núcleo de tableta comprimido que comprende:
 - i. 50-98% de clorhidrato de metformina;
 - ii. 0,1-40% agente aglutinante;
 - iii. 0-20% de un mejorador de absorción; y
 - iv. 0-5% de un lubricante;
 - b. opcionalmente un recubrimiento de sello que rodea el núcleo; y
 - c. una membrana de liberación sostenida que comprende:
 - i. 50-99% de un polímero;
 - ii. 0-40% de un mejorador de flujo; y
 - iii. 0-25% de un plastificante.dicha membrana tiene al menos un pasaje formado en ella para la liberación del clorhidrato de metformina.
9. La dosis farmacéutica de la reivindicación 1, en donde dicho núcleo está libre de un polímero gelificante o expansivo.
10. La dosis farmacéutica de la reivindicación 1, en donde dicha liberación de dicho clorhidrato de metformina proporciona un $T_{\max}$ de 6-12 horas.
11. La dosis farmacéutica de la reivindicación 1, en donde dicha liberación de dicho clorhidrato de pioglitazona proporciona un $T_{\max}$ de 1-4 horas.
12. Una forma de dosis farmacéutica que comprende:
 - a. Una tableta osmótica que comprende:
 - i. Un núcleo de tableta comprimido que comprende al menos un excipiente farmacéuticamente aceptable y solo una droga activa que consiste de clorhidrato de metformina; y

- ii. Una membrana de liberación sostenida que rodea el núcleo de tableta comprimido en donde el clorhidrato de metformina es liberado de la tableta osmótica tal que el pico de metformina en plasma se obtiene de 6 – 12 horas después de la administración de la forma de dosis después de la comida; y
- b. una capa de liberación inmediata que rodea la membrana de liberación controlada de la tableta osmótica, que comprende:
 - i. clorhidrato de pioglitazona y
 - ii. un aglutinante soluble en agua de baja viscosidad que exhibe una viscosidad entre 2 mPa.s y 6 mPa.s cuando se prueba como una solución acuosa al 2% y 20°C, y en donde dicho aglutinante soluble en agua de baja viscosidad es hidroxipropil celulosa;

en donde no menos del 95% de la pioglitazona es liberada de la forma de dosis dentro de 30 minutos cuando se prueba de acuerdo con la Farmacopea 26 de Estados Unidos, con el aparato 1 a 100 rpm, 37°C y 900 ml de solución tampón de KCl-HCl 0,3M, pH 2,0, y luego de almacenarse a 40°C y 75% de humedad relativa por 3 meses la forma de dosis contiene un total no mayor al 0,5% de las siguientes impurezas de pioglitazona:

- vi. (+/-)-5-[p-[2-(5-etil-2-piridil)etoxi]benzil]-5-hidroxi-2,4-tiazolidinediona;
- vii. (z)-5-[p-[2-(5-etil-2-piridil)etoxi]benziliden]-2,4-tiazolidinediona;
- viii. (+/-)-5-[p-[2-(5-etil-2-piridil)etoxi]benzil]-3-[2-(5-etil-2-piridil)etil]-2,4-tiazolidinediona;
- ix. (+/-)-etil-2-carbamoyltio-3-[4-[2-(5-etil-2-piridil)etoxi]fenil]propionato; y
- x. Etil-3-p-[2-(5-etil-2-piridil)etoxi]fenil-propionato

como se determina mediante una cromatografía líquida de alto desempeño y cada una de las impurezas de pioglitazona está presente en una cantidad no mayor al 0,20%.

13. La dosis farmacéutica de la reivindicación 12, en donde cada una de las impurezas de pioglitazona está presente en una cantidad no mayor al 0,10%.

14. La dosis farmacéutica de la reivindicación 12, en donde el núcleo de tableta comprimido es una mezcla homogénea de al menos un excipiente farmacéuticamente aceptable y clorhidrato de metformina.

Docket No. 141-490

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Lodin et al.

Serial No.: 11/093,742

Group Art Unit: 1611

Filed: March 30, 2005

Examiner: Welter, Rachael E.

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

New York, New York 10036
August 2, 2010

Via Electronic Filing System
Hon. Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF KAZUHIRO OKOCHI UNDER 37 C.F.R. § 1.132

Sir:

I, Kazuhiro Okochi, declare and state as follows:

1. I am currently employed by Takeda Pharmaceutical Company Limited, the co-owner of the above identified patent application, and I am one of the named inventors listed on the above identified patent application.
2. I am associate director and I am responsible for all aspects of technology assessment of pharmaceutical technology at Takeda Pharmaceutical Company Limited.
3. I received a master from the Kyoto University. A copy of my curriculum vitae is attached as Exhibit A.

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4. I have read and understand United States Published Patent Application No. 2005/0226928. It is my understanding that this Published Patent Application Corresponds to the above-identified patent application.

5. I have also reviewed: WO 01/35940 (hereinafter "Lewis"); U.S. Patent No. 6,838,093 (hereinafter "Flanner") and U.S. Patent No. 5,948,440 (hereinafter "Arora").

6. It is my understanding that the Examiner has relied upon these references to reject the claims of the above captioned patent application.

5. It is my further understanding that the above-identified application currently contains the following claim:

47. A pharmaceutical dosage form comprising:

(a) an osmotic tablet comprising:

- (i) a compressed tablet core comprising at least one pharmaceutically acceptable excipient and only one active drug that consists of metformin hydrochloride, and
- (ii) a sustained release membrane surrounding the compressed tablet core wherein the metformin hydrochloride is released from the osmotic tablet so the peak plasma level of metformin is obtained about 6-12 hours after administration of the dosage form following a meal; and

(b) an immediate release layer surrounding the sustained release membrane of the osmotic tablet comprising pioglitazone hydrochloride and a low viscosity water soluble binder that exhibits a viscosity between 2 and 6 mPa.S when tested as a 2% aqueous solution at 20°C;

wherein not less than 90% of the pioglitazone is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia 26, with Apparatus 1 at 100 rpm, 37°C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0 and the total amount of pioglitazone impurities selected from the group consisting of:

- (i) (+/-)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-5-hydroxy-2,4-thiazolidinedione;
- (ii) (z)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzylidene]-2,4-thiazolidinedione;
- (iii) (+/-)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-3-[2-(5-ethyl-2-pyridyl)ethyl]-2,4-thiazolidinedione;

(iv) (+/-)-ethyl-2-carbamoyltio-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl]
propionate; and
(v) ethyl-3-p-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl-propionate
that are present in the dosage form are not more than 0.6% as determined by
high performance liquid chromatography.

6. I have been asked to organize and review data related to the stability of pioglitazone hydrochloride in formulations where the pioglitazone hydrochloride has been applied as an immediate release layer to a sustained release membrane surrounding a metformin core. A summary of the formulations and data reviewed is attached hereto as Exhibit B.

7. The stability data for three separate formulations was reviewed during the preparation of the present declaration.

8. The first formulation (formulation A) reviewed was prepared in accordance with Example 7 of the present application and contained the following formulation:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	9.00 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Hydroxypropyl Cellulose, NF (HPC-SSL)	9.0 mg/tablet
Lactose Monohydrate, NF	30.0 mg/tablet
Polyethylene Glycol 8000, NF	0.450 mg/tablet
Titanium Dioxide, USP	0.90 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

9. The second formulation (formulation B) reviewed was prepared in accordance with Example 8 of the present application and contained the following formulation:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	

Opadry Clear (YS-1-7006)	9.00 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Hydroxypropyl Cellulose, NF (HPC-SSL)	9.0 mg/tablet
Lactose Monohydrate, NF	30.0 mg/tablet
Polyethylene Glycol 8000, NF	0.450 mg/tablet
Titanium Dioxide, USP	0.90 mg/tablet
Color Coating	
Hydroxypropyl Cellulose, NF (HPC-SSL)	5.32 mg/tablet
Polyethylene Glycol 8000, NF	0.84 mg/tablet
Titanium Dioxide, USP	0.84 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

10. A third formulation (formulation C) reviewed was prepared with the following formulation:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	9.00 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Povidone, USP (Kollidon K-30))	3.0 mg/tablet
Lactose Monohydrate, NF	90.0 mg/tablet
Poloxamer 188, NF (Lutrol F-68)	15.00 mg/tablet
Sodium Starch Glycolate, NF	30.00 mg/tablet
Color Coating	
Hydroxypropyl Cellulose, NF (HPC-SSL)	5.32 mg/tablet
Polyethylene Glycol 8000, NF	0.84 mg/tablet
Titanium Dioxide, USP	0.84 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

11. Formulations A-C were packed in a 100 cc high density polyethylene (HDPE) bottles containing one 3g SORB-IT® desiccant canister and subjected to accelerated stability conditions

of 40°C and 75% relative humidity for 0.5 months, 1 month, 2 months and 3 months. After storage, the final tablets were tested for pioglitazone related compounds by high performance liquid chromatography (HPLC). The results of the test are summarized in the table below:

Formulation	Initial impurities	0.5 M	1 M	2 M	3 M
Formulation A	0.18%	0.18%	0.19%	0.16%	0.16%
Formulation B	0.15%	0.14%	0.18%	0.14%	0.18%
Formulation C	0.14%	0.19%	0.29%	0.43%	0.75%

12. As shown in the above table, Formulation C is unstable compared with Formulations A and B, which were prepared in accordance with Examples 7 and 8 of the present application. The total pioglitazone related impurities in Formulation C exceeded the upper claim limit of not more than 0.6% of pioglitazone related impurities.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements and like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

August 2, 2010

Dated

Kazuhiro Okochi

Kazuhiro Okochi

EXHIBIT A

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Curriculum Vitae

Name: Kazuhiro Okochi

<u>Date</u>	<u>Education</u>
March 1987	Graduate College of Pharmacy, Kyoto University
March 1989	Master degree from Graduate School of Pharmaceutical Sciences, Kyoto University

<u>Date</u>	<u>Job</u>
From April 1989 until now	Takeda Pharmaceutical Company

During August 1994 to July 1995
Visiting scientist, College of Pharmacy, University of Kentucky

<u>Date</u>	<u>Industry Activities</u>
From 2001 to 2003	Osaka Pharmaceutical Manufacturers Association
From 2003 until now	Japan Pharmaceutical Manufacturers Association (JPMA) ICH Q8 JPMA topic deputy leader, Q-IWG Expert

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EXHIBIT B

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Table 1 - Components and Composition of Formulation A and Formulation B

	Component	Quantity per Tablet (mg)	
		Formulation A	Formulation B
Core Tablet	Metformin HCl membrane coated tablet	1201	1201
Seal Coat	Opadry Clear (YS-1-7006)	9	9
Pioglitazone Coating	Pioglitazone HCl	33.06	33.06
	Hydroxypropyl Cellulose,NF (HPC-SSL)	9	9
	Lactose Monohydrate,NF	30	30
	Polyethylene Glycol 8000,NF	0.45	0.45
	Titanium Dioxide,USP	0.9	0.9
Color Coating	Hydroxypropyl Cellulose,NF (HPC-SSL)		5.32
	Polyethylene Glycol 8000,NF		0.84
	Titanium Dioxide,USP		0.84
Polishing Coat	Candelilla Wax Powder	0.4	0.4
	Total	1283.81	1290.81

Table 2 -Components and Composition of Formulation C

	Component	Quantity per Tablet (mg)
		Formulation C
Core Tablet	Metformin HCl membrane coated tablet	1201
Seal Coat	Opadry Clear (YS-1-7006)	9
Pioglitazone Coating	Pioglitazone HCl	33.06
	Povidone,USP (Kollidon K-30)	3
	Lactose Monohydrate,NF	90
	Poloxamer 188, NF (Lutrol F-68)	15
	Sodium Starch Glycolate, NF (Explotab)	30
Color Coating	Hydroxypropyl Cellulose,NF (HPC-SSL)	5.32
	Polyethylene Glycol 8000,NF	0.84
	Titanium Dioxide,USP	0.84
Polishing Coat	Candelilla Wax Powder	0.4
	Total	1388.46

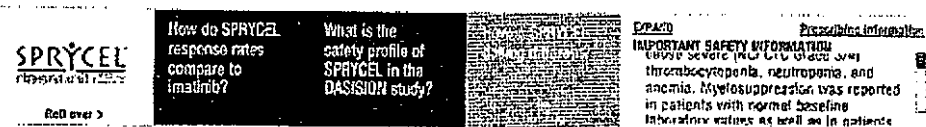
Table 3

Total impurities (%) of pioglitazone in each formulation after storage at 40°C /75%RH

Formulation	Specification for total impurities	Initial	0.5M	1M	2M	3M
Formulation A	NMT 0.6%	0.18	0.18	0.19	0.16	0.16
Formulation B	NMT 0.6%	0.15	0.14	0.18	0.14	0.18
Formulation C	NMT 0.6%	0.14	0.19	0.29	0.43	0.75

NMT : not more than

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Phase 1 multicenter dose-escalation study of ezatiostat hydrochloride (TLK199 tablets), a novel glutathione analog prodrug, in patients with myelodysplastic syndrome

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Author Affiliations

1. Presented in abstract form at the 49th Annual Meeting of the American Society of Hematology, Atlanta, GA, December 8, 2007.³¹

Abstract

Phase 1 testing of ezatiostat, a glutathione S-transferase P1-1 inhibitor, for the treatment of myelodysplastic syndrome was conducted in a multidose-escalation study. Patients received 10 dose levels (200, 400, 1000, 1400, 2000, 2400, 3000, 4000, 5000, and 6000 mg) of ezatiostat tablets in divided doses on days 1 to 7 of a 21-day cycle for a maximum of 8 cycles. The safety and pharmacokinetics of ezatiostat were evaluated. Forty-five patients with low to intermediate-2 International Prognostic Scoring System risk myelodysplastic syndrome were enrolled. No dose-limiting toxicities were observed. The most common grade 1 or 2, respectively, treatment-related adverse events were nonhematologic: nausea (56%, 9%), diarrhea (36%, 7%), vomiting (24%, 7%), abdominal pain (9%, 0%), constipation (4%, 9%), anorexia (3%, 7%), and dyspepsia (3%, 7%). Concentration of the primary active metabolite, TLK236, increased proportionate to ezatiostat dosage. Seventeen hematologic improvement (HI) responses by International Working Group criteria were observed at dose levels of 200 to 6000 mg/day with 11 HI responses at doses of 4000 to 6000 mg/day. HI responses occurred in all lineages including 3 bilineage and 1 complete cytogenetic response. Decreased number of red blood cell and platelet transfusions and in some cases transfusion independence were attained. Extended dose schedules of ezatiostat tablets are under investigation. This study was registered at <http://www.clinicaltrials.gov> as NCT00280631.

Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal hematopoietic stem cell disorders characterized by dysplasia in 1 or more myeloid, erythroid, and megakaryocytic lineages, leading to ineffective blood cell production and a variable risk of transformation to acute myelogenous leukemia (AML).¹⁻⁴ The treatment options available to patients with MDS are largely based upon the patient's age and prognosis as determined by the International Prognostic Scoring System (IPSS).⁵ For patients in the low to intermediate 1 (INT-1) IPSS risk categories, the goal of treatment is to improve ineffective hematopoiesis while providing the appropriate supportive care. In higher risk patients, the goal is to extend survival and delay transformation to AML.

Current therapeutic strategies for patients with low or INT-1 risk include supportive care⁶ and low-intensity therapy such as chemotherapy with low-dose cytarabine, azacitidine, decitabine, or biologic response modifiers (eg, amifostine, pentoxifylline, lisofylline, interferon alpha, anti-thymocyte globulin [ATG], cyclosporine, retinoids, and vitamin D analogs), or nonchemotherapeutic agents such as thalidomide or thalidomide analogs.^{7,8}

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The National Comprehensive Cancer Network (NCCN) Practice Guidelines recommend the use of erythropoietin (EPO) and other stem cell factors for anemia.⁷ For patients with refractory anemia (RA) and a serum EPO level of less than 500 mU/mL, EPO may be given subcutaneously for 2 to 3 months. Concomitant oral iron may be beneficial even without iron deficiency in the absence of iron overload. In RA with ringed sideroblasts (RARS), EPO can be combined synergistically with granulocyte colony-stimulating factor (G-CSF) for 3 months. G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) should not be administered routinely for infection prophylaxis, but should be considered for recurrent or resistant infections in neutropenic patients.

To date, only a few treatments have had an impact on the natural history of MDS. Recent results from a clinical trial with azacitidine in MDS patients have shown that the drug improves survival and quality of life for patients with MDS compared with best supportive care.^{9,10} Allogeneic bone marrow transplantation is a potentially curative procedure with a high treatment-related mortality (40% to 50%), but is applicable to only a minority of patients of younger age (those < 60 years old) with good performance status and a suitable donor.^{11,12} Otherwise, management is largely supportive, consisting of treatment of infections, transfusions of red cells for anemia, platelet transfusions to reduce bleeding, and use of hematopoietic growth factors.

Recently, azacitidine was approved by the Food and Drug Administration (FDA) based upon a 16% response rate in azacitidine-treated patients compared with 0 percent receiving best supportive care in a 191-patient study.^{9,10} In 2006, Revlimid (lenalidomide), a thalidomide analog, was approved by the FDA for treatment of patients with transfusion-dependent anemia due to low or INT-1 risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Dacogen (decitabine), a hypomethylating agent, was also approved by the FDA in 2006 for treatment of patients with MDS including previously treated and untreated, de novo and secondary MDS of all French-American-British (FAB) subtypes and INT-1, INT-2, and high-risk IPSS groups. Attempts to use differentiating agents such as all-*trans* retinoic acid or vitamin D analogs have been disappointing,^{13,14} although one study reported a beneficial effect of vitamin D in the progression to acute leukemia.¹⁵ Trials of low-dose cytarabine have demonstrated hematologic response rates of 10% to 25%.¹⁶

Growth factors may improve cytopenias but do not induce complete remissions and may not prolong survival. Recently, weekly dosing of recombinant human erythropoietin alpha therapy resulted in improvement in erythropoiesis in a subset of MDS patients who were unresponsive to conventional dosing.^{17,18} Intensive chemotherapy induces complete remissions in 40% to 50% of patients but is associated with serious morbidity and mortality, with repeated and prolonged periods of hospitalization required and consequent impaired quality of life.

In conclusion, the need for new drugs with novel mechanisms of action remains. Ezatiostat hydrochloride (TLK199 tablets), a glutathione analog prodrug, is currently being developed for the treatment of cytopenias associated with MDS or chemotherapy. Ezatiostat is a synthetic tripeptide analog of glutathione that has been shown to stimulate the proliferation of myeloid precursors.¹⁹ Ezatiostat is metabolized to TLK117. TLK117 selectively binds to and inhibits glutathione S-transferase P1-1 (GST P1-1), an enzyme that is overexpressed in many human cancers. GST P1-1 is known to bind to and inhibit Jun-N-terminal kinase (JNK), a key regulator of cellular proliferation, differentiation, and apoptosis²⁰ (Figure 1). TLK117 facilitates dissociation of GST P1-1 from JNK, leading to activation of JNK and the subsequent promotion of growth and maturation of hematopoietic progenitors in preclinical models, while promoting apoptosis in human leukemia cell lines. Ezatiostat has been shown to stimulate the multilineage differentiation of hematopoietic progenitors in vitro and overcomes the block in myeloblast differentiation (ineffective myelopoiesis) in leukemia cell lines.^{19,21,22}

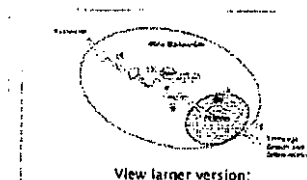


Figure 1

Ezatiostat HCl (TLK199). (1) Ezatiostat enters the cell and is hydrolyzed to its corresponding diacid. (2) The diacid form of ezatiostat

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binds to GST P1-1 and disrupts the interaction of GST P1-1 with JNK. (3) JNK is activated by phosphorylation and in turn activates c-Jun. (4) c-Jun and other regulators promote transcription of genes that lead to proliferation and differentiation of normal hematopoietic cells or apoptosis of malignant cells. (5) Signaling pathways are activated to promote growth and differentiation of hematologic progenitors that form neutrophils, erythrocytes, and platelets.

The absorption, distribution, metabolism, and excretion (ADME) properties of TLK199 were characterized in the rat and dog. The primary metabolite of TLK199 is the phenylglycine monoester (TLK236). Unchanged TLK199 was not detected in blood, although the metabolites TLK117 and TLK236 were detected, indicating that the systemic clearance of the parent compound was both rapid and extensive. In a 14-day multiple dose study, up to 10 mg/kg TLK199 twice daily was administered to dogs orally. TLK199 was absorbed but was quickly biotransformed primarily to TLK236. Concentrations of TLK199 and TLK235, glutamate monomer, were either very low or below the detection limit. TLK117 is the predominant metabolite in the rat.

Toxicology studies included a 14-day repeat dose study in rats and dogs. Rats exhibited no significant toxicity following daily oral administration of TLK199 at doses up to 1000 mg/kg per day for 14 days. Dogs exhibited no significant toxicity following daily oral administration of TLK199 at doses as high as 20 mg/kg for 14 days.

On the basis of safety and promising hematologic activity of studies with the intravenous formulation of ezatiostat,^{23,24} we initiated a phase I study with an oral formulation. The goal of this study was to determine the maximum tolerated dose (MTD) or optimal biologic dose (OBD), the pharmacokinetics, safety profile, and preliminary evidence of hematologic improvement.

Methods

Patients

This study was conducted in accordance with the International Conference on Harmonization and Good Clinical Practice standards. Institutional review board (IRB) approval was obtained from all participating institutions: University of Massachusetts Medical School, Loyola University Medical School, and University of South Florida. (Note: J.G. moved to Southern Illinois University Simmons Cooper Cancer Institute, Springfield, IL; however, this institution did not participate in this study.) All patients provided written informed consent before study participation in accordance with the Declaration of Helsinki.

Eligible patients were 18 years or older, with histologically confirmed diagnosis of primary MDS, either newly diagnosed or for whom prior treatment was ineffective, and with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were required to have adequate hepatic and renal function. No prior treatment with hematopoietic growth factors within 3 weeks of study entry was permitted. Other inclusion criteria were as follows: documented significant cytopenia for more than 2 months and ineligibility for stem cell bone marrow transplantation (BMT). Patients were excluded for prior allogeneic BMT, cytogenetic abnormalities consistent with de novo AML (such as t(15,17), t(9,11), t(8,21), t(9,22), t(8,16), and inv16),^{25,26} proliferative chronic myelomonocytic leukemia (CMML), prior leukemia, rapidly progressive AML, chronic myelogenous leukemia (CML) blast crisis, use of oral corticosteroids (> 10 mg), history of hepatitis B/C, HIV, or an active infection requiring intravenous antibiotics.

Study design

This phase I study of ezatiostat was conducted in patients with all World Health Organization (WHO) classification types of MDS.²⁷ The objectives of the study were to evaluate safety, pharmacokinetics, and the hematologic improvement (HI) response rate. A cohort of patients was evaluated under fed/fast conditions to determine the effect of food on the pharmacokinetics of ezatiostat. Ezatiostat tablets were administered at 10 dose-escalation levels of 200, 400, 1000, 1400, 2000, 2400, 3000, 4000, 5000, and 6000 mg divided into 2 oral doses twice daily on days 1 to 7 of a 21-day treatment cycle. The dose schedule for

ezatiostat tablets was chosen to mimic the schedule that led to hematologic improvement in the clinical phase 1-2a study of the intravenous liposomal formulation of TLK199 product in MDS patients.²⁴ In addition, the dose schedule for TLK199 tablets mimics the schedule that led to steady-state pharmacokinetics after 3 to 5 days with the oral formulation nonclinical pharmacokinetic studies in animals. A minimum of 3 patients were treated at each dose level. If no more than none of 3 or 1 of 6 patients experienced a dose-limiting toxicity (DLT), 3 subsequent patients were enrolled at the next higher dose level. Dose-escalation continued until 2 or more patients in a cohort experienced a treatment-related DLT or dose escalation was completed based on the determination of the OBD. The MTD was defined as the highest dose at which none of 3 patients experienced a DLT or 1 full dose level below the level where a DLT was observed. If biologic activity (correction of neutropenia; improvement in anemia, platelet count, or blast count; reduction in red blood cells [RBCs] or platelet transfusion requirements) occurred before the MTD was established, the OBD was selected for future phase 2 studies. At the MTD or a dose level below the MTD, at least 6 additional patients were treated to further evaluate toxicity.

Patients were allowed to receive up to a maximum of 8 cycles of treatment unless unacceptable toxicity occurred. Treatment cycles continued until the patient experienced a lack of MDS response, disease progression, or unacceptable toxicity. The morning dose of ezatiostat tablets was administered after an overnight fast and the evening dose, approximately 12 hours later on an empty stomach (at least 3 hours after an evening meal). Twelve patients were enrolled to evaluate the pharmacokinetics of ezatiostat tablets under fed and fasted conditions. Under fed conditions, patients received the morning dose 30 minutes after a standard high-calorie meal followed by pharmacokinetic evaluation. Adverse events (AEs) were graded in accordance with the National Cancer Institute-Common Toxicity Criteria for Adverse Events, version 3.0 (NCI-CTCAE, version 3.0; Bethesda, MD). A hematologic DLT was defined as a grade 4 hematologic AE complicated by infection, severe hemorrhage, or marrow aplasia persisting more than 4 weeks. A nonhematologic DLT was defined as any treatment-related grade 3 or 4 nonhematologic AE occurring during the first treatment cycle.

Drug formulation and administration

Ezatiostat tablets are formulated as 100-mg and 500-mg tablets. Each tablet contains ezatiostat hydrochloride in a formulation containing the following excipients: mannitol, croscarmellose sodium, hypromellose, magnesium stearate, and Opadry Clear (Opadry Clear is a mixture of hypromellose and polyethylene glycol 400). Divided daily doses were administered orally approximately every 12 hours, 1 tablet at a time with adequate fluids.

Baseline and follow-up assessments

All patients underwent a screening evaluation including a complete medical history, a physical examination with vital signs, an assessment of ECOG performance status, an electrocardiogram, and a chest x-ray. Pretreatment laboratory evaluation included complete blood count (CBC) with differential and platelet count, serum erythropoietin, ferritin and transferrin levels, serum chemistry profile, urinalysis, and pregnancy test. On day 1 of each subsequent treatment cycle, a physical examination including vital signs and laboratory assessments (CBC with differential, platelet count, and chemistry profile) was obtained, use of concomitant medication(s) was documented, and AEs were assessed. Complete blood count with differential and platelet count was repeated weekly.

Dose modifications

Patients who experienced a treatment-related nonhematologic grade 3 or higher toxicity had treatment delayed by up to a maximum of 3 weeks until recovery to grade 1 or baseline and continued treatment at a reduced dose. Patients who did not meet the minimum retreatment criteria on day 21 of a treatment cycle had the subsequent cycle delayed and the AE re-evaluated. If recovery did not occur after a delay of 21 days, treatment was discontinued and patients were followed until resolution of the AE. Each dose of ezatiostat was reduced by the amount of 1 tablet for each dose reduction required.

Efficacy

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Hematologic Improvement (HI) response assessment was performed every 2 treatment cycles and was based upon the laboratory values indicating the best response during the previous 2 cycles. Although HI response assessments were performed every 2 cycles, treatment was to continue for at least 4 cycles before a decision to withdraw the patient from study treatment due to lack of MDS response was made.

The objective HI response was based on the standardized criteria for assessing MDS response as proposed by the International Working Group (IWG; 2000) for MDS.^{28,29} In addition to the peripheral cytopenia assessment of HI, bone marrow assessments were reviewed beyond 4 months.

Patients with HI in the erythroid (E), neutrophil (N), and platelet (P) cell lines were summarized by cell lineage as HI-E, HI-N, and HI-P, respectively, based on the number of cytopenic peripheral blood cell lineages at baseline. The primary analysis was conducted with the IWG 2000 criteria and an exploratory analysis using IWG 2006 criteria was also performed.

Ezatiostat tablets pharmacokinetic assessment

Blood and urine samples were collected at specific time intervals to assess the pharmacokinetics of ezatiostat. Blood samples were collected on days 1 and 7 of the first treatment cycle. On day 1, urine samples were collected for 6 hours after ingestion of ezatiostat tablets. Plasma and urinary concentrations of ezatiostat and its metabolites (TLK235, TLK236, and TLK117) were analyzed from 400 µL whole blood supernatant or urine supernatant (after protein precipitation with 0.05 M acetic acid in acetonitrile). After evaporation to dryness and reconstitution, the extracts were analyzed by liquid chromatography-atmospheric pressure ionization mass spectrometry/mass spectrometry (LC-API/MS/MS). Run times were approximately 10 minutes. The lower limit of quantitation (LLQ) for ezatiostat and metabolites is 10 µg/mL. Twelve patients had pharmacokinetic evaluation under fed and fasted conditions.

Statistical analysis

Demographic and baseline MDS disease characteristics of all treated patients were summarized descriptively. The sample size, total number of cycles administered, median, and range of cycles per patient were summarized overall and by the following total daily dose levels of ezatiostat tablets: 200, 400, 1000, 1400, 2000, 2400, 3000, 4000, 5000, and 6000 mg.

The safety of ezatiostat was evaluated by the frequency, severity, and relationship to ezatiostat tablets of treatment-emergent AEs graded according to the NCI-CTCAE version 3.0 that occurred during the study treatment and follow-up period of 30 days after the last study drug treatment. The incidence and percentage of AEs related to study treatment judged by investigators were summarized overall and by dose level.

Objective HI response rate including HI-E, HI-N, and HI-P, unilineage, and bilineage HI rate by IWG criteria (2000 and 2006),^{28,29} was calculated in the efficacy-evaluable population. The count and percentage of patient reported outcomes of clinical benefit were also reported.

Results

Patient demographic characteristics

Forty-five patients (33 males and 12 females; Table 1) with histologically confirmed MDS were enrolled in the trial and treated at 3 centers in the United States between February 15, 2006, and October 15, 2007. The majority of patients were white (98%) with an ECOG performance status of 1 (56%). Ages ranged from 53 to 84 years (median, 71 years). Twenty-two patients (49%) had normal cytogenetics, 16 (36%) had abnormal cytogenetics, and 7 (26%) had unknown cytogenetics. The majority of patients, 28 (62%), had an INT-1 risk IPSS; 14 (31%) were low risk, and a minority of patients, 3 (7%), had an INT-2 risk MDS disease. The WHO subtypes included 9 patients (20%) with RA, 11 (24%) RARS, 3 (7%) refractory anemia with excess blasts (RAEB-I), 1 (2%) RAEB-II, 8 (18%) refractory cytopenias with multilineage dysplasia (RCMD), 2 (4%) RCMD-with ringed sideroblasts (RS), 5 (11%) MDS-unclassified (U), and 2 (4%) CMML. The majority of patients, 27 (60%), were red blood cell (RBC) transfusion dependent (defined as patients who required at least 4 units RBC transfusion over an 8-week time period before treatment), and only 5 patients (11%) were

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platelet transfusion dependent. Thirty-five (78%) patients had baseline anemia, 21 patients (47%) had baseline neutropenia, and 25 patients (56%) reported thrombocytopenia at baseline. Overall, 16 patients (26%) had a single lineage cytopenia; 22 (49%), bilineage cytopenia; and 7 (16%), trilineage cytopenia.

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Table 1	
Patient demographics and MDS disease characteristics	

Patients received a median of 1 prior therapy (range, 0-5 prior therapies); 20 (44%) received prior recombinant erythropoietin; 16 (36%), immunotherapy; 15 (33%), chemotherapy; 8 (18%), prior G-CSF; 7 (16%), corticosteroids; and 5 (11%), investigational agents.

Ezatiostat tablets study treatment administration

Ten dose levels ranging from 200 to 6000 mg were evaluated (Table 2). Forty-five patients received a total of 228 cycles of ezatiostat tablets. The median number of cycles per patient was 5 (range, 1-12 cycles). No DLTs were observed. Dose reductions due to AEs were infrequent with a total of 4 patients (9%) receiving a dose reduction (2 patients at the 3000 mg/day dose level, 1 patient at the 5000 mg/day dose level, and 1 patient at the 6000 mg/day dose level) for nausea.

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Table 2	
Ezatiostat tablets: treatment administration	

A total of 5 patients had a dose delay (1 each occurring at the 1000, 2400, 3000, 4000, and 6000 mg/day dose level). Two of the dose delays were due to AEs with the remaining 3 due to scheduling difficulties.

Safety

Ezatiostat tablets were well tolerated with no treatment-related deaths reported. The most common treatment-related AEs were nonhematologic (Tables 3,4). A total of 3 grade 4 hematologic AEs (neutropenia) occurred at 3000 mg, 4000 mg, and 6000 mg (n = 1 at each dose level, respectively); however, there were no grade 1, grade 2, or grade 3 ezatiostat tablet treatment-related hematologic AEs reported at any dose level. There was 1 grade 3 (pyrexia) and no grade 4 nonhematologic AEs. Nausea, diarrhea, vomiting, abdominal pain, constipation, anorexia, dyspepsia, and abnormal odor were the most frequently observed nonhematologic AEs with ezatiostat tablets. The majority of patients were instructed to take the tablets without food, until the fed/fast cohort enrolled at the end of the study. There were a total of 22 serious adverse events (SAEs) reported, 18 were unrelated to ezatiostat and 4 were ezatiostat tablet treatment related (esophagitis [n = 2], reflux esophagitis [n = 1], and fever [n = 1]). Three patients discontinued treatment with ezatiostat tablets due to AEs. One patient experienced a grade 3 esophageal ulceratus with hematochezia. One patient experienced an AE, mild elevation of hepatic enzymes, that the investigator considered to be possibly related to ezatiostat tablets and discontinued study treatment after 4 cycles. Because only 6 patients each were in the fed/fast 6000-mg cohort, a meaningful analysis of adverse events with and without food ingestion could not be conducted due to the small sample size. Further study of ingestion of ezatiostat tablets with food will be conducted.

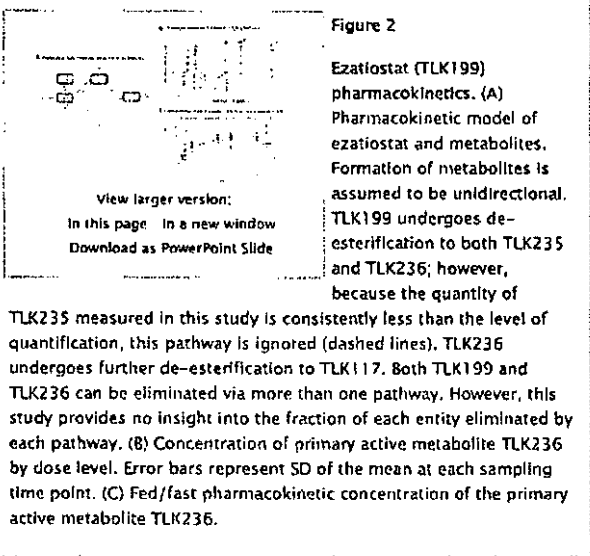
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Table 3	
Hematologic and nonhematologic adverse events related to ezatiostat tablets in 5% or more of patients: by grade	

Pharmacokinetic analysis
Concentrations of TLK199, TLK235, TLK236, and TLK117 were determined in whole blood by a

Hematologic and nonhematologic adverse events related to ezatiostat tablets in 5% or more of patients: by dose level

high-performance liquid chromatography (HPLC) assay. The limit of quantification was 10 µg/mL for all 4 entities. The pharmacokinetic model for ezatiostat and its metabolites (Figure 2A) was derived from the

concentrations of ezatiostat and metabolites in blood of patients administered ezatiostat intravenous formulation. The proposed pharmacokinetic model using nonlinear mixed effects was modeled by NONMEM (ICON Development Solutions, Ellicott City, MD). Ezatiostat undergoes de-esterification to both TLK235 and TLK236. Both TLK236 and TLK235 undergo further de-esterification to TLK117. This model is being further tested with the patient data collected in this and future studies.



Exposure to the primary active metabolite, TLK236, increased with ezatiostat tablet dose (Figure 2B). Ezatiostat tablets achieved a comparable exposure to ezatiostat administered intravenously with a liposomal formulation. Comparative fed/fast ezatiostat pharmacokinetics demonstrated similar results (Figure 2C). Food did not inhibit or delay absorption of ezatiostat tablets, thus patients will be allowed to ingest food on future studies. In summary, the exposure of the primary metabolite, TLK236, increases proportionate to ezatiostat dose. Fed/fast analysis revealed similar results. It was determined in this study that ezatiostat tablets may be ingested either 1 hour before or 1 hour after eating without affecting bioavailability.

Efficacy analysis

Forty-five patients were in the Intent-to-treat population. Hematologic improvement responses were observed in all 3 cell lines at dose levels of 200 to 6000 mg/day in the efficacy evaluable population (Table 5). The IWG criteria were revised during the course of the study; therefore, HI-E analyses were performed using the original IWG 2000 criteria as the primary analysis and with the new IWG 2006 criteria as an exploratory analysis (Table 5). Eleven of the 17 HI responses were observed in the 4000 to 6000 mg/day dose range, reflecting a dose response. One bilineage response was reported at 5000 mg/day and 2 bilineage responses were reported at the 6000 mg/day dose level. One bilineage response was correlated with a complete cytogenetic response.

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Table 5

Efficacy

Of the 23 patients who were RBC transfusion dependent, 8 (35%) achieved transfusion independence and 14 (61%) had a reduction in the RBC transfusion requirements of 4 units/8 weeks (Table 5). One of 5 platelet transfusion-dependent patients achieved independence from platelet transfusions. Since

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this was a phase I study, a formal quality of life validated questionnaire was not incorporated; however, clinical benefit was assessed by key MDS-related symptoms in an informal questionnaire. These patient-reported outcomes were considered exploratory analyses: patients with HI responses in this study did report improvement in clinical symptoms (Table 6).

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Table 6	
Patient reported outcomes	

Discussion

This phase I study was the first clinical study of ezatiostat tablets in patients with MDS. The 7-day dose schedule of tablet administration represents one half the number of days of the maximum dose schedule evaluated in rats and dogs (ie, 14 days). Ezatiostat doses up to 6000 mg/day were evaluated without reaching a DLT. Adverse events were primarily mild or moderate in grade, severe events were relatively few, and an MTD was not defined.

Ezatiostat has shown significant stimulatory activity in vitro in human bone marrow progenitor cultures, as well as in several in vivo preclinical models of myelopoiesis. GST P1-1-null mice consistently demonstrate higher than normal neutrophil levels, in addition to a significant increase in the growth rate of their embryonal-derived fibroblast cells compared with the wild type.³⁰ These findings are consistent with reports that GST P1-1 is a negative regulator of cellular growth and differentiation exerting its effect by binding to JNK.

In this oral study of ezatiostat tablets, levels of the major metabolite, TLK236, were comparable with the TLK236 exposure achieved with the intravenous formulation of ezatiostat. Comparable pharmacokinetic parameters were seen between the fed and fasted states in this clinical study.

Seventeen HI responses (IWG 2000 criteria) were observed that included lineages at all dose levels evaluated with 11 of the HI responses observed in the 4000 to 6000 mg/day dose range, suggesting a possible relationship between dose and HI response. Three bilineage responses were observed with 1 associated with a complete cytogenetic response. Hematologic improvement in all 3 lineages was observed in several MDS subtypes in this dose-escalation study. The MDS subtypes of responding patients included: RA, RARS, RCMD, and RSMDS-U. Due to the small sample size and different dose cohort assignments across subtypes, conclusions regarding which subtypes might most benefit from ezatiostat hydrochloride therapy cannot be made in this phase I study. Further study will be needed to identify the MDS subtypes that respond at ezatiostat hydrochloride's optimal dose and dose schedule.

An exploratory analysis suggests that the HI responses were also accompanied by improvement in clinical symptoms. Red blood cell (RBC) transfusion independence was achieved by IWG 2006 criteria in 8 patients (35%). Fourteen patients (61%) with RBC transfusion dependence achieved a 4-unit/8-week reduction in transfusion requirements. Twelve patients (52%) had transfusion requirements reduced by 50% (IWG 2000 criteria). One patient achieved platelet transfusion independence. A follow-up bone marrow evaluation was supposed to have been obtained at 4 months. Due to the insufficient number of follow-up bone marrows obtained, a meaningful data analysis of pre- and post-ezatiostat treatment effects on bone marrow was not performed. In a previous study of ezatiostat administered intravenously, an increase in bone marrow cellularity and maturation was reported.^{23,24} It is clear that early indications of efficacy on this 1-week dosing schedule are promising; however, to further enhance the efficacy observed with ezatiostat tablets, phase 2 testing will evaluate extended dosing schedules in MDS.

In conclusion, the tolerability and HI responses seen with ezatiostat tablets across all 3 cell lineages, including independence or reduction of RBC and platelet transfusion requirements, indicate clinical safety, tolerability, and early indications of hematologic improvement in patients with MDS. These findings support the further development of extended schedules of ezatiostat tablets in MDS and other hematologic malignancies.

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Authorship

Contribution: A.L., A.R., J.G., M.J., and G.L.B. designed the research protocol; A.R., N.G., S.S., J.G., J.L., M.M., and A.L. were involved in treating patients and collecting data; L.M. conducted the statistical analysis; and A.R., N.G., A.L., M.J., J.G.K., and G.L.B. wrote the paper with contributions from the other authors. All authors approved the final version of the paper.

Conflict-of-interest disclosure: G.L.B., M.J., J.G.K., and L.M. are employed by Telik, whose investigational drug candidate was studied in the present work. J.G. is a consultant to Telik. The remaining authors declare no competing financial interests.

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Handbook of Pharmaceutical Excipients

FOURTH EDITION

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Hydroxypropyl Cellulose

1 Nonproprietary Names

BP: Hydroxypropylcellulose
JP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulosum
USPNF: Hydroxypropyl cellulose

2 Synonyms

Cellulose; hydroxypropyl ether; E463; hyplose; Klucel; Methocel; Nisso HPC; oxypropylated cellulose.

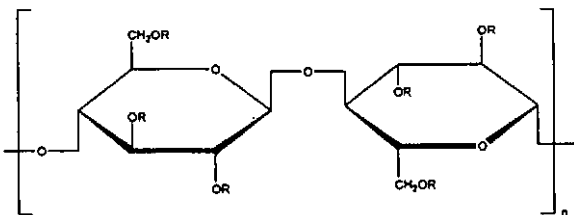
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

4 Empirical Formula Molecular Weight

The PhEur 2002 and USPNF 20 describe hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight ranges from 50 000–1 250 000; see also Section 10.

5 Structural Formula



R is H or $[\text{CH}_2\text{CH}(\text{CH}_3)\text{O}]_m\text{H}$

6 Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations; see Table I.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating, and extended-release-matrix former. Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes.^(1–3) Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.⁽⁶⁾ The release rate of a drug increases with decreasing viscosity of

hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose along with an amount of methyl cellulose or ethanolic solutions may be used.^(7–9) Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant; see Hydroxypropyl Cellulose, Low-substituted.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations.^(10–12)

Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Table I: Uses of hydroxypropyl cellulose.

Use	Concentration (%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

8 Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. See also Sections 4 and 5.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for hydroxypropyl cellulose.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Apparent viscosity	+	+	+
Appearance of solution	+	+	—
pH (1 in 100)	5.0–7.5	5.0–8.5	5.0–8.0
Loss on drying	≤5.0%	≤7.0%	≤5.0%
Residue on ignition	≤0.5%	—	≤0.2%
Sulfated ash	—	≤1.6%	—
Arsenic	≤2 ppm	—	≤3 ppm
Chlorides	+	≤0.5%	—
Lead	—	—	≤0.001%
Heavy metals	≤20 ppm	≤20 ppm	20 µg/g
Silica	—	≤0.6%	—
Organic volatile impurities	—	—	+
Sulfate	≤0.048%	—	—
Assay of hydroxypropoxy groups	53.4–77.5%	—	≤80.5%

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10 Typical Properties

Acidity/alkalinity: pH = 5.0–8.5 for a 1% w/v aqueous solution.

Density (bulk): $\approx 0.5 \text{ g/cm}^3$

Interfacial tension: 12.5 mN/m for a 0.1% w/v aqueous solution compared with mineral oil.

Melting point: softens at 130°C; chars at 260–275°C.

Moisture content: hydroxypropyl cellulose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air. Typical equilibrium moisture content values at 25°C are 4% w/w at 50% relative humidity and 12% w/w at 84% relative humidity. See Table III. See also Figure 1.

Table III: Moisture content of Klucel (Aqualon).

Grade	Molecular weight	Moisture (%)
Klucel EF	$\approx 80\,000$	0.59
Klucel LF	$\approx 95\,000$	2.21
Klucel JF	$\approx 140\,000$	1.44
Klucel GF	$\approx 370\,000$	1.67
Klucel MF	$\approx 850\,000$	1.52
Klucel HF	$\approx 1\,150\,000$	4.27

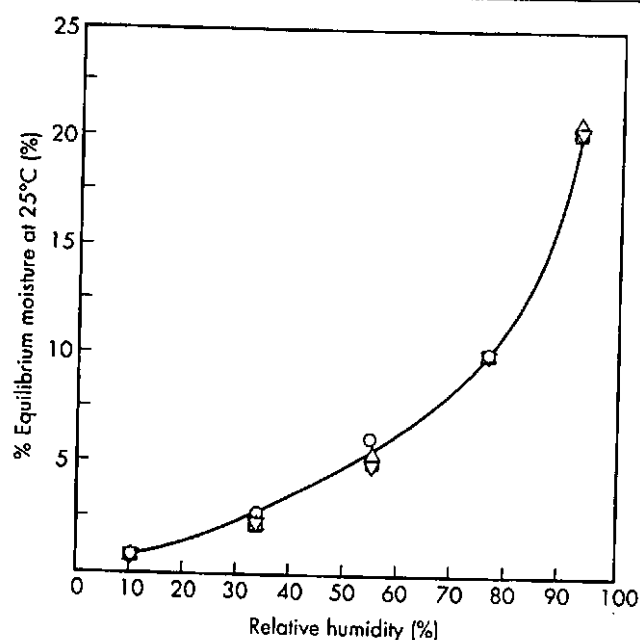


Figure 1: Equilibrium moisture content of various grades of hydroxypropyl cellulose.

○ Klucel GF (Aqualon, Lot #4996).

▽ Klucel JF (Aqualon, Lot #4753).

△ Klucel LF (Aqualon, Lot #4965).

□ Klucel EF (Aqualon, Lot #1223).

Particle size distribution:

Klucel (regular grind), 95% through a US #30 mesh (590 μm), and 99% through a US #20 mesh (840 μm)

Klucel (X-grind), 100% through a US #60 mesh (250 μm), and 80% through a US #100 mesh (149 μm)

Refractive index: $n_D^{20} = 1.3353$ for a 2% w/v aqueous solution.

Solubility: soluble 1 in 10 parts dichloromethane, 1 in 2.5 parts ethanol, 1 in 2 parts methanol, 1 in 5 parts propan-2-ol, 1 in 5 parts propylene glycol, and 1 in 2 parts water; practically insoluble in aliphatic hydrocarbons, aromatic

hydrocarbons, carbon tetrachloride, petroleum distillates, glycerin, and oils.

Hydroxypropyl cellulose is freely soluble in water below 38°C, forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40 and 45°C. Hydroxypropyl cellulose is soluble in many cold or hot polar organic solvents such as dimethyl formamide, dimethyl sulfoxide, dioxane, ethanol, methanol, propan-2-ol (95%), and propylene glycol. There is no tendency for precipitation in hot organic solvents. However, the grade of hydroxypropyl cellulose can have a marked effect upon solution quality in some organic liquids that are borderline solvents, such as acetone, butyl acetate, cyclohexanol, dichloromethane, lactic acid, methyl acetate, methyl ethyl ketone, propan-2-ol (99%), and *tert*-butanol. The higher-viscosity grades of hydroxypropyl cellulose tend to produce slightly inferior solutions. However, the solution quality in borderline solvents can often be greatly improved by the use of small quantities (5–15%) of a cosolvent. For example, dichloromethane is a borderline solvent for Klucel HF and solutions have a granular texture, but a smooth solution may be produced by adding 10% methanol.

Hydroxypropyl cellulose is compatible with a number of high-molecular-weight, high-boiling waxes and oils, and can be used to modify certain properties of these materials. Examples of materials that are good solvents for hydroxypropyl cellulose at an elevated temperature are acetylated monoglycerides, glycerides, pine oil, polyethylene glycol, and polypropylene glycol.

Specific gravity: 1.2224 for particles; 1.0064 for a 2% w/v aqueous solution at 20°C.

Surface tension: see Table IV.

Table IV: Surface tension (mN/m) of aqueous solutions of Nisso HPC (Nippon Soda Co. Ltd.) at 20°C.

Grade	Surface tension (mN/m) at 20°C for aqueous solutions of stated concentration			
	0.01%	0.1%	1.0%	10.0%
Nisso HPC-L	51.0	49.1	46.3	45.8
Nisso HPC-M	54.8	49.7	46.3	—

Viscosity (dynamic): a wide range of viscosity types are commercially available; see Table V. Solutions should be prepared by gradually adding the hydroxypropyl cellulose to a vigorously stirred solvent. Increasing concentration produces solutions of increased viscosity. See also Section 11 for information on solution stability.

Table V: Viscosity of aqueous solutions of Klucel (Aqualon) at 25°C.

Grade	Viscosity (mPa s) of various aqueous solutions of stated concentration			
	1%	2%	5%	10%
Klucel HF	1500–3000	—	—	—
Klucel MF	—	4000–6500	—	—
Klucel GF	—	150–400	—	—
Klucel JF	—	—	150–400	—
Klucel LF	—	—	75–150	—
Klucel EF	—	—	—	200–600

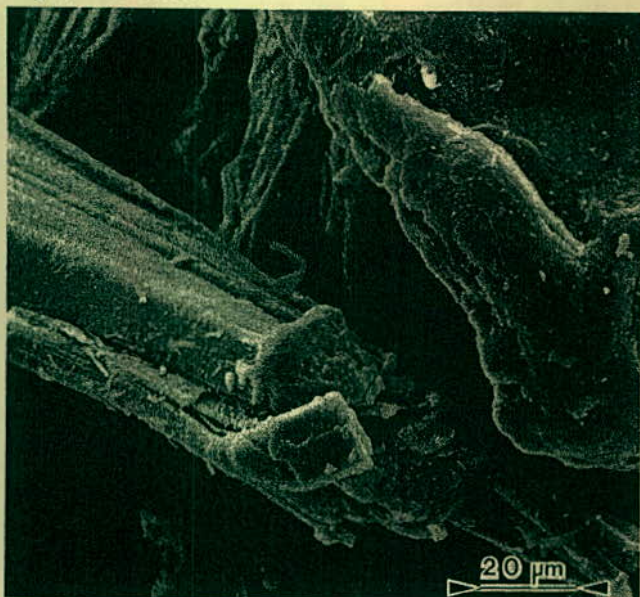
SEM: 1

Excipient: Hydroxypropyl cellulose (Klucel)
 Manufacturer: Aqualon
 Magnification: 60 ×



SEM: 2

Excipient: Hydroxypropyl cellulose (Klucel)
 Manufacturer: Aqualon
 Magnification: 600 ×



11 Stability and Storage Conditions

Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying.

Aqueous solutions of hydroxypropyl cellulose are stable at pH 6.0–8.0, with the viscosity of solutions being relatively unaffected. However, at low pH aqueous solutions may undergo acid hydrolysis, resulting in chain scission and hence a decrease in solution viscosity. The rate of hydrolysis increases with increasing temperature and hydrogen ion concentration.

At high pH, alkali-catalyzed oxidation may degrade the polymer and result in a decrease in viscosity of solutions. This degradation can occur owing to the presence of dissolved oxygen or oxidizing agents in a solution.

Increasing temperature causes the viscosity of aqueous solutions to decrease gradually until the viscosity drops suddenly at about 45°C owing to the limited solubility of hydroxypropyl cellulose. However, this process is reversible and on cooling the original viscosity is restored.

The high level of substitution of hydroxypropyl cellulose improves the resistance of the polymer to degradation by molds and bacteria.⁽⁹⁾ However, aqueous solutions are susceptible to degradation under severe conditions and a viscosity decrease may occur. Certain enzymes produced by microbial action will degrade hydroxypropyl cellulose in solution.⁽¹³⁾ Therefore, for prolonged storage, an antimicrobial preservative should be added to aqueous solutions. Solutions of hydroxypropyl cellulose in organic solvents do not generally require preservatives.

Ultraviolet light will also degrade hydroxypropyl cellulose and aqueous solutions may therefore decrease slightly in viscosity if exposed to light for several months.

Aqueous hydroxypropyl cellulose solutions have optimum stability when the pH is maintained between pH 6.0 and 8.0, and also when the solution is protected from light, heat, and the action of microorganisms.

Hydroxypropyl cellulose powder should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions.

The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration; see Table VI. Hydroxypropyl cellulose may not tolerate high concentrations of other dissolved materials.

Table VI: Compatibility of hydroxypropyl cellulose (Nisso HPC) with inorganic salts in aqueous solutions.^(a)

Salt	Concentration of salt (% w/w)						
	2	3	5	7	10	30	50
Aluminum sulfate	S	S	I	I	I	I	I
Ammonium nitrate	S	S	S	S	S	I	I
Ammonium sulfate	S	S	I	I	I	I	I
Calcium chloride	S	S	S	S	S	T	I
Dichromic acid	S	S	S	S	S	S	S
Disodium hydrogenphosphate	S	S	I	I	I	I	I
Ferric chloride	S	S	S	S	S	I	I
Potassium ferrocyanide	S	S	S	I	I	I	I
Silver nitrate	S	S	S	S	S	S	T
Sodium acetate	S	S	S	S	I	I	I
Sodium carbonate	S	S	I	I	I	I	I
Sodium chloride	S	S	S	S	I	I	I
Sodium nitrate	S	S	S	S	S	I	I
Sodium sulfate	S	S	I	I	I	I	I
Sodium sulfite	S	S	I	I	I	I	I
Sodium thiosulfate	T	T	T	I	I	I	I

^(a) S, completely soluble; T, turbid white; I, insoluble.

The balance of the hydrophilic-lipophilic properties of the polymer, which are required for dual solubility, reduces its ability to hydrate with water and it therefore tends to be salted out in the presence of high concentrations of other dissolved materials.

The precipitation temperature of hydroxypropyl cellulose is lower in the presence of relatively high concentrations of other dissolved materials that compete for the water in the system; see Table VII.

Table VII: Variation in precipitation temperature of hydroxypropyl cellulose (Klucel H) in the presence of other materials.

Ingredients and concentrations	Precipitation temperature (°C)
1% Klucel H	41
1% Klucel H + 1.0% sodium chloride	38
1% Klucel H + 5.0% sodium chloride	30
0.5% Klucel H + 10% sucrose	41
0.5% Klucel H + 30% sucrose	32
0.5% Klucel H + 40% sucrose	20
0.5% Klucel H + 50% sucrose	7

13 Method of Manufacture

A purified form of cellulose is reacted with sodium hydroxide to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then reacted with propylene oxide at elevated temperature and pressure. The propylene oxide can be substituted on the cellulose through an ether linkage at the three reactive hydroxyls present on each anhydroglucose monomer unit of the cellulose chain. Etherification takes place in such a way that hydroxypropyl substituent groups contain almost entirely secondary hydroxyls. The secondary hydroxyl present in the side chain is available for further reaction with the propylene oxide, and 'chaining-out' may take place. This results in the formation of side chains containing more than 1 mole of combined propylene oxide.

14 Safety

Hydroxypropyl cellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hydroxypropyl cellulose is generally regarded as an essentially nontoxic and nonirritant material.⁽¹⁴⁾ However, the use of hydroxypropyl cellulose as a solid ocular insert has been associated with rare reports of discomfort or irritation, including hypersensitivity and edema of the eyelids. Adverse reactions to hydroxypropyl cellulose are rare. However, it has been reported that a single patient developed contact dermatitis due to hydroxypropyl cellulose in a transdermal estradiol patch.⁽¹⁵⁾

The WHO has not specified an acceptable daily intake for hydroxypropyl cellulose since the levels consumed were not considered to represent a hazard to health.⁽¹⁶⁾ Excessive consumption of hydroxypropyl cellulose may, however, have a laxative effect.

LD₅₀ (rat, IV): 0.25 g/kg⁽¹⁷⁾

LD₅₀ (rat, oral): 10.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl cellulose

dust may be irritant to the eyes; eye protection is recommended. Excessive dust generation should be avoided to minimize the risk of explosions.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets; topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose, low-substituted; hypromellose.

18 Comments

Hydroxypropyl cellulose is a thermoplastic polymer that can be processed by virtually all fabrication methods used for plastics.

It is also used in hot-melt extruded films for topical use. When it is produced with chlorpheniramine maleate, the matrix is stabilized, allowing film processing at lower temperatures.⁽¹⁸⁾ Mucoadhesive hydroxypropyl cellulose microspheres have been prepared for powder inhalation preparations.⁽¹⁹⁾

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22 Date of Revision

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Hypromellose

1 Nonproprietary Names

BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Hypromellosem
USP: Hypromellose

2 Synonyms

Benecel MHPC; cellulose, hydroxypropyl methyl ether; E464; hydroxypropyl methylcellulose; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Pharmacoat*; *Spectracel 6*; *Spectracel 15*; *Tylopur*.

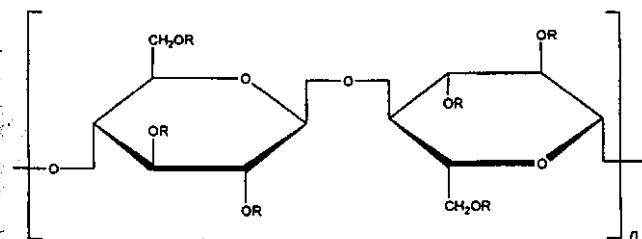
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl methyl ether [9004-65-3]

4 Empirical Formula Molecular Weight

The PhEur 2002 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 25 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH₃). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH₂CH(OH)CH₃), calculated on a dried basis. Molecular weight is approximately 10 000–1 500 000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

5 Structural Formula



where R is H, CH₃, or CH₃CH(OH)CH₂

6 Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder,⁽¹⁾ in film-coating,^(2–7) and as an extended-release tablet matrix.^(8–12) Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

Hypromellose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hypromellose produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

8 Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.

Ash: 1.5–3.0%, depending upon the grade.

Autoignition temperature: 360°C

Density (bulk): 0.341 g/cm³

Density (tapped): 0.557 g/cm³

Density (true): 1.326 g/cm³

Melting point: browns at 190–200°C; chars at 225–230°C.

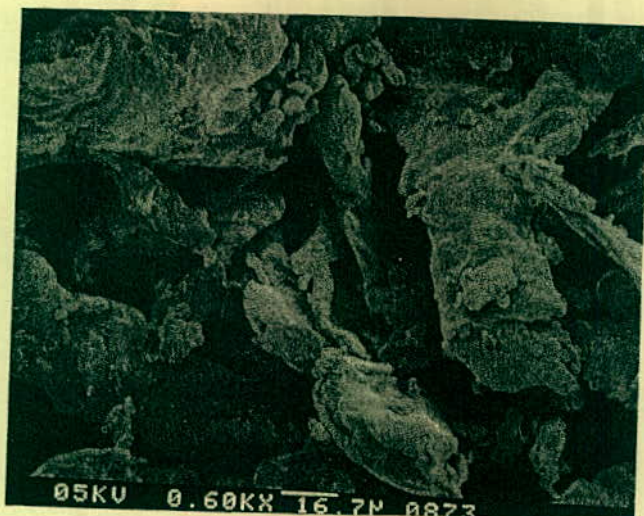
Glass transition temperature is 170–180°C.

Moisture content: hypromellose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air. See Figure 1.

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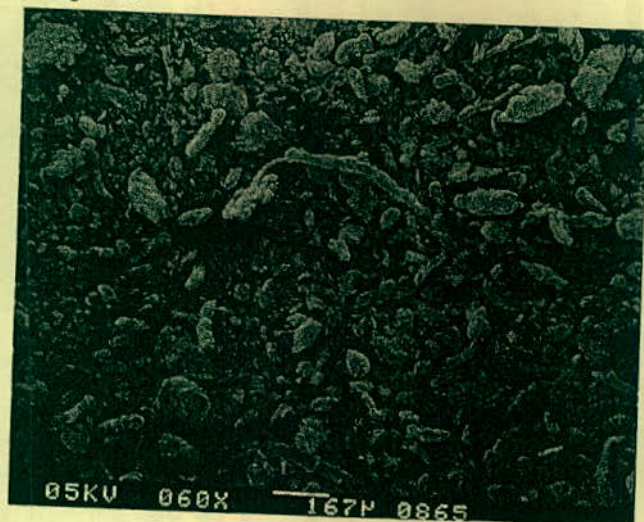
SEM: 1

Excipient: Hypromellose
 Manufacturer: Dow Chemical Co.
 Lot No.: ME20012N11
 Magnification: 600 ×
 Voltage: 5 kV



SEM: 2

Excipient: Hypromellose
 Manufacturer: Dow Chemical Co.
 Lot No.: ME20012N11
 Magnification: 60 ×
 Voltage: 5 kV



Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. *See also* Section 11.

Specific gravity: 1.26

Table I: Pharmacopeial specifications for hypromellose.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
pH (1% w/w solution)	5.0–8.0	5.5–8.0	—
Apparent viscosity	+	+	+
Loss on drying	≤5.0%	≤10.0%	≤5.0%
Residue on ignition	≤1.5%	—	—
For viscosity grade >50 mPa s	—	—	≤1.5%
For viscosity grade ≤50 mPa s	—	—	≤3.0%
For type 1828 of all viscosities	—	—	≤5.0%
Sulfated ash	—	≤1.0%	—
Chlorides	≤0.284%	≤0.5%	—
Heavy metals	≤10 ppm	≤20 ppm	≤0.001%
Iron	≤100 ppm	—	—
Arsenic	≤2 ppm	—	—
Organic volatile impurities	—	—	+
Methoxy content			
Type 1828	—	—	16.5–20.0%
Type 2208	19.0–24.0%	—	19.0–24.0%
Type 2906	27.0–30.0%	—	27.0–30.0%
Type 2910	28.0–30.0%	—	28.0–30.0%
Hydroxypropoxy content			
Type 1828	—	—	23.0–32.0%
Type 2208	4.0–12.0%	—	4.0–12.0%
Type 2906	4.0–7.5%	—	4.0–7.5%
Type 2910	7.0–12.0%	—	7.0–12.0%

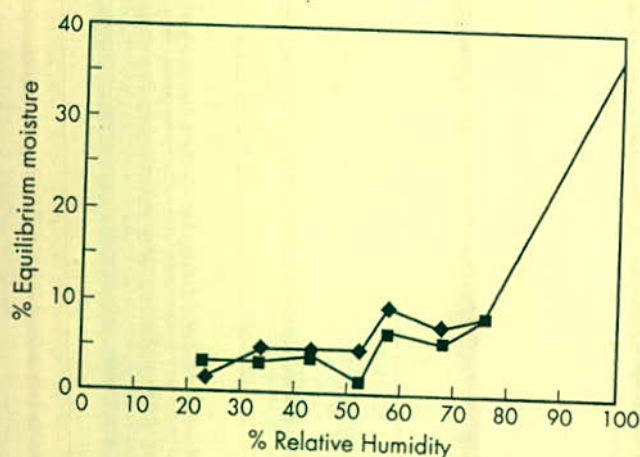


Figure 1: Absorption-desorption isotherm for hypromellose.

◆: Sorption
 ■: Desorption

Viscosity (dynamic): a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions; *see* Table II.

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Table II: Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.). Viscosities measured at 20°C.

Methocel grade	Nominal	Viscosity (mPa s)
K100LVP	100	80-120
K4M	4000	3 000-5 600
K15MP	15 000	12 000-21 000
K100MP	100 000	80 000-120 000
E4MP	4000	3 500-5 600
E10MP CR	10 000	8 000-13 000
E3 PREM.IV	—	2.4-3.6
E5 PREM.IV	—	4-6
E6 PREM.IV	—	5-7
E15 PREM.IV	—	12-18
E50 PREM.IV	—	40-60
K3 PREM.IV	—	2.4-3.6

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20-30% of the required amount of water. The water should be vigorously stirred and heated to 80-90°C, then the remaining hypromellose added. Cold water should then be added to produce the required volume.

When a water-miscible organic solvent such as ethanol, glycol, or mixtures of ethanol and dichloromethane is used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5-8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

11 Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying.

Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 50-90°C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.⁽¹³⁾ However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

13 Method of Manufacture

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce

methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

14 Safety

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.⁽¹⁴⁾ The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.⁽¹⁵⁾

LD₅₀ (mouse, IP): 5 g/kg⁽¹⁶⁾
LD₅₀ (rat, IP): 5.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose; hypromellose phthalate; methylcellulose.

18 Comments

Powdered or granular, surface-treated grades of hypromellose are also available that are dispersible in cold water. These are not recommended for oral use.

19 Specific References

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22 Date of Revision

25 October 2002.