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AS: 97.288

Señores
SUPERINTENDENCIA DE INDUSTRIA Y C(
DIVISION DE NUEVAS CREACIONES
E. S. D.

REF.: Expediente No. 05 058.715 - Solicitud de Patente FASE NACIONAL
Corresp. a la Solicitud Internacional PCT/EP2003/014422.
a nombre de: **FERRER INTERNACIONAL S.A.**
Titulada: COMPOSICIONES VAGINALES DE SERTACONAZOL.

CARLOS HUMBERTO PALACIO EASTMAN, vecino de Bogotá, portador de la tarjeta profesional No. 62154 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad **FERRER INTERNACIONAL S.A.**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 07-67,204 por valor de $202.000.

De la Señora Jefe atentamente,

CARLOS HUMBERTO PALACIO EASTMAN
C.C. No. 79.311.882 de Bogotá
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Bogotá, 29 de noviembre de 2007
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD Y CASTRO	CONSIGNACION	BANCO POPULAR	050-00110-6	51181692	17/08/2007	16,740,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	202,000.00
		TOTAL : $	202,000.00

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE : _____

IBO DE CAJA APLICADO AL EXPEDIENTE No._____

Industria y Comercio
SUPERINTENDENCIA

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-58715

EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

NUMERO FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No

576 DE FECHA **31** DE **MAYO** DE **2007** EL TERMINO HABIL SEÑALADO POR

LA LEY EXPIRA EL **31** DE **AGOSTO DE 2007**

NOTA: Dentro del plazo de los tres (3) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 y en concordancia con el artículo 85 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO _ **X** _____

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09/145,172	1 September 1998 (01.09.98)	US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, 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, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: A PHARMACEUTICAL COMPOSITION FOR TREATING DYSMENORRHEA AND PREMATURE LABOR

(57) Abstract

The present invention teaches a composition comprising a β–adrenergic agonist in a bioadhesive carrier. Preferably, the composition comprises terbutaline in polycarbophil. The present invention additionally teaches the local administration of a β–adrenergic agonist for the purpose of treating or preventing dysmenorrhea or premature labor. Using this composition and the method of treatment provides sufficient local levels of the drug to provide therapeutic efficacy, but avoids many untoward adverse events.

A PHARMACEUTICAL COMPOSITION FOR TREATING DYSMENORRHEA AND PREMATURE LABOR

This application claims the benefit of United States Provisional Application No. 60/058,789, filed September 12, 1997, which is incorporated herein by reference.

Field of the Invention

The invention relates to a pharmaceutical composition and the local administration thereof for the purpose of treating or preventing dysmenorrhea or premature labor.

Background of the Invention

Both dysmenorrhea and premature labor affect significant numbers of American women; however, treatment regimens are still lacking for both conditions. Dysmenorrhea, menstrual cramps, affects on average over 50% of women and results in frequent absenteeism or loss of activity. *Andersch, B., Milsom I., An Epidemiologic study of young women with dysmenorrhea, A.J.O.G., 144:655-60 (1982).* Young women report a somewhat higher incidence of dysmenorrhea than the average, with estimates ranging from 67% to 72%. *Harlow, S.D., Parck M., A longitudinal study of risk factors for the occurrence, duration and severity of menstrual cramps in a cohort of college women, Br. J. Obstet. Gynaecol., 103:1134-42 (1996).* Severe pain has been reported by 7 to 15% of women. *Id.*

In the United States alone an estimated 140 million work and school hours are lost per year due to this condition. *Klein, J.R., Litt, I.F., Epidemiology of adolescent dysmenorrhea, Pediatrics, 68:6661-64 (1981).* About 42% of United States university students between the ages of 17 and 19 have had to be absent from their daily activities at least once due to dysmenorrhea. *Id.* Approximately 15% of young women have one to three days of incapacitation each month and dysmenorrhea is the leading cause of short-term school absenteeism among adolescent young women. *Id.* This disease, with its constant regularity, results in notable social, educational, and economic losses in this country.

Dysmenorrhea consists of painful uterine cramping and is often accompanied by associated symptoms including nausea, vomiting, diarrhea, and

for compositions with other active substances such as progesterone (Crinone®) (*see* U.S. Pat. No. 5,543,150) and Nonoxynol-9 (Advantage-S) (*see* U.S. Pat. No. 5,667,492).

Additionally, it is important that pharmaceutical compositions do not interfere with all contractions and the homeostasis of menstruation. As menstrual blood does not clot, normal, regularized contractions are helpful to stop the bleeding. If there are no contractions, then the patient may not stop bleeding and may hemorrhage. Thus, it is an object of the invention to interfere with the dyskinetic contractions causing dysmenorrhea, without stopping contractions entirely.

Summary of the Invention

The present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a β-adrenergic agonist together with a pharmaceutically acceptable bioadhesive carrier and the local administration of a β-adrenergic agonist for the purpose of treating or preventing dysmenorrhea or premature labor. Using this composition and the method of treatment provides sufficient local levels of the drug to provide therapeutic efficacy, but avoids many untoward adverse events.

Brief Description of the Drawings

FIG. 1 illustrates the serum terbutaline levels in a single dose study. Doses were 4 mg, 2 mg, and 1 mg. The terbutaline gel was administered transvaginally once.

FIG. 2 illustrates the serum terbutaline levels in a multiple dose study. Doses were 4 mg, 2 mg, and 1 mg. The terbutaline gel was administered transvaginally once daily for six days.

FIG. 3 illustrates the serum terbutaline levels in a single dose study. The dose given was 8 mg. The terbutaline gel was administered transvaginally once.

FIG. 4 illustrates the serum terbutaline levels in a multiple dose study. The dose given was 8 mg. The terbutaline gel was administered transvaginally once daily for six days.

FIG. 5 illustrates mean heart rates in a single dose study. Doses were 8 mg, 4 mg, 2 mg, and 1 mg. The terbutaline gel was administered transvaginally once.

FIG. 6 illustrates mean heart rates in a multiple dose study. Doses were 8 mg, 4 mg, 2 mg, and 1 mg. The terbutaline gel was administered transvaginally once daily for six days.

FIG. 7 illustrates the myometrial terbutaline influx in an *ex vivo* uterine perfusion model.

Detailed Description Of the Invention

The present invention is related to a composition comprising therapeutically effective amount of a β-adrenergic agonist together with a pharmaceutically acceptable bioadhesive carrier. Preferably terbutaline is used as the β-adrenergic agonist. The present invention preferably comprises a β_2 specific adrenergic agonist. Other acceptable β-adrenergic agonists include ritodrine, isoxsuprine, fenoterol, salambutol, hexoprenaline, metaproterenol, bitolterol and pirbuterol. The invention comprises a uterine smooth muscle relaxant for both pregnant and non-pregnant women and has been specifically designed for vaginal administration. The bioadhesive carrier, which may be in a gel formulation, contains a polycarbophil base designed to give controlled and prolonged release of terbutaline, or another β-adrenergic agonist, through the vaginal mucosa. This route of administration avoids first-pass metabolism problems. The direct delivery to the uterus allows for lower systemic drug concentrations. These two properties help avoid many significant adverse events.

The present invention is additionally related to a method of preventing or treating dysmenorrhea comprising administering the composition vaginally. Additionally, the present invention includes a method of preventing or treating premature labor comprising administering the composition vaginally. Most preferably, in preventing or treating both conditions, 1 to 1.5 g of the composition is administered; although, acceptable amounts of the composition to be administered include 0.5 to 2.5 g. The composition administered can contain between 1 to less than about 8 mg of terbutaline per dose, preferably containing 1 to 4 mg, and most preferably containing 2 to 4 mg. Dosages of 8 or more mg are

not recommended, however, because side effects may be noted in some individuals at such levels. The composition can be administered every 12 to 48 hours, but is preferably administered every 24 hours. The composition can be administered during dysmenorrhea or optionally including one or more days prior to the anticipated onset of dysmenorrhea. Similarly, the composition may be administered during premature labor or to prevent the onset of anticipated premature labor.

The present invention comprises a dosing regimen and manner of treating dysmenorrhea. In practicing the invention, a patient need not wait until the onset of menses and the occurrence of pain to begin treatment. The present invention comprises administration of the composition as soon as the patient realizes that she is nearing the onset of menses, for example within a day or two. This method of administration is based on pharmacokinetic data below, and prevents the process of dyskinetic contractions from occurring, rather than treating them once the contractions have already begun.

Another important aspect of the invention is that the uterorelaxant formulation can correct dysmenorrhea and its dyskinetic contractions, without interfering with the normal contractions and bleeding during menstruation. Dysmenorrhea appears to involve dyskinetic contractions, which are erratic and abnormal. This is in contrast to other theories of dysmenorrhea as comprises solely an increase in the amplitude and frequency of contraction. The inventors believe that in dysmenorrhea the nature of contractions change so that there are not only antegrade contractions (fundus to cervix), but also retrograde contractions (cervix to fundus), and non-functional fibrillations. The composition of the present invention appears to provide relief by way of a selective action on the dyskinetic contractions without preventing the normal, regularized contractions necessary for menstruation.

The specific drug delivery formulation chosen and used in the examples below comprises a cross-linked polycarboxylic acid polymer formulation, generally described in U.S. Patent No. 4,615,697 to Robinson (hereinafter "the '697 patent"), which is incorporated herein by reference. In general, at least about eighty percent of the monomers of the polymer in such a formulation should

contain at least one carboxyl functionality. The cross-linking agent should be present at such an amount as to provide enough bioadhesion to allow the system to remain attached to the target epithelial surfaces for a sufficient time to allow the desired dosing to take place.

For vaginal administration, such as in the examples below, preferably the formulation remains attached to the epithelial surfaces for a period of at least about twenty-four to forty-eight hours. Such results may be measured clinically over various periods of time, by testing samples from the vagina for pH reduction due to the continued presence of the polymer. This preferred level of bioadhesion is usually attained when the cross-linking agent is present at about 0.1 to 6.0 weight percent of the polymer, with about 1.0 to 2.0 weight percent being most preferred, as long as the appropriate level of bioadhesion results. Bioadhesion can also be measured by commercially available surface tensiometers utilized to measure adhesive strength.

The polymer formulation can be adjusted to control the release rate of the β-adrenergic agonist, such as terbutaline, by varying the amount of cross-linking agent in the polymer. Suitable cross-linking agents include divinyl glycol, divinylbenzene, N,N-diallylacrylamide, 3,4-dihydroxy-1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene and similar agents.

A preferred polymer for use in such a formulation is Polycarbophil, U.S.P., which is commercially available from B.F. Goodrich Speciality Polymers of Cleveland, OH under the trade name NOVEON®-AA1. The United States Pharmacopeia, 1995 edition, United States Pharmacopeial Convention, Inc., Rockville, Maryland, at pages 1240-41, indicates that polycarbophil is a polyacrylic acid, cross-linked with divinyl glycol.

Other useful bioadhesive polymers that may be used in such a drug delivery system formulation are mentioned in the '697 patent. For example, these include polyacrylic acid polymers cross-linked with, for example, 3,4-dihydroxy-1,5-hexadiene, and polymethacrylic acid polymers cross-linked with, for example, divinyl benzene.

Typically, these polymers would not be used in their salt form, because this would decrease their bioadhesive capability. Such bioadhesive polymers may

be prepared by conventional free radical polymerization techniques utilizing initiators such as benzoyl peroxide, azobisisobutyronitrile, and the like. Exemplary preparations of useful bioadhesives are provided in the '697 patent.

The bioadhesive formulation may be in the form of a gel, cream, tablet, pill, capsule, suppository, film, or any other pharmaceutically acceptable form that adheres to the mucosa and does not wash away easily. Different formulations are further described in the '697 Patent, which is incorporated herein by reference.

Additionally, the additives taught in the '697 patent may be mixed in with the cross-linked polymer in the formulation for maximum or desired efficacy of the delivery system or for the comfort of the patient. Such additives include, for example, lubricants, plasticizing agents, preservatives, gel formers, tablet formers, pill formers, suppository formers, film formers, cream formers, disintegrating agents, coatings, binders, vehicles, coloring agents, taste and/or odor controlling agents, humectants, viscosity controlling agents, pH-adjusting agents, and similar agents.

The specific preparation (COL-2301) used in the studies discussed in the examples consists of the following ingredients.

Table 1: Preferred Compositions

Active Ingredient mg/g	1.0	2.0	4.0
Terbutaline (sulfate) % (w/w)	0.1%	0.2%	0.4%
Purified Water	755.4	754.4	752.4
Glycerin	139.0	139.0	139.0
Light liquid paraffin	42.0	42.0	42.0
Carbomer 934P	30.0	30.0	30.0
Polycarbophil	20.0	20.0	20.0
Methylparaben	1.8	1.8	1.8
Sorbic acid	0.8	0.8	0.8
Sodium Hydroxide	0.0-2.0	0.0-2.0	0.0-2.0
LABRAFIL® M2130	10	10	10

Sorbic acid is a preservative, which may be substituted by any other approved preservative, such as benzoic acid or propionic acid.

Carbomer is a gel former, preferably Carbopol 934P, but may be substituted by other gel formers including, but not limited to, Carbomer 974P, Carbomer 980, methyl cellulose or propyl cellulose.

LABRAFIL® M2130 is a lubricant/whitening agent to provide lubricity and add color to the gel; alternatives may be used, and coloring may be left out altogether.

Glycerin is a humectant; alternative humectants include, for example, propylene glycol or dipropylene glycol.

Preparation of the formulation involves hydration of the polymers, separate mixing of water-soluble ingredients (the "polymer phase") and oil-soluble ingredients (the "oil phase"), heating and mixing of the two phases, and homogenization of the mixture. All ingredients in COL-2301 are well known and readily available from suppliers known in the industry.

The polymer phase may generally be prepared by mixing the water (with about 3% excess volume of water to account for evaporative losses), sorbic acid, and methylparaben together. This mixture is heated to 75°C. The solution is

cooled, generally to room temperature, and then the polycarbophil and Carbomer are added. The polymers are hydrated by mixing for several hours, generally about 2-3 hours until a uniform, smooth, homogenous, lump-free gel-like polymer mixture is obtained. When the polymers are completely hydrated, the terbutaline is added and mixed in, until a homogeneous suspension is obtained.

The oil phase is generally prepared by melting together the LABRAFIL® M2130, glycerin, and light liquid paraffin, by heating to 75 to 78°C. The mixture is cooled to about 60°C., while the polymer phase is warmed to about the same temperature. The polymer phase is then added to the heated oil phase. The two phases are mixed thoroughly, producing a uniform, creamy white product. Sodium hydroxide is added, as needed, to produce a pH of about 2.5-4.5, generally about 4. When the mixture has cooled, it is de-aerated.

As will be apparent to those skilled in the art, the composition of the formulation can be varied to affect certain properties of the formulation. For example, the concentration of the bioadhesive polymer can be adjusted to provide greater or lesser bioadhesion. The viscosity can be varied by varying the pH or by changing the concentration of the polymer or gel former. The relative concentrations of the oils compared to the water can be varied to modulate the release rate of the terbutaline from the drug delivery system. The pH can also be varied as appropriate or to affect the release rate or bioadhesiveness of the formulation.

One of the surprising, but important aspects of the present formulation is that it allows the drug to be administered effectively even during menses. The particular bioadhesive qualities prevent the composition from being diluted or washed away, as would be expected with other bioadhesive preparations. This characteristic increases the utility of the present formulation.

Additionally, in light of the information disclosed in U.S. Pat. No. 5,543,150, it now appears that this bioadhesive formulation can provide local vaginal administration of different drugs to yield significant local drug levels while maintaining serum levels low enough to avoid most undesired side effects. It was a surprising result that this formulation serves as an acceptable carrier for two different active ingredients -- progesterone, and now terbutaline. Now, given its

concentrations for each tested dose). Terbutaline concentrations increased slowly reaching C_{max} after 13-14 hours and thereafter remained flat (steady state) for 24 hours with a mean steady state concentration (C_{ss}) of approximately 300 pg/mL with the 0.4% concentration. Concentrations were still detectable for up to 48 hours (mean ± SEM (Standard Error of the Mean) of 113.11 ± 32.25 pg/mL for the 0.4% concentration). Terbutaline absorption exhibited dose-dependent pharmacokinetics as reflected by the increase in AUC_{0-48} values (see Table 2 and Figure 1) to increases in terbutaline dosing. Mean $t_{1/2}$ estimates varied from 18 to 29 hours according to the dose administered and markedly exceeded measured $t_{1/2}$ after terbutaline administration by intravenous or subcutaneous routes, as had been found in the prior art.

TABLE 2: Single Dose Study, Pharmacokinetic Parameters

Single Dose Study		Pharmacokinetic Parameters (mean ± SEM)				
Terbutaline Dose	n	C_{max} (pg/mL)	T_{max} (h)	C_{ss} (pg/mL)	$t_{1/2}$ (h)	$AUC_{0\ to\ 48}$ (pg.h/mL))
0.1%	10	117 ± 59	13 ± 6	56 ± 41	18 ± 12	2281 ± 1836
0.2%	10	297 ± 170	13 ± 6	191 ±108	29 ± 15	8011 ± 4699
0.4%	10	479 ± 149	14 ± 7	294 ± 115	24 ± 16	11893 ± 5277

Example 2: The Pharmacokinetic Parameters of the Terbutaline Composition,
A Multiple Dose Study

The multiple dose study was an open-label study conducted in 12 healthy female volunteers with a mean age ± SD of 25 ± 4.13 years. The dose used in this study was 0.4%. This study consisted of a 30 day screening period, a 6 day treatment period, and a 2 day follow-up. The drug was administered transvaginally once daily at 9:00 a.m. All subjects were given an

(mean ± SEM: 287 ± 96 pg/mL). The mean C_{ss} was 10 to 15 times less than therapeutic concentrations of terbutaline for intravenous preterm labor therapy described in the prior art. *See Lyrenas, S, Grahnen A, Lindberg B. et al., Pharmacokinetics of Terbutaline During Pregnancy, Eur. J. Clin. Pharmacol., 29:619-23 (1986).* Comparison of the AUC_{0-24} for days 1 and 6 revealed a two-fold increase. Mean $t_{1/2}$ estimates were 51 hours on day 6.

TABLE 3: Multiple Dose Study, Pharmacokinetic Parameters

Multiple Dose Study			Pharmacokinetic Parameters (mean ± SEM)				
Terbutaline Dose	Day	n	C_{max} (pg/mL)	T_{max} (h)	C_{ss} (pg/mL)	$t_{1/2}$ (h)	$AUC_{0\ to\ 48}$ (pg.h/mL)
0.4%	1	11	477 ± 259	9 ± 6	287 ± 96	---	6896 ± 2304
0.4%	6	11	769 ± 465	9 ± 5	563 ± 339	51 ± 91	13512 ± 8135

Example 3: A Dose Comparison

Both the single and multiple dose studies discussed in the preceding examples also evaluated the 0.8% w/w concentration. The average age ± SD for the single and multiple dose studies at the 0.8 dose were 26 ± 3.42 and 26 ± 4.12, respectively. The pharmacokinetic parameters from the study follow in Tables 4 and 5.

TABLE 4: Single Dose Study, Pharmacokinetic Parameters

Single Dose Study		Pharmacokinetic Parameters (mean ± SEM)				
Terbutaline Dose	n	C_{max} (pg/mL)	T_{max} (h)	C_{ss} (pg/mL)	$t_{1/2}$ (h)	$AUC_{0\ to\ 48}$ (pg.h/mL)
0.8%	8	787 ± 434	10 ± 3	579 ± 300	20 ± 7	23222 ± 13530

TABLE 5: Multiple Dose Study, Pharmacokinetic Parameters

Multiple Dose Study			Pharmacokinetic Parameters (mean ± SEM)				
Terbutaline Dose	Day	n	C_{max} (pg/mL)	T_{max} (h)	C_{ss} (pg/mL)	$t_{1/2}$ (h)	$AUC_{0\ to\ 48}$ (pg.h/mL)
0.8%	1	10	794 ± 394	11 ± 5	567 ± 322	---	13618 ± 7718
0.8%	6	10	1537± 906	9 ± 2	1135 ± 679	19 ± 4	27246 ± 16299

As can be seen in Figures 3 and 4, the serum terbutaline levels in both cases did not reach known levels for toxicity (3000 pg/ml), nor did they even therapeutic concentrations for other conditions such as asthma (1600 pg/ml). A number of patients in the study (40%), however, experienced side effects such as tachycardia at this dose. The occurrence of adverse events at this dose was an unexpected result of the invention, as again the serum levels did not reach known levels for toxicity. This dose can be a method of practicing the invention, but is certainly not the most preferred embodiment.

Example 4: Human *Ex Vivo* Uterine Perfusion Model

This model verifies the preferential direct delivery of terbutaline from the vagina to the uterus. In this study, uteri obtained from women undergoing hysterectomies for benign diseases were immediately connected to an organ

WE CLAIM:

1. A pharmaceutical composition comprising a therapeutically effective amount of a ß-adrenergic agonist together with a pharmaceutically acceptable bioadhesive carrier.

2. The composition of claim 1 wherein the ß-adrenergic agonist is terbutaline.

3. The composition of claim 2 wherein the bioadhesive carrier comprises a cross-linked carboxylic polymer.

4. The composition of claim 3, wherein the concentration of terbutaline is from 0.1 to 0.4% weight/weight.

5. The composition of claim 4, wherein the polymer is polycarbophil.

6. The composition of claim 5, wherein the β-adrenergic agonist is terbutaline and the composition is prepared so that a dosage of about 1 to 1.5 g of composition delivers from about 1 to 4 mg of terbutaline.

7. A method of preventing or treating dysmenorrhea comprising administering vaginally to a host in need thereof the pharmaceutical composition of claim 1.

8. The method of claim 7, wherein the β-adrenergic agonist is terbutaline and the dosage of composition administered contains from 1 to 4 mg of terbutaline.

9. The method of claim 7, wherein the composition is administered every 12 to 48 hours during dysmenorrhea.

10. The method of claim 7, wherein the composition is administered every 24 hours during dysmenorrhea.

11. A method of preventing or treating premature labor comprising administering the composition of claim 1 vaginally, in a therapeutically effective amount.

12. The method of claim 11, wherein the β-adrenergic agonist is terbutaline and the dosage of composition administered contains from 1 to 4 mg of terbutaline.

13. The method of claim 11, wherein the composition is administered every 12 to 48 hours to prevent or treat premature labor.

14. The method of claim 11, wherein the composition is administered every 24 hours to prevent or treat premature labor.

15. A pharmaceutical composition for vaginal administration of a treating agent to achieve local efficacy without detrimental blood levels of the treating agent, comprising a therapeutically effective amount of a treating agent together with polycarbophil.

16. A method of vaginally administering the composition of claim 15, in a therapeutically effective amount.

17. A pharmaceutical composition for vaginal administration of a treating agent during menses, comprising polycarbophil and a therapeutically effective amount of a treating agent.

18. Use of a β-adrenergic agonist together with a bioadhesive cross-linked carboxylic polymer carrier for the preparation of a pharmaceutical composition for the prevention or treatment of dysmenorrhea or premature labor.

US005135943A

United States Patent [19]

Foguet et al.

[11] Patent Number: 5,135,943

[45] Date of Patent: Aug. 4, 1992

95 D2
95

[54] 1H-IMIDAZOLE DERIVATIVE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME

[75] Inventors: **Rafael Foguet; Marcial Moreno; Manuel Raga; Rosa M. Cuberes; Jose M. Castello; Jose A. Ortiz,** all of Barcelona, Spain

[73] Assignee: **Ferrer Internacional S.A.,** Barcelona, Spain

[21] Appl. No.: **649,764**

[22] Filed: **Feb. 1, 1991**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 451,823, Dec. 15, 1989, abandoned, which is a continuation-in-part of Ser. No. 366,756, Jun. 14, 1989, abandoned, which is a continuation of Ser. No. 694,645, Jan. 24, 1985, abandoned.

[30] **Foreign Application Priority Data**

Feb. 2, 1984 [ES] Spain 529608
Jun. 1, 1984 [ES] Spain 533353
Aug. 6, 1984 [ES] Spain 535656

[51] **Int. Cl.**[5] **A61K 31/415**; A61K 31/38; C07D 403/12

[52] **U.S. Cl.** **514/397**; 548/336

[58] **Field of Search** 548/336; 514/397

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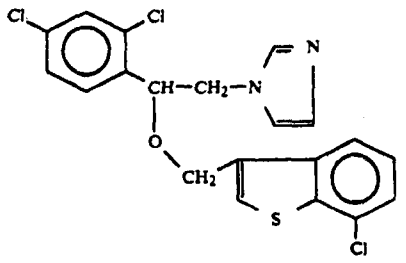
Primary Examiner—Johann Richter
Attorney, Agent, or Firm—Michael J. Striker

[57] **ABSTRACT**

The 1H-imidazole derivative compound of formula I:



(I)

and its nontoxic addition salts, particularly the nitrate addition salt, are more effective as antimycotic agents and are unexpectedly safer than the corresponding prior art compounds, especially the compound in which the sulfur atom of the benzothiophene ring of the above compound is replaced by an oxygen atom. Pharmaceutical compositions containing an effective amount of the compound of formula I, e.g. 1 to 5% by weight, in a pharmaceutical carrier are safer, more effective, and, in some cases, more reliable with fewer side effects than currently used antimycotic preparations.

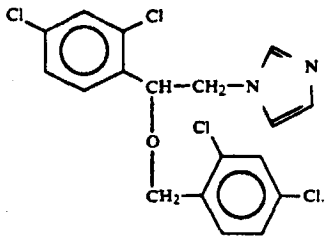
14 Claims, No Drawings

1H-IMIDAZOLE DERIVATIVE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAMEBACKGROUND OF THE INVENTION

This application is a continuation-in-part of application Ser. No. 451,823, filed Dec. 15, 1989, which is, in turn, a continuation-in-part application of Ser. No. 366,756, filed Jun. 14, 1989 and abandoned Apr. 5, 1990; which is a continuation of application Ser. No. 694,645, filed Jan. 24, 1985 and abandoned Jul. 27, 1989.

This invention relates to antimycotic pharmaceutical compositions and, more particularly, to 1H-imidazole derivative compounds and pharmaceutical compositions containing those compounds, especially antimycotic pharmaceutical compositions, i.e. pharmaceutical compositions for the treatment of infections in humans and animals, which are due to infection by fungi and yeast microorganisms. The invention also relates to fungicidal compositions for application to crops to destroy fungi and other microorganisms.

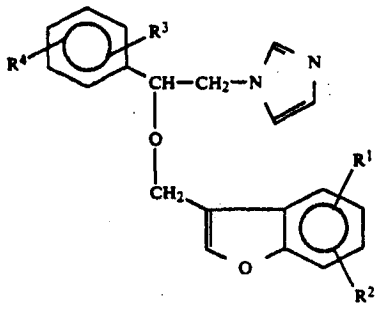
A number of compounds with antimycotic and/or fungicidal properties, which are useful in pharmaceutical compositions, are currently known. These include the commercially successful Miconazole having the formula II



(II)

Miconazole has a structure chemically similar to the 1H-imidazole derivative compounds of the invention. Miconazole is effective against a number of yeasts, dermatophytes and fungi. This effectiveness can be measured by culturing these microorganisms in vitro and applying a preparation containing the antimycotic compound, Miconazole. The results of this type of *in vitro* experiment is expressed in terms of the Minimum Inhibitory Concentration (MIC), i.e. the minimum concentration which inhibits the growth of the microorganism. For example, the MIC for Miconazole against a particular *Candida albicans* strain is found to be 10.7 micrograms/milliliter. The effectiveness of Miconazole as an antimycotic compound is measured in vivo by applying a suspension containing the drug to the skin of a number of animals and measuring the proportion of animals on which growth of the microorganism is inhibited as a function of time. Typically, after 25 days, about ½ of the animals were cured, when treated with a cream containing 2 % by weight Miconazole. Of course, any pharmaceutical preparation for treating a disease in a human must satisfy certain toxicity requirements. Therefore, toxicity tests are required to show that the preparation may be administered safely. Toxicity tests have been performed on the IH-imidazole derivative compounds of the invention and on Miconazole and other known compounds having antimycotic properties. In toxicity tests the LD_{50} (the dose at which 50 % mortality occurs) is measured. For Miconazole, for example, the LD_{50} in mouse is about 2500 mg/kg for oral administration, 600 mg/kg for intraperitoneal administration and over 5000 mg/kg for subcutaneous administration.

Other compounds having a structure similar to applicants' compound include those described in U.S. Pat. No. 4,402,968, issued to Martin, Sep. 6, 1983. These compounds are also imidazole derivative compounds and have the following general formula III as claimed in the Martin Patent:



(III)

wherein R^1, R^2, R^3 and R^4 may be a hydrogen atom or a halogen atom, especially a chlorine atom. The in vitro fungicidal activity of one compound of formula III, in which all the R groups are chlorine radicals, was reported in the patent against several fungi. Measured in vitro against *Candida albicans* this compound has a MIC of about 10 micrograms per milliliter. A method of measurement of in vivo fungicidal activity was also described. However, as will be seen from the results described below, these compounds are comparatively toxic.

Other compounds having antimycotic properties are described in U.S. Pat. No. 4,272,545, issued to Walker. However, these antimycotic compounds have a structure which is considerably different from the structure of either the applicants or those of the Martin Patent. They have also been tested in vivo and in vitro and found effective against a large variety of fungi and yeast.

The current prior art antimycotic compounds, which are closest in structure to the applicants' compound, namely those of the Martin Patent, have an unexpectedly undesirably high toxicity, as measured in a variety of ways in comparison to the compounds described herein. Furthermore, the compounds of the present invention are more effective as in vitro fungicidal agents.

Other toxicological properties of the antimycotic compounds described in the Martin Patent are also poor. These poor toxicological properties imply that it is comparatively more dangerous to expose a human or pet to the compounds of the Martin Patent than to the compounds of the invention. The data, which will be presented below, also imply that 1H-imidazole derivative compounds of the invention can be applied in larger amounts, but as safely, as a correspondingly smaller concentration of the compounds of the Martin patent.

SUMMARY OF THE INVENTION

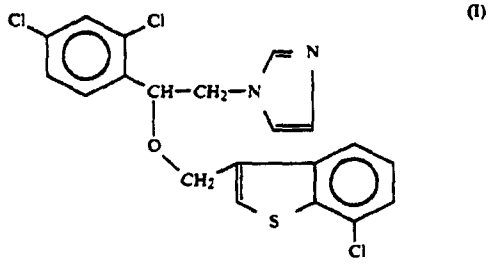
It is an object of the present invention to provide new 1H-imidazole derivative compounds having improved antimycotic and/or antifungicidal activity, but which

are also unexpectedly safer, in comparison to the comparable prior art compounds.

It is another object of the present invention to provide new antimycotic 1H-imidazole derivative compounds, which are more effective, are safer to use on humans and pets and also in larger amounts than the current comparable prior art compounds and which are more reliable and faster acting for some microorganism infections.

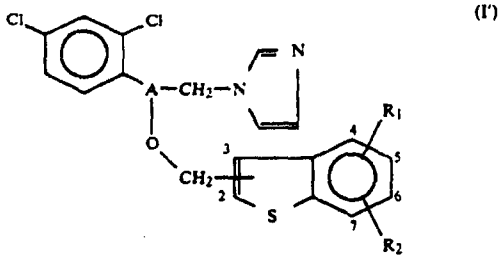
According to the invention, the 1H-imidazole derivative compounds having the above-mentioned improved pharmaceutical properties, including improved antimycotic activity and toxicological properties, comprise 1-[2-(7-chloro-3-benzo[b]thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole, and nontoxic addition salts thereof, preferably the mononitrate and the heminaphthanlene-1,5-disulphonate.

The novel 1H-imidazole derivative compound of the invention also has the following general formula I:



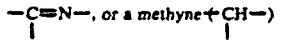
(I)

A number of other new 1H-imidazole derivative compounds of the following general formula I' have also been prepared and tested:



(I')

wherein A is an imino-,



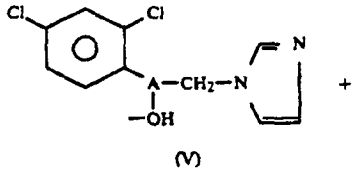
group, R_1 and R_2 are independently hydrogen or halogen selected from chlorine, bromine or fluorine in any of the 2, 4, 5, 6 or 7 positions of the benzo[b]thiophene group, and the methylene -CH_2-group is bonded to the benzo[b]thiophene group in its 2 or 3 position. These compounds also show antimycotic properties.

The antimycotic compound of the invention, the compound of formula I, will be hence forth referred to as Sertaconazole, for convenience. Pharmaceutical preparations with antimycotic properties are described hereinbelow.

The compound of formula I had a melting point of 146–7° C. The corresponding nitrate addition salt had a melting point of 156–7° C. Mass spectra and elemental analysis also confirmed the structure of the compound of formula I. See Manuel Raga, Celia Palacin, Josep Ma. Castello and Jose Ortiz and Ma. Cuberes and Marcial Moreno-Manas, Eur. J.Med. Chem. 21, pp 329-332(1986).

PREPARATION OF THE DERIVATIVE COMPOUNDS

The compounds of the present invention may be prepared according to the following scheme:



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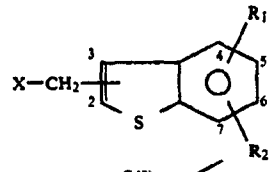
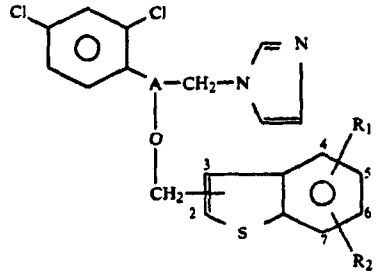


(VI)



In the starting compounds of the formula V, A has the same meaning as stated above, and in the starting compounds of the formula VI, X is chlorine or bromine, R_1 and R_2 have the same meaning stated above and likewise, the methylene group (—CH_2—) is bonded to the benzo[b]thiophene group in the same position as defined above. A similar process is used to prepare the compounds described in the Martin reference referred to in the Background Section.

The reaction between the oxime or the alcohol of the formula V and the halides of the formula VI occurs conveniently in the presence of a suitable mineral base strong enough to ionize the compounds of the formula V such as hydroxides, or alkaline or alkaline-earth hydrides, with potassium hydroxide and sodium hydride, preferably employed.

The reaction is advantageously performed within a wide temperature range (from −55° C. to 100° C.) and in an aprotic solvent selected from an alkanone with up to 6 carbon atoms or a polyalkylated amide, with acetone or hexamethylphosphorotriamide preferably employed.

After purification, the acid addition salts may be obtained by treating with respective acids in a medium composed of an organic solvent. The organic solvent is an alcohol with 1 to 4 carbons, preferably ethanol or n-butanol, or may be a ketone such as acetone. A sol-

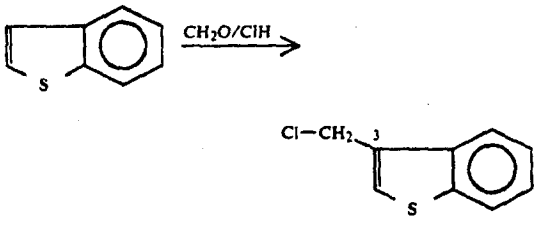
vent which is a mixture of an organic solvent and water may also be used.

The described reaction steps lead to the compounds of the formula I according to the present invention.

The oxime and alcohol used as starting material of the formula V are already known and are obtained according to the processes described by Von. G. Mixich and K. Thiele (Arzneimittel-Forschung, 29(II), Nr.10, 1510-3, 1979)—oxime, .Z configuration—and by E.F. Godefroi, et al (J. Med. Chem., 12, 784–9, 1969)—Alcohol, for example by treating 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl) ethanone with hydroxylamine or sodium borohydride, respectively.

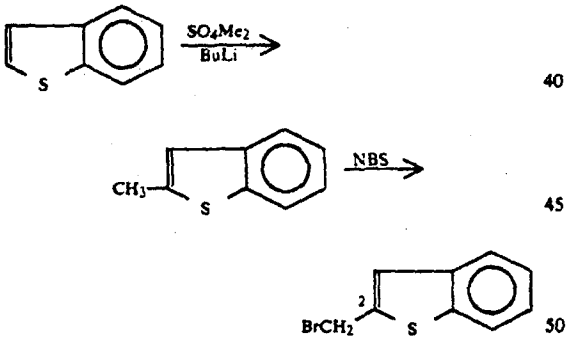
The halides of the formula VI are obtained by the known methods of organic chemistry, e.g.:

a) from benzo[b]thiophene either by chloromethylation (R. Neidlen and E.P. Mrugowski: Arch. Pharm. [Weinheim, Ger.,] 308(7), 513–9, 1975):



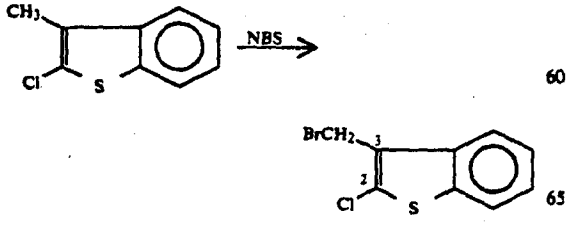
(VI, X = Cl, R_1 = R_2 = H, 3 position)

or by methylation and final bromination (D.A. Shirley and M.D. Cameron: JACS, 74, 664, 1952; U.S. Pat. No. 4,282,227):



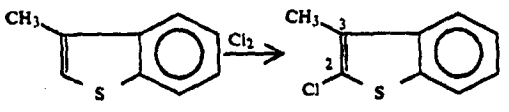
(VI, X = Br, R_1 = R_2 = H, 2 position)

b) from 2- chloro-3-methylbenzo[b]thiophene by bromination (European Pat. No. 54,233):



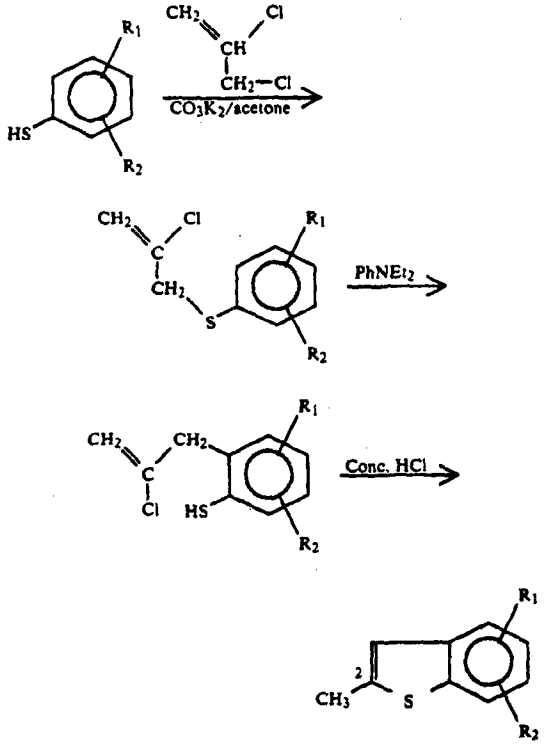
(VI, X = Br, R_1 = 2-Cl, R_2 = H, 3 position)

and 2- chloro-3-methylbenzo[b]thiophene is in turn obtained by chlorination of 3- methylbenzo[b]thiophene (V.I. Dronov et al, CA, 79, 115388f):



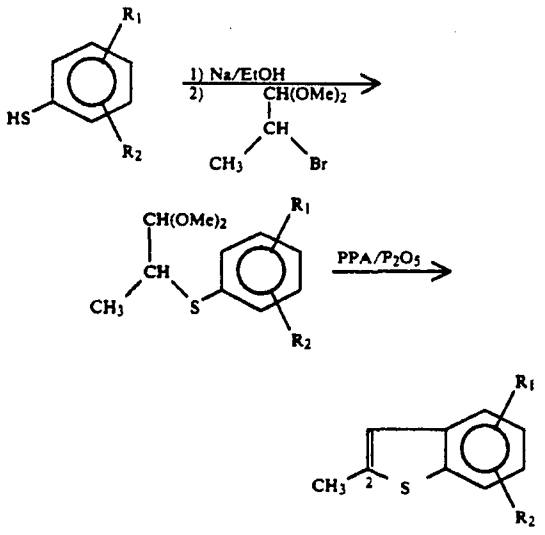
(VI, X = H, R_1 = 2-Cl, R_2 = H, 3 position)

c) from the corresponding thiophenol by total synthesis, for example, 2- chloro-2-propenyl-phenylthioether is formed by treating 2,3- dichloropropene, transposition in N,N-diethylaniline and cyclization with concentrated hydrochloric acid (W.K. Anderson and E.J. LaVoie, J. Chem. Soc., Chem. Commun., (5), 174, 1974; W.K. Anderson et al, J. Chem. Soc., Perkin Trans. 1, (1), 1–4, 1975):



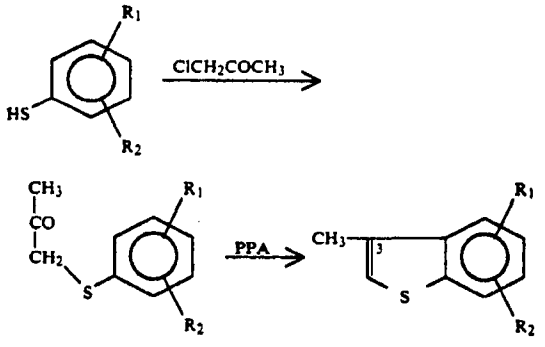
(VI, X = H, 2 position)

or by an alternative process also from the corresponding thiophenol by total synthesis, for example by forming respective 2- phenylthiopropionaldehyde acetal by treatment with 2-bromopropionaldehyde in sodium ethoxide and cyclization with an admixture of polyphosphoric acid and phosphorous pentoxide (Yasuo Matsuki and Fusaji Shoji, Nippon Kagaku Zasshi, 86,(10), 1067–72. 1965):



(VI, X = H, 2 position)

d) in a similar manner the 3-position compounds are also obtained from the corresponding thiophenol by total synthesis and forming respective phenylthioacetone by treatment with chloroacetone and cyclization with polyphosphoric acid (N.B. Chapman, et al, J. Chem. Soc. C., (5), pp. 512-22, 1968; N.B. Chapman, et al, ibid, (5), 2747-51, 1968):



(VI, X = H, 3 position)
PPA: Polyphosphoric acid
NBS: N-bromosuccinimide

Halogenation of intermediates (VI, X=H) with N-bromosuccinimide or with N-chlorosuccinimide in carbon tetrachloride, under the conditions described by N.B. Chapman, et al; J. Chem. Soc. C., (5), 512-22, 1968) and N.B. Chapman, et al (ibid., (5), 2747-51, 1968), leads to the intermediates (VI, X=Br or Cl).

The starting thiophenol, when R_1 or R_2 are halogen in metaposition, leads to correspondingly substituted 4- or 6- position benzo[b]thiophenes, enabling the isomers to be separated by customary methods of organic chemistry. Column chromatography is a preferred method of separation.

COMPARATIVE STUDY OF PHARMACOLOGICAL PROPERTIES

Comparative in vitro and in vivo antimycotic activities of the compound of formula I, Sertaconazole, versus Miconazole and the compounds of the Martin patent, which have the closest structure to Sertaconazole, are reported hereinbelow. Clinical data are also included. The data show that Sertaconazole has a higher antimycotic activity than these prior art compounds. Furthermore, toxicological data for these compounds also shows that Sertaconazole is surprisingly and unexpectedly safer to administer to humans and pets in a method of treating an infection due to fungi or yeast.

The compounds of the Martin patent, which are the closest in structure to Sertaconazole, also have an unexpectedly large toxicity and are much less safe than Miconazole. In view of this finding, it is not surprising that Miconazole is the more frequently used compound commercially. As a result, comparison has been made with Miconazole as well as with the compounds described in the Martin patent.

1. In vitro Fungicidal Activity Measurements

Minimum Inhibitory Concentrations (MICS) of Sertaconazole and Miconazole against 107 yeasts, 47 dermatophytes and 4 fungi were determined by a two-fold dilution method. The results of these measurements are shown in the following Table 1.

These results show that Sertaconazole has a somewhat different, but similar, spectrum of in vitro activity in comparison to Miconazole. Particularly, Sertaconazole is more active against *Candida albicans* (43.9 % higher), *Candida s.p.* (47.4% higher) and *Scopulariopsis* (75 % higher). Thus Sertaconazole is more effective than the most common commercially used product in the case of several microorganisms.

Minimum Inhibitory Concentrations (MICS) of Sertaconazole were also measured in comparison to four of the compounds described in the Martin Patent, including a compound, referred to herein as Martin Compound 1, which has the same structure as Sertaconazole, expect that the sulfur in the benzothiophene ring is replaced by an oxygen.

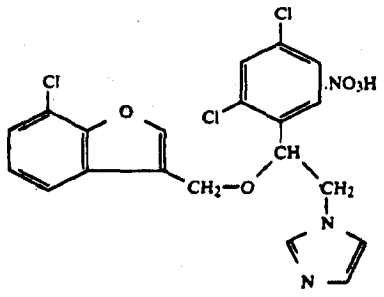
TABLE I

Minimum Inhibitory Concentration of Sertaconazole and Miconazole against Different Microorganisms

Microorganism	# strains	Sertaconazole microgram/ml	Miconazole microgram/ml
Yeasts			
Candida albicans	52	6.0	10.7
Candida tropicalis	10	5.6	5.6
Torulopsis glabrata	10	1.5	1.1
Candida s.p.	15	0.5	0.95
Malasezzia furfur	20	25/8	19/2.8
Dermatophytes			
Trichophyton rubrus	10	0.4	0.3
Trichophyton mentagrophytes	30	2.6	2.8
Microsporum canis	4	2.8	2.0
Others	3	2.5	4.0
Fungi			
Scopulariopsis brevicaulis	4	8.0	32.0
Gram-positive germs	21	0.97	0.88

The structure of the Martin Compound 1 is as follows:

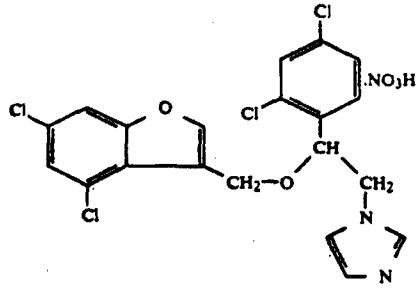
M1



The structure of Martin Compound 2 and 3 is the same as the Martin Compound 1 except that the chlorine substituent on the benzothiophene ring is in the 6 and the 5 position, respectively, instead of the 7 position. Furthermore, the methylene group (—CH_2—) is bonded to the benzo[b]furan group in the Martin Compound 3 in the 2 position instead of the 3 position.

The structure of the Martin Compound 4 is as follows:

M4



The results of comparative in vitro testing of Sertaconazole and these four Martin compounds are shown in the following Table II against 16 microorganisms.

The reading time is the time interval from the time of inoculation to the time of measurement.

Table II also shows the geometric mean of all measurements. Calculation of these geometric mean values shows that Sertaconazole is 24 % more effective than Martin Compound 1; 54 % more effective than Martin Compound 2; 16 % more effective than Martin Compound 3 and 54 % more effective than Martin Compound 4.

Thus, Sertaconazole shows an increased antimycotic activity in relation to all the Martin Compounds studied, including Martin Compound 1, in which only a benzothiophene ring sulfur is replaced by oxygen

Theoretical calculations of bond angles and electron densities made by the method of Del Re, et al. Biochem.Biophys.Acta, 75, 153–182(1963) have confirmed that significant differences in chemical properties can occur, because of replacement of the oxygen atom in the benzothiophene ring with the sulfur atom. For example,

TABLE II

			MIC values (μg/ml)								
Microorganism	SZ	M1		SZ	M2		SZ	M3		SZ	M4	
C. albicans 14	1	2	*a*	0.25	0.25	*d*	0.5	0.5	*d*	0.5	0.5	*d*
C. albicans 15	0.5	1	*a*	0.06	0.06	*d*	0.03	0.06	*d*	0.03	0.03	*d*
C. albicans 31	8	8	*b*	4	4	*e*	4	4	*e*	4	8	*e*
C. albicans 32	8	8	*b*	4	4	*e*	4	4	*e*	4	8	*e*
C. albicans ATCC E-10231	1	2	*a*	0.5	0.5	*d*	0.5	0.5	*d*	0.5	0.5	*d*
C. pseudotropicalis 21	0.03	0.03	*c*	0.03	0.06	*f*	0.03	0.03	*f*	0.03	0.03	*f*
C. krusei 24	1	1	*a*	0.25	0.05	*d*	0.125	0.125	*d*	0.125	0.5	*d*
C. krusei 24	0.25	0.25	*b*	0.25	0.5	*e*	0.25	0.25	*e*	0.25	0.5	*e*
C. parapsilosis 19	1	1	*c*	0.25	1	*f*	0.25	0.5	*f*	0.25	0.5	*f*
C. parapsilosis 19	0.5	0.5	*b*	0.25	1	*e*	0.5	1	*e*	0.5	0.5	*e*
C. stellatoidea 36232	1	1	*c*	0.25	0.5	*f*	0.5	0.5	*f*	0.5	0.5	*f*
C. stellatoidea 36232	0.25	0.5	*a*	0.06	0.06	*d*	0.06	0.125	*d*	0.06	0.06	*d*
C. stellatoidea 36232	4	4	*b*	1	1	*e*	0.5	4	*e*	0.5	0.5	*e*
C. guillermondii	0.5	0.5	*a*	0.25	0.5	*d*	0.25	0.25	*d*	0.25	0.5	*d*
C. guillermondii	0.25	0.5	*b*	0.25	0.5	*e*	0.125	0.25	*e*	0.125	0.5	*e*
C. tropicalis 25	8	8	*b*	8	8	*e*	4	8	*e*	4	8	*e*
Geometric means	0.876	1.09		0.366	0.565		0.336	0.497		0.336	0.518	
Increase of Sertaconazole activity	24%			54%			16%			54%		

SZ Sertaconazole
M1, M2, M3, M4 Martin compounds
[a] Casitone medium. Reading time 60 h
[b] YNB medium. Reading time 60 h
[c] Sabouraud medium. Reading time 60 h
[d] Casitone medium. Reading time 48 h
[e] YNB medium. Reading time 48 h
[f] Sabouraud medium. Reading time 48 h

applicants have found by this theoretical method that the sulfur atom in Sertaconzole is significantly less negatively charged than the corresponding oxygen atom in Martin Compound 1. Furthermore, the theoretical results for the electron densities and the bond angles show that, relative to Martin Compound 1, Sertaconzaole has decreased polarity, increased lipophylicity, increased molecular volume, decreased gastrointestinal absorption and decreased toxicity.

2. In Vivo Activity

Dermal infection in albino female guinea pigs by Trichophyton mcntagrophytes has been studied. Animals were distributed in three groups: a) a control group of infected untreated animals; b) a scrtaconazole group of infected and treated animals; and c) a miconazole group of infected and treated animals. Animals were depleted and a 0.4 ml suspension of the microorganism was applied on the depleted area. Treatment with each of the test drugs was made by application of 1 g of 2% cream on the depleted area on the 4th, 5th and

6th day after infection. The results are shown in the following Table III:

TABLE III

Relationship of Negative Cultures to Total Cultures (% microbiological healing) at days 18, 25 and 32 Postinfection.

Treatment group	18 days	25 days	32 days
Control	0/24(0%)	0/24(0%)	5/24(21%)
Compound 25	27/48(56%)	36/48(75%)	40/48(84%)
Miconazole	3/48(6%)	13/48(28%)	21/48(44%)

Although in the in vitro experiment with *Trich. metagrophytes*, Sertaconazole was not much more active than Miconazole, in this in vivo experiment with the same microorganism Sertaconazole was surprisingly remarkably more active than Miconazole. 9 times higher on the 18th day, 2.7 times higher on the 25th day and 1.9 times higher on the 32nd day postinfection. These results show that although only small structural changes are involved large surprising changes in the rates of cure occur. These results are consistent with clinical trials.

Besides the above in vivo experiments vaginal infection by *Candida albicans* was studied in female mice. Standard methods were used. Seven days after infection sertaconazole was found to heal 75 % of the animals treated whereas miconazole only healed 12.5 %. Similar results were found in experiments where repeated dosages of active compound were used after infection. These in vivo results confirmed the surprising speed of action of Sertaconazole in comparison to the prior art compounds.

3. Toxicological Comparisons

Toxicity of Sertaconazole, Microazole and Martin's compounds 1, 2 and 3, as shown below, has been tested by standard methods. Both acute toxicity, subacute toxicity and chronic toxicity were studied

Oral, intraperitoneal and subcutaneous acute toxicity of sertaconazole and miconazole have been investigated. LD50 in mouse and rat, male and female, were measured. The results are shown in Table IV following:

TABLE IV

Lethal Dose(LD50) of Sertaconazole and Miconazole through Three Different Administration Routes in Males

Administration	Animal	Sertaconazole mg/kg	Miconazole mg/kg
Oral	mouse	>8000	2,560
Oral	rat	>8000	920
Intraperi-toneal	mouse	>8000	662
	rat	>8000	1,185
Subcutaneous	mouse	>8000	>5000
	rat	>8000	>5000

Table IV shows that Sertaconazole is an order of magnitude less toxic by oral and intraperitoneal routes than the prior art compound, Miconazole. Subcutaneous acute toxicity was also significantly less for Sertaconazole than Miconazole. This shows that a pharmaceutical preparation containing Sertaconazole is significantly safer to give to a person or pet suffering from an infection due to microorganisms than Miconazole (assuming equal amounts of the active ingredient are used, which is most likely since Sertaconazole is more effective than Miconazole).

In a study of prolonged subacute toxicity of Miconazole in rats, among other effects, significant hepatomegalias in females with a dosage of under 30 mg/kg p.o. and in males with a dosage of under 60 mg/kg p.o. were observed. In contrast, Sertaconazole did not show this effect, caused by hepatocite microsomal enzymes, up to a dosage of 300 mg/kg.

Chronic toxicity of Miconazole in rats resulted in a conclusion that 100 mg/kg or more dosage caused 32 % mortality, while no mortality was observed with Sertaconazole, even at dosage levels of 300 mg/kg.

Based on these finds a safe dosage for Miconazole is about 10 mg/kg, while a safe dosage for Sertaconzole is about 150 mg/kg, i.e about 15 times higher.

Similar toxicological experiments were performed for Sertaconazole, Sertaconazole nitrate, Martin Compounds 1, 2, 3 and 4. The results are shown in Table V hereinbelow. They show that Sertaconazole is unexpectedly and surprisingly less toxic than the Martin compounds.

Sertaconazole is 8 to 15 times less toxic than the Martin Compound 1, the compound of the prior art having a structure which is closest to that of Sertaconazole.

TABLE V

Compound	Toxicological Data LD_{50} (mg/kg) (Swiss mice i.p.)	LD_0 (mg/kg) (Swiss mice i.p.)
Sertaconazole base	8000	4000
Sertaconazole nitrate	8000	2000
Martin compound 1	518	285
Martin compound 2	640	235
Martin compound 3	640	423
Martin compound 4	<1000[a]	Not determined

[a]Approximate value.

Furthermore and in addition to the results shown in Table V, the mice given Martin Compounds 1 and 3 revealed evident signs of intoxication in the central nervous system, which possibly caused the death of most animals. Such signs included convulsions and Straub tail(vertical righting of the tail). These signs were not observed in mice given Sertaconazole at any dosage level. Post mortem examination showed that 80 % of the mice given Martin Compound 3 had generalized pulmonary edema and congestion to such an extent that alone could have caused their death.

Thus, Sertaconzole is unexpectedly and surprisingly safer than the closest prior art, Martin Compound 1 This implies that a higher concentration of Sertaconazole can be used safely in a pharmaceutical preparation to treat an infection in humans and pets than Martin Compound 1. However, since Sertaconazole is also more effective as an in vitro fungicidal agent, it is not necessary to use a higher concentration.

In conclusion, Sertaconazole has been shown to be unexpectedly and surprisingly better as an antimycotic agent than the closest prior art compounds.

4. Clinical Evaluation of Pharmaceutical Preparations for Treating Infections in Humans

Human clinical trials were performed with Sertaconazole nitrate and Miconazole nitrate acid addition salts. Randomized double blind trials were carried out with 502 patients suffering from cutaneous mycosis as confirmed by microscopic examination and microbiological culture. 247 patients were treated with 2 % Sertaconazole cream and the remaining 255 patients were treated with 2 % Miconazole cream. All patients received scheduled treatment for 28 days and were followed up for an additional 28 days for possible re-

lapses. The most important conclusions from these clinical trials were that Sertaconazole was 20.8% more effective than Miconazole. Also it was 100 % effective against *Trichophyton rubrum*, which produces a particularly stubborn infection, as compared to 79 % for Miconazole. Furthermore, there were 5 cases of contact dermatitis in the experiments with Miconazole, while Sertaconazole showed no such side effects.

Sertaconazole generally shows an antibacterial and antiprotozoal activity as well as an antimycotic behavior.

PHARMACEUTICAL COMPOSITIONS

For their pharmaceutical, veterinary and clinical use the compounds of the present invention or their pharmaceutically acceptable acid addition salts can be administered, in solid, semi-solid or liquid form in tablets, coated tablets, capsules, powders, suppositories, liquid solutions, suspensions, creams, lotions, ointments and the like, together with pharmaceutically acceptable non-toxic carriers or excipients normally employed. They can also be administered by the in3ectable route, rectal route and by vaginal-intrauterine route in the form of ovulum, vaginal tablets, ointment, cream, pessary, lotion, etc. They can be administered by the topical route in the form of cream, lotion, ointment, emulsion, solution shampoo, powder, gel and so forth.

Topical application is the preferred method of administration in clinical usage. Topical pharmaceutical compositions containing the compounds of the present invention exhibit antiyeast, antifungal, antiprotozoal and antibacterial activity over a wide range of concentrations, for example, from about 0.1 % to 15 % by weight of the composition, to be applied on the infected skin or mucosa, preferably in 2 to 3 daily applications.

For systematic (oral or parenteral) or rectal administration, it is expedient to administer the active ingredient in amounts between 1 and 50 mg/kg body weight for a day, preferably distributed over several applications. Exact dosage however depends on a variety of factors including of course patient's nature and condition.

Examples of pharmaceutical preparations for the treatment and control of infections due to yeast, fungi, protozoa and bacteria using compound 25 of the invention as the effective ingredient are provided in the following paragraphs

Example 1. Topical Formulation: Dermal Cream	
Sertaconazole nitrate	0.2-3 g
Benzyl alcohol	1.00 g
2-Octyldodecanol	5.75 g
Liquid paraffin	5.75 g
Stearic alcohol	5.75 g
Cetyl alcohol	5.75 g
Myristhylic alcohol	3.00 g
Tween 60	3.50 g
Span 60	1.50 g
Distilled water s.q.f.	100 g
Example 2. Topical Preparation: Vaginal Cream	
Sertaconazole nitrate	0.2-3 g
Hydrogen ricinus oil	100 mg.
Corn starch	100 mg
Magnesium stearate	6 mg
Microcrystalline cellulose s.q.f.	1 tablet
Example 3. Oral Formulation: Tablets	
Sertaconazole nitrate	200 mg
Corn starch	80 mg
Lactose	160 mg
Polyvinylpyrrolidone	15 mg
Colloidal silicic anhydride	1 mg
Magnesium stearate	2.5 mg
Microcrystalline cellulose s.q.f.	500 mg

Thus, the amount of the compound of formula I, or an acid addition salt thereof, administered to a patient to treat an infection caused by fungi or yeasts on a daily dosage basis amounts to from about 100 mg to about 800 mg. For topical application to treat infections of the skin 0.1 to 5 % of the compound of formula I, or an acid addition salt thereof, in the pharmaceutical carrier is preferably used.

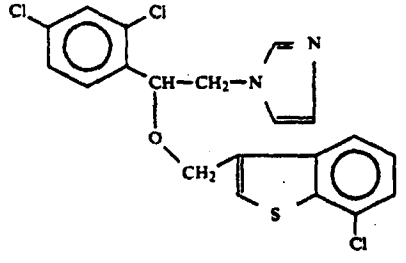
Also the compounds of the present invention, can be used to treat crop diseases caused by fungi or yeasts. The compounds can be administered by watering, atomizing, spraying or dusting, and also in the form of a powder, cream, paste or spray at the rate of 0.1 to 15 kg per hectare.

While the invention has been illustrated and described as embodied in 1H-imidazole derivative compounds and pharmaceutical compositions containing the same for treating infections caused by fungi and yeasts in humans and pets and in crops, it is not intended to be limited to the details shown, since various modifications and structural changes may be made without departing in any way from the spirit of the present invention.

Without further analysis, the foregoing will so fully reveal the gist of the present invention that others can, by applying current knowledge, readily adapt it for various. applications without omitting features that, from the standpoint of the prior art, fairly constitute essential characteristics of the generic or specific aspects of the invention.

We claim:

1. A 1H-imidazole derivative compound of formula I:



(I)

or a nontoxic addition salt thereof.

2. A pharmaceutical composition for treating infections caused by fungi or yeasts in humans and pets, comprising said compound of claim 1 in an effective amount and in combination with a pharmaceutically acceptable carrier.

3. A pharmaceutical composition according to claim 2, in dosage unit form including 100 to 800 mg of said compound.

4. A pharmaceutical composition according to claim 3 for topical application, wherein said compound is present in a concentration from 0.1 to 5 %.

5. A pharmaceutical composition composed of 0.1 to 5 % by weight of said compound of claim 1 in a pharmaceutically acceptable carrier, said compound being present in an amount of from 100 to 800 mg.

6. Method of treating infection caused by fungi or yeast in humans and pet animals, comprising administering an effective amount of the composition according to claim 2.

7. Method of claim 6, wherein said effective amount comprises a daily dose of 100 to 800 mg of said compound.

8. Method of claim 6, wherein said administering comprises oral, injection, rectal, vaginal or topical route administering.

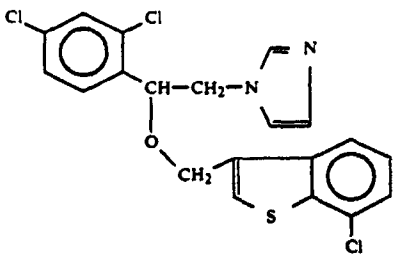
9. Method of treating disease caused by fungi or yeast in crops, comprising applying onto or within the locus of said crops, an effective amount of a compound of claim 1 in combination with carrier means.

10. Method of claim 9, wherein said effective amount comprises 0.1 to 15 kg per hectare of soil.

11. Method of claim 9, wherein said applying comprises watering, atomizing, spraying, dusting or pasting.

12. Compound according to claim 1, wherein said acid addition salt is a nitrate salt.

13. A pharmaceutical composition for treating fungal and yeast infections in humans and pets, comprising 100 to 800 mg of a member selected from the group consisting of a 1H-imidazole derivative compound of formula I:



(I)

and nontoxic addition salts thereof in a pharmaceutically acceptable carrier.

14. A pharmaceutical composition according to claim 13, wherein said nontoxic addition salts include a mononitrate addition salt of said 1H-imidazole derivative compound.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
CARLOS HUMBERTO PALACIO EASTMAN
Apoderado

ASUNTO	Radicación	05058715
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	No 5 9 8 0
	Folios	107

Patente de Invención ☐ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☐ Cap. I ☐ Cap. II ☐

No. Sol. Internacional PCT/EP2003/014422
Fecha de Presentación Internal. 2003/12/17

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 18 a 31

Reivindicaciones: Folios 55 a 58

Prioridad: Fecha: 2002/12/18, País: EP, Número: PCT/EP02/14488.

2. Objeto de la invención

- Título de la solicitud: COMPOSICIONES VAGINALES DE SERTACONAZOL.
  Número de folio: 1

El problema planteado en esta solicitud es la necesidad de composiciones útiles monodosis mucoadhesivas para el tratamiento de la candidiasis vulvovaginal.

Para solucionar este problema técnico la solicitud en estudio proporciona una composición de sertaconazol.

Clasificación Internacional de Patentes (IPC.): A61K9/00

3. **De la solicitud de Patente**

4. **Unidad de invención** *(artículo 25 D 486)*
Reivindicaciones 21 - 24: Se refiere a un pack de aplicación vulvar de sertaconazol. Los componentes del pack (crema concentrada o gel concentrado de uso interior, envase, aplicador, crema convencional de uso exterior, tubo, instrucciones, etc.) pertenecen a diferentes campos técnicos o a varias invenciones de manera que no dan cabida al principio de unidad de invención.

5. **Excepción a la patentabilidad** *(artículo 20 D486 literal a)-d)*
Reivindicaciones 26-27: Se refiere a un procedimiento para el tratamiento de la candidiasis vulvovaginal por lo tanto no se acepta según la legislación vigente.

6. **Reivindicaciones relativas a un uso o a un segundo uso** *(artículos 14 y 21 D 486)*
Reivindicación 25: Se refiere al uso de la composición para la fabricación de una forma de administración por lo tanto no se aceptan según la legislación vigente.

7. **Determinación del Estado de la Técnica**

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2002/12/18

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D_1	WO 99/13862	A PHARMACEUTICAL COMPOSITION FOR TREATING DYSMENORRHEA AND PREMATURE LABOR	1999/03/25
D_2	US 5135943	1H-IMIDAZOLE DERIVATIVE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME	1992/08/04

8. **Análisis de patentabilidad (artículo 14 D486)**

Nivel inventivo *(artículo18 D486)*

La presente Solicitud de Patente reivindica:

Reivindicaciones 1 - 20: Composición vaginal mucoadhesiva de dosis única en crema o gel que comprende:

a) sertaconazol o sertaconazol nitrato 2-10%
b) excipientes lipófilos 10-40%.
c) excipientes mucoadhesivo.
d) uno o más conservantes 0.01-0.3 %.

Dicha composición se ve afectada por los siguientes documentos del Estado de la Técnica:

D_1 que enseña una composición con un principio activo en un vehículo bioadherible, preferiblemente en policarbofil. Enseña la administración local de un agonista β-adrenérgico para tratar o prevenir la dismenorrea o la labor prematura. Usar esta composición provee suficientes niveles locales del principio activo para proveer eficacia terapéutica y evita muchos efectos adversos.

D_2 que enseña composiciones conteniendo sertaconazol o sertaconazol nitrato (cl 13), que pueden ser preparadas en forma sólida, semisólida, liquida, tabletas cubiertas, cápsulas, polvos, supositorios, suspensiones, cremas, lociones, ungüentos y similares. Por ruta rectal intrauterina vaginal como ovulo, tableta vaginal, ungüento, crema, etc, en rangos de 0.1-15% por peso de la composición.

TABLA 1		
CARACTERÍSTICAS REIVINDICADAS	**D_1**	**D_2**
Composición vaginal	**SI** F 84 ln 20, F 89 ln 28-33, F 93 R7, F 94 R16	**SI** F 102 cl 14
dosis única	**SI** F 83 ln 22, 27, F 90 estudio tabla 2, folio 92 tabla 4	**SI** F 102 reiv 3
crema o gel,	**SI** F 84 ln 18, F 87 ln 4	**SI** F 102 cl 14
PRINCIPIO ACTIVO: sertaconazol o sertaconazol nitrato 2-10%	**PARCIALMENTE** F 81, abstract, F 89 ln 28-33	**SI** F 97 cl 3

La única **diferencia con D_1** es que esta solicitud **posee como principio activo sertaconazol o su sal** pero esta diferencia no parece conceder un efecto técnico inesperado ya que de la misma forma como lo indica la solicitud, D1 también ofrece las mismas ventajas conferidas por la composición mucoadhesiva como lo son: el hecho de que un principio activo se mantenga en la mucosa por varios días con administración en unidosis y eventos secundarios sistémicos irrelevantes (ver anterioridad página 8 ln 20-24, página 10 ln 2-4, 6-7, página 13 ln 28-33).

No puede determinarse un efecto técnico que logre la diferencia con la anterioridad encontrada ya que a pesar de que se muestra en la tabla I la concentración mínima inhibitoria del sertaconazol contra el bifonazol y econazol superando a la mayoría de los antifúngicos imidazólicos como fungicida frente a

C. albicans y que se muestra en la página 11 folio 28 un estudio de disolución y permeación transdermica in Vitro del sertaconazol nitrato en comparación con una crema convencional de sertaconazol nitrato al 2%, comprobándose que a los 5 dias la cesión del principio activo es de 81%, éstos datos no conceden superioridad contra la anterioridad ya que son las mismas ventajas obtenidas por D1 e igualmente las ventajas del sertaconazol son inherentes al compuesto como tal, lo cual es demostrado también por los estudios de D2 (folios 99-102) y no a la composición que se pretende proteger en esta solicitud estando previamente todos sus componentes o características esenciales sugeridas en D1 para obtener las ventajas que se lograron.

El problema técnico objetivo de la invención podría redefinirse en: "como lograr una composición alternativa de sertaconazol mucoadhesiva a lo previamente conocido".

Por consiguiente resultaría obvio el diseño de este tipo de composiciones para un experto en la materia ya que D2 enseñaba composiciones de sertaconazol en crema y gel con los mismos porcentajes de la solicitud, vía vaginal y dosis única.

En conclusión la solicitud no tiene nivel inventivo.

9. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones *afectadas*	Requisito que afecta
D_1	WO 99/13862	1-20	NIVEL INVENTIVO
D_2	US 5135943	1-20	NIVEL INVENTIVO

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 22 MAYO 2009

CONCEPTO TÉCNICO No. 258	**EXAMINADOR TÉCNICO** Código No. 202087

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EXAMEN TÉCNICO DE FONDO			
Nº Radicación	05-058715	Fecha de presentación	16/06/2005
Nº Solicitud Internacional	PCT/EP2003/014422	Fecha Solicitud Internacional	2003/12/17
Nº Prioridad	PCT/EP02/14488	Fecha de Prioridad	2002/12/18

Palabras clave	

CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA
A61K9/00; A61K9/06; A61K31/4178; A61K47/32; A61K9/00; A61K9/06; A61K31/4164; A61K47/32

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES			
NO20053398	IS7928	AU2003290071	
MXPA05006505	HR20050574	AT400270	
MA27498	CN1726032		
KR20050084294	CA2509830		
JP2006513182	BR0317555		
Patente Original	Wo 2004/054576		

BASES DE DATOS CONSULTADAS
EPOLINE ESPACENET

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Oficina	Fecha	Reiv. afectadas

ANTERIORIDADES ENCONTRADAS		
Documento	*Relevancia*	*Reiv. afectadas*
WO 99/13862	PARTICULAR (Y)	**1-20**

LITERATURA NO PATENTES		
Documento	Relevancia	Reiv. afectadas

Observaciones

Fecha del examen	03/2009

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Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION NO 44296

Por la cual se niega una patente de invención

Rad. PCT/05-58715

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 4, numeral 5 del decreto 2153 de 1992, y

CONSIDERANDO:

PRIMERO: Que la solicitud de patente de invención titulada "COMPOSICIONES VAGINALES DE SERTACONAZOL", que corresponde a la solicitud internacional PCT/EP 2003/014422 de fecha 17 de diciembre del 2003, fue radicada en esta Superintendencia el 16 de junio del 2005 bajo el número 05058715, para que se dé comienzo a la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un período de treinta días adicionales.(...) Si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente".*

CUARTO: Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 81 a 107 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del mismo, por lo cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.

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Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION № 44296

Por la cual se niega una patente de invención

Rad. PCT/05-58715

RESUELVE:

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPOSICIONES VAGINALES DE SERTACONAZOL", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Carlos Humberto Palacio Eastman, en su calidad de apoderado de Ferrer Internacional S.A., o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 31 AGO. 2009

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

GUSTAVO VALBUENA QUIÑONES

Doctor
CARLOS HUMBERTO PALACIO EASTMAN
Carrera 7 Nº 71 – 21, Torre B, Piso 4.
Bogotá D.C.

202021