



No. 05-129656- -00004-0000

Fecha: 2007-09-27 16:40:03 Dep. 2020 NUECREACIONE
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 400 OPOS/OBSERVTER Folios: 58

**FORMULARIO UNICO DE OPOSICION
2000-12**

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OPOSICION A:

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

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Número del expediente: 05 129.656

Solicitante: GRUPO INTERNACIONAL FARMACEUTICO GRUFARMA S.A.

**SOLICITUD
PUBLICADA**

Apoderado: MARIA DEL PILAR GALINDO

Título de la nueva creación o denominación del signo:

"COMPOSICIÓN FARMACÉUTICA QUE CONTIENE (S)-I-(2S,3S)-3-
HEXIL-4-OXO-OXETAN-2-ILMETILDODECIL N-FORMIL-L-
LEUCINATO."

Gaceta: 577 de 29 de Junio 2007, Número de Publicación 99

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OPOSICION PRESENTADA POR:

OPOSITOR

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(2) Lafrancol S.A.

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**REPRESENTANTE
O APODERADO
(74)**

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IDENTIFICACION

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Número: 79'152.473 de Usaquén
TP 44655

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FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial), 16 (una invención se considera nueva cuando no es obvia, ni se deriva de manera evidente del estado de la técnica) y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia)

Justificación: Ver anexo

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Comprobante de pago No. 07 - 78.568 (Oposición) Fecha Septiembre 27 de 2007
07 - 78.569 (Prórroga) Fecha Septiembre 27 de 2007
07 - 78.570
07 - 78.581 Septiembre 27 de 2007

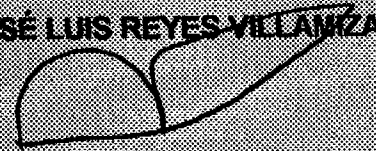
6

Anexos:

- ☐ Comprobante de pago de la tasa
- ☐ Poderes, si fuere el caso
- ☐ Pruebas de los fundamentos de la oposición
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso
- ☐ Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- ☐ Copia de la oposición para el traslado al solicitante.

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NOMBRE: JOSÉ LUIS REYES VILLANZAR

FIRMA: 

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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 05-129-656

TÍTULO SOLICITADO: "Composición farmacéutica que contiene (S)-l-(2S, 3S)-3-hexil-4-oxo-oxetan-2-ilmetil dodecil N-formil-L-leucinato"

PUBLICACIÓN: Gaceta 577 de 29-06-2007, número de publicación 99

SOLICITANTE: Grupo Internacional Farmacéutico GRUFARMA S.A.

APODERADO: María del Pilar Galindo.

TRÁMITE: Presentación de Oposición

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

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente 05-129-656 por no cumplir con lo dispuesto por el Título II – Capítulo I, artículos 14, 16 y 18 de la Decisión 486 de 2000, con base en los fundamentos que me permito exponer a continuación.

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II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS S.A., Y LAFRANCOL S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias y composiciones farmacéuticas carentes de nivel inventivo, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud en curso reivindica una composición farmacéutica que contiene como principio activo (S)-1-[(2S,3S)-3-hexil-4-oxo-oxetan-2-ilmetil] dodecil N-formil-L-leucinato (Orlistat), conjuntamente con auxiliares de formulación apropiados, un estabilizante, para formar gránulos irregulares de tamaño de partícula en el rango de 0,1mm a 0,25mm, utilizados en la fabricación de formas farmacéuticas orales como cápsulas.

3.1. La composición farmacéutica de las reivindicaciones 1 a 11 carece de nivel inventivo.

Es claro para ese despacho que los inhibidores de lipasa -Orlistat, entre otros-, sus propiedades, e indicación terapéutica como inhibidor de lipasa gastrointestinal, se conocen en publicaciones desde 1985; es este el caso de lo revelado en la solicitud europea EP 0 129748, equivalente a la patente americana US 4,598,089 y concedida en 1986-07-01. Estas patentes, según información de la División de Nuevas Creaciones de la SIC, tal como le consta al Despacho, no fueron solicitadas ni concedidas en Colombia, y en consecuencia, nunca tuvieron ni tienen en la actualidad protección patentaria en Colombia.

De igual manera, es conocido internacionalmente el empleo comercial de orlistat en productos farmacéuticos bajo diversas formulaciones y formas de presentación, todos ellos para el tratamiento de la obesidad¹.

De forma que al examinar el objetivo verdadero de los gránulos y los excipientes, con los que se presenta el principio inhibidor THL, tampoco nos encontramos con nada que tenga ni novedad ni altura inventiva. Para no alargar más este aparte con repeticiones sobre lo que es obvio, concluimos que la patente 4,598,089 revela una anterioridad evidente del compuesto

¹ Como ejemplo hago notar que el producto XENICAL fue aprobado por FDA el 23 de abril 23 de 1999.

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tetrahidrolipstatina, THL, como inhibidor de la lipasa junto con excipientes adecuados y que es útil en el control o prevención de la obesidad.

Este compuesto, denomínese así o THL como venimos haciéndolo, según se ha demostrado, no podía ser patentado en Colombia, ya que su estructura química estaba en el estado de la técnica desde mucho antes (por lo menos desde 1986) a la fecha de presentación de la solicitud materia de la patente acusada y de las prioridades que ésta reivindica. La molécula cuya patente se solicita es por todos los aspectos, la misma de la anterioridad descrita y no es, por lo tanto, novedosa ni mucho menos producto de una actividad inventiva.

En el mismo sentido es notorio – y por ello no requiere demostración adicional – que todos y cada uno de excipientes descritos y empleados en la composición farmacéutica pretendida han sido revelados con anterioridad a la fecha de la publicación de la solicitud (29-06-2007).

Teniendo en cuenta los hechos expuestos hasta el momento, sería necesario evaluar si para la fecha de publicación reseñada se conocían en la literatura especializada composiciones farmacéuticas de Orlistat como principio activo, en presencia de excipientes como los definidos en la solicitud de patente colombiana y con el tamaño de partícula descrito y si en tales composiciones se hacía referencia a los porcentajes en peso de los componentes sobre el peso total de la formulación.

En efecto, nótese cómo las composiciones pretendidas en la solicitud en curso son anticipadas por lo revelado en la patente americana US 4,598,089 -antes mencionada-, en especial en la columna 7, líneas 3 a 51, donde se describe que los compuestos de fórmula (I) entre los que se encuentra Orlistat ó Tetrahidrolipstatina, pueden ser administrados en preparaciones farmacéuticas por vía oral como tabletas, tabletas cubiertas, grageas, cápsulas duras y de gelatina blanda, soluciones, emulsiones o suspensiones.

Estas formulaciones pueden ser procesadas con vehículos farmacéuticos inertes, inorgánicos u orgánicos; para el caso de tabletas, grageas y cápsulas duras y de gelatina blanda se pueden emplear como ejemplos de excipientes lactosa, almidón de maíz o derivados, talco, ácido esteárico; además pueden contener agentes preservantes, solubilizantes, agentes endulzantes, agentes colorantes, agentes saborizantes, antioxidantes, entre otros.

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La patente americana US 6,734,314, publicada el 11 de mayo de 2004 y titulada "PREPARATION OF ORLISTAT AND ORLISTAT CRYSTALLINE FORMS", revela en las columna 10, 11 y 12, que el principio activo **Orlistat** puede ser formulado en una variedad de composiciones farmacéuticas junto con uno o más excipientes dependiendo de la forma escogida; para el caso de composiciones sólidas se pueden emplear diluentes como por ejemplo, celulosa microcristalina, celulosa microfina, lactosa, almidón, almidón pregelatinizado, carbonato de calcio, sulfato de calcio, dextrina, fosfato de calcio, caolín, carbonato de magnesio, maltodextrina, manitol, sorbitol, talco, entre muchos otros; también señala que las composiciones sólidas de la invención incluyen polvos, granulados, agregados y composiciones compactadas y que las formas de dosificación corresponden a **cápsulas** que contienen dicha composición, preferiblemente polvos o granulados en **cápsulas duras** o blandas.

Por su parte, la solicitud internacional PCT/WO 9834607 publicada en 13-08-1998 revela en la página 2 un producto que contiene THL como ingrediente activo, estabilizantes, excipientes farmacéuticamente aceptables y se caracteriza porque están en forma de partículas con un diámetro en el rango entre 0.25mm y 2mm, como vemos, esta anterioridad anticipa de manera evidente lo que se pretende con la actual solicitud colombiana (especialmente reivindicaciones 1 y 2), es decir, no sólo revela composiciones que contienen Orlistat o THL, sino que dicho principio activo se encuentra acompañado de excipientes adecuados y de un estabilizante y por si fuera poco, se encuentran en forma de gránulos con un determinado rango de tamaño de partícula.

Si bien es cierto no coinciden los rangos de tamaño de partícula declarados en uno y otro documento, no lo es menos que, para cualquier persona medianamente versada en la materia y teniendo en cuenta que en el estado del arte se encuentra un documento que revela un rango de tamaños entre 0.25 y 2mm, sería obvio darse a la tarea de proponer un rango menor a 0,25mm o superior a 2mm para evitar infracciones de derechos de patentes o simplemente para darle una ligera modificación que, como en el caso que nos ocupa, no permite la comprensión del problema técnico ni de la solución "aportada por la invención", además no demuestra las ventajas con respecto a lo ya revelado, en consecuencia, el nivel inventivo del capítulo reivindicatorio de la solicitud de patente colombiana 05-129-656 se encuentra claramente afectado por obra de lo revelado tanto en las patentes americanas US 4,598,089, y US 6,734,314 y la WO 98/34607.

Así mismo, se insiste en el hecho de que los excipientes incluidos en la formulación de la solicitud en trámite, son ampliamente conocidos como auxiliares de formulación en composiciones farmacéuticas y cosméticas; tal es el caso de lo revelado en la página 2 de la WO 98/34607 –tantas veces mencionada-, en donde se describe que el estabilizante puede incluir, pero no se limita a Hidroxipropilmetilcelulosa, hidroxipropilcelulosa, polivinilpirrolidona y lactosa; más adelante, en su capítulo reivindicatorio menciona que adicionalmente a los estabilizantes preferidos PVP y/o lactosa, el producto puede contener otros excipientes tales como agentes dluentes (sucrosa, CMC o almidón de maíz), ligantes como pasta de almidón; surfactantes como laurilsulfato de sodio o dioctilsulfosuccinato; y/o desintegrantes como almidón glicolato sódico, PVP entrelazada, croscarmelosa sódica, o HPC con sustituyentes bajos.

Más específicamente, en la página 3 describe que las composiciones preferidas contienen:

- * entre 20 y 75% de THL;
- * entre 20 y 60% de celulosa microcristalina;
- * entre 1 y 10% de almidón glicolato sódico;
- * entre 1 y 8% de laurilsulfato de sodio;
- * entre 1 y 10% de PVP; y
- * entre 0 y 1% de talco;

y las reivindicaciones 3 a 6 de la solicitud colombiana en trámite revelan:

- * THL entre el 10 y el 60%;
- * Fosfato de calcio dibásico entre el 5 y 70%
- * almidón de maíz entre 1 y 15%;
- * Laurilsulfato de sodio entre 0,5 y 6%
- * Talco entre 0,5 y 5%;
- * Estearato de magnesio entre 0,2 y 4%;
- * Almidón glicolato de sodio entre 2 y 8%;
- * Croscarmelosa sódica entre 1,5 y 4%;
- * Polisorbato 80 entre 0,5 y 3,5%;
- * PVP entre 1 y 8%.

La reivindicación 9 por su parte revela:

- * 46,15% de THL;
- * 42,31% de Fosfato de calcio dibásico;
- * 3,85% de almidón de maíz;
- * 1,92% de Laurilsulfato de sodio;

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* 3,85% de PVP;

* 1,92% de Estearato de magnesio;

Si tenemos en cuenta lo anterior y lo comparamos vemos claramente que las formulaciones descritas son muy similares entre sí porque tienen excipientes en común y el principio activo es el mismo (Ver los datos en negrilla).

Si bien es cierto existen excipientes que son distintos en uno u otro caso, su empleo no supone un asombroso aporte técnico, ya que una persona medianamente versada en la materia técnica, conociendo las características, propiedades y aplicaciones de THL, conociendo la función que cumplen los excipientes dentro de una formulación, y conociendo composiciones que los emplean de manera combinada, derivaría efectivamente, tras la etapa de preformulación, una composición que incluya el mismo principio activo y excipientes de la misma clase y aplicación farmacotécnica.

En este orden de ideas, el conocimiento previo de estas y otras sustancias, hace que carezca de nivel inventivo la composición pretendida en la solicitud colombiana en cuestión.

Ahora bien, en lo que se refiere a los porcentajes de peso de los componentes sobre el peso total de la composición, y teniendo en cuenta escrito más arriba (ver lo que se encuentra en negrilla), es interesante revisar que porcentajes se encuentran dentro del rango descrito en la anterioridad o muy cercanos a ellos, por tanto, el documento reseñado revelaba con anterioridad a la fecha de prioridad de la solicitud en curso, composiciones de THL con excipientes comunes, tal como se revelan en la solicitud en curso y con los mismos propósitos, en porcentajes de peso similares a los ahora propuestos, hecho que elimina el nivel inventivo de las composiciones pretendidas.

En cuanto a la composición de la reivindicación 11 de la solicitud en trámite y la composición de la reivindicación 14, ejemplos 4 y 5 de la WO 98/34607, ya no dada en porcentaje sino en mg, y que se caracterizan por:

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Formulación cápsula (CO-05-129-656)	
Componente	mg
THL	120
Fosfato de calcio dibásico	110
Croscarmelosa sódica	10
Laurilsulfato de sodio	5
Polivinilpirrolidona	10
Estearato de magnesio	5
Total	260mg

Formulación cápsula (WO 98/34607)		
Componente	mg	mg
THL	120	120
Celulosa microcristalina	93.6	93.6
Almidón glicolato de sodio	7.2	7.2
Laurilsulfato de sodio	7.2	7.2
Polivinilpirrolidona	12	12
Talco	0.24	
Total	240,24mg	240mg

Pese a que la simple determinación de los rangos de ingrediente activo no constituye siquiera remotamente un principio de nivel inventivo, pues tal definición hace parte del necesario proceso de pre-formulación para cualquier fármaco, es del caso hacer notar que la solicitud en curso menciona el empleo de orlistat en dosis de 120 mg, si se compara con las formulaciones de la solicitud internacional WO 98/34607 se observa que dicho principio activo se encuentra en las mismas cantidades.

También hago notar que la patente US 4,598,089 tantas veces citada revela en su reivindicación 4 composiciones de orlistat con dosis de ingrediente activo comprendidas entre 0.1 y 100 mg por Kg. de peso corporal por día, rango que haciendo sustituciones aritméticas menores puede equivaler al revelado en la presente solicitud. En idéntico sentido, llamo la atención al hecho de que la reivindicación 3 de la patente US 5,643,874 de 1997-07-01, cuya equivalente, tramitada bajo el expediente 94-034-076, fue negada en Colombia por esa entidad, revela una composición farmacéutica combinada de inhibidores de lipasa e inhibidores de glucosidasa, en la cual el rango de dosis del inhibidor de lipasa preferido - que es, precisamente, orlistat -, está comprendido entre 10 y 200 mg., rango que evidentemente incluye el pretendido en la presente solicitud.

Por último, hago notar que la bibliografía correspondiente al producto XENICAL® (Roche) da cuenta, con anterioridad a la fecha de prioridad de esta

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solicitud, de cápsulas que contienen 120 mg. de orlistat², dosis que ampara la mayoría del rango pretendido en la solicitud, e incluye la dosis preferida en la solicitud en curso.

Por lo expuesto, carece de nivel inventivo la caracterización de la composición farmacéutica oral en función de la dosis de orlistat presente en ella.

En idéntico sentido hago notar que el juego de porcentajes o partes de peso del ingrediente activo y los auxiliares frente al peso total de la formulación carece por completo de nivel inventivo, pues esa determinación, rutinaria y previa al proceso de formulación y lanzamiento de cualquier producto farmacéutico, tan sólo depende de realizar pruebas que permitan escoger los rangos de peso preferidos de la composición de que se trate, en función de las propiedades y características del principio activo y de los auxiliares, y desde luego, de la forma de administración deseada para la formulación respectiva.

La definición de los porcentajes o partes en peso de un comprimido es una práctica obligatoria y común en farmacotecnia, y carece por ello de nivel inventivo. Pese a que esta afirmación, por obvia, no merecería una demostración bibliográfica, llamo la atención del despacho hacia lo dicho al respecto en Remington³, a cuyo tenor "The successful performance of many of the operations in pharmacy depends on a thorough knowledge of the principles of balance and a correct understanding of its care and use; because weighing is nearly always the preliminary step in any compounding. (...) In pharmacy, weighing usually refers to ascertaining a definite weight of material to be used in compounding a prescription or manufacturing a dosage form (...) An unused set of standard weights should be kept on hand so that at least once a year the weights (...) can be tested, adjusted or rejected, if necessary". (Subrayado fuera de texto).

La cita anterior demuestra sin más, que la determinación del peso de los principios activos, del peso total la forma que lo contiene, y de la relación porcentual o en partes entre aquel y este, es un paso conocido, necesario y previo a la formulación de cualquier producto farmacéutico, y que por ello es

²PHYSICIAN'S DESK REFERENCE, 50th Edition, 1996, pp 2809-2812

³ Remington – The Science and Practice of Pharmacy, 20th Edition, 2000, Páginas 96 y 99.

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predecible y obvio para una persona con medianos conocimientos técnicos en la materia, sin que pueda ser fundamento de nivel inventivo.

EN CONCLUSIÓN

Las anterioridades y referencias expuestas demuestran que el objeto de la invención consiste en una simple yuxtaposición de elementos y características conocidas. Aunque es obvio que las invenciones pueden partir de elementos conocidos, no lo es menos que la patentabilidad en esa clase de creaciones está determinada por el aporte de quien toma tales elementos, los combina en forma creativa y obtiene un efecto sorprendente, situación que no se verifica en el presente caso.

IV. FUNDAMENTOS DE DERECHO

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

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En Desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI. PRUEBAS

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

- 6.1. Copia íntegra de la patente americana US 4,598,089 de 01-07-1986;
- 6.2. Copia de la primera página y columnas 9 a 14 de la patente americana US 6,734,314 de 11-05-2004.

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- 6.3. Copia de la primera página y páginas 1 a 5, 11 y capítulo reivindicatorio de la solicitud internacional WO/9834607 de 13-08-1998.

VII. ANEXOS

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

1. Certificados de existencia y representación legal de Tecnoquímicas S.A., y Lafranco S.A.
2. Poderes para actuar otorgados por Tecnoquímicas S.A., y Lafranco S.A.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. Las mencionadas en el acápite de pruebas.

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A. las recibirá en la secretaría de su Despacho o en su sede localizada en la Calle 23 # 7-39, de la ciudad de Cali y Lafranco S.A. las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. No. 79.152.473 (Usaquén)

T.P.A. No. 44655 del C. S. J.

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

PCT

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:	A61K 31/365, 916	AI
(11) International Publication Number:	WO 98/34607	
(43) International Publication Date:	13 August 1998 (13.08.98)	

(21) International Application Number:	PCT/EP98/00395
(22) International Filing Date:	24 January 1998 (24.01.98)
(30) Priority Data:	5 February 1997 (05.02.97) US 60/037,384 09/003,137 US
(71) Applicant: F. HOFFMANN-LA ROCHE AG (CH/CH); Grenzacherstrasse 124, CH-4070 Basle (CH).	
(72) Inventors: SHAH, Navin; Hargovindas; 203 Beverly Hill Road, Clifton, NJ 07012 (US). ZIEGLER, Max; Violaweg 81, CH-4303 Kaiseraugst (CH).	
(74) Agent: MAHER, Jean; Grenzacherstrasse 124, CH-4070 Basle (CH).	
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KR, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	Published With international search report.

(54) Title: TETRAHYDRO-11PSTATIN CONTAINING COMPOSITIONS

(57) Abstract

Product containing tetrahydropstatin as the active ingredient and pharmaceutically acceptable excipients, characterized in that it is in the form of particles with a diameter of 0.25 to 2 mm; and pharmaceutical preparations or compositions for oral administration containing the product.

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TETRAHYDROLIPSTATIN CONTAINING COMPOSITIONS

5 Tetrahydrolipstatin („THL“) is an inhibitor of pancreatic lipase and is known by the generic name orlistat. The use of THL as medicament, particularly as anti-obesity agent, and pharmaceutical compositions containing THL as active agent are described in US Patent No. 4,598,089.

10 Due to its low melting point of about 44°C, THL undergoes both hydrolytic and thermal degradation, particularly when stored in a humid atmosphere or above 35°C in a dry atmosphere. Furthermore, conventional dosage forms such as described in US Patent No. 4,598,089, for example, tablets or hard gelatin capsules, cannot easily be formulated from powder mix or by conventional wet granulation procedure due to picking and sticking phenomena during tablet
15 compression or encapsulation. Thus, there was a need for THL containing products and dosage forms which would be stable against moisture and heat during production and storage.

20 In one of its aspects, the present invention relates to a product containing THL as active ingredient, stabilizers, pharmaceutically acceptable excipients, characterized in that it is in the form of particles with a diameter in the range of from about 0.25 mm to about 2 mm.

25 These particles are typically in the form of particles or pellets. The preferred pellet form requires the presence of microcrystalline cellulose. Preferably, the diameter of the pellets ranges from about 0.5 to about 1.5 mm.

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Surprisingly, it was found that THL containing particles do not feature the sticking and picking phenomena and exhibit superior THL stability.

5 The subject invention will now be described in terms of its preferred embodiments. These embodiments are set forth to aid in understanding the invention but are not to be construed as limiting.

10 The subject invention provides particles, such as granules and pellets, useful in producing pharmaceutical compositions, such as a unit dosage form. The use of particles in the form of pellets is preferred.

15 Surprisingly, it was found that THL containing particles (also called multiple units) minimize the sticking and picking phenomena encountered during tablet compression or encapsulation. In one of its aspects, the present invention relates to a unit dosage form comprising a plurality of pellets having a diameter in the range of from 0.25 to 2 mm wherein each particle comprises tetrahydrolipstatin, a stabilizer and at least one pharmaceutically acceptable excipient. When the particles are in the form of pellets, it is critical to employ microcrystalline cellulose.

20 The term „stabilizer“ refers to an agent having a rate of moisture uptake greater than the rate of moisture uptake for THL. Such stabilizer acts to retard hydrolytic degradation of the THL. Preferably, the stabilizer has a moisture content of greater than five percent (5%) at fifty percent (50%) relative humidity. The selection of a
25 stabilizer having the above qualities is within the skill of the artisan having read the present specification. Examples of such stabilizers include, but are not limited to, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, and lactose.

30 Preferably, the average diameter of the particles ranges from 0.5 to 1.5 mm. Diameters referred to throughout the specification are average diameters. Although it is preferred that all particles are within the

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recited ranges, it is acceptable for very minor or trace amounts of undersize or oversize particles to be present.

5 A further object of the invention is a product as described above which comprises a specific combination of THL with stabilizers, and excipients, particularly a product which contains polyvinylpyrrolidone and/or lactose as stabilizers.

Preferably, the product contains either (a) lactose and at least 3% by weight of the product is polyvinylpyrrolidone or (b) at least 5% by weight of the product is polyvinylpyrrolidone.

10 Preferred compositions typically contain from about 20% to about 75% by weight THL, and from about 3% to about 60% by weight stabilizer. Preferred pellets additionally contain from about 10% to about 60% by weight microcrystalline cellulose. More preferably, such pellets contain about 25% to about 75% by weight THL; from about 20% to
15 about 60% by weight microcrystalline cellulose; from about 1% to about 10% by weight sodium starch glycolate; from about 1% to about 8% by weight sodium lauryl sulfate; from about 1% to about 10% by weight polyvinylpyrrolidone; and from about 0% to about 1% by weight talc.

20 Most preferably, such pellets contain about 50% by weight THL; about 39% by weight microcrystalline cellulose; about 3% by weight sodium starch glycolate; about 3% by weight sodium lauryl sulfate; about 5% polyvinyl pyrrolidone; and about 0.1% by weight talc.

25 Such products are chemically stable and can be filled on fast running encapsulation machines without presenting the sticking and picking phenomena.

30 In addition to the preferred stabilizers, polyvinylpyrrolidone and/or lactose, the product of the invention (the particles) contains other excipients, such as diluting agents, for example, sucrose or preferably microcrystalline cellulose (mandatory for pellets of the present invention); binders, for example, starch paste; surfactants, for example, sodium lauryl sulfate or sodium dioctylsulfosuccinate; and/or

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disintegrants, for example, sodium starch glycolate. The pellets can also contain corn starch as a diluent and disintegrant, and triglycerides.

5 Pellets are preferably prepared by extrusion of a wet mass followed by spheronization. They can also be prepared by granulation on a rotating base plate in fluidized bed equipment, by agglomeration granulation on an inclined disc equipment, or in high shear mixers.

10 The process for preparing the pellets is known *per se*. See, for example, J.W. Conine and H.R. Hadley, D & CI, April 1970, p. 38-41: Small Solid Pharmaceutical Spheres; A.D. Reynold, Manufacturing Chemist & Aerosol News, June 1970, p. 40-43: A new technique for the production of spherical particles; C.W. Woodruff and N.O. Nuessle, J. Pharm. Sci. 61 (5), p. 787-790 (1972): Effect of Processing Variables on Particles obtained by Extrusion-Spheronization Processing; and H.J. 15 Malinowski and W.E. Smith, J. Pharm. Sci. 64 (10), p. 1688-1692 (1975); Use of Factorial Design to Evaluate Granulations Prepared by Spheronization.

Typically, the pelletization process by extrusion and spheronization comprises the following unit operations:

- 20 - wetting and kneading a powder mass containing the active substance THL and additional excipients with an appropriate, mostly aqueous solution of an appropriate binder to get a wet, pasty mass. Alternatively, the binder may be contained in the powder mix before wetting and kneading;
- 25 - forcing this wetted mass by means of an appropriate equipment (extruder) through tiny holes of a perforated plate, to get spaghetti-like, wet strands. The diameter of the holes may vary within wide limits, for example, between 0.4 and 1.0 mm, according to the specific product to be 30 obtained.

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- breaking the strands into short pieces which are at the same time formed to more or less spherical particles by means of a fast spinning, mostly structured plate, in a vertical cylinder (spheronizer).
- 5 - drying the wet spheres by means of any suitable drying equipment, for example, a fluid bed dryer or a tray drier.
- optionally, the dried spheres may be fractionated into appropriate sized fractions, or the main material may be freed from undersized or
10 oversized material by an appropriate sieving or screening process. Preferably, the temperature is maintained below 35°C during the whole process.

15 A further aspect of the invention are pharmaceutical preparations or compositions for oral administration, comprising the particles. They can be simply filled in a PVC container from which the particles can be taken with a dosing spoon. Other oral dosage forms are sachets in which the particles are filled, alone or together with appropriate excipients, such as skim milk powder, microcrystalline cellulose,
20 sodium carboxymethylcellulose and talc, to form a powder for reconstitution. Another possibility is to embed the particle in a matrix excipient, for example, microcrystalline cellulose, followed by compression to tablets, particularly chewable tablets. The particle, can also be filled in capsules, for example, hard gelatin capsules.

25 The following Examples are illustrative but in no way limit the invention.

1. Polyvinyl pyrrolidone and sodium lauryl sulfate is dissolved in water.
2. THL, microcrystalline cellulose, and sodium starch glycolate are mixed for 10 minutes and granulated with the solution of step 1.
- 5 3. Granules are dried at or below 30°C and passed through # 20 mesh screen.
4. Granules are filled in a # 1 hard gelatin capsule.

Example 6

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Preparation of Granules and Formulations containing THL

Ingredient	mg/capsule
1. THL	120
2. Lactose anhydrous	93.6
3. Sodium starch glycolate	7.2
4. Polyvinyl pyrrolidone	12.0
5. Sodium lauryl sulfate	7.2
Total	240.00

1. Polyvinyl pyrrolidone and sodium lauryl sulfate is dissolved in water.
- 15 2. THL, lactose anhydrous, and sodium starch glycolate is mixed for 10 minutes and granulated with the solution of step 1.
3. Granules are dried at or below 30°C and passed through # 20 mesh screen.
4. Granules are filled in a # 1 hard gelatin capsule.

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5 The subject invention has been described in terms of its preferred
embodiments. Upon reading the specification, a skilled artisan will
become cognizant of various alternative embodiments. These variations
are to be considered within the scope and spirit of the invention which is
only to be limited by the claims that follow and their equivalents.

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67Claims

1. A pharmaceutical composition comprising a plurality of particles having an average diameter of from about 0.25 mm to about 2 mm, each particle comprising tetrahydrolipstatin, a stabilizer, and at least one pharmaceutically acceptable excipient, provided that when the particles are in the form of pellets, each pellet contains microcrystalline cellulose.

2. The composition of claim 1, wherein the particles are pellets or granules, particularly wherein the pellets or granules have an average diameter of from about 0.5 mm to about 1.5 mm.

3. The composition of claim 2, wherein the stabilizer is selected from the group consisting of polyvinylpyrrolidone, lactose, a combination of polyvinylpyrrolidone and lactose, hydroxypropylmethyl cellulose, and hydroxypropyl cellulose.

4. The composition of claim 3, wherein at least 5% by weight of the composition is polyvinylpyrrolidone.

5. The composition of claim 3, wherein the stabilizer is a combination of lactose and polyvinylpyrrolidone wherein at least 3% by weight of the composition is polyvinylpyrrolidone.

6. The composition of claim 2, wherein the pharmaceutically acceptable excipient is a surfactant, diluent, or disintegrant.

7. The composition of claim 6, wherein the pharmaceutically acceptable excipient is a surfactant, particularly wherein the surfactant is sodium lauryl sulfate or sodium dioctylsulfosuccinate.

8. The composition of claim 6, wherein the pharmaceutically acceptable excipient is a diluent, particularly wherein the diluent is microcrystalline cellulose, sucrose or corn starch.

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9. The composition of claim 6, wherein the excipient is a disintegrant, particularly wherein the disintegrant is sodium starch glycolate, cross-linked polyvinyl pyrrolidone, cross-carmolose sodium, or low-substituted hydroxypropyl cellulose.

5 10. The composition of claim 2 which comprises from about 20% to about 75% by weight tetrahydrolipstatin; from about 3% to about 60% by weight stabilizer; and from about 10% to about 60% by weight microcrystalline cellulose.

10 11. The composition of claim 10 which comprises about 25% to about 75% by weight tetrahydrolipstatin; from about 20% to about 60% by weight microcrystalline cellulose; from about 1% to about 10% by weight sodium starch glycolate; from about 1% to about 8% by weight sodium lauryl sulfate; from about 1% to about 10% by weight polyvinylpyrrolidone; and from about 0% to about 1% by weight talc.

15 12. The composition of claim 11 which comprises about 50% by weight tetrahydrolipstatin; about 39% by weight microcrystalline cellulose; about 3% by weight sodium starch glycolate; about 3% by weight sodium lauryl sulfate; about 5% by weight polyvinylpyrrolidone; and about 0.1% by weight talc.

20 13. The composition of any one of claims 1, 2 and 10-12 which is in unit dosage form.

25 14. A pharmaceutical composition as in claim 1, which comprises about 120 mg of tetrahydrolipstatin; about 93.6 mg of microcrystalline cellulose; about 7.2 mg of sodium starch glycolate; about 7.2 mg of sodium lauryl sulfate; about 12 mg polyvinylpyrrolidone; and about 0.24 mg talc.

15. The composition of claim 14 which is in unit dosage form.



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Keri et al.

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(54) **PREPARATION OF ORLISTAT AND
ORLISTAT CRYSTALLINE FORMS**

(58) Field of Search 549/328, 263;
435/123

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(65) **Prior Publication Data**

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(57) **ABSTRACT**

Related U.S. Application Data

(60) Provisional application No. 60/337,218, filed on Dec. 4,
2001.

The present invention is directed to a process of converting
lipstatin to orlistat by catalytic hydrogenation. The present
invention further discloses novel crystalline solid orlistat
forms, designated form I and form II and methods for their
preparation.

(51) Int. Cl.⁷ **C07D 305/12**

37 Claims, 2 Drawing Sheets

(52) U.S. Cl. **549/328; 549/263; 435/123**

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20-25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 2-1).

Example 11

0.7 gram orlistat was dissolved in 0.7 mL n-Propanol. Hexane of 0.7 mL was added to the solution. It was dried at 20-25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 3-1).

Example 12

0.7 gram orlistat was dissolved in 1.0 mL isopropanol. Water of 0.3 mL was added to the solution. It was dried at 20-25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 4).

Example 13

0.7 gram orlistat was dissolved in 0.7 mL isopropanol. Hexane of 0.7 mL was added to the solution. It was dried at 20-25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 4-1).

Example 14

0.7 gram orlistat was dissolved in 1.0 mL acetone. Water of 0.3 mL was added to the solution. It was dried at 20-25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 5).

Example 15

0.7 gram orlistat was dissolved in 0.7 mL acetone. Hexane of 0.7 mL was added to the solution. It was dried at 20-25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 5-1).

Example 16

0.7 gram orlistat was dissolved in 0.7 mL ethyl acetate. Hexane of 0.7 mL was added to the solution. It was dried at 20-25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 8-1).

Example 17

0.7 gram orlistat was dissolved in 0.7 mL isobutyl acetate. Hexane of 0.7 mL was added to the solution. It was dried at 20-25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 9-1).

Example 18

0.7 gram orlistat was dissolved in 0.7 mL methyl isobutyl ketone. Hexane of 0.7 mL was added to the solution. It was dried at 20-25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 10-1).

Example 19

0.7 gram orlistat was dissolved in 0.7 mL methanol. Hexane of 0.7 mL was added to the solution. It was dried at 20-25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 13-1).

Example 20

0.7 gram orlistat was dissolved in 0.7 mL methanol. Water of 0.3 mL was added to the solution. It was cooled at 0-5° C. for 1 hour. Filtered crystals were dried at 20-25° C. for 1 hour and at 38° C. for 1 hour (sample number 14-1).

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Example 21

0.7 gram orlistat was dissolved in 7.0 mL hexane. Crystals were filtered after 20 hours cooling at 0-5° C. Drying was carried out at 20-25° C. for 1 hour and at 38° C. for 1 hour (sample number 16).

Example 22

The melting points (DSC) and enthalpy of the following orlistat samples were measured and presented in the following table. The crystalline forms (XRD) of the orlistat samples were also presented.

Sample Numbers	melting endotherm ° C. (DSC)	enthalpy (Δ) (J/gram)	Crystalline forms (XRD)
1-1	46.3	87	I > II
2	47.0	92	I > II
2-1	47.1	85	I > II
3-1	46.7	87	I > II
4	46.5	91	I > II
4-1	46.8	92	I > II
5	46.2	90	I > II
5-1	46.9	90	I > II
8-1	46.9	93	I > II
9-1	46.5	85	I > II
10-1	46.5	88	I > II
13-1	46.7	91	I
14-1	46.2	90	I > II
16	46.6	93	II

">" refers to "substantially excess". For example "I > II" means that form I is in substantially excess amount than form II

One of ordinary skill in the art would appreciate that the experimental conditions require optimization in order to crystallize and obtain further purified crystalline orlistat.

Pharmaceutical Formulations of Orlistat Crystalline Forms:

Orlistat crystalline forms I and II are useful for treating obesity. They can be formulated into a variety of compositions for administration to a mammal including humans and animals.

Pharmaceutical compositions of the present invention contain orlistat crystalline form I or orlistat crystalline form II. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention can contain one or more excipients. Excipients are added to the composition for a variety of purposes. Diluents increase the bulk of a solid pharmaceutical composition and can make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form like a tablet can include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include for example acacia, alginate acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl

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methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach can be increased by the addition of a disintegrant to the composition. Disintegrants include for example alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polypasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polyacrylic potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

Glidants can be added to improve the flowability of non-compacted solid composition and improve the accuracy of dosing. Excipients that can function as glidants include for example colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease release of the product from the dye. Lubricants include for example magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that can be included in the composition of the present invention include for example maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

Solid and liquid compositions can also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, Orlistat crystalline form I or II, and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

Liquid pharmaceutical compositions can contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that can be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention can also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include for example acacia, alginic acid hentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, pro-

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pylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar can be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid can be added at levels safe for ingestion to improve storage stability.

A liquid composition according to the present invention can also contain a buffer such as gluconic acid, lactic acid, citric acid or acetic acid, sodium gluconate, sodium lactate, sodium citrate or sodium acetate.

Selection of excipients and the amounts to use can be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. The dosages can be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and lozenges as well as liquid syrups, suspensions and elixirs.

A dosage form of the present invention is a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell can be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients can be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filling can be prepared by wet granulation. In wet granulation some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, which causes the powders to clump up into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate can then be tableted or other excipients can be added prior to tableting, such as a glidant and/or a lubricant.

A tableting composition can be prepared conventionally by dry blending. For instance, the blended composition of the actives and excipients can be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules can be compressed subsequently into a tablet.

As an alternative to dry granulation, a blended composition can be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well-suited to direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

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A capsule filling of the present invention can comprise any of the aforementioned blends and granulates that were described with reference to tableting, only they are not subjected to a final tableting step.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosure of which are incorporated by reference in their entireties.

What is claimed is:

1. A crystalline solid orlistat, or hydrate or solvate thereof, characterized by data selected from the group consisting of a XRD pattern with peaks at 5.8, 18.5, 19.5 and 22.3 ± 0.2 degrees two-theta and a DSC melting endotherm at about 46.7°C .

2. The crystalline solid orlistat of claim 1, wherein the crystalline solid orlistat is characterized by the XRD pattern with peaks at 5.8, 18.5, 19.5 and 22.3 ± 0.2 degrees two-theta.

3. The crystalline solid orlistat of claim 2, wherein the crystalline solid orlistat is further characterized by a XRD pattern substantially as depicted in FIG. 1.

4. The crystalline solid orlistat of claim 1, wherein the crystalline solid orlistat is characterized by the DSC melting endotherm at about 46.7°C .

5. A crystalline solid orlistat, or hydrate or solvate thereof, characterized by data selected from the group consisting of a XRD pattern with peaks at 4.8, 5.6, 14.9, 17.3, 19.2 and 22.0 ± 0.2 degrees two-theta, and a DSC melting endotherm at about 46.6°C .

6. The crystalline solid orlistat of claim 5, wherein the crystalline solid orlistat is characterized by the XRD pattern with peaks at 4.8, 5.6, 14.9, 17.3, 19.2 and 22.0 ± 0.2 degrees two-theta.

7. The crystalline solid orlistat of claim 6, wherein the crystalline solid orlistat is further characterized by a XRD pattern substantially as depicted in FIG. 2.

8. The crystalline solid orlistat of claim 5, wherein the crystalline solid orlistat is characterized by a DSC melting endotherm at about 46.6°C .

9. A process of preparing crystalline solid orlistat, or hydrate or solvate thereof, characterized by data selected from the group consisting of a XRD pattern with peaks at 5.8, 18.5, 19.5 and 22.3 ± 0.2 degrees two-theta and a DSC melting endotherm at about 46.7°C , comprising the steps of:

- (a) dissolving orlistat in a solvent;
- (b) adding an anti-solvent or water to the solvent; and
- (c) isolating the crystalline solid orlistat.

10. The process of claim 9, wherein the solvent is a lower alkyl alcohol, acetone, acetonitrile, acetone, ethyl acetate, isobutyl acetate, methyl isobutyl ketone, and hexane.

11. The process of claim 10, wherein the lower alkyl alcohol is selected from the group consisting of methanol, ethanol, n-propanol, and isopropanol.

12. The process of claim 9, wherein the anti-solvent is a hydrocarbon.

13. The process of claim 12, wherein the hydrocarbon is selected from the group consisting of hexane, cyclohexane and heptane.

14. The process of claim 9, wherein the solvent is methanol and the anti-solvent is hexane.

15. The process of claim 9, wherein the steps (a) to (c) are repeated at least once to increase the purity of the crystalline solid orlistat.

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16. The crystalline solid orlistat prepared in accordance with the process of claim 9.

17. The crystalline solid orlistat of claim 16, wherein the crystalline solid orlistat is characterized by a XRD pattern with peaks at 5.8, 18.5, 19.5 and 22.3 ± 0.2 degrees two-theta.

18. The crystalline solid orlistat of claim 17, wherein the crystalline solid orlistat is further characterized by a XRD pattern substantially as depicted in FIG. 1.

19. The crystalline solid orlistat of claim 16, wherein the crystalline solid orlistat is characterized by a DSC melting endotherm at about 46.7°C .

20. A process for preparing a crystalline solid orlistat, or hydrate or solvate thereof, characterized by data selected from the group consisting of a XRD pattern with peaks at 4.8, 5.6, 14.9, 17.3, 19.2 and 22.0 ± 0.2 degrees two-theta, and a DSC melting endotherm at about 46.6°C , comprising the steps of:

- (a) mixing orlistat in hexane to form a mixture at a first temperature;
- (b) lowering the first temperature of the mixture sufficiently to precipitate; and
- (c) isolating crystalline solid orlistat.

21. The process of claim 20, wherein the steps (a) to (c) are repeated at least once to increase the purity of the crystalline solid orlistat.

22. The crystalline solid orlistat prepared in accordance with the process of claim 20.

23. The crystalline solid orlistat of claim 22, wherein the crystalline solid orlistat is characterized by the XRD pattern with peaks at 4.8, 5.6, 14.9, 17.3, 19.2 and 22.0 ± 0.2 degrees two-theta.

24. The crystalline solid orlistat of claim 23, wherein the crystalline solid orlistat is further characterized by a XRD pattern substantially as depicted in FIG. 2.

25. The crystalline solid orlistat of claim 22, wherein the crystalline solid orlistat is characterized by the DSC melting endotherm at about 46.6°C .

26. A process of preparing a mixture of crystalline solid orlistat, or hydrate or solvate thereof, characterized by data selected from the group consisting of a XRD pattern with peaks at 5.8, 18.5, 19.5 and 22.3 ± 0.2 degrees two-theta, a DSC melting endotherm at about 46.7°C , a XRD pattern with peaks at 4.8, 5.6, 14.9, 17.3, 19.2 and 22.0 ± 0.2 degrees two-theta, and a DSC melting endotherm at about 46.6°C , comprising the steps of:

- (a) dissolving orlistat in a solvent; and
- (b) inducing crystallization to obtain the mixture of crystalline solid orlistat.

27. The process of claim 26, wherein the solvent is at least one alcohol selected from the group consisting of methanol, ethanol, n-propanol, 1-propanol, 2-propanol, isopropanol, 1-butanol, i-butanol, sec-butanol, tert-butanol, N,N-dimethyl formamide, dimethyl sulfoxide, acetonitrile, acetone, ethyl acetate, isobutyl acetate, methyl isobutyl ketone, and acetic acid.

28. The process of claim 26, wherein solvent is an aliphatic hydrocarbon.

29. The process of claim 28, wherein the aliphatic hydrocarbon is selected from the group consisting of hexane, pentane and heptane.

30. The process of claim 26, wherein the solvent contains water.

31. The process of claim 26, wherein the solvent is methanol.

32. The process of claim 26, wherein the mixture of methanol and water is present in a v/v ratio of about 1:0.3.

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United States Patent [19]

Hadvary et al.

[11] Patent Number: 4,598,089

[45] Date of Patent: Jul. 1, 1986

[54] LEUCINE DERIVATIVES

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[21] Appl. No.: 621,827

[22] Filed: Jun. 18, 1984

[30] Foreign Application Priority Data

Jun. 22, 1983 [CH] Switzerland 3415/83

[51] Int. Cl.⁴ C07D 305/12; C12P 17/02; A61K 31/365

[52] U.S. Cl. 514/449; 549/263; 549/328; 514/909; 435/123; 435/886

[58] Field of Search 549/263, 328; 435/123; 514/449

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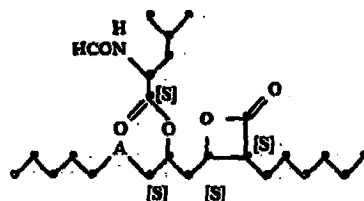
Primary Examiner—Glenn H. Hollrah

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Attorney, Agent, or Firm—Jon S. Saxe; Bernard S. Leon; George W. Johnston

[57] ABSTRACT

Novel compounds of the formula



wherein A signifies the group



or $-(CH_2)_5-$,

which inhibit pancreas lipase and can be used for the control or prevention of obesity and hyperlipaemia, are disclosed. The inventive compounds can be produced by the cultivation of microorganism *Streptomyces toxytricini*, identified as NRRL 15443.

20 Claims, No Drawings

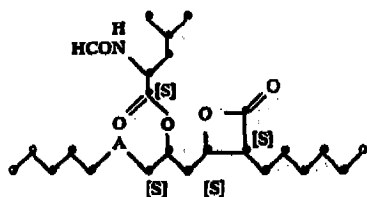
LEUCINE DERIVATIVES

BACKGROUND

The present invention concerns N-formylleucine derivatives which are useful in the treatment of obesity and hyperlipaemia.

SUMMARY OF THE INVENTION

The present invention is concerned with compounds of the formula

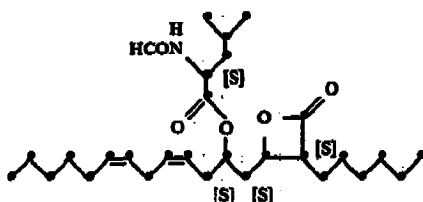


wherein A signifies the group

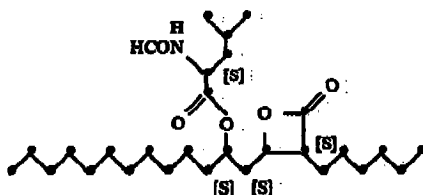


or $-(CH_2)_5-$.

Formula I above embraces (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic acid lactone of the formula



(i.e., lipstatin,) and (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeranyloxy]-2-hexyl-3-hydroxy-hexadecanoic acid lactone of the formula



(i.e., tetrahydrolipstatin).

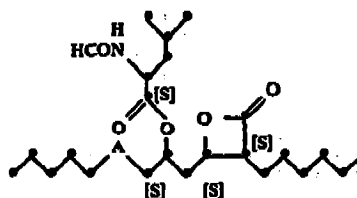
These compounds are novel and have valuable pharmacological properties. In particular, they inhibit pancreas lipase and can be used in the control or prevention of obesity and hyperlipaemia.

Objects of the present invention are the compounds of formula I above per se and as pharmaceutically active substances, the manufacture of these compounds, medicaments and industrially-produced foodstuffs containing a compound of formula I, their production as well as the use of these compounds in the control or prevention of illnesses. More particularly, the invention

concerns methods for preventing or treating obesity or hyperlipaemia in an afflicted mammal.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is concerned with compounds of the formula

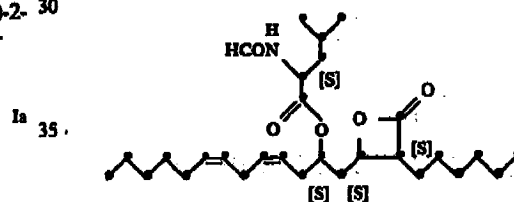


wherein A signifies the group

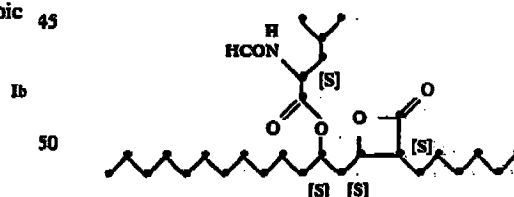


or $-(CH_2)_5-$.

Formula I above embraces (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic acid lactone of the formula



which is referred to hereinafter as lipstatin, and (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic acid lactone of the formula



which is referred to hereinafter as tetrahydrolipstatin.

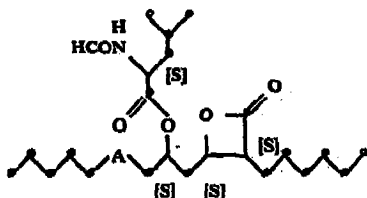
These compounds are novel and have valuable pharmacological properties. In particular, they inhibit pancreas lipase and can be used in the control or prevention of obesity and hyperlipaemia.

The present invention is also concerned with pharmaceutical compositions for preventing and treating obesity or hyperlipaemia comprising a compound of formula I and a pharmaceutically acceptable carrier material.

The invention also concerns methods for preventing or treating obesity or hyperlipaemia in an afflicted mammal wherein compound I is administered to the mammal in an amount which is effective in preventing or treating obesity or hyperlipaemia.

The invention also is directed to a commercially-produced foodstuff comprising compound I admixed with a material suitable for consumption.

As used herein, [S] indicates the absolute configuration of compound I in the S-form. More particularly, the applicable carbon atoms in formula I having the S-configuration are noted with enlarged circles in the following formula:



wherein A is as above.

The digestion of fats (triglycerides) taken in with the food is effected in the intestine by pancreas lipase. The pancreas lipase cleaves the primary ester bonds of triglycerides, whereby free fatty acids and 2-monoglycerides result as products. These products can then be resorbed and utilized. By inhibiting the pancreas lipase the aforementioned cleavage of the food fats and therefore also the resorption and utilization of these substances is partially prevented; the triglycerides are excreted in unchanged form.

The inhibition of pancreas lipase by the compounds of formula I can be demonstrated experimentally by registering tritrimetrically the oleic acid liberated in the cleavage of triolein by pig pancreas lipase. An emulsion which contains 1 mM taurodeoxycholate, 9 mM taurodeoleate, 0.1 mM cholesterol, 1 mM egg lecithin, 15 mg/ml BSA (i.e., bovine serum albumine), 2 mM Tris-HCl, 100 mM sodium chloride, 1 mM calcium chloride and the substrate triolein is treated with the compound of formula I dissolved in ethanol or dimethyl sulphoxide (10% of the emulsion volume) and the reaction is started by the addition of 100 μ l (175 U) of pig pancreas lipase. The pH is held at 8 during the reaction by the addition of sodium hydroxide. The IC_{50} is calculated from the consumption of sodium hydroxide determined during 10 minutes. The IC_{50} is that concentration at which the lipase reactivity is inhibited to half of the maximum. Table I hereinafter contains IC_{50} values determined for the compounds of formula I and data concerning the acute toxicity (LD_{50} after single oral administration to mice).

TABLE I

Test compound	IC_{50} in μ g/ml	LD_{50} in mg/kg p.o.
Lipstatin	0.07	>4000
Tetrahydrolipstatin	0.18	—

The inhibition of the resorption of fats taken in with the food, which is brought about by the inhibition of pancreas lipase, can be demonstrated in a double-labelling experiment on mice. For this purpose, there is administered to the test animals a test meal, which contains ^3H -triolein and ^{14}C -oleic acid, and a compound of formula I. By measuring the radioactivity there is then determined the amount of ^3H -triolein and ^{14}C -oleic acid (in % of the amount administered) excreted with the feces. The results set forth in Table II hereinafter show that in comparison to untreated control animals the

excretion of unaltered triglyceride increases greatly and the excretion of oleic acid remains largely unchanged.

TABLE II

Test compound	Number of experimental animals	Dosage	Excretion in % of the amount administered	
			Triolein	Oleic acid
Controls	12	—	15 $\pm$ 0.3	10.1 $\pm$ 0.6
Lipstatin	6	40 mg/kg*	56.8 $\pm$ 1.3	13.8 $\pm$ 5.6

*The experiments were carried out with a preparation which contained about 10% lipstatin. The dosage specified is the amount of lipstatin administered.

The compounds of formula I can be manufactured in accordance with the invention by the following procedure:

(a) for the manufacture of the compound of formula Ia, aerobically cultivating a microorganism of the species *Streptomyces toxytricini* which produces this compound in an aqueous culture medium which contains suitable carbon and nitrogen sources and inorganic salts and separating the compound of formula Ia produced from the culture broth, or

(b) for the manufacture of the compound of formula Ib, hydrogenating the compound of formula Ia.

Streptomyces strains which produce lipstatin, the compound of formula Ia, can be isolated from soil samples from various locations. An example is the microorganism isolated from a soil sample found in Mallorca, Spain, which was given the laboratory designation *Streptomyces* sp. 85-13 and which has been identified by CBS, Baarn (Netherlands) as *Streptomyces toxytricini* Preobrazhenskaya & Sveshnikova (see Bergey's Manual of Determinative Bacteriology, 8th Edition, page 811). It thereupon received the new designation *Streptomyces toxytricini* 85-13. A lyophilized sample of this strain was deposited on the 14th June 1983 at the Agricultural Research Culture Collection, Peoria, Ill., under the designation NRRL 15443.

A description of the identification of *Streptomyces* sp. 85-13 is given hereinafter:

Media

The composition of the media used is described in Int. J. Syst. Bacteriol 1966, 16, 3; 313-321.

Nonomura diagram

Nonomura used the results of the International *Streptomyces* Project (ISP) for the classification of the *Streptomyces* species (J. Ferment. Technol. 1974, 52, 2).

Colours

The names and code numbers of the aerial mycelium come from Tresner & Backus "System of color wheels for streptomycete taxonomy". The colours of the reverse of the colonies come from H. Prauser's selection from Baumann's "Farbtonkarte Atlas I".

Methodology

This was carried out according to the ISP methods (see Int. J. Syst. Bacteriol, 1966, 16, 3; 313-340).

I. Agar cultures after 16 days at 28° C. (double determination)

(a) Oatmeal agar

Growth: abundant; colonies: thin, spreading; aerial mycelium: velutinous, pinkish brown (Light Brown 57); reverse of the colonies: yellowish (Pr. Coc-3-m) with

broad purple-grey (Pr. Oc-6-x) margin; soluble pigments: doubtful.

(b) Starch-salt agar

Growth: good; colonies: thin, spreading; aerial mycelium: velutinous, pinkish brown (Light Brown 57) with white sectors; reverse of the colonies: dark straw coloured [Pr. Co- (Cr) 5a], margin and some other areas pinkish (Pr. Oc-5-b) with some dark reddish brown [Pr. O-5-S(r)] spots; soluble pigments: doubtful. The diastatic action is excellent.

(c) Glycerine-asparagine agar

Growth: good; colonies: thin, spreading; aerial mycelium: velutinous, pale pinkish brown (R4ec: Grayish Yellowish Pink); reverse of the colonies: orange (Pr. Oc-3-m/r); soluble pigments: pale pinkish brown.

(d) Yeast malt agar

Growth: good; colonies: thin, spreading; aerial mycelium: reddish brown (4ge: Light Grayish Reddish Brown 45); reverse of the colonies: yellow (Pr. Co-4-5) and dark brown (Pr. Oc-5-r); soluble pigments: very pale yellowish brown.

II. Agar cultures after 62 days at 28° C. (double determination)

(a) Oatmeal agar

Growth: good; colonies: thin, spreading; aerial mycelium: powdery velutinous, cinnamon coloured [R-4ie: Light Brown (57)-Cork Tan] with broad, paler margin [R. 5gc: Light Reddish Brown (4.2)-Peach Tan]; reverse of the colonies: yellowish-brown with ochre-yellow (Pr. Co-3-a) margin, slightly greyish towards the bright (Pr. Oc-4-r) centre; soluble pigments: pale ochre-brown.

(b) Starch-salt agar

As an oatmeal agar, but with a more greyish brown reverse (Pr. Oc-6-c) and with dark brown (Pr. Oc-4-r) spots and rings at the ends of the cross-hatches.

(c) Glycerine-asparagine agar

As on starch-salt agar, but paler light beige (5ec: Grayish yellowish Pink 32-Dusty Peach); Reverse: ochre-yellow [Pr. Co- (Cr)-4-b], paler in the centre; no soluble pigments.

(d) Yeast-malt agar

Growth: fair; colonies: almost as on oatmeal agar, but with very thin, pale grey margin; reverse: dark yellow (Pr. Co-4-b), dark brown in submarginal areas; soluble pigments: doubtful.

III. Melanoid pigments

Peptone-yeast extract agar: negative after 24 hours, positive after 48 hours; tyrosine agar: positive after 24 hours, positive after 48 hours.

IV. Morphology of the sporulating aerial mycelium
Section: spira-retinaculum apertum. Sympodial branched type. Spirals often irregular, with up to 5 coils often of different diameters.

V. Utilization of carbon sources No growth or only sparing growth on arabinose, xylose, inositol, mannitol, fructose, rhamnose, saccharose, raffinose.

VI. Spores

Oval to cylindrical-oval, sometimes of irregular size, smooth-walled. Spore chains with more than 10 spores.

VII. Nonomura diagram

15 R(Gy) 100 SRA sm(±) (±) (±) ———

All Streptomyces strains which produce the lipase inhibitor lipstatin are suitable for the purpose of the present invention, especially Streptomyces toxytricini 85-13, NRRL 15443, and its subcultures, mutants and variants.

The cultivation of these microorganisms for the manufacture of lipstatin can be carried out according to various fermentation methods. It can be carried out, for example, in shaking flasks or in 10 l or 200 l and 1000 l fermentors. A fixed amount of spore material or mycelium or a lipstatin-producing strain is introduced into a liquid medium which contains suitable carbon and nitrogen sources and salts required for the growth and the mixture is aerobically incubated at a temperature of 20°-37° C. for 1-6 days. Suitable carbon sources are, for example, dextrin, glucose, starch, ribose and glycerine. Suitable nitrogen sources are, for example, yeast extract, peptone or soya meal. Preferred salts are ammonium, magnesium and calcium salts. The fermentation is carried out at pH 6-8.

The isolation of the lipstatin is carried out according to methods which are known per se and which are familiar to any person skilled in the art. For example, it can be carried out as follows:

After completion of the fermentation the fermentation broth is centrifuged, whereupon 60-90% of the activity is found in the cell mass and the remainder is found in the centrifugate. The cell mass can then be treated with a low alcohol such as methanol and ethanol and extracted with the same solvent. The centrifugate can be extracted with a suitable organic solvent (e.g. with methylene chloride or ethyl acetate). The material produced from the extracts contains the desired lipstatin and can be enriched and purified by chromatographic methods. Suitable methods are, for example, multiplicative extraction with the system hexane/-methanol/water (50:40:9), filtration chromatography over silica gel while eluting with chloroform, column chromatography on silica gel while eluting with hexane, ethyl acetate and mixtures thereof, chromatography on apolar carrier materials while eluting with polar solvents such as methanol (reversed-phase chromatography) and high pressure liquid chromatography.

The Examples hereinafter contain detail information relating to the cultivation of Streptomyces toxytricini 85-13 and the isolation of the lipstatin.

Tetrahydrolipstatin, the compound of formula Ib, can be manufactured by hydrogenating lipstatin in the presence of a suitable catalyst. Examples of catalysts which can be used are palladium/carbon, platinum oxide, palladium and the like. Suitable solvents are, for example, lower alcohols such as methanol and ethanol. The hy-

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drogenation is preferably carried out at low hydrogen pressures and at room temperature (about 23° C.)

The compounds of formula I can be used as medicaments, for example in the form of pharmaceutical preparations. Illustratively, the pharmaceutical preparations can be administered orally, for example in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. If desired, the compounds also can be administered parenterally.

For the manufacture of pharmaceutical preparations the compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatine capsules are lactose, maize starch or derivatives thereof, talc, stearic acid or its salts and the like. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active ingredient no carriers are, however, generally required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water polyols, saccharose, invert sugar, glucose and the like.

Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, colouring agents, flavouring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I are also an object of the present invention as is a process for the manufacture of these medicaments, which process comprises bringing a compound of formula I and, if desired, one or more other therapeutically valuable substances into a galenical administration form. As mentioned earlier, the compounds of formula I can be used in the control or prevention of illnesses and especially in the control or prevention of obesity and hyperlipaemia. The dosage can vary within wide limits and is, of course, fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 100 mg/kg body weight of compound I is appropriate.

Preferably, the pharmaceutical compositions of formula I in unit dosage form contain about 5% to 95% by weight of compound I to the total composition. A range of 10% to 50% is preferred.

The compounds of formula I can also be added to industrially-produced foodstuffs, especially to fats, oils, butter, margarine, chocolate and other confectionery goods. Such industrially-produced foodstuffs and their production are also objects of the present invention.

The following Examples illustrate the present invention in more detail, but are not intended to limit its extent. All temperatures are given in degrees Celsius (°C.). Room temperature is about 23° C. Unless otherwise indicated, percentages and ratios relating to solvents and expressed in volume, and the remaining percentages are expressed in weight. Unless indicated otherwise, all Examples were carried out as written. A Lobar column Lichoprep RP-8, size C, is a lowpressure reverse phase column, commercially available from Merck Co.

EXAMPLE 1

(a) Fermentation:

A shaking flask containing pre-culture medium 391 is inoculated with spores of *Streptomyces toxytricini* 85-13 (or vegetative mycelium thereof) and aerobically incubated as a shaking culture at 28° C. for 72 hours. About 2-5 vol.% of this culture is used to inoculate a fermentor preculture of 10 l containing pre-culture medium 391. Incubation is carried out at 28° for 3 days with aeration of 1 vvm and stirring at 400 rpm. This 10 l pre-culture is used to inoculate a 200 l production fermentor containing production medium N7. Fermentation is carried out at 28° for 124 hours with aeration of 1.0 vvm and stirring at 150 rpm. Regular analyses show after 124 hours an extracellular lipase-inhibiting activity of 53 IC₅₀/ml.

The pre-culture medium 391 (pH 7.0) has the following composition: 3% maize starch, 4% dextrin, 3% soya meal, 0.2% (NH₄)₂SO₄, 0.6% CaCO₃ and 0.8% soya oil. The pH was adjusted to 7. The production medium N 7 (pH 7.0) has the following composition: 1% potato starch, 0.5% glucose, 1% ribose, 0.5% glycerine, 0.2% peptone, 2% soya meal and 0.2% (NH₄)₂SO₄.

(b) Working-up:

The fermentation broth is centrifuged by means of a tube centrifuge, whereby there are obtained 175 l of culture filtrate and 12 kg of mycelium. The mycelium is discarded. The culture filtrate is heated to 80° for 10 minutes, cooled, again centrifuged and concentrated to 50 l at 30° in vacuo. This concentrate is extracted with 50 l of hexane using a continuously operating extractor, the emulsion obtained is mixed with 50 l of hexane/ethyl acetate (1:1) and the organic phase is separated. This is dried over sodium sulphate and evaporated, there being obtained 199 g of crude extract I. The aqueous phase is diluted with water to 100 l and extracted with 100 l of ethyl acetate. After evaporation of the ethyl acetate solution, there are obtained 49 g of crude extract II. The aqueous phase is subsequently extracted once more with 100 l of ethyl acetate, whereby 78 g of crude extract III are obtained after evaporation.

(c) Purification:

The crude extracts II and III are filtered in three portions over in each case 1 kg of silica gel 60 (0.040-0.063 mm particle size), whereby the elution is carried out with chloroform (column: 10×100 cm). 18.3 g of enriched material are obtained in this manner. 178 g of this substance are again filtered over 1 kg of silica gel while eluting with chloroform. 5.29 g of active material are thus obtained. 802 mg of this substance are purified by reversed-phase chromatography on a commercially obtainable Lobar column (Lichoprep RP-8, size C) while eluting with methanol. There are obtained 158 mg of (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryl-oxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic acid lactone (lipstatin) which is a yellowish oil at room temperature. It is waxy-crystalline at low temperatures.

Microanalysis (dried for 20 hours in a high vacuum at 50°):

Calculated for C₂₉H₄₉N₁O₅ (491.713): C 70.84, H 10.04, N 2.85. Found C 70.85, H 9.97, N 2.59.

Optical rotation: [α]_D²⁰ = -19.0° (c=1 in chloroform).

Mass spectrum (chemical ionization with NH_3 as the reagent gas): Peaks at, inter alia, m/z 509 ($\text{M} + \text{NH}_4^+$) and 492 ($\text{M} + \text{H}^+$).

IR spectrum (film): Bands at, inter alia, 3318, 3012, 2928, 2558, 2745, 1823, 1740, 1673, 1521, 1382, 1370, 1250, 1191 cm^{-1} .

The absolute configuration could be established by chemically degrading the lipstatin and comparing the fractions obtained with known substances.

EXAMPLE 2

(a) Fermentation

A 200 l fermentor containing production medium N 16 is inoculated with a pre-culture of *Streptomyces toxytricini* 85-13 (shaking flasks and then 10 l fermentation) prepared in accordance with Example 1. The production medium N 16 corresponds to production medium N 7 used in Example 1, but also contains 0.1% pig lard. The fermentation is carried out as described in Example 1 for 120 hours. After 120 hours, the intracellular lipase-inhibiting activity amounts to 71 IC_{50}/ml of fermentation broth and the extracellular lipase-inhibiting activity amounts to 4 IC_{50}/ml of fermentation broth.

(b) Working-up

After completion of the fermentation, the fermentation broth is heated to 80° for 10 minutes, subsequently cooled and the cell mass is separated using a tube centrifuge. By two-fold centrifugation there are obtained 11.4 kg of mycelium; the culture filtrate is discarded. The mycelium is triturated in 70 l of methanol for 30 minutes, whereupon the suspension obtained is suction filtered. The filter cake is again triturated with 50 l of methanol and suction filtered. The combined methanolic extracts are concentrated to 1.8 l. This concentrate is extracted three times with 2 l of butyl acetate each time. 160 g of crude extract are obtained from the combined organic phases after evaporation.

(c) Purification

This crude extract is purified by multiplicative extraction with the system hexane/methanol/water (5:4:0.9). The active substance is firstly transferred from the lower phase (lp) into the upper phase (up). 160 g of crude extract are dissolved in 4 l of lp and stirred in a stirring vessel with 4 l of up. After separating the up, the lp is extracted a second time with 4 l of fresh up. A stable emulsion forms and to this there are added 4 l of lp and 4 l of up, whereupon a good phase separation is achieved. After separating the up, the lp is extracted twice more with 8 l of fresh up. The combined up give 90.3 g of extract after evaporation. The extraction lp is discarded. The active substance is now transferred from the up into the lp. 90.3 g of the above extract are dissolved in 4 l of up and extracted with 4 l of lp. After phase separation, the up is extracted a further three times with fresh lp. The up is subsequently discarded. The combined lp are concentrated to 0.7 l of aqueous phase and this is extracted eight times with a total of 0.2 l of ethyl acetate. 23.8 g of product are obtained after evaporation. The extracted aqueous phase is discarded. The further purification of this material is carried out by filtration over 1 kg of silica gel 60 (0.040-0.063 mm particle size; column 10×100 cm) while eluting with chloroform. There are obtained 649 mg of product which is chromatographed on a Lobar column (Lichoprep RP-8, size C) while eluting with methanol (reversed-phase chromatography). There are obtained 204

mg of lipstatin which is pure according to thin-layer chromatography.

EXAMPLE 3

138 mg of lipstatin are dissolved in 10 ml of ethanol and the solution is treated with 60 mg of 5 percent palladium/carbon and stirred at room temperature for 3 hours in a hydrogen atmosphere (balloon). The catalyst is subsequently centrifuged off. The hydrogenation product is chromatographed over a short silica gel column (1×5 cm) with chloroform. There are obtained 112 mg of (2S,3S,5S)-5-[(S)-2-formamido-4-methylvaleryl-oxy]-2-hexyl-3-hydroxyhexadecanoic acid lactone (tetrahydrolipstatin) as a waxy, slightly yellow solid.

Optical rotation: $[\alpha]_D^{20} = -32.0^\circ$ ($c=1$ in chloroform).

Mass spectrum (chemical ionization with NH_3 is the reagent gas): Peaks at, inter alia, m/z 513 ($\text{M} + \text{NH}_4^+$); 496 ($\text{M} + \text{H}^+$) and 452 ($\text{M} + \text{H}^+ - \text{CO}_2$).

IR spectrum (film): Bands at, inter alia, 3332, 2956, 2921, 2853, 1838, 1731, 1709, 1680, 1665, 1524, 1383, 1249 and 1200 cm^{-1} .

$^1\text{H-NMR}$ spectrum (270 MHz, CDCl_3): 0.89 (6H); 0.97 (6H); 1.15-1.5 (27H); 1.5-1.85 (6H); 1.9-2.25 (2H); 3.24 (1H); 4.32 (1H); 4.68 (1H); 5.03 (1H); 6.43 (1H); 8.07 and 8.21 (1H) ppm.

EXAMPLE 4

(a) Fermentation

A 2 l shaking culture flask containing pre-culture medium 391 is inoculated with spores of an agar slant culture of *Streptomyces toxytricini* 85-13 and aerobically incubated at 28° C. for 72 hours. Thereafter, the 2 l preculture is transferred into a 50 l fermentor containing production medium N 16 and incubated at 28° C. for 77 hours with 0.5 vvm aeration. This 50 l pre-culture is used to inoculate a 1000 l fermentor containing medium N 16. This production fermentation is carried out at 28° C. and 0.5 vvm aeration for 91 hours, whereby a lipstatin titre of 73 IC_{50}/ml intracellularly and 16 IC_{50}/ml extracellularly is achieved. The entire fermentation broth is cooled to 2° C. and centrifuged, whereby there are obtained 41 kg of moist biomass which are frozen at -20° C.

(b) Working-up

37 kg of mycelium are melted at 4° C. and homogenized with about 40 l of water in a mixer. The thinly liquid suspension obtained is treated with 140 l of methanol and stirred for 20 minutes. The mixture is subsequently suction filtered over a cloth filter, whereupon the filter cake is extracted further with 140 l of methanol. The methanol extracts are concentrated at 30° C. to about 22 l. The concentrate obtained is diluted with water to 50 l and extracted three times in a stirring vessel with 50 l of hexane/ethyl acetate (1:1) each time. In the second and third extractions there are obtained emulsions which can be broken by the addition of about 1.4 kg and 0.5 kg of sodium chloride, respectively. The combined organic extracts are concentrated, dried over sodium sulphate and evaporated to an oily residue. 428 g of crude extract are obtained.

(c) Purification

This crude extract is filtered in four portions over in each case 1 kg of silica gel 60 (0.040-0.063 mm particle

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size), whereby the elution is carried out with chloroform (column: 10×100 cm). There are obtained 70 g of enriched preparation which is filtered in two portions over in each case 1 kg of silica gel 60 while eluting with hexane/ethyl acetate (gradient from 9:1 to 4:1). There are obtained 4.2 g of active material which is purified in four portions by reversed-phase chromatography on a Lobar column (Lichoprep RP-8, size C) while eluting with methanol. 1.77 g of lipstatin are obtained.

EXAMPLE A

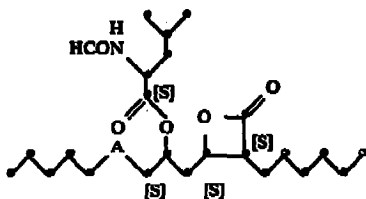
Manufacture of soft gelatine capsules of the following composition:

Amount per capsule	
Lipstatin	50 mg
NEOBEE M-5	450 µl

The solution of the active substance in NEOBEE M-5 is filled into soft gelatine capsules of suitable size. NEOBEE M-5 is a mixture of triglycerides commonly used for pharmaceutical preparations.

We claim:

1. A compound of the formula



wherein A is the group



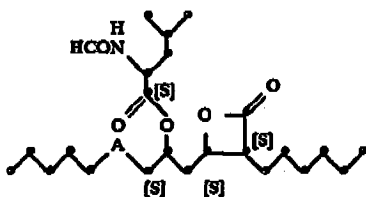
or $-(CH_2)_5-$.

2. The compound of claim 1, (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

3. The compound of claim 1, (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

4. A pharmaceutical composition for administration to a patient comprising

(a) about 5% to about 95% of a compound of formula



wherein A is the group

12



or $-(CH_2)_5-$

said composition being present in a amount sufficient to supply about 0.1 to about 100 mg of compound I per kilogram of body weight of the patient per day; and

(b) 5% to 95% of a pharmaceutically acceptable inert carrier material, said composition being formulated in a unit dosage form.

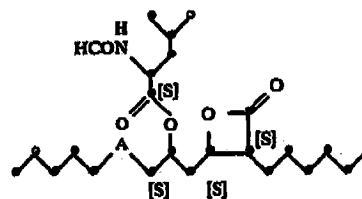
5. The composition of claim 4 wherein said composition is formulated in an oral unit dosage form.

6. The composition of claim 5 wherein said oral unit dosage form is a tablet, dragee, capsule, solution, emulsion or suspension.

7. The composition of claim 4 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

8. The composition of claim 4 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

9. A method of treating obesity in an afflicted mammal comprising administering to the mammal a compound of the formula



wherein A is the group



or $-(CH_2)_5-$

in an amount which is effective in treating obesity.

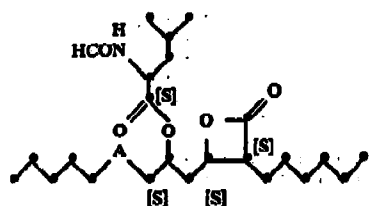
10. The method of claim 9 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

11. The method of claim 9 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

12. The method of claim 9 wherein compound I is administered in a daily dose of about 0.1 mg to 100 mg/kg body weight of the mammal.

13. A method of treating hyperlipaemia in an afflicted mammal comprising administering to the mammal a compound of the formula

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wherein A is the group



or $-(CH_2)_5-$,

in an amount which is effective in treating hyperlipemia.

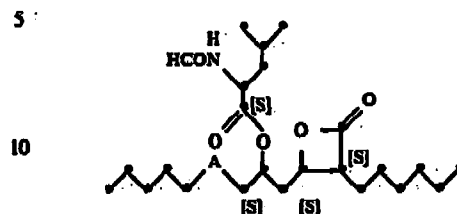
14. The method of claim 13 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

15. The method of claim 13 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

16. The method of claim 13 wherein compound I is administered in a daily dose of about 0.1 mg to 100 mg/kg body weight of the mammal.

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17. A method of preventing obesity in a mammal comprising administering to the mammal a compound of the formula



wherein A is the group



or $-(CH_2)_5-$,

in an amount which is effective in preventing obesity by inhibiting pancrease lipase.

18. The method of claim 17 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-Formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

19. The method of claim 17 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

20. The method of claim 17 wherein compound I is administered in a daily dose of about 0.1 mg to 100 mg/kg body weight of the mammal.



AA 3286377

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

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

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

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y
representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente

conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida

mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
enero de 1957, reformada en distintas oportunidades, según consta en el certificado
expedido por la Cámara de Comercio de Cali -----

SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial
pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de

Bogotá, identificado con C.C. # 79.152.473 de Bogotá, abogado en ejercicio, portador
de la T.P 44655 del C.S.de la J., domiciliado en Bogotá, D.C., República de Colombia

con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante

con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad

industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos

represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente

ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo

concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y

oposición a patentes de invención, modelos y dibujos industriales y el registro de

licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad,

medidas cautelares, concesión de licencias y en general los procesos administrativos o contencioso-administrativos relacionados con esos derechos u otros de

diferente naturaleza; acciones y procesos que promovamos o se nos promuevan; y c) para

defenderlos y hacerlos valer en los términos de la ley.

REPUBLICA DE COLOMBIA
NOTARIO NOVENO
BOGOTA, D.C.

Como Notario Veintitres de Alta Circulo
hago constar que esta fotocopia es
con su fotocopia autentica que he
a la vista
13 AGO 2007
WILLY VALENTIN
NOTARIO VEINTITRES
BOGOTA D.C.

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LUZ MERY CORREA
ELABORACION DE ESCRITURAS
Notaría 3 de Cali

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

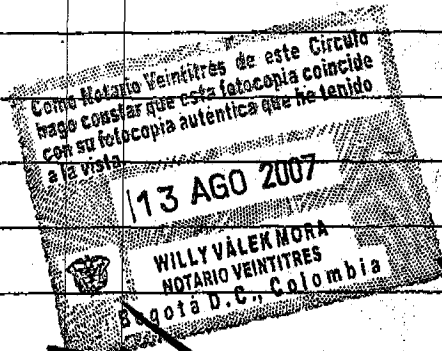
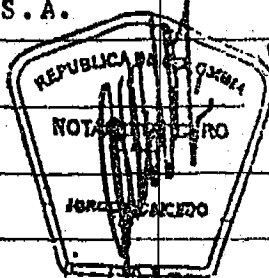
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.

Se agregan comprobantes. Derechos \$30.000,00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDANDO "OCTUBRE" VALE.

91 Juan m. Barberi

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:40:18

Operacion : 02CP20924075

PAGINA No. 1

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CERTIFICA:

NOMBRE: TECNOQUIMICAS S A

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL : ---C 23 7 39

DIRECCION NOTIFICACION JUDICIAL: ---C 23 7 39

CIUDAD: CALI

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

AFILIADO

CERTIFICA:

NIT : 890300466-5

CERTIFICA:

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

CERTIFICA:

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

CERTIFICA:

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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 2

CERTIFICA:

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

CERTIFICA:

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

CERTIFICA:

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
INS LIBRO				
E.P. 4075	05/09/1957	NOTARIA SEGUNDA DE CALI	27/09/1957	16922
E.P. 5718	28/11/1957	NOTARIA SEGUNDA DE CALI	30/12/1957	17242
E.P. 5507	31/12/1957	NOTARIA PRIMERA DE CALI	13/03/1958	17529
E.P. 3124	16/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	18365
E.P. 3325	29/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	18366
E.P. 5726	17/12/1958	NOTARIA PRIMERA DE CALI	12/05/1959	19258
E.P. 2374	12/05/1959	NOTARIA PRIMERA DE CALI	03/06/1959	19368
E.P. 2793	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961	22616
E.P. 2794	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961	22617
E.P. 6365	30/12/1961	NOTARIA PRIMERA DE CALI	23/01/1962	23489
E.P. 1383	21/03/1962	NOTARIA PRIMERA DE CALI	28/03/1962	23850
E.P. 3396	28/05/1963	NOTARIA PRIMERA DE CALI	11/06/1963	26016

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 3

E.P. 8853	30/12/1963	NOTARIA PRIMERA DE CALI	23/01/1964
27107			
E.P. 5718	28/11/1957	NOTARIA SEGUNDA DE CALI	10/02/1964
27181			
E.P. 2743	29/04/1964	NOTARIA PRIMERA DE CALI	06/05/1964
27681			
E.P. 2744	29/04/1964	NOTARIA PRIMERA DE CALI	06/05/1964
27682			
E.P. 7057	21/10/1964	NOTARIA PRIMERA DE CALI	22/10/1964
28591			
E.P. 1693	26/04/1965	NOTARIA PRIMERA DE CALI	28/04/1965
29569			
E.P. 1799	10/05/1966	NOTARIA PRIMERA DE CALI	11/05/1966
31623			
E.P. 2498	18/11/1966	NOTARIA CUARTA DE CALI	25/11/1966
32757			
E.P. 2792	27/12/1966	NOTARIA CUARTA DE CALI	05/01/1967
33009			
E.P. 2209	25/09/1967	NOTARIA CUARTA DE CALI	04/10/1967
34591			
E.P. 6933	20/12/1967	NOTARIA SEGUNDA DE CALI	28/12/1967
35082			
E.P. 6363	14/11/1968	NOTARIA SEGUNDA DE CALI	26/11/1968
37141			
E.P. 7711	31/12/1968	NOTARIA SEGUNDA DE CALI	04/02/1969
37615			
E.P. 5597	30/09/1969	NOTARIA SEGUNDA DE CALI	18/10/1969
39341			
E.P. 5211	27/08/1970	NOTARIA SEGUNDA DE CALI	04/09/1970
41379			
E.P. 6576	07/10/1971	NOTARIA SEGUNDA DE CALI	14/10/1971
44154			
E.P. 7286	08/11/1971	NOTARIA SEGUNDA DE CALI	10/11/1971
44367			
E.P. 8042	03/12/1971	NOTARIA SEGUNDA DE CALI	21/12/1971
44716			
E.P. 6209	05/10/1973	NOTARIA SEGUNDA DE CALI	15/10/1973
5505 IX			
E.P. 8741	31/12/1973	NOTARIA SEGUNDA DE CALI	08/03/1974
7636 IX			
E.P. 9270	31/12/1974	NOTARIA SEGUNDA DE CALI	31/01/1975
11772 IX			
E.P. 9504	31/12/1974	NOTARIA SEGUNDA DE CALI	04/04/1975
12441 IX			
E.P. 7566	05/12/1975	NOTARIA SEGUNDA DE CALI	09/01/1976
15581 IX			
E.P. 2671	09/05/1980	NOTARIA SEGUNDA DE CALI	22/10/1980
41529 IX			

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operacion : 02CP20924075

PAGINA No. 4

E.P. 779	10/03/1982	NOTARIA DECIMA	DE CALI	03/08/1982
54655 IX				
E.P. 4324	10/11/1982	NOTARIA DECIMA	DE CALI	30/06/1983
61172 IX				
E.P. 41269	18/03/1986	NOTARIA DECIMA	DE CALI	01/04/1986
83730 IX				
E.P. 5089	24/09/1986	NOTARIA DECIMA	DE CALI	29/09/1986
87933 IX				
E.P. 7064	04/11/1987	NOTARIA DECIMA	DE CALI	19/11/1987
2552 IX				
E.P. 7065	04/11/1987	NOTARIA DECIMA	DE CALI	19/11/1987
2553 IX				
E.P. 5929	14/07/1989	NOTARIA DECIMA	DE CALI	26/07/1989
20225 IX				
E.P. 8569	29/09/1989	NOTARIA DECIMA	DE CALI	02/10/1989
22250 IX				
E.P. 10571	04/12/1992	NOTARIA DECIMA	DE CALI	15/12/1992
60929 IX				
E.P. 10249	18/12/1995	NOTARIA DECIMA	DE CALI	20/12/1995
10214 IX				
E.P. 2359	22/05/1997	NOTARIA TERCERA	DE CALI	27/05/1997
3813 IX				
E.P. 2624	30/06/2000	NOTARIA TERCERA	DE CALI	07/07/2000
4740 IX				
E.P. 3814	15/09/2000	NOTARIA TERCERA	DE CALI	18/09/2000
6381 IX				
E.P. 3588	30/07/2004	NOTARIA TERCERA	DE CALI	04/08/2004
8542 IX				
E.P. 1224	24/05/2006	NOTARIA TERCERA	DE CALI	30/05/2006
6565 IX				

CERTIFICA:

VIGENCIA: 01 DE ENERO DEL AÑO 2057

CERTIFICA:

OBJETO SOCIAL. LA SOCIEDAD TIENE POR OBJETO: A) LA FABRICACION, EL ENVASADO, LA IMPORTACION, LA EXPORTACION, LA VENTA Y DISTRIBUCION DE PRODUCTOS BIOLÓGICOS Y QUÍMICOS, MEDICAMENTOS O PRODUCTOS FARMACÉUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRÍCOLAS Y ALIMENTOS NATURALES Y/O PRODUCTOS DE CONSUMO POPULAR DE CUALQUIER NATURALEZA Y SERVICIOS EN GENERAL. B) INVERTIR EN SOCIEDADES O EMPRESAS DE CUALQUIER NATURALEZA O ESPECIE DE LA SOCIEDAD MERCANTIL, NACIONAL O EXTRANJERA, QUE TENGAN COMO ACTIVIDAD O NEGOCIO PROPIO DE SU OBJETO LA FABRICACION, DISTRIBUCION Y

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 5

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

CERTIFICA:

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

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

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

FUNCIONES DE LA ASAMBLEA DE ACCIONISTAS. ENTRE OTRAS LAS SIGUIENTES: 1) ACORDAR LA FUSION DE LA SOCIEDAD, SU TRANSFORMACION, LA ENAJENACION O EL ARRENDAMIENTO DE LA EMPRESA SOCIAL, LA DISOLUCION O LA PRORROGA Y CUALQUIER REFORMA, AMPLIACION MODIFICACION DEL CONTRATO SOCIAL. 9) AUTORIZAR LA ADQUISICION DE ACCIONES PROPIAS, CON SUJECION A LOS REQUISITOS ESTABLECIDOS POR LA LEY. 10) ADOPTAR EN GENERAL, TODAS LAS MEDIDAS QUE RECLAMEN EL CUMPLIMIENTO DE LOS ESTATUTOS O EL INTERES DE LA SOCIEDAD.

EN LA JUNTA DIRECTIVA SE ENTIENDE DELEGADO EL MAS AMPLIO MANDATO PARA

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AFIJSO FOR CALI 14. INT 620037115 NIS 64207

CERTIFICADO NACIONAL

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Operacion : 02CP20924075

PAGINA No. 6

ADMINISTRAR LA SOCIEDAD Y POR CONSIGUIENTE, TENDR? ATRIBUCIONES SUFICIENTES PARA ORDENAR QUE SE EJECUTE O CELEBRE CUALQUIER ACTO O CONTRATO COMPRENDIDO DENTRO DEL OBJETO SOCIAL Y PARA ADOPTAR LAS DETERMINACIONES NECESARIAS EN ORDEN A QUE LA SOCIEDAD CUMPLA SUS FINES Y DE MANERA ESPECIAL, TENDR? LAS SIGUIENTES FUNCIONES ENTRE OTRAS: C) NOMBRAR Y REMOVER LIBREMENTE AL PRESIDENTE EJECUTIVO, A LOS VICEPRESIDENTES EJECUTIVOS Y A LOS VICEPRESIDENTES ADMINISTRATIVOS. E) DISPONER EL ESTABLECIMIENTO O LA CLAUSURA DE SUCURSALES O AGENCIAS, DENTRO O FUERA DEL DOMICILIO SOCIAL. F) FIJAR LAS POLITICAS DE LA SOCIEDAD EN LOS DIFERENTES ORDENES DE SU ACTIVIDAD, ESPECIALMENTE EN MATERIA FINANCIERA, ECONOMICA Y LABORAL; APROBAR PLANES DE INVERSION Y DE PRODUCCION; DECIDIR SOBRE NUEVAS LINEAS DE PRODUCCION Y VENTA, ESTABLECER NORMAS GENERALES EN MATERIA DE PRECIOS Y DE VENTAS DE LOS PRODUCTOS ELABORADOS POR LA SOCIEDAD O DE LOS MATERIALES Y DEMAS ELEMENTOS EN QUE ELLA NEGOCIE Y DICTAR NORMAS Y REGLAMENTOS PARA LA ORGANIZACION Y EL FUNCIONAMIENTO DE TODAS LAS DEPENDENCIAS DE LA SOCIEDAD. G) DETERMINAR LA APLICACION QUE DEBA DARSE A LAS UTILIDADES QUE, CON EL CARACTER DE RESERVAS DE INVERSION, HAYAN SIDO APROPIADAS POR LA ASAMBLEA DE ACCIONISTAS. H) AUTORIZAR PREVIAMENTE LAS OPERACIONES QUE TENGAN POR OBJETO: 1) ADQUIRIR, HIPOTECAR Y EN CUALQUIER OTRA FORMA GRAVAR O LIMITAR EL DOMINIO DE BIENES RAICES CUYA CUANTIA SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE; 2) CONSTITUIR PRENDA SOBRE BIENES SOCIALES O DARLOS EN ANTICRESIS PARA ACTOS O CONTRATOS CUYA CUANTIA SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE; 3) AUTORIZAR INVERSIONES EN BIENES DE CAPITAL O EFECTUAR REPARACIONES O MEJORAS DE LOS MISMOS, CUANDO UNAS U OTRAS IMPLIQUEN, EN CADA CASO, COSTOS O DESEMBOLSOS EN CUANTIA O SUPERIOR A CIENTO MIL DOLARES AMERICANOS (\$US100.000.00). 4) AUTORIZAR LOS CONTRATOS DE MUTUO QUE PUEDAN CELEBRAR LA SOCIEDAD LOS REPRESENTANTES LEGALES CUANDO SU CUANTIA SEA SUPERIOR A \$100.000.000.00 MONEDA LEGAL COLOMBIANA O A US\$300.000.00. L) AUTORIZAR AL REPRESENTANTE LEGAL PARA QUE SOLICITE, LLEGADO EL CASO, QUE SE ADMITA A LA COMPANIA A LA CELEBRACION DE CONCORDATO PREVENTIVO CON SUS ACREEDORES. M) SERVIR DE ORGANO CONSULTIVO Y ASESOR DE LOS REPRESENTANTES DE LA COMPANIA.

LA ADMINISTRACION INMEDIATA DE LA COMPANIA, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES EJECUTIVOS, DESIGNADOS POR LA JUNTA DIRECTIVA PARA PERIODOS DE UN AÑO, REELEGIBLES INDEFINIDAMENTE Y REMOVIBLES LIBREMENTE POR ELLA EN CUALQUIER TIEMPO, QUIENES COMO REPRESENTANTES LEGALES PODRAN ACTUAR CONJUNTA O SEPARADAMENTE CON IGUALDAD DE FUNCIONES Y CALIDADES. TODOS LOS EMPLEADOS DE LA COMPANIA CON EXCEPCION DE LOS DESIGNADOS POR LA ASAMBLEA DE ACCIONISTAS Y LOS DEPENDIENTES DEL REVISOR FISCAL, SI LOS HUBIERE, ESTARAN SOMETIDOS EN EL DESEMPEÑO DE SUS CARGOS A LOS REPRESENTANTES LEGALES.

LOS REPRESENTANTES LEGALES SON MANDATARIOS CON REPRESENTACION INVESTIDOS DE FUNCIONES EJECUTIVAS Y ADMINISTRATIVAS Y COMO TALES TIENEN A SU CARGO LA REPRESENTACION LEGAL DE LA COMPANIA, LA GESTION COMERCIAL Y FINANCIERA, LA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA EMPRESA, LAS CUALES CUMPLIRAN CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS Y A LAS DISPOSICIONES LEGALES Y CON SUJECION A LAS ORDENES E INSTRUCCIONES DE LA JUNTA DIRECTIVA.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 7

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

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

CERTIFICA:

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

ORIGEN: JUNTA DIRECTIVA

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

FUE(ON) NOMBRADO(S):

PRESIDENTE EJECUTIVO
FRANCISCO JOSE BARBERI OSPINA
C.C.14445880

VICEPRESIDENTE EJECUTIVO
JUAN MANUEL BARBERI OSPINA ✓
C.C.14949561

VICEPRESIDENTE EJECUTIVO
JUAN BAUTISTA DE LOS RIOS GUTIERREZ

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha: 20070924

Hora Certificado 17:40:18

Operacion: 02CP20924075

PAGINA No. 8

C.C.17108621

VICEPRESIDENTE EJECUTIVO

EMILIO SARDI APARICIO

C.C.14434582

CERTIFICA:

DOCUMENTO: ACTA No. 38 DEL 03 DE FEBRERO DE 1992

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 05 DE JUNIO DE 1992 No. 54016 DEL LIBRO IX

DOCUMENTO: ACTA No. 54 DEL 31 DE MARZO DE 2000

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 24 DE MAYO DE 2000 No. 3622 DEL LIBRO IX

DOCUMENTO: ACTA No. 65 DEL 27 DE JULIO DE 2006

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 04 DE AGOSTO DE 2006 No. 9191 DEL LIBRO IX

FUE (RON) NOMBRADO (S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

FRANCISCO JOSE BARBERI OSPINA

C.C.14445880

SEGUNDO RENGLON

JUAN MANUEL BARBERI OSPINA

C.C.14949561

TERCER RENGLON

JUAN BAPTISTA DE LOS RIOS GUTIERREZ

C.C.17108621

CUARTO RENGLON

EMILIO SARDI APARICIO

C.C.14434582

QUINTO RENGLON

DIEGO HUMBERTO QUIJANO REISSNER

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CAMARA DE COMERCIO DE CALI

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PAGINA No. 9

C.C.16615708

SUPLENTES

PRIMER RENGLON

GUSTAVO ADOLFO SANCHEZ LESMES

C.C.16625960

SEGUNDO RENGLON

VICTOR RICARDO ROSA GARCIA

C.C.6811102

TERCER RENGLON

ANTONIO JAIRO RAMIREZ ECHAVE

C.C.16741040

CUARTO RENGLON

ERNESTO TRUJILLO PEREZ

C.C.14984104

QUINTO RENGLON

ANA MARIA ALVAREZ

C.C.31170896

CERTIFICA:

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

ORIGEN: ASAMBLEA DE ACCIONISTAS

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

FUE (RON) NOMBRADO(S):

REVISOR FISCAL

DELOITTE & TOUCHE LTDA D & T LTDA

NIT.860005813-4

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 26 DE AGOSTO DE 2004

ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA

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

FUE (RON) NOMBRADO(S):

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:40:18

Operacion : 02CP20924075

PAGINA No. 10

REVISOR FISCAL PRINCIPAL
LUIS FERNANDO QUICENO BENAVIDES
C.C.6106227

REVISOR FISCAL SUPLENTE
JESUS DARIO LOPEZ CASELLA
C.C.16789097

CERTIFICA:

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

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

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

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CAMARA DE COMERCIO DE CALI

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PAGINA No. 11

QUE POR ESCRITURA NRO. 2719 DEL 15 DE JULIO DE 1999 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE AGOSTO DE 1999 BAJO EL NRO. 323 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A SAMUEL GOMEZ UPEGUI, MAYOR DE EDAD, VECINO DE CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 16.633.490, GERENTE DEL DISTRITO DE VENTAS DEL OCCIDENTE COLOMBIANO DE LA SOCIEDAD, CON SEDE EN CALI, UBICADO EN LA CALLE 23 NRO. 4-66, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO O POLICIVO, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES DE CARACTER LABORAL, CIVIL, COMERCIAL Y POLICIVO, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORGUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESA FACULTAD PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRAPROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 4) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 5) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:40:18

Operacion : 02CP20924075

PAGINA No. 12

QUE POR ESCRITURA NRO. 2873 DEL 10 DE JULIO DE 2001 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 06 DE SEPTIEMBRE DE 2001 BAJO EL NRO. 213 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A MARIA TERESA CANON DE GUZMAN, IDENTIFICADA CON LA CEDULA DE CIUDADANIA NRO. 31.238.104 DE CALI, CARLOS ARTURO PENA NIETO IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 19.483.439 DE BOGOTA Y ANGELA MARIA CORREA CARDONA IDENTIFICADA CON LA CEDULA DE CIUDADANIA No.66.835.555 DE CALI, LA PRIMERA COMO PRINCIPAL Y EL SEGUNDO COMO PRIMER SUPLENTE Y LA TERCERA COMO SEGUNDA SUPLENTE, PARA QUE REPRESENTEN A LA SOCIEDAD EN TODOS LOS ASUNTOS CAMBIARIOS, CON FACULTAD PARA FIRMAR DECLARACIONES DE CAMBIOS SEA POR CREDITOS EN MONEDA EXTRANJERA, POR MOVIMIENTOS DE LAS CUENTAS CORRIENTES DE COMPENSACION, IMPORTACIONES DE BIENES Y SERVICIOS, TRANSFERENCIAS Y OTROS CONCEPTOS, REGISTRO DE PRESTAMO EN MONEDA EXTRANJERA OTORGADOS A LA EMPRESA EN SU CONDICION DE RESIDENTE Y TODOS AQUELLOS DOCUMENTOS O DECLARACIONES QUE DEBAN HACERSE ANTE EL BANCO DE LA REPUBLICA U OTRAS ENTIDADES GUBERNAMENTALES RESPECTO DE OPERACIONES EN EL MERCADO CAMBIARIO. LOS APODERADOS SUSCRIBIRAN TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A TECNOQUIMICAS S. A. ANTE LAS AUTORIDADES CAMBIARIAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL PARA QUE ASUMA LA PERSONERIA A NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIMEN CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES DE CARACTER CAMBIARIO Y EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. LOS APODERADOS SE CENIRAN RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER NOTIFICACION O REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA:

QUE POR ESCRITURA NRO. 307 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 298 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A JORGE ROBERTO OBANDO RODRIGUEZ, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 14.960.183 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA: 1o.) PROMUEVA O DESISTA DE ACCIONES ANTE CORPORACIONES, ENTIDADES O FUNCIONARIOS DEL ORDEN JUDICIAL O GUBERNATIVO, YA SEA EN PROCESOS, ACTUACIONES O ACTOS SIMPLES, DILIGENCIAS O GESTIONES EN QUE TECNOQUIMICAS S.A. TENGA INTERES COMO ACTOR, DEMANDANDO O TERCERO INTERVINIENTE EN RELACION CON LOS ASUNTOS DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA, EN QUE LA EMPRESA SEA PARTE ACTIVA O PASIVA, CON CAPACIDAD PARA NOTIFICARSE Y CONTESTAR Y HACERSE PARTE DE ELLOS EN NOMBRE DE TECNOQUIMICAS S.A. 2o.) SUSCRIBA Y DE POR TERMINADO LOS CONTRATOS DE TRABAJO DEL PERSONAL VINCULADO A LA EMPRESA. 3o.) CONSTITUYA APODERADOS EN DESARROLLO DE ESTA REPRESENTACION LABORAL, REVOQUE Y SUSTITUYA DICHOS PODERES CUANDO LO ESTIME PROCEDENTE. 4o.) TRANSIGA, CONCILIE, DESISTA Y COMPROMETA A

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PAGINA No. 13

LA EMPRESA EN TODOS LOS TRAMITES ADMINISTRATIVOS Y PROCESOS JUDICIALES, DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA EN LOS QUE LA EMPRESA SEA PARTE DEMANDANTE, DEMANDADA O TERCERO INTERVINIENTE. PARAGRAFO. LA FACULTAD PARA TRANSIGIR O CONCILIAR SE LIMITA A LA SUMA DE QUINIENTOS (500) SALARIOS LEGALES MENSUALES. 5o.) OTORQUE PODERES Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES JUDICIALES DE CARACTER CIVIL, COMERCIAL Y PENAL TENDIENTES A LA RECUPERACION DE LOS CREDITOS A FAVOR DE LA SOCIEDAD, BIEN SEA REPRESENTADOS EN FACTURAS, CHEQUES, TITULOS VALORES O CUALQUIER OTRO DOCUMENTO REPRESENTATIVO DE CREDITO, HASTA POR SUMA EQUIVALENTE A QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE TECNOQUIMICAS S.A. A LAS AUDIENCIAS DE CONCILIACION QUE PROGRAMEN LOS JUZGADOS CIVILES MUNICIPALES Y DEL CIRCUITO, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD HASTA POR LA CUANTIA INDICADA. 6o. REPRESENTA A TECNOQUIMICAS S.A. DENTRO DE LOS TRAMITES DE CONCORDATOS, PROCESOS DE REESTRUCTURACION ECONOMICA PREVISTO EN LA LEY 550 DE 1999 Y LAS NORMAS QUE LA ADICIONEN O MODIFIQUEN Y LIQUIDACIONES OBLIGATORIAS QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE ACREEDORES O ANTE LOS JUZGADOS CIVILES, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER, NOMBRAR APODERADOS, PRESENTAR LOS CREDITOS, APORTAR LAS PRUEBAS QUE ESTIME NECESARIAS, ASISTIR A LAS AUDIENCIAS PRELIMINARES Y DEFINITIVAS, ACORDAR FORMULAS DE PAGO, RECIBIR Y EN GENERAL PARA EJERCER TODAS AQUELLAS GESTIONES NECESARIAS PARA OBTENER EL RECONOCIMIENTO Y PAGO DE LOS CREDITOS PRESENTADOS. LAS FACULTADES AQUI ESTABLECIDAS ESTAN LIMITADAS PARA LOS CREDITOS HASTA POR CUANTIA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. PARAGRAFO. IGUALMENTE QUEDA FACULTADO PARA ACEPTAR Y REPRESENTAR A TECNOQUIMICAS CUANDO LA EMPRESA SEA NOMBRADA EN JUNTA DE ACREEDORES O EN ORGANOS EQUIVALENTES O SIMILARES, EN LOS PROCESOS QUE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES. 7o.) REPRESENTA A TECNOQUIMICAS S.A. EN LOS PROCEDIMIENTOS DE CONCILIACION QUE LOS DEUDORES DE LA SOCIEDAD CONVOQUEN ANTE LAS ENTIDADES FACULTADAS PARA ELLO CON EL FIN OBTENER UN ACUERDO EN EL PAGO DE LAS ACREENCIAS, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER Y RECIBIR, FACULTADES QUE SE LIMITAN HASTA POR LA SUMA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. 8o.) REVISE LOS EXPEDIENTES DE LOS PROCESOS JUDICIALES DE CARACTER EJECUTIVO EN QUE LA SOCIEDAD SEA PARTE DEMANDANTE, EN TODO EL TERRITORIO NACIONAL, PARA LA RECUPERACION DE SUS ACREENCIAS. 9o.) APRUEBE Y SUSCRIBA ACUERDOS PRIVADOS DE PAGO Y CONCILIACIONES DE OBLIGACIONES A FAVOR DE TECNOQUIMICAS POR LA VENTA DE SUS PRODUCTOS HASTA POR LA SUMA DE (500) SALARIOS MINIMOS LEGALES MENSUALES.

CERTIFICA:

QUE POR ESCRITURA NRO. 309 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 300 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A DANIEL AMEZQUITA, MAYOR DE EDAD, VECINO DE BARRANQUILLA,

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CERTIFICADO NACIONAL

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PAGINA No. 14

IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 8.681.962 DE BARRANQUILLA, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL DE LA ZONA ATLANTICA DE LA SOCIEDAD, CON SEDE EN BARRANQUILLA, PARA EL EJERCICIO DE LA SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VENTILE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO, EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y

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PAGINA No. 15

PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

QUE POR ESCRITURA NRO. 310 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 301 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A CARLOS ORLANDO MUTIS, MAYOR DE EDAD, VECINO DE BUCARAMANGA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 91.200.418 DE BUCARAMANGA, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL ORIENTE DE LA SOCIEDAD, CON SEDE EN BUCARAMANGA, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO, Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD

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PAGINA No. 16

SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO, EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

QUE POR ESCRITURA NRO. 308 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE MARZO DE 2002 BAJO EL NRO. 318 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A HERNANDO ANGULO MOYANO, MAYOR DE EDAD, VECINO DE BOGOTA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 19.322.139 DE BOGOTA, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE.

PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O

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PAGINA No. 17

RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO, EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

QUE POR ESCRITURA NRO. 4.202 DEL 31 DE MAYO DE 1995 NOTARIA DECIMA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 24 DE SEPTIEMBRE DE 2003 BAJO EL NRO. 134 DEL LIBRO V SE CONFIERE PODER ESPECIAL A ANTONIO JAIRO RAMIREZ ECHAVE, ABOGADO TITULADO Y EN EJERCICIO, CON TARJETA PROFESIONAL No. 58.401 DEL MINISTERIO DE JUSTICIA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 16.741.040 DE CALI PARA QUE REPRESENTA A TECNOQUIMICAS S.A., EN LOS SIGUIENTES ACTOS: A) SOLICITAR Y ADELANTAR ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO TODOS LOS TRAMITES ATINENTES A LA OBTENCION DE LICENCIAS DE VENTA Y LICENCIAS DE FUNCIONAMIENTO, RENOVACIONES, CERTIFICACIONES, AMPLIACIONES, INSCRIPCIONES Y MODIFICACIONES EN GENERAL; B) TODOS LOS TRAMITES ANTE EL INVIMA ATINENTES A LA OBTENCION DE REGISTRO SANITARIO, RENOVACION DEL MISMO, REFORMULACIONES, ADICIONES DE NUESTRA LINEA DE PRODUCTOS, CAMBIOS DE TITULAR Y DE FABRICANTE, CESIONES, CERTIFICACIONES DE FORMULA Y EXCLUSIVIDAD, MODIFICACIONES DE FABRICAR Y VENDER A IMPORTAR Y VENDER Y VICEVERSA, E IGUALMENTE CERTIFICACIONES SOBRE LA LINEA COMPLETA DE NUESTROS PRODUCTOS, A CUYO OBJETO LO FACULTO PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS PASOS NECESARIOS, PRESENTAR SOLICITUDES, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPLOTACIONES, SOLICITAR TESTIMONIOS, RECIBIR DOCUMENTOS, FORMULAR APELACIONES Y RECLAMOS, DESISTIR Y PERCIBIR. ASI MISMO DICHO APODERADO ESTA AUTORIZADO PARA HACER CUANTO FUERE NECESARIO ANTE LAS AUTORIDADES ADMINISTRATIVAS PARA LOS FINES ARRIBA INDICADOS CON TODAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE FUEREN NECESARIAS INCLUIDAS LAS DE SUSTITUIR Y DELEGAR EL

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PAGINA No. 18

 PRESENTE PODER SI LO ESTIMARE CONVENIENTE Y EN CASO NECESARIO REVOCAR DICHAS SUSTITUCIONES. PUDIENDO ATENDER ASI MISMO LAS NOTIFICACIONES QUE DIRECTA O INDIRECTAMENTE SE GENERE DE LOS ACTOS, ACTUACIONES, DILIGENCIAS O GESTIONES QUE TENGAN RELACION DE CAUSALIDAD POR LOS SUSODICHOS TRAMITES Y 3) EN GENERAL PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. ANTONIO JAIRO RAMIREZ ECHAVE SE CENIRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O SU REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA:

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

CERTIFICA:

QUE POR ESCRITURA NRO. 4265 DEL 16 DE SEPTIEMBRE DE 2005 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE OCTUBRE DE 2005 BAJO EL NRO. 168 DEL LIBRO V EL SE?OR JUAN BAUTISTA DE LOS RIOS GUTIERREZ MAYOR DE EDAD, DOMICILIADO EN CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 17108621

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Hora Certificado 17:40:18

Operacion : 02CP20924075

PAGINA No. 19

DE BOGOTA, QUIEN ACTUA EN SU CALIDAD DE REPRESENTANTE LEGAL DE TECNOQUIMICAS S. A. SOCIEDAD COMERCIAL ORGANIZADA Y EXISTENTE CONFORME A LAS LEYES COLOMBIANAS, CON DOMICILIO Y SEDE PRINCIPAL EN CALI. EN DICHA CONDICION CONFIERE PODER AMPLIO Y SUFICIENTE A LAS SIGUIENTES PERSONAS: CLAUDETTE VERNOT HERNANDEZ ABOGADA TITULADA Y EN EJERCICIO, IDENTIFICADA CON LA CEDULA DE CIUDADANIA No. 51722517 DE BOGOTA, PORTADORA DE LA TARJETA PROFESIONAL DE ABOGADO No. 57111 DEL C.S. DE LA J., ANDRES FELIPE ZAPATA OCAMPO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79598546 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 107240 DEL C.S. DE LA J. Y JUAN MANUEL SERRANO CASTILLO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79875670 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 124953 DE C.S. DE LA J., TODOS CON DOMICILIO EN LA CIUDAD DE BOGOTA, D.C., PARA QUE EN NOMBRE DE MI REPRESENTADA ACTUEN EN TODOS LOS ASUNTOS DE PROPIEDAD INTELECTUAL Y LOS DERIVADOS DE ELLA, CON FACULTAD PARA RECIBIR NOTIFICACIONES, NOMBRAR APODERADOS JUDICIALES O EXTRAJUDICIALES EN ESTOS ASUNTOS.

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

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IMPRESO POR DANIELA P. A. N. 11 00-00-7113 7453 04-2007

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

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Operacion : 02CP20924075

PAGINA No. 20

SOLICITUD DE AUTORIZACIONES PARA PROMOCIONES, RIFAS Y JUEGOS ANTE ETESA O ANTE LAS AUTORIDADES COMPETENTES DEL ORDEN LOCAL, DISTRITAL O DEPARTAMENTAL; Y EN GENERAL CUALQUIERA OTRA PETICION ANTE LAS AUTORIDADES ADMINISTRATIVA, ASI COMO PARA NOTIFICARSE DE CUALQUIER PROVIDENCIA Y RENUNCIAR A TERMINOS. EN TODOS LOS ASUNTOS ARRIBA DETERMINADOS LA APODERADA QUEDA FACULTADA PARA SUSTITUIR TOTAL O PARCIALMENTE ESTE MANDATO, TRANSIGIR, CONCILIAR EXTRAJUDICIAL O JUDICIALMENTE, ADMITIR LOS HECHOS DEL PROCESO PERO NO PARA CONFESAR, DESISTIR, CANCELAR, RECIBIR, RENUNCIAR Y RATIFICAR LOS ACTOS DE AGENTES OFICIOSOS.

CERTIFICA:

QUE POR ESCRITURA NRO. 2065 DEL 15 DE MAYO DE 2006 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 30 DE MAYO DE 2006 BAJO EL NRO. 76 DEL LIBRO V , SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A PAULINA MARIA AGUDELO, MAYOR DE EDAD, VECINA DE MEDELLIN, IDENTIFICADA CON LA CEDULA DE CIUDADANIA NRO.43723508 DE ENVIGADO, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ANTIOQUIA DE LA SOCIEDAD, CON SEDE EN MEDELLIN, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO, CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORQUE Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operacion : 02CP20924075

PAGINA No. 21

DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A., EN NINGUN CASO, QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

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

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 17 DE NOVIEMBRE DE 2005, INSCRITO EN LA CAMARA DE COMERCIO EL 23 DE NOVIEMBRE DE 2005 BAJO EL NRO. 13.158 DEL LIBRO IX, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR TECNOQUIMICAS S.A.

CONTROLANTE: TECNOQUIMICAS S.A.
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA

CONTROLADA: INDUGRAFICAS S.A.
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE INDUGRAFICAS S.A. CORRESPONDEN AL DESARROLLO DE NEGOCIOS RELACIONADOS CON LAS ARTES GRAFICAS, LA DISTRIBUCION DE LAS MISMAS YA SEA DE SUS PRODUCTOS PROPIOS O POR CONTRATO, TANTO EN EL MERCADO NACIONAL COMO

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

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Operacion : 02CP20924075

PAGINA No. 22

EN EL INTERNACIONAL.

UNIDAD DE PROPOSITO Y ADMINISTRACION. ENTRE TECNOQUIMICAS E INDUGRAFICAS S.A. EXISTE UNIDAD DE PROPOSITO Y DIRECCION YA QUE LOS PLANES Y OBJETIVOS DE ESTA ULTIMA ESTAN DETERMINADAS POR LA PRIMERA.

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

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 17 DE NOVIEMBRE DE 2005, INSCRITO EN LA CAMARA DE COMERCIO EL 23 DE NOVIEMBRE DE 2005 BAJO EL NRO. 13.159 DEL LIBRO IX, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR TECNOQUIMICAS S.A.

CONTROLANTE: TECNOQUIMICAS S.A.

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

CONTROLADA: TECNOFAR TQ S.A.

DOMICILIO: VILLA, RICA DEPARTAMENTO DEL CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE TECNOFAR TQ S.A. CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION DE PRODUCTOS BIOLOGICOS, QUIMICOS, MEDICAMENTOS Y PRODUCTOS FARMACEUTICOS, PRODUCTOS VETERINARIOS Y AGRICOLAS, ALIMENTOS, COSMETICOS Y DE TOCADOR, PRODUCTOS DE ASEO PARA EL HOGAR Y LA FABRICACION Y DISTRIBUCION DE ENVASES PLASTICOS PARA TODO TIPO DE USO.

UNIDAD DE PROPOSITO Y ADMINISTRACION. ENTRE TECNOQUIMICAS Y TECNOFAR, EXISTE UNIDAD DE PROPOSITO Y DIRECCION YA QUE LOS PLANES Y OBJETIVOS DE ESTA ULTIMA ESTAN DETERMINADAS POR LA PRIMERA.

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

CERTIFICA:

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

MATRIZ: TECNOQUIMICAS S.A.

DOMICILIO: SANTIAGO DE CALI.

NACIONALIDAD: COLOMBIANA

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

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Operacion : 02CP20924075

PAGINA No. 23

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

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

NACIONALIDAD: COLOMBIANA

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

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

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.7050-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: ---C 23 7 39 DE CALI
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.311234-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: -K 7 22 122 DE CALI
FECHA MATRICULA : 22 DE ABRIL DE 1992
RENOVO : POR EL A?O 2007

CERTIFICA:

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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

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Operacion : 02CP20924075

PAGINA No. 24

RENOVO : POR EL AÑO 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.606730-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A JAMUNDI
UBICADO EN: --CARRETERA JAMUNDI KM. 23 DE JAMUNDI
FECHA MATRICULA : 14 DE ABRIL DE 2003
RENOVO : POR EL AÑO 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.606736-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A YUMBO
UBICADO EN: --CL. 15 NRO. 30 98 AUTOPISTA CALI-YUMBO KILOMETRO 4 DE YUMBO
FECHA MATRICULA : 14 DE ABRIL DE 2003
RENOVO : POR EL AÑO 2007

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 30 DE MARZO DE 2007.

CERTIFICA:

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

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

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

DADO EN CALI A LOS 24 DIAS DEL MES DE SEPTIEMBRE DEL AÑO 2007 HORA: 05:17:40



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

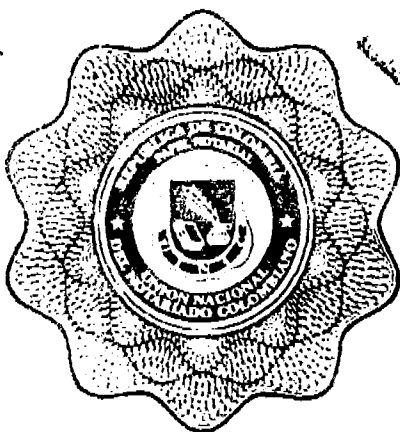
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REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE

JULIO - - - - -

DEL AÑO DOS MIL DOS (2002). -----

ACTO: -----

1.- PODER ESPECIAL.-----

OTORGADO POR: LAFRANCOL S.A., con Nit. No. - - -

890.301.463-8 - - - - -

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No.

79.152.473 de Usaquén - Bogotá.-----

DIANA BEATRIZ LOPEZ

NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL,

DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA,

ANTE MI, DIANA BEATRIZ LOPEZ, - - - - -

NOTARIA TREINTA Y TRES (33) - - - - -

DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE

SE CONSIGNA EN LOS SIGUIENTES TERMINOS:-----

COMPARECIO: JUAN MARIA RENDON, mayor de edad,

vecino de Bogotá, D.C, identificado con la cédula de

ciudadanía número 17.125.100 - -

EL NOTARIO NOVENO AUTENTICA ESTA COPIA POR
TENER CORRESPONDENCIA CON LA FOTOCOPIA
AUTENTICA QUE HA SIDO PRESENTADA.

Expedida en Bogotá - - -

24 SET-2007

Y manifestó:-----

PRIMERO: Que obra en su carácter de Representante

Legal de en nombre y representación de LAFRANCOL

S.A, sociedad comercial organizada y existente

conforme a las leyes colombianas, con domicilio y

sede principal en Cali - Valle, constituida mediante

escritura pública número

De la Notaría

De fecha

Reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali - Valle.-----

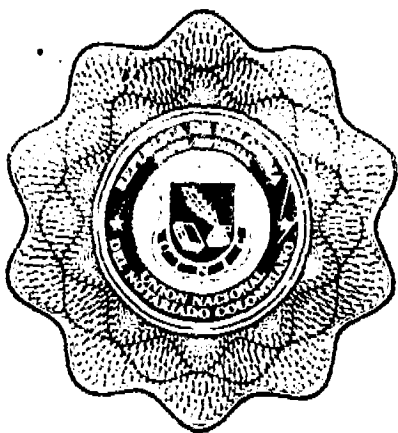
SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE a **JOSE LUIS REYES VILLAMIZAR**, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 79.152.473 de Usaquén, abogado en ejercicio, portador de la T.P.No. 446 55 del C.S. de la J., domiciliado en Bogotá, D.C, República de Colombia, con dirección en la carrera 17 No. 88-23, Oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de Lafrancol S.A., a cuyo efecto lo autorizo, par que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las el orden administrativo, contencioso, administrativo y judicial, en todo lo concerniente a los siguientes asuntos:-----

a.- Obtención, formulación de oberservaciones y oposición a patentes de invención, modelos y diseños industriales y el registro de licencias de uso de esos derechos.-----

b.- Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso- administrativos relacionados con estos derechos u otros de diferente naturaleza, acciones y procesos que

EL NOTARIO NOVENO AUTENTICA ESTA COPIA POR
TENER CORRESPONDENCIA CON LA FOTOCOPIA
AUTENTICA QUE HA SIDO PRESENTADA.

24 SET 2007



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AA 8567152

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promueva Lafrancol S.A., o se
promuevan contra esta y.-----

c.- Para que en todos los asuntos
arriba determinados, tanto en
los términos señalados por los
artículos 42 y complementarios

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

Manifestamos que de la veracidad de las
declaraciones del contenido y autenticidad de los
documentos anexos en éste instrumento público sólo
respondemos los comparecientes.-

HASTA AQUI LA MINUTA PRESENTADA

EL NOTARIO NOVENO AUTENTICA ESTA COPIA POR
TENER CORRESPONDENCIA CON LA FOTOCOPIA
AUTENTICA QUE HA SIDO PRESENTADA.

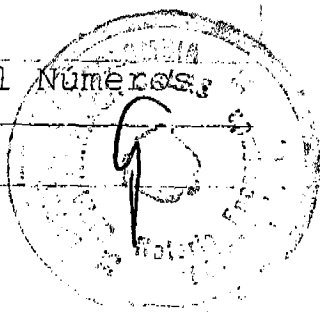
24 SET 2007

FE

OTORGAMIENTO Y AUTORIZACION: Leído el presente
instrumento Público por los comparecientes y
advertidos de la formalidad de su contenido, dentro
del término legal, lo hallaron conforme con sus
intenciones y lo aprobaron en todas sus partes y
firmaron junto con la Suscrita Notaria quien da fe y
lo autoriza. -----

Se utilizaron las hojas de papel Notarial Números

AA 8567146, 8567152.



DERECHOS NOTARIALES: \$ 49.600.00

RESOLUCION No. 4188 del 28 de Diciembre del 2001

JUAN MARIA RENDON

C.C. No. 17.125.100 de Bogotá

LAFRANCOL S.A.

Nit. No. 890.301.463-8

TEL: 622-04-66.

ACEPTO :

JOSE LUIS REYES VILLAMIZAR

C.C. No. 29.152.473

TEL: 621-2631

DIANA BEATRIZ LOPEZ

DIANA BEATRIZ LOPEZ

NOTARIA 33 DE BOGOTA D.C.

n.c.a.

Es segunda COPIA (FOTOCOPIA)

tomada de su original que se expide conforme al

Artículo 79 del Decreto 960 de 1970 en 06

hojas útiles con destino a Jose Luis Reyes

Villamizar

Santafé de

BOGOTÁ, Dcto. 1772/79

05 JUL. 2002

EL NOTARIO NOVENO AUTENTICA ESTA COPIA POR
TENER CORRESPONDENCIA CON LA FOTOCOPIA
AUTENTICA QUE HA SIDO PRESENTADA.

24 SET 2007

FERNANDO



Quien



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 1

null

CERTIFICA:

NOMBRE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
DOMICILIO: CALI VALLE
DIRECCION COMERCIAL : ---K 1 46 84
DIRECCION NOTIFICACION JUDICIAL: ---K 1 46 84
CIUDAD: CALI
MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTUBRE DE 1958
DIRECCION ELECTRONICA : esperanzacortes@lafrancol.net
AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA:

REFORMAS

DOCUMENTO

FECHA.DOC ORIGEN

FECHA.INS NRO.

INS LIBRO

E.P. 1104	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959
19467			
E.P. 2309	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959
20089			
E.P. 1725	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962
24528			
E.P. 1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963
26360			
E.P. 2422	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963
26717			
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado : 17:38:54

Operacion : 02CP20924074

PAGINA No. 2

28406	E.P.	101	31/01/1966	NOTARIA CUARTA DE CALI
31039	E.P.	552	21/03/1968	NOTARIA CUARTA DE CALI
35711	E.P.	4964	12/12/1972	NOTARIA CUARTA DE CALI
2975	IX	1956	30/05/1973	NOTARIA CUARTA DE CALI
4337	IX	4964	12/12/1972	NOTARIA CUARTA DE CALI
5994	IX	5579	12/11/1973	NOTARIA CUARTA DE CALI
5995	IX	4406	30/09/1974	NOTARIA CUARTA DE CALI
10887	IX	192	03/02/1978	NOTARIA CUARTA DE CALI
25355	IX	3479	07/09/1979	NOTARIA CUARTA DE CALI
34204	IX	4274	12/12/1984	NOTARIA NOVENA DE CALI
73088	IX	1155	21/05/1985	NOTARIA SEPTIMA DE CALI
76917	IX	1553	20/06/1986	NOTARIA SEPTIMA DE CALI
85997	IX	1458	09/06/1987	NOTARIA SEPTIMA DE CALI
3508	IX	7222	14/12/1988	NOTARIA TERCERA DE CALI
13847	IX	4530	04/09/1989	NOTARIA TERCERA DE CALI
21508	IX	3865	02/08/1990	NOTARIA TERCERA DE CALI
31708	IX	8305	13/12/1995	NOTARIA TERCERA DE CALI
557	IX	4559	16/11/1999	NOTARIA TERCERA DE CALI
7911	IX	6004	02/12/2004	NOTARIA TERCERA DE CALI
13371	IX	6241	27/12/2006	NOTARIA TERCERA DE CALI
625	IX			

CERTIFICA

VIGENCIA: 29 DE SEPTIEMBRE DEL AÑO 2057

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 3

CERTIFICA:

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISIOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL. TAMBIEN TENDRA UN REVISOR FISCAL.

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) AÑOS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

PARAGRAFO PRIMERO. SUPLENTE: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTE: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMMVLV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

FUNCIONES DEL GERENTE: A) ... B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y

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IMPRESO POR: CAMARA DE COMERCIO DE BOGOTA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 4

DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS.
EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1.- COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2.- ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS. CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y COMPROMISOS RESPECTIVOS. HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

GERENTE GENERAL Y REPRESENTANTE LEGAL
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

PRIMER SUPLENTE DEL GERENTE
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

SEGUNDO SUPLENTE DEL GERENTE
ROBERTO M. VENTURA CRISPINO
C.C.9086003

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924 Hora Certificado 17:38:54

Operacion : 02CP20924074 PAGINA No. 5

PRESIDENTE
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

VICEPRESIDENTE
ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2032 DEL LIBRO IX

FUE(ON) NOMBRADO(S)

TERCER SUPLENTE DEL GERENTE
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2031 DEL LIBRO IX

FUE(ON) NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

SEGUNDO RENGLON

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 6

ROSA VICTORIA VENTURA DE VISBAL
C.C.38992048

TERCER RENGLON
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

SUPLENTE

PRIMER RENGLON
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

SEGUNDO RENGLON
ROBERTO M. VENTURA CRISPINO
C.C.9086003

TERCER RENGLON
ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

REVISOR FISCAL
ALFREDO LOPEZ & CIA. LTDA

NIT.800026893-5

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 20 DE OCTUBRE DE 2006

ORIGEN: ALFREDO LOPEZ & CIA LTDA

INSCRIPCION: 07 DE NOVIEMBRE DE 2006 No. 12672 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL
ALFREDO LOPEZ CAMPO

***** CONTINUA *****



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 7

C.C.8241912

**REVISOR FISCAL SUPLENTE
GEOVANA GONZALEZ GALINDO
C.C.66959852**

CERTIFICA:

**CAPITAL AUTORIZADO: \$7,500,000,000
NUMERO DE ACCIONES: 750,000,000
VALOR NOMINAL: \$10
CAPITAL SUSCRITO: \$6,000,000,000
NUMERO DE ACCIONES: 600,000,000
VALOR NOMINAL: \$10
CAPITAL PAGADO: \$6,000,000,000
NUMERO DE ACCIONES: 600,000,000
VALOR NOMINAL: \$10**

CERTIFICA:

**QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL
UBICADO EN: ---K 1 46 84 DE CALI
RENOVO : POR EL A?O 2007**

CERTIFICA:

**QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A
UBICADO EN: --K 1 46A 70 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL A?O 2007**

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO

***** CONTINUA *****

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 8

EL NRO. 369810-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO

LAFRANCOL S A

UBICADO EN: -K 1A 46 A 32 DE CALI

FECHA MATRICULA: 29 DE ABRIL DE 1994

RENOVOMARIA DE COM: POR EL APO 2007

CERTIFICA: A CAMARA DE COMERCIO DE BOGOTA CAMARA DE COMERCIO

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 29 DE MARZO DE 2007

CERTIFICA: DE COMERCIO DE BOGOTA CAMARA DE COMERCIO DE BOGOTA

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

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

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 24 DIAS DEL MES DE SEPTIEMBRE DEL APO 2007 HORA: 05:16:15

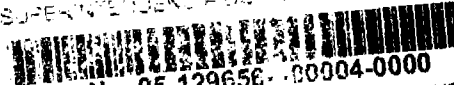
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 78,568
: SEPTIEMBRE 27 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-129656-00004-0000

Fecha: 2007-09-27 16:40:00 Dep. 2020 NUECREACION
Trib. 2 PATENTES Lib. 1 REGDEPOSITO
Act. 400 CPOSIOSSERVER Folios: 58

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69812082	27/09/2007	2,048,000.00

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

RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04	PRESENTACION DE OBSERVACIONES	
12	MARCAS Y LEMAS COMERCIALES	256,000.00
	TOTAL :	\$ 256,000.00

SON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

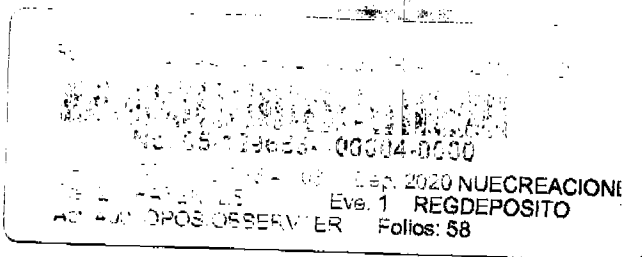
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 78,569
FECHA : SEPTIEMBRE 27 DE 2007



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69812082	27/09/2007	2,048,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEHAS COMERCIALES	256,000.00
		TOTAL :	\$ 256,000.00

SON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

SF 117
104
104

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 78,581
FECHA : SEPTIEMBRE 27 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69812084	27/09/2007	576,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	
		31 PRORROGA DE TERMINOS	72,000.00
		TOTAL :	\$ 72,000.00

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(54) Title: TETRAHYDROLIPSTATIN CONTAINING COMPOSITIONS			
(57) Abstract Product containing tetrahydrolipstatin as the active ingredient and pharmaceutically acceptable excipients, characterized in that it is in the form of particles with a diameter of 0.25 to 2 mm; and pharmaceutical preparations or compositions for oral administration containing the product.			

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TETRAHYDROLIPSTATIN CONTAINING COMPOSITIONS

5 Tetrahydrolipstatin („THL“) is an inhibitor of pancreatic lipase and is known by the generic name orlistat. The use of THL as medicament, particularly as anti-obesity agent, and pharmaceutical compositions containing THL as active agent are described in US Patent No. 4,598,089.

10 Due to its low melting point of about 44°C, THL undergoes both hydrolytic and thermal degradation, particularly when stored in a humid atmosphere or above 35°C in a dry atmosphere. Furthermore, conventional dosage forms such as described in US Patent No. 4,598,089, for example, tablets or hard gelatin capsules, cannot easily be formulated from powder mix or by conventional wet granulation procedure due to picking and sticking phenomena during tablet
15 compression or encapsulation. Thus, there was a need for THL containing products and dosage forms which would be stable against moisture and heat during production and storage.

20 In one of its aspects, the present invention relates to a product containing THL as active ingredient, stabilizers, pharmaceutically acceptable excipients, characterized in that it is in the form of particles with a diameter in the range of from about 0.25 mm to about 2 mm.

25 These particles are typically in the form of particles or pellets. The preferred pellet form requires the presence of microcrystalline cellulose. Preferably, the diameter of the pellets ranges from about 0.5 to about 1.5 mm.

Surprisingly, it was found that THL containing particles do not feature the sticking and picking phenomena and exhibit superior THL stability.

The subject invention will now be described in terms of its preferred embodiments. These embodiments are set forth to aid in understanding the invention but are not to be construed as limiting.

The subject invention provides particles, such as granules and pellets, useful in producing pharmaceutical compositions, such as a unit dosage form. The use of particles in the form of pellets is preferred.

Surprisingly, it was found that THL containing particles (also called multiple units) minimize the sticking and picking phenomena encountered during tablet compression or encapsulation. In one of its aspects, the present invention relates to a unit dosage form comprising a plurality of pellets having a diameter in the range of from 0.25 to 2 mm wherein each particle comprises tetrahydrolipstatin, a stabilizer and at least one pharmaceutically acceptable excipient. When the particles are in the form of pellets, it is critical to employ microcrystalline cellulose.

The term "stabilizer" refers to an agent having a rate of moisture uptake greater than the rate of moisture uptake for THL. Such stabilizer acts to retard hydrolytic degradation of the THL. Preferably, the stabilizer has a moisture content of greater than five percent (5%) at fifty percent (50%) relative humidity. The selection of a stabilizer having the above qualities is within the skill of the artisan having read the present specification. Examples of such stabilizers include, but are not limited to, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, and lactose.

Preferably, the average diameter of the particles ranges from 0.5 to 1.5 mm. Diameters referred to throughout the specification are average diameters. Although it is preferred that all particles are within the

recited ranges, it is acceptable for very minor or trace amounts of undersize or oversize particles to be present.

A further object of the invention is a product as described above which comprises a specific combination of THL with stabilizers, and excipients, particularly a product which contains polyvinylpyrrolidone and/or lactose as stabilizers.

Preferably, the product contains either (a) lactose and at least 3% by weight of the product is polyvinylpyrrolidone or (b) at least 5% by weight of the product is polyvinylpyrrolidone.

Preferred compositions typically contain from about 20% to about 75% by weight THL, and from about 3% to about 60% by weight stabilizer. Preferred pellets additionally contain from about 10% to about 60% by weight microcrystalline cellulose. More preferably, such pellets contain about 25% to about 75% by weight THL; from about 20% to about 60% by weight microcrystalline cellulose; from about 1% to about 10% by weight sodium starch glycolate; from about 1% to about 8% by weight sodium lauryl sulfate; from about 1% to about 10% by weight polyvinylpyrrolidone; and from about 0% to about 1% by weight talc.

Most preferably, such pellets contain about 50% by weight THL; about 39% by weight microcrystalline cellulose; about 3% by weight sodium starch glycolate; about 3% by weight sodium lauryl sulfate; about 5% polyvinyl pyrrolidone; and about 0.1% by weight talc.

Such products are chemically stable and can be filled on fast running encapsulation machines without presenting the sticking and picking phenomena.

In addition to the preferred stabilizers, polyvinylpyrrolidone and/or lactose, the product of the invention (the particles) contains other excipients, such as diluting agents, for example, sucrose or preferably microcrystalline cellulose (mandatory for pellets of the present invention); binders, for example, starch paste; surfactants, for example, sodium lauryl sulfate or sodium dioctylsulfosuccinate; and/or

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disintegrants, for example, sodium starch glycolate. The pellets can also contain corn starch as a diluent and disintegrant, and triglycerides.

Pellets are preferably prepared by extrusion of a wet mass followed by spheronization. They can also be prepared by granulation on a rotating base plate in fluidized bed equipment, by agglomeration granulation on an inclined disc equipment, or in high shear mixers.

The process for preparing the pellets is known *per se*. See, for example, J.W. Conine and H.R. Hadley, D & CI, April 1970, p. 38-41; Small Solid Pharmaceutical Spheres; A.D. Reynold, Manufacturing Chemist & Aerosol News, June 1970, p. 40-43; A new technique for the production of spherical particles; C.W. Woodruff and N.O. Nuessle, J. Pharm. Sci. 61 (5), p. 787-790 (1972); Effect of Processing Variables on Particles obtained by Extrusion-Spheronization Processing; and H.J. Malinowski and W.E. Smith, J. Pharm. Sci. 64 (10), p. 1688-1692 (1975); Use of Factorial Design to Evaluate Granulations Prepared by Spheronization.

Typically, the pelletization process by extrusion and spheronization comprises the following unit operations:

- wetting and kneading a powder mass containing the active substance THL and additional excipients with an appropriate, mostly aqueous solution of an appropriate binder to get a wet, pasty mass. Alternatively, the binder may be contained in the powder mix before wetting and kneading;

- forcing this wetted mass by means of an appropriate equipment (extruder) through tiny holes of a perforated plate, to get spaghetti-like, wet strands. The diameter of the holes may vary within wide limits, for example, between 0.4 and 1.0 mm, according to the specific product to be obtained.

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- breaking the strands into short pieces which are at the same time formed to more or less spherical particles by means of a fast spinning, mostly structured plate, in a vertical cylinder (spheronizer).

5 - drying the wet spheres by means of any suitable drying equipment, for example, a fluid bed dryer or a tray drier.

- optionally, the dried spheres may be fractionated into appropriate sized fractions, or the main material may be freed from undersized or
10 oversized material by an appropriate sieving or screening process. Preferably, the temperature is maintained below 35°C during the whole process.

A further aspect of the invention are pharmaceutical preparations
15 or compositions for oral administration, comprising the particles. They can be simply filled in a PVC container from which the particles can be taken with a dosing spoon. Other oral dosage forms are sachets in which the particles are filled, alone or together with appropriate excipients, such as skim milk powder, microcrystalline cellulose,
20 sodium carboxymethylcellulose and talc, to form a powder for reconstitution. Another possibility is to embed the particle in a matrix excipient, for example, microcrystalline cellulose, followed by compression to tablets, particularly chewable tablets. The particle, can also be filled in capsules, for example, hard gelatin capsules.

25 The following Examples are illustrative but in no way limit the invention.

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1. Polyvinyl pyrrolidone and sodium lauryl sulfate is dissolved in water.
 2. THL, microcrystalline cellulose, and sodium starch glycolate are mixed for 10 minutes and granulated with the solution of step 1.
 - 5 3. Granules are dried at or below 30°C and passed through # 20 mesh screen.
 4. Granules are filled in a # 1 hard gelatin capsule.

Example 6

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Preparation of Granules and Formulations containing THL

Ingredient	mg/capsule
1. THL	120
2. Lactose anhydrous	93.6
3. Sodium starch glycolate	7.2
4. Polyvinyl pyrrolidone	12.0
5. Sodium lauryl sulfate	7.2
Total	240.00

1. Polyvinyl pyrrolidone and sodium lauryl sulfate is dissolved in water.
- 15 2. THL, lactose anhydrous, and sodium starch glycolate is mixed for 10 minutes and granulated with the solution of step 1.
3. Granules are dried at or below 30°C and passed through # 20 mesh screen.
4. Granules are filled in a # 1 hard gelatin capsule.

5 The subject invention has been described in terms of its preferred embodiments. Upon reading the specification, a skilled artisan will become cognizant of various alternative embodiments. These variations are to be considered within the scope and spirit of the invention which is only to be limited by the claims that follow and their equivalents.

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Claims

1. A pharmaceutical composition comprising a plurality of particles having an average diameter of from about 0.25 mm to about 2 mm, each particle comprising tetrahydrolipstatin, a stabilizer, and at least one pharmaceutically acceptable excipient, provided that when the particles are in the form of pellets, each pellet contains microcrystalline cellulose.
2. The composition of claim 1, wherein the particles are pellets or granules, particularly wherein the pellets or granules have an average diameter of from about 0.5 mm to about 1.5 mm.
3. The composition of claim 2, wherein the stabilizer is selected from the group consisting of polyvinylpyrrolidone, lactose, a combination of polyvinylpyrrolidone and lactose, hydroxypropylmethyl cellulose, and hydroxypropyl cellulose.
4. The composition of claim 3, wherein at least 5% by weight of the composition is polyvinylpyrrolidone.
5. The composition of claim 3, wherein the stabilizer is a combination of lactose and polyvinylpyrrolidone wherein at least 3% by weight of the composition is polyvinylpyrrolidone.
6. The composition of claim 2, wherein the pharmaceutically acceptable excipient is a surfactant, diluent, or disintegrant.
7. The composition of claim 6, wherein the pharmaceutically acceptable excipient is a surfactant, particularly wherein the surfactant is sodium lauryl sulfate or sodium dioctylsulfosuccinate.
8. The composition of claim 6, wherein the pharmaceutically acceptable excipient is a diluent, particularly wherein the diluent is microcrystalline cellulose, sucrose or corn starch.

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9. The composition of claim 6, wherein the excipient is a disintegrant, particularly wherein the disintegrant is sodium starch glycolate, cross-linked polyvinyl pyrrolidone, cross-carmolose sodium, or low-substituted hydroxypropyl cellulose.

5 10. The composition of claim 2 which comprises from about 20% to about 75% by weight tetrahydrolipstatin; from about 3% to about 60% by weight stabilizer; and from about 10% to about 60% by weight microcrystalline cellulose.

10 11. The composition of claim 10 which comprises about 25% to about 75% by weight tetrahydrolipstatin; from about 20% to about 60% by weight microcrystalline cellulose; from about 1% to about 10% by weight sodium starch glycolate; from about 1% to about 8% by weight sodium lauryl sulfate; from about 1% to about 10% by weight polyvinylpyrrolidone; and from about 0% to about 1% by weight talc.

15 12. The composition of claim 11 which comprises about 50% by weight tetrahydrolipstatin; about 39% by weight microcrystalline cellulose; about 3% by weight sodium starch glycolate; about 3% by weight sodium lauryl sulfate; about 5% by weight polyvinylpyrrolidone; and about 0.1% by weight talc.

20 13. The composition of any one of claims 1, 2 and 10-12 which is in unit dosage form.

25 14. A pharmaceutical composition as in claim 1, which comprises about 120 mg of tetrahydrolipstatin; about 93.6 mg of microcrystalline cellulose; about 7.2 mg of sodium starch glycolate; about 7.2 mg of sodium lauryl sulfate; about 12 mg polyvinylpyrrolidone; and about 0.24 mg talc.

15. The composition of claim 14 which is in unit dosage form.



US006734314B2

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

(10) Patent No.: **US 6,734,314 B2**
(45) Date of Patent: **May 11, 2004**

(54) **PREPARATION OF ORLISTAT AND
ORLISTAT CRYSTALLINE FORMS**

(58) Field of Search 549/328, 263;
435/123

(75) Inventors: **Vilmos Keri, Debrecen (HU); Andrea
Csorvasi, Debrecen (HU); Judith
Aronhime, Rehovot (IL)**

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(73) Assignee: **Biogal Gyogyszergyar Rt., Debrecen
(HU)**

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

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(21) Appl. No.: **10/313,601**

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Primary Examiner—**Ba K. Trinh**

(65) **Prior Publication Data**

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(74) *Attorney, Agent, or Firm*—**Kenyon & Kenyon**

Related U.S. Application Data

(60) Provisional application No. 60/337,218, filed on Dec. 4,
2001.

(57) **ABSTRACT**

The present invention is directed to a process of converting
lipstatin to orlistat by catalytic hydrogenation. The present
invention further discloses novel crystalline solid orlistat
forms, designated form I and form II and methods for their
preparation.

(51) Int. Cl.⁷ **C07D 305/12**

(52) U.S. Cl. **549/328; 549/263; 435/123**

37 Claims, 2 Drawing Sheets

20–25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 2-1).

Example 11

0.7 gram orlistat was dissolved in 0.7 mL n-Propanol. Hexane of 0.7 mL was added to the solution. It was dried at 20–25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 3-1).

Example 12

0.7 gram orlistat was dissolved in 1.0 mL isopropanol. Water of 0.3 mL was added to the solution. It was dried at 20–25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 4).

Example 13

0.7 gram orlistat was dissolved in 0.7 mL isopropanol. Hexane of 0.7 mL was added to the solution. It was dried at 20–25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 4-1).

Example 14

0.7 gram orlistat was dissolved in 1.0 mL acetone. Water of 0.3 mL was added to the solution. It was dried at 20–25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 5).

Example 15

0.7 gram orlistat was dissolved in 0.7 mL acetone. Hexane of 0.7 mL was added to the solution. It was dried at 20–25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 5-1).

Example 16

0.7 gram orlistat was dissolved in 0.7 mL ethyl acetate. Hexane of 0.7 mL was added to the solution. It was dried at 20–25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 8-1).

Example 17

0.7 gram orlistat was dissolved in 0.7 mL isobutyl acetate. Hexane of 0.7 mL was added to the solution. It was dried at 20–25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 9-1).

Example 18

0.7 gram orlistat was dissolved in 0.7 mL methyl isobutyl ketone. Hexane of 0.7 mL was added to the solution. It was dried at 20–25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 10-1).

Example 19

0.7 gram orlistat was dissolved in 0.7 mL methanol. Hexane of 0.7 mL was added to the solution. It was dried at 20–25° C. for 24 hours. It was further dried at 38° C. for 48 hours without any filtration (sample number 13-1).

Example 20

0.7 gram orlistat was dissolved in 0.7 mL methanol. Water of 0.3 mL was added to the solution. It was cooled at 0–5° C. for 1 hour. Filtered crystals were dried at 20–25° C. for 1 hour and at 38° C. for 1 hour (sample number 14-1).

Example 21

0.7 gram orlistat was dissolved in 7.0 mL hexane. Crystals were filtered after 20 hours cooling at 0–5° C. Drying was carried out at 20–25° C. for 1 hour and at 38° C. for 1 hour (sample number 16).

Example 22

The melting points (DSC) and enthalpy of the following orlistat samples were measured and presented in the following table. The crystalline forms (XRD) of the orlistat samples were also presented.

Sample Numbers	melting endotherm ° C. (DSC)	enthalpy (Δ) (J/gram)	Crystalline forms (XRD)
1-1	46.3	87	I > II
2	47.0	92	I > II
2-1	47.1	85	I > II
3-1	46.7	87	I > II
4	46.5	91	I > II
4-1	46.8	92	I > II
5	46.2	90	I > II
5-1	46.9	90	I > II
8-1	46.9	93	I > II
9-1	46.5	85	I > II
10-1	46.5	88	I > II
13-1	46.7	91	I
14-1	46.2	90	I > II
16	46.6	93	II

">" refers to "substantially excess". For example "I > II" means that form I is in substantially excess amount than form II.

One of ordinary skill in the art would appreciate that the experimental conditions require optimization in order to crystallize and obtain further purified crystalline orlistat.

Pharmaceutical Formulations of Orlistat Crystalline Forms:

Orlistat crystalline forms I and II are useful for treating obesity. They can be formulated into a variety of compositions for administration to a mammal including humans and animals.

Pharmaceutical compositions of the present invention contain orlistat crystalline form I or orlistat crystalline form II. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention can contain one or more excipients. Excipients are added to the composition for a variety of purposes. Diluents increase the bulk of a solid pharmaceutical composition and can make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form like a tablet can include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include for example acacia, alginate acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl

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methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach can be increased by the addition of a disintegrant to the composition. Disintegrants include for example alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polypasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polyacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

Glidants can be added to improve the flowability of non-compacted solid composition and improve the accuracy of dosing. Excipients that can function as glidants include for example colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease release of the product from the dye. Lubricants include for example magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that can be included in the composition of the present invention include for example maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

Solid and liquid compositions can also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, Orlistat crystalline form I or II, and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

Liquid pharmaceutical compositions can contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that can be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention can also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include for example acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, pro-

pylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar can be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid can be added at levels safe for ingestion to improve storage stability.

A liquid composition according to the present invention can also contain a buffer such as gluconic acid, lactic acid, citric acid or acetic acid, sodium gluconate, sodium lactate, sodium citrate or sodium acetate.

Selection of excipients and the amounts to use can be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. The dosages can be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and lozenges as well as liquid syrups, suspensions and elixirs.

A dosage form of the present invention is a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell can be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients can be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filling can be prepared by wet granulation. In wet granulation some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, which causes the powders to clump up into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate can then be tableted or other excipients can be added prior to tableting, such as a glidant and/or a lubricant.

A tableting composition can be prepared conventionally by dry blending. For instance, the blended composition of the actives and excipients can be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules can be compressed subsequently into a tablet.

As an alternative to dry granulation, a blended composition can be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well-suited to direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

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A capsule filling of the present invention can comprise any of the aforementioned blends and granulates that were described with reference to tableting, only they are not subjected to a final tableting step.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosure of which are incorporated by reference in their entireties.

What is claimed is:

1. A crystalline solid orlistat, or hydrate or solvate thereof, characterized by data selected from the group consisting of a XRD pattern with peaks at 5.8, 18.5, 19.5 and 22.3 ± 0.2 degrees two-theta and a DSC melting endotherm at about 46.7°C .

2. The crystalline solid orlistat of claim 1, wherein the crystalline solid orlistat is characterized by the XRD pattern with peaks at 5.8, 18.5, 19.5 and 22.3 ± 0.2 degrees two-theta.

3. The crystalline solid orlistat of claim 2, wherein the crystalline solid orlistat is further characterized by a XRD pattern substantially as depicted in FIG. 1.

4. The crystalline solid orlistat of claim 1, wherein the crystalline solid orlistat is characterized by the DSC melting endotherm at about 46.7°C .

5. A crystalline solid orlistat, or hydrate or solvate thereof, characterized by data selected from the group consisting of a XRD pattern with peaks at 4.8, 5.6, 14.9, 17.3, 19.2 and 22.0 ± 0.2 degrees two-theta, and a DSC melting endotherm at about 46.6°C .

6. The crystalline solid orlistat of claim 5, wherein the crystalline solid orlistat is characterized by the XRD pattern with peaks at 4.8, 5.6, 14.9, 17.3, 19.2 and 22.0 ± 0.2 degrees two-theta.

7. The crystalline solid orlistat of claim 6, wherein the crystalline solid orlistat is further characterized by a XRD pattern substantially as depicted in FIG. 2.

8. The crystalline solid orlistat of claim 5, wherein the crystalline solid orlistat is characterized by a DSC melting endotherm at about 46.6°C .

9. A process of preparing crystalline solid orlistat, or hydrate or solvate thereof, characterized by data selected from the group consisting of a XRD pattern with peaks at 5.8, 18.5, 19.5 and 22.3 ± 0.2 degrees two-theta and a DSC melting endotherm at about 46.7°C , comprising the steps of:

(a) dissolving orlistat in a solvent;

(b) adding an anti-solvent or water to the solvent; and

(c) isolating the crystalline solid orlistat.

10. The process of claim 9, wherein the solvent is a lower alkyl alcohol, acetone, acetonitrile, acetone, ethyl acetate, isobutyl acetate, methyl isobutyl ketone, and hexane.

11. The process of claim 10, wherein the lower alkyl alcohol is selected from the group consisting of methanol, ethanol, n-propanol, and isopropanol.

12. The process of claim 9, wherein the anti-solvent is a hydrocarbon.

13. The process of claim 12, wherein the hydrocarbon is selected from the group consisting of hexane, cyclohexane and heptane.

14. The process of claim 9, wherein the solvent is methanol and the anti-solvent is hexane.

15. The process of claim 9, wherein the steps (a) to (c) are repeated at least once to increase the purity of the crystalline solid orlistat.

16. The crystalline solid orlistat prepared in accordance with the process of claim 9.

17. The crystalline solid orlistat of claim 16, wherein the crystalline solid orlistat is characterized by a XRD pattern with peaks at 5.8, 18.5, 19.5 and 22.3 ± 0.2 degrees two-theta.

18. The crystalline solid orlistat of claim 17, wherein the crystalline solid orlistat is further characterized by a XRD pattern substantially as depicted in FIG. 1.

19. The crystalline solid orlistat of claim 16, wherein the crystalline solid orlistat is characterized by a DSC melting endotherm at about 46.7°C .

20. A process for preparing a crystalline solid orlistat, or hydrate or solvate thereof, characterized by data selected from the group consisting of a XRD pattern with peaks at 4.8, 5.6, 14.9, 17.3, 19.2 and 22.0 ± 0.2 degrees two-theta, and a DSC melting endotherm at about 46.6°C , comprising the steps of:

(a) mixing orlistat in hexane to form a mixture at a first temperature;

(b) lowering the first temperature of the mixture sufficiently to precipitate; and

(c) isolating crystalline solid orlistat.

21. The process of claim 20, wherein the steps (a) to (c) are repeated at least once to increase the purity of the crystalline solid orlistat.

22. The crystalline solid orlistat prepared in accordance with the process of claim 20.

23. The crystalline solid orlistat of claim 22, wherein the crystalline solid orlistat is characterized by the XRD pattern with peaks at 4.8, 5.6, 14.9, 17.3, 19.2 and 22.0 ± 0.2 degrees two-theta.

24. The crystalline solid orlistat of claim 23, wherein the crystalline solid orlistat is further characterized by a XRD pattern substantially as depicted in FIG. 2.

25. The crystalline solid orlistat of claim 22, wherein the crystalline solid orlistat is characterized by the DSC melting endotherm at about 46.6°C .

26. A process of preparing a mixture of crystalline solid orlistat, or hydrate or solvate thereof, characterized by data selected from the group consisting of a XRD pattern with peaks at 5.8, 18.5, 19.5 and 22.3 ± 0.2 degrees two-theta, a DSC melting endotherm at about 46.7°C , a XRD pattern with peaks at 4.8, 5.6, 14.9, 17.3, 19.2 and 22.0 ± 0.2 degrees two-theta, and a DSC melting endotherm at about 46.6°C , comprising the steps of:

(a) dissolving orlistat in a solvent; and

(b) inducing crystallization to obtain the mixture of crystalline solid orlistat.

27. The process of claim 26, wherein the solvent is at least one alcohol selected from the group consisting of methanol, ethanol, n-propanol, 1-propanol, 2-propanol, isopropanol, 1-butanol, i-butanol, sec-butanol, tert-butanol, N,N-dimethyl formamide, dimethyl sulfoxide, acetonitrile, acetone, ethyl acetate, isobutyl acetate, methyl isobutyl ketone, and acetic acid.

28. The process of claim 26, wherein solvent is an aliphatic hydrocarbon.

29. The process of claim 28, wherein the aliphatic hydrocarbon is selected from the group consisting of hexane, pentane and heptane.

30. The process of claim 26, wherein the solvent contains water.

31. The process of claim 26, wherein the solvent is methanol.

32. The process of claim 26, wherein the mixture of methanol and water is present in a v/v ratio of about 1:0.3.

United States Patent [19]

Hadvary et al.

[11] Patent Number: 4,598,089

[45] Date of Patent: Jul. 1, 1986

[54] LEUCINE DERIVATIVES

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[21] Appl. No.: 621,827

[22] Filed: Jun. 18, 1984

[30] Foreign Application Priority Data

Jun. 22, 1983 [CH] Switzerland 3415/83

[51] Int. Cl.⁴ C07D 305/12; C12P 17/02; A61K 31/365

[52] U.S. Cl. 514/449; 549/263; 549/328; 514/909; 435/123; 435/886

[58] Field of Search 549/263, 328; 435/123; 514/449

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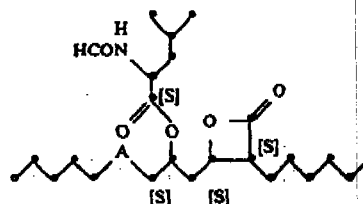
Primary Examiner—Glennon H. Hollrah

Assistant Examiner—Dara Dinner

Attorney, Agent, or Firm—Jon S. Saxe; Bernard S. Leon; George W. Johnston

[57] ABSTRACT

Novel compounds of the formula



wherein A signifies the group



or $-(CH_2)_5-$,

which inhibit pancreas lipase and can be used for the control or prevention of obesity and hyperlipaemia, are disclosed. The inventive compounds can be produced by the cultivation of microorganism *Streptomyces toxytricini*, identified as NRRL 15443.

20 Claims, No Drawings

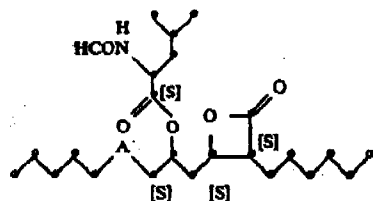
LEUCINE DERIVATIVES

BACKGROUND

The present invention concerns N-formylleucine derivatives which are useful in the treatment of obesity and hyperlipaemia.

SUMMARY OF THE INVENTION

The present invention is concerned with compounds of the formula

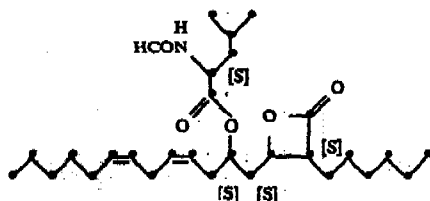


wherein A signifies the group

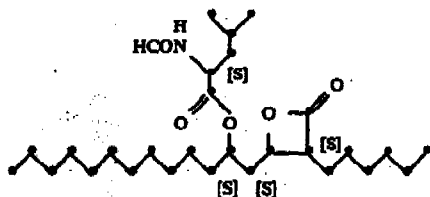


or $-(CH_2)_5-$.

Formula I above embraces (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic acid lactone of the formula



(i.e., lipstatin) and (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic acid lactone of the formula



(i.e., tetrahydrolipstatin).

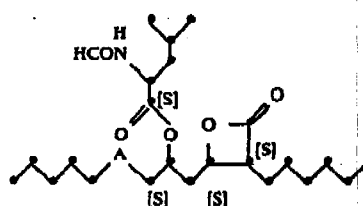
These compounds are novel and have valuable pharmacological properties. In particular, they inhibit pancreas lipase and can be used in the control or prevention of obesity and hyperlipaemia.

Objects of the present invention are the compounds of formula I above per se and as pharmaceutically active substances, the manufacture of these compounds, medicaments and industrially-produced foodstuffs containing a compound of formula I, their production as well as the use of these compounds in the control or prevention of illnesses. More particularly, the invention

concerns methods for preventing or treating obesity or hyperlipaemia in an afflicted mammal.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is concerned with compounds of the formula

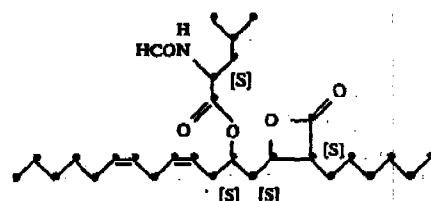


wherein A signifies the group

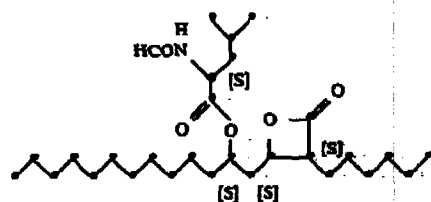


or $-(CH_2)_5-$.

Formula I above embraces (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic acid lactone of the formula



which is referred to hereinafter as lipstatin, and (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic acid lactone of the formula



which is referred to hereinafter as tetrahydrolipstatin.

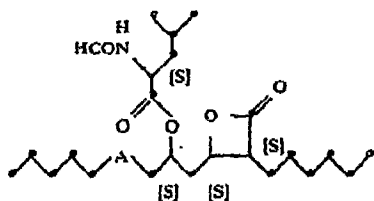
These compounds are novel and have valuable pharmacological properties. In particular, they inhibit pancreas lipase and can be used in the control or prevention of obesity and hyperlipaemia.

The present invention is also concerned with pharmaceutical compositions for preventing and treating obesity or hyperlipaemia comprising a compound of formula I and a pharmaceutically acceptable carrier material.

The invention also concerns methods for preventing or treating obesity or hyperlipaemia in an afflicted mammal wherein compound I is administered to the mammal in an amount which is effective in preventing or treating obesity or hyperlipaemia.

The invention also is directed to a commercially-produced foodstuff comprising compound I admixed with a material suitable for consumption.

As used herein, [S] indicates the absolute configuration of compound I in the S-form. More particularly, the applicable carbon atoms in formula I having the S-configuration are noted with enlarged circles in the following formula:



wherein A is as above.

The digestion of fats (triglycerides) taken in with the food is effected in the intestine by pancreas lipase. The pancreas lipase cleaves the primary ester bonds of triglycerides, whereby free fatty acids and 2-monoglycerides result as products. These products can then be resorbed and utilized. By inhibiting the pancreas lipase the aforementioned cleavage of the food fats and therefore also the resorption and utilization of these substances is partially prevented; the triglycerides are excreted in unchanged form.

The inhibition of pancreas lipase by the compounds of formula I can be demonstrated experimentally by registering tritrimetrically the oleic acid liberated in the cleavage of triolein by pig pancreas lipase. An emulsion which contains 1 mM taurodeoxycholate, 9 mM taurodeolate, 0.1 mM cholesterol, 1 mM egg lecithin, 15 mg/ml BSA (i.e., bovine serum albumine), 2 mM Tris-HCl, 100 mM sodium chloride, 1 mM calcium chloride and the substrate triolein is treated with the compound of formula I dissolved in ethanol or dimethyl sulphoxide (10% of the emulsion volume) and the reaction is started by the addition of 100 μ l (175 U) of pig pancreas lipase. the pH is held at 8 during the reaction by the addition of sodium hydroxide. The IC_{50} is calculated from the consumption of sodium hydroxide determined during 10 minutes. The IC_{50} is that concentration at which the lipase reactivity is inhibited to half of the maximum. Table I hereinafter contains IC_{50} values determined for the compounds of formula I and data concerning the acute toxicity (LD_{50} after single oral administration to mice).

TABLE I

Test compound	IC_{50} in μ g/ml	LD_{50} in mg/kg p.o.
Lipstatin	0.07	>4000
Tetrahydrolipstatin	0.18	—

The inhibition of the resorption of fats taken in with the food, which is brought about by the inhibition of pancreas lipase, can be demonstrated in a double-labelling experiment on mice. For this purpose, there is administered to the test animals a test meal, which contains ^3H -triolein and ^{14}C -oleic acid, and a compound of formula I. By measuring the radioactivity there is then determined the amount of ^3H -triolein and ^{14}C -oleic acid (in % of the amount administered) excreted with the feces. The results set forth in Table II hereinafter show that in comparison to untreated control animals the

excretion of unaltered triglyceride increases greatly and the excretion of oleic acid remains largely unchanged.

TABLE II

Test compound	Number of experimental animals	Dosage	Excretion in % of the amount administered	
			Triolein	Oleic acid
Controls	12	—	1.5 ± 0.3	10.1 ± 0.6
Lipstatin	6	40 mg/kg*	56.8 ± 13	13.8 ± 3.6

*The experiments were carried out with a preparation which contained about 10% lipstatin. The dosage specified is the amount of lipstatin administered.

The compounds of formula I can be manufactured in accordance with the invention by the following procedure:

(a) for the manufacture of the compound of formula Ia, aerobically cultivating a microorganism of the species *Streptomyces toxytricini* which produces this compound in an aqueous culture medium which contains suitable carbon and nitrogen sources and inorganic salts and separating the compound of formula Ia produced from the culture broth, or

(b) for the manufacture of the compound of formula Ib, hydrogenating the compound of formula Ia.

Streptomyces strains which produce lipstatin, the compound of formula Ia, can be isolated from soil samples from various locations. An example is the microorganism isolated from a soil sample found in Mallorca, Spain, which was given the laboratory designation *Streptomyces* sp. 85-13 and which has been identified by CBS, Baarn (Netherlands) as *Streptomyces toxytricini* Preobrazhenskaya & Sveshnikova (see Bergey's Manual of Determinative Bacteriology, 8th Edition, page 811). It thereupon received the new designation *Streptomyces toxytricini* 85-13. A lyophilized sample of this strain was deposited on the 14th June 1983 at the Agricultural Research Culture Collection, Peoria, Ill., under the designation NRRL 15443.

A description of the identification of *Streptomyces* sp. 85-13 is given hereinafter:

Media

The composition of the media used is described in Int. J. Syst. Bacteriol 1966, 16, 3; 313-321.

Nonomura diagram

Nonomura used the results of the International *Streptomyces* Project (ISP) for the classification of the *Streptomyces* species (J. Ferment. Technol. 1974, 52, 2).

Colours

The names and code numbers of the aerial mycelium come from Tresner & Backus "System of color wheels for streptomycete taxonomy". The colours of the reverse of the colonies come from H. Prauser's selection from Baumann's "Farbtonkarte Atlas I".

Methodology

This was carried out according to the ISP methods (see Int. J. Syst. Bacteriol, 1966, 16, 3; 313-340).

I. Agar cultures after 16 days at 28° C. (double determination)

(a) Oatmeal agar

Growth: abundant; colonies: thin, spreading; aerial mycelium: velutinous, pinkish brown (Light Brown 57); reverse of the colonies: yellowish (Pr. Co-3-m) with

25 134
A21
121

broad purple-grey (Pr. Oc-6-x) margin; soluble pigments: doubtful.

(b) Starch-salt agar

Growth: good; colonies: thin, spreading; aerial mycelium: velutinous, pinkish brown (Light Brown 57) with white sectors; reverse of the colonies: dark straw coloured [Pr. Co- (Cr) 5a], margin and some other areas pinkish (Pr. Oc-5-b) with some dark reddish brown [Pr. O-5-S(r)] spots; soluble pigments: doubtful. The diastatic action is excellent.

(c) Glycerine-asparagine agar

Growth: good; colonies: thin, spreading; aerial mycelium: velutinous, pale pinkish brown (R4ec: Grayish Yellowish Pink); reverse of the colonies: orange (Pr. Oc-3-m/r); soluble pigments: pale pinkish brown.

(d) Yeast malt agar

Growth: good; colonies: thin, spreading; aerial mycelium: reddish brown (4ge: Light Grayish Reddish Brown 45); reverse of the colonies: yellow (Pr. Co-4-5) and dark brown (Pr. Oc-5-r); soluble pigments: very pale yellowish brown.

II. Agar cultures after 62 days at 28° C. (double determination)

(a) Oatmeal agar

Growth: good; colonies: thin, spreading; aerial mycelium: powdery velutinous, cinnamon coloured [R-4ie: Light Brown (57)-Cork Tan] with broad, paler margin [R. 5gc: Light Reddish Brown (4.2)-Peach Tan]; reverse of the colonies: yellowish-brown with ochre-yellow (Pr. Co-3-a) margin, slightly greyish towards the bright (Pr. Oc-4-r) centre; soluble pigments: pale ochre-brown.

(b) Starch-salt agar

As an oatmeal agar, but with a more greyish brown reverse (Pr. Oc-6-c) and with dark brown (Pr. Oc-4-r) spots and rings at the ends of the cross-hatches.

(c) Glycerine-asparagine agar

As on starch-salt agar, but paler light beige (5ec: Grayish yellowish Pink 32-Dusty Peach); Reverse: ochre-yellow [Pr. Co- (=Cr)-4-b], paler in the centre; no soluble pigments.

(d) Yeast-malt agar

Growth: fair; colonies: almost as on oatmeal agar, but with very thin, pale grey margin; reverse: dark yellow (Pr. Co-4-b), dark brown in submarginal areas; soluble pigments: doubtful.

III. Melanoid pigments

Peptone-yeast extract agar: negative after 24 hours, positive after 48 hours; tyrosine agar: positive after 24 hours, positive after 48 hours.

IV. Morphology of the sporulating aerial mycelium
Section: spira-retinaculum apertum. Sympodial branched type. Spirals often irregular, with up to 5 coils often of different diameters.

V. Utilization of carbon sources No growth or only sparing growth on arabinose, xylose, inositol, mannitol, fructose, rhamnose, saccharose, raffinose.

VI. Spores

Oval to cylindrical-oval, sometimes of irregular size, smooth-walled. Spore chains with more than 10 spores.

VII. Nonomura diagram

15 R(Gy) 100 SRA sm(±) (±) (±)-----

All Streptomyces strains which produce the lipase inhibitor lipstatin are suitable for the purpose of the present invention, especially Streptomyces toxytricini 85-13, NRRL 15443, and its subcultures, mutants and variants.

The cultivation of these microorganisms for the manufacture of lipstatin can be carried out according to various fermentation methods. It can be carried out, for example, in shaking flasks or in 10 l or 200 l and 1000 l fermentors. A fixed amount of spore material or mycelium or a lipstatin-producing strain is introduced into a liquid medium which contains suitable carbon and nitrogen sources and salts required for the growth and the mixture is aerobically incubated at a temperature of 20°-37° C. for 1-6 days. Suitable carbon sources are, for example, dextrin, glucose, starch, ribose and glycerine. Suitable nitrogen sources are, for example, yeast extract, peptone or soya meal. Preferred salts are ammonium, magnesium and calcium salts. The fermentation is carried out at pH 6-8.

The isolation of the lipstatin is carried out according to methods which are known per se and which are familiar to any person skilled in the art. For example, it can be carried out as follows:

After completion of the fermentation the fermentation broth is centrifuged, whereupon 60-90% of the activity is found in the cell mass and the remainder is found in the centrifugate. The cell mass can then be treated with a low alcohol such as methanol and ethanol and extracted with the same solvent. The centrifugate can be extracted with a suitable organic solvent (e.g. with methylene chloride or ethyl acetate). The material produced from the extracts contains the desired lipstatin and can be enriched and purified by chromatographic methods. Suitable methods are, for example, multiplicative extraction with the system hexane/methanol/water (50:40:9), filtration chromatography over silica gel while eluting with chloroform, column chromatography on silica gel while eluting with hexane, ethyl acetate and mixtures thereof, chromatography on apolar carrier materials while eluting with polar solvents such as methanol (reversed-phase chromatography) and high pressure liquid chromatography.

The Examples hereinafter contain detail information relating to the cultivation of Streptomyces toxytricini 85-13 and the isolation of the lipstatin.

Tetrahydrolipstatin, the compound of formula Ib, can be manufactured by hydrogenating lipstatin in the presence of a suitable catalyst. Examples of catalysts which can be used are palladium/carbon, platinum oxide, palladium and the like. Suitable solvents are, for example, lower alcohols such as methanol and ethanol. The hy-

drogenation is preferably carried out at low hydrogen pressures and at room temperature (about 23° C.)

The compounds of formula I can be used as medicaments, for example in the form of pharmaceutical preparations. Illustratively, the pharmaceutical preparations can be administered orally, for example in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. If desired, the compounds also can be administered parenterally.

For the manufacture of pharmaceutical preparations the compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatine capsules are lactose, maize starch or derivatives thereof, talc, stearic acid or its salts and the like. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active ingredient no carriers are, however, generally required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water polyols, saccharose, invert sugar, glucose and the like.

Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, colouring agents, flavouring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I are also an object of the present invention as is a process for the manufacture of these medicaments, which process comprises bringing a compound of formula I and, if desired, one or more other therapeutically valuable substances into a galenical administration form. As mentioned earlier, the compounds of formula I can be used in the control or prevention of illnesses and especially in the control or prevention of obesity and hyperlipaemia. The dosage can vary within wide limits and is, of course, fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 100 mg/kg body weight of compound I is appropriate.

Preferably, the pharmaceutical compositions of formula I in unit dosage form contain about 5% to 95% by weight of compound I to the total composition. A range of 10% to 50% is preferred.

The compounds of formula I can also be added to industrially-produced foodstuffs, especially to fats, oils, butter, margarine, chocolate and other confectionery goods. Such industrially-produced foodstuffs and their production are also objects of the present invention.

The following Examples illustrate the present invention in more detail, but are not intended to limit its extent. All temperatures are given in degrees Celsius (°C.). Room temperature is about 23° C. Unless otherwise indicated, percentages and ratios relating to solvents and expressed in volume, and the remaining percentages are expressed in weight. Unless indicated otherwise, all Examples were carried out as written. A Lobar column Lichoprep RP-8, size C, is a lowpressure reverse phase column, commercially available from Merck Co.

EXAMPLE 1

(a) Fermentation:

A shaking flask containing pre-culture medium 391 is inoculated with spores of *Streptomyces toxytricini* 85-13 (or vegetative mycelium thereof) and aerobically incubated as a shaking culture at 28° C. for 72 hours. About 2-5 vol.% of this culture is used to inoculate a fermentor preculture of 10 l containing pre-culture medium 391. Incubation is carried out at 28° for 3 days with aeration of 1 vvm and stirring at 400 rpm. This 10 l pre-culture is used to inoculate a 200 l production fermentor containing production medium N7. Fermentation is carried out at 28° for 124 hours with aeration of 1.0 vvm and stirring at 150 rpm. Regular analyses show after 124 hours an extracellular lipase-inhibiting activity of 53 IC₅₀/ml.

The pre-culture medium 391 (pH 7.0) has the following composition: 3% maize starch, 4% dextrin, 3% soya meal, 0.2% (NH₄)₂SO₄, 0.6% CaCO₃ and 0.8% soya oil. The pH was adjusted to 7. The production medium N 7 (pH 7.0) has the following composition: 1% potato starch, 0.5% glucose, 1% ribose, 0.5% glycerine, 0.2% peptone, 2% soya meal and 0.2% (NH₄)₂SO₄.

(b) Working-up:

The fermentation broth is centrifuged by means of a tube centrifuge, whereby there are obtained 175 l of culture filtrate and 12 kg of mycelium. The mycelium is discarded. The culture filtrate is heated to 80° for 10 minutes, cooled, again centrifuged and concentrated to 50 l at 30° in vacuo. This concentrate is extracted with 50 l of hexane using a continuously operating extractor, the emulsion obtained is mixed with 50 l of hexane/ethyl acetate (1:1) and the organic phase is separated. This is dried over sodium sulphate and evaporated, there being obtained 199 g of crude extract I. The aqueous phase is diluted with water to 100 l and extracted with 100 l of ethyl acetate. After evaporation of the ethyl acetate solution, there are obtained 49 g of crude extract II. The aqueous phase is subsequently extracted once more with 100 l of ethyl acetate, whereby 78 g of crude extract III are obtained after evaporation.

(c) Purification:

The crude extracts II and III are filtered in three portions over in each case 1 kg of silica gel 60 (0.040-0.063 mm particle size), whereby the elution is carried out with chloroform (column: 10×100 cm). 18.3 g of enriched material are obtained in this manner. 178 g of this substance are again filtered over 1 kg of silica gel while eluting with chloroform. 5.29 g of active material are thus obtained. 802 mg of this substance are purified by reversed-phase chromatography on a commercially obtainable Lobar column (Lichoprep RP-8, size C) while eluting with methanol. There are obtained 158 mg of (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic acid lactone (lipstatin) which is a yellowish oil at room temperature. It is waxy-crystalline at low temperatures.

Microanalysis (dried for 20 hours in a high vacuum at 50°):

Calculated for C₂₉H₄₉N₁O₅ (491.713): C 70.84, H 10.04, N 2.85. Found C 70.85, H 9.97, N 2.59.

Optical rotation: [α]_D²⁰ = -19.0° (c=1 in chloroform).

Mass spectrum (chemical ionization with NH_3 as the reagent gas): Peaks at, inter alia, m/z 509 ($\text{M} + \text{NH}_4^+$) and 492 ($\text{M} + \text{H}^+$).

IR spectrum (film): Bands at, inter alia, 3318, 3012, 2928, 2558, 2745, 1823, 1740, 1673, 1521, 1382, 1370, 1250, 1191 cm^{-1} .

The absolute configuration could be established by chemically degrading the lipstatin and comparing the fractions obtained with known substances.

EXAMPLE 2

(a) Fermentation

A 200 l fermentor containing production medium N 16 is inoculated with a pre-culture of *Streptomyces toxytricini* 85-13 (shaking flasks and then 10 l fermentation) prepared in accordance with Example 1. The production medium N 16 corresponds to production medium N 7 used in Example 1, but also contains 0.1% pig lard. The fermentation is carried out as described in Example 1 for 120 hours. After 120 hours, the intracellular lipase-inhibiting activity amounts to 71 IC_{50}/ml of fermentation broth and the extracellular lipase-inhibiting activity amounts to 4 IC_{50}/ml of fermentation broth.

(b) Working-up

After completion of the fermentation, the fermentation broth is heated to 80° for 10 minutes, subsequently cooled and the cell mass is separated using a tube centrifuge. By two-fold centrifugation there are obtained 11.4 kg of mycelium; the culture filtrate is discarded. The mycelium is triturated in 70 l of methanol for 30 minutes, whereupon the suspension obtained is suction filtered. The filter cake is again triturated with 50 l of methanol and suction filtered. The combined methanolic extracts are concentrated to 1.8 l. This concentrate is extracted three times with 2 l of butyl acetate each time. 160 g of crude extract are obtained from the combined organic phases after evaporation.

(c) Purification

This crude extract is purified by multiplicative extraction with the system hexane/methanol/water (5:4:0.9). The active substance is firstly transferred from the lower phase (lp) into the upper phase (up). 160 g of crude extract are dissolved in 4 l of lp and stirred in a stirring vessel with 4 l of up. After separating the up, the lp is extracted a second time with 4 l of fresh up. A stable emulsion forms and to this there are added 4 l of lp and 4 l of up, whereupon a good phase separation is achieved. After separating the up, the lp is extracted twice more with 8 l of fresh up. The combined up give 90.3 g of extract after evaporation. The extraction lp is discarded. The active substance is now transferred from the up into the lp. 90.3 g of the above extract are dissolved in 4 l of up and extracted with 4 l of lp. After phase separation, the up is extracted a further three times with fresh lp. The up is subsequently discarded. The combined lp are concentrated to 0.7 l of aqueous phase and this is extracted eight times with a total of 0.2 l of ethyl acetate. 25.8 g of product are obtained after evaporation. The extracted aqueous phase is discarded. The further purification of this material is carried out by filtration over 1 kg of silica gel 60 (0.040-0.063 mm particle size; column 10×100 cm) while eluting with chloroform. There are obtained 649 mg of product which is chromatographed on a Lobar column (Lichoprep RP-8, size C) while eluting with methanol (reversed-phase chromatography). There are obtained 204

mg of lipstatin which is pure according to thin-layer chromatography.

EXAMPLE 3

138 mg of lipstatin are dissolved in 10 ml of ethanol and the solution is treated with 60 mg of 5 percent palladium/carbon and stirred at room temperature for 3 hours in a hydrogen atmosphere (balloon). The catalyst is subsequently centrifuged off. The hydrogenation product is chromatographed over a short silica gel column (1×5 cm) with chloroform. There are obtained 112 mg of (2S,3S,5S)-5-[(S)-2-formamido-4-methylvaleryloxy]-2-hexyl-3-hydroxyhexadecanoic acid lactone (tetrahydrolipstatin) as a waxy, slightly yellow solid.

Optical rotation: $[\alpha]_D^{20} = -32.0^\circ$ ($c=1$ in chloroform).

Mass spectrum (chemical ionization with NH_3 is the reagent gas): Peaks at, inter alia, m/z 513 ($\text{M} + \text{NH}_4^+$); 496 ($\text{M} + \text{H}^+$) and 452 ($\text{M} + \text{H}^+ - \text{CO}_2$).

IR spectrum (film): Bands at, inter alia, 3332, 2956, 2921, 2853, 1838, 1731, 1709, 1680, 1665, 1524, 1383, 1249 and 1200 cm^{-1} .

$^1\text{H-NMR}$ spectrum (270 MHz, CDCl_3): 0.89 (6H); 0.97 (6H); 1.15-1.5 (27H); 1.5-1.85 (6H); 1.9-2.25 (2H); 3.24 (1H); 4.32 (1H); 4.68 (1H); 5.03 (1H); 6.43 (1H); 8.07 and 8.21 (1H) ppm.

EXAMPLE 4

(a) Fermentation

A 2 l shaking culture flask containing pre-culture medium 391 is inoculated with spores of an agar slant culture of *Streptomyces toxytricini* 85-13 and aerobically incubated at 28° C. for 72 hours. Thereafter, the 2 l preculture is transferred into a 50 l fermentor containing production medium N 16 and incubated at 28° C. for 77 hours with 0.5 vvm aeration. This 50 l pre-culture is used to inoculate a 1000 l fermentor containing medium N 16. This production fermentation is carried out at 28° C. and 0.5 vvm aeration for 91 hours, whereby a lipstatin titre of 73 IC_{50}/ml intracellularly and 16 IC_{50}/ml extracellularly is achieved. The entire fermentation broth is cooled to 2° C. and centrifuged, whereby there are obtained 41 kg of moist biomass which are frozen at -20° C.

(b) Working-up

37 kg of mycelium are melted at 4° C. and homogenized with about 40 l of water in a mixer. The thin liquid suspension obtained is treated with 140 l of methanol and stirred for 20 minutes. The mixture is subsequently suction filtered over a cloth filter, whereupon the filter cake is extracted further with 140 l of methanol. The methanol extracts are concentrated at 30° C. to about 22 l. The concentrate obtained is diluted with water to 50 l and extracted three times in a stirring vessel with 50 l of hexane/ethyl acetate (1:1) each time. In the second and third extractions there are obtained emulsions which can be broken by the addition of about 1.4 kg and 0.5 kg of sodium chloride, respectively. The combined organic extracts are concentrated, dried over sodium sulphate and evaporated to an oily residue. 428 g of crude extract are obtained.

(c) Purification

This crude extract is filtered in four portions over in each case 1 kg of silica gel 60 (0.040-0.063 mm particle

size), whereby the elution is carried out with chloroform (column: 10×100 cm). There are obtained 70 g of enriched preparation which is filtered in two portions over in each case 1 kg of silica gel (60 while eluting with hexane/ethyl acetate (gradient from 9:1 to 4:1). There are obtained 4.2 g of active material which is purified in four portions by reversed-phase chromatography on a Lobar column (Lichoprep RP-8, size C) while eluting with methanol. 1.77 g of lipstatin are obtained.

EXAMPLE A

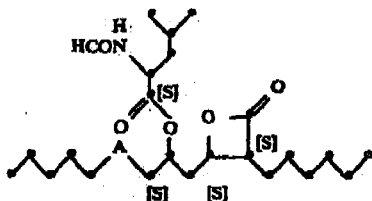
Manufacture of soft gelatine capsules of the following composition:

Amount per capsule	
Lipstatin	30 mg
NEOBEE M-5	450 μ l

The solution of the active substance in NEOBEE M-5 is filled into soft gelatine capsules of suitable size. NEOBEE M-5 is a mixture of triglycerides commonly used for pharmaceutical preparations.

We claim:

1. A compound of the formula



wherein A is the group



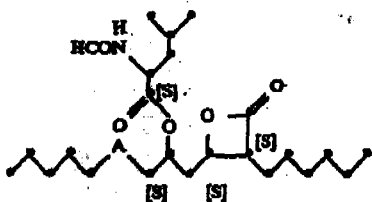
or $-(CH_2)_5-$.

2. The compound of claim 1, (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

3. The compound of claim 1, (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

4. A pharmaceutical composition for administration to a patient comprising

(a) about 5% to about 95% of a compound of formula



wherein A is the group



or $-(CH_2)_5-$

said composition being present in a amount sufficient to supply about 0.1 to about 100 mg of compound I per kilogram of body weight of the patient per day; and

(b) 5% to 95% of a pharmaceutically acceptable inert carrier material, said composition being formulated in a unit dosage form.

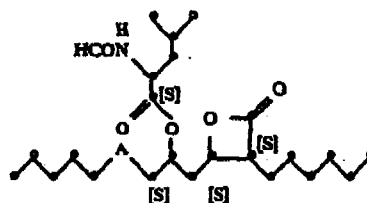
5. The composition of claim 4 wherein said composition is formulated in an oral unit dosage form.

6. The composition of claim 5 wherein said oral unit dosage form is a tablet, dragee, capsule, solution, emulsion or suspension.

7. The composition of claim 4 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

8. The composition of claim 4 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

9. A method of treating obesity in an afflicted mammal comprising administering to the mammal a compound of the formula



wherein A is the group



or $-(CH_2)_5-$

in an amount which is effective in treating obesity.

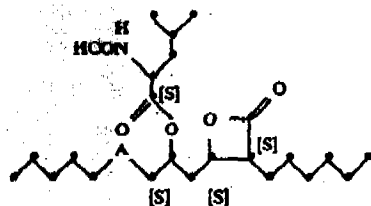
10. The method of claim 9 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

11. The method of claim 9 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

12. The method of claim 9 wherein compound I is administered in a daily dose of about 0.1 mg to 100 mg/kg body weight of the mammal.

13. A method of treating hyperlipaemia in an afflicted mammal comprising administering to the mammal a compound of the formula

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wherein A is the group



or $-(CH_2)_5-$,

in an amount which is effective in treating hyperlipaemia.

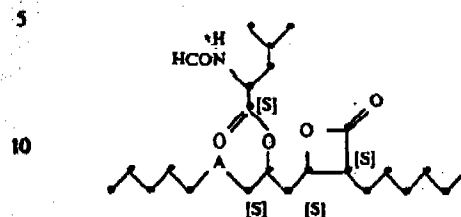
14. The method of claim 13 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

15. The method of claim 13 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

16. The method of claim 13 wherein compound I is administered in a daily dose of about 0.1 mg to 100 mg/kg body weight of the mammal.

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17. A method of preventing obesity in a mammal comprising administering to the mammal a compound of the formula



wherein A is the group



or $-(CH_2)_5-$,

in an amount which is effective in preventing obesity by inhibiting pancreas lipase.

18. The method of claim 17 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-Formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

19. The method of claim 17 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

20. The method of claim 17 wherein compound I is administered in a daily dose of about 0.1 mg to 100 mg/kg body weight of the mammal.

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