

Clarke, Modet & C<sup>o</sup>

COLOMBIA

103

SEÑORES  
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
DIVISIÓN DE NUEVAS CREACIONES  
E.S.D

SUPERINDUSTRIA Y COMERCIO  
Radicacion : 02102954 00000003 Folios: 2  
Fecha (AMD): 2004-09-28 16:15:27  
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION  
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REF EXPEDIENTE No. : **02102954**  
SOLICITANTE : **ZONAGEN, INC**  
SLICITUD FECHA : **NOVIEMBRE 13, 2002**  
PATENTE : **TERAPIA DE COMBINACIÓN PARA MODULAR LA  
RESPUESTA SEXUAL HUMANA**

**ASUNTO: SOLICITUD ESTUDIO DE FONDO**

DILIA RODRÍGUEZ D'ALEMAN, en mi condición de apoderada de la Sociedad solicitante, por el presente escrito atentamente solicito a Usted que habiéndose surtido la publicación de la presente solicitud, en la Gaceta de la Propiedad Industrial No.539 de fecha Abril 30, 2004 se proceda con el estudio de Fondo.

Para tal fin me permito anexar la tasa correspondiente No. 04.72399.

Agradezco continuar con el presente trámite.

Señor Jefe,



DILIA RODRÍGUEZ D'ALEMAN  
T.P.No. 20824 del CSJ

P-461

MR

104 104

SUPERINDUSTRIA Y COMERCIO

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MIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 72,399  
FECHA : SEPTIEMBRE 10 DE 2004

\*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE               | TIPO PAGO    | BANCO         | CUENTA      | No. PAGO | FECHA PGO  | Vr. PAGO     |
|---------------------------|--------------|---------------|-------------|----------|------------|--------------|
| CLARKE MODET Y CO. COLOMB | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 23291592 | 10/09/2004 | 3,568,000.00 |

\*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. | RENTISTICO              | CONCEPTO                             | TOTAL CONCEPTO |
|-------|-------------------------|--------------------------------------|----------------|
| 1     | 50005-01-01 SOLICITUDES | 95 EXAMEN DE PATENTABILIDAD DE INVEN | 353,000.00     |
|       |                         | TOTAL :                              | \$ 353,000.00  |

SON: TRESCIENTOS CINCUENTA Y TRES MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

**DIVISION DE NUEVAS CREACIONES**

**RADICACIÓN EXPEDIENTE No. 02-102954**

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION**  
**FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 539, DE**  
**FECHA 30 DE ABRIL DE 2004, EL TERMINO HABIL SEÑALADO POR LA LEY**  
**EXPIRA EL 02 DE AGOSTO DE 2004.**

**NOTA:** Dentro del plazo de los seis (6) 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 de la Decisión 486/2000.

**SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.**

**SI** \_\_\_\_\_ **NO**   X   \_\_\_\_\_

# United States Patent [19]

Virag

[11] Patent Number: 5,145,852

[45] Date of Patent: Sep. 8, 1992

US005145852A

## [54] VASO-ACTIVE MEDICAMENT TO TREAT IMPOTENCE

[76] Inventor: Ronald Virag, 5, avenue Clodoald, F-92210 Saint-Cloud, France

[21] Appl. No.: 550,779

[22] Filed: Jul. 10, 1990

[51] Int. Cl.<sup>5</sup> ..... A01N 43/58; A01N 43/60; A01N 43/42; A01N 43/50

[52] U.S. Cl. .... 514/253; 514/255; 514/256; 514/280; 514/307; 514/316; 514/386; 514/739; 514/929

[58] Field of Search ..... 514/307, 530, 280, 573, 514/253, 690, 248, 535, 542

## [56] References Cited

### U.S. PATENT DOCUMENTS

4,311,707 1/1982 Birnbaum et al. .... 514/530  
4,801,587 1/1989 Voss et al. .... 514/248

## FOREIGN PATENT DOCUMENTS

0346297 5/1989 Italy .

## OTHER PUBLICATIONS

CA: 109(19)—163408 (Nov. 1988).

Primary Examiner—Leonard Schenkman

Assistant Examiner—T. J. Criares

Attorney, Agent, or Firm—Browdy and Neimark

## [57] ABSTRACT

The invention pertains to the field of vasoactive medicines.

The vasoactive medicine, of the type composed of a combination of main active ingredients with papaverine, is characterized by the fact that it comprises at least one alpha blocker and a phosphodiesterase inhibitor representing a total of 5 to 20% by weight of the papaverine.

Application to treatment of impotence in men.

7 Claims, 1 Drawing Sheet

+ Bloqueador α  
Dopaminérgico  
p<sup>r</sup> tratar impotencia en hombres.  
fenibutina  
apomorfina  
(p.e. 012)

## VASO-ACTIVE MEDICAMENT TO TREAT IMPOTENCE

This invention pertains to a vasoactive medicine that is applicable in particular to the treatment of impotence in men.

A considerable amount of research work in this field has made it possible, first of all, to identify the mechanism and the various phases of erection, then to define the necessary properties, particularly vasoactive, of active and tolerable products. In particular, multiple clinical studies have made it possible to select papaverine and to clarify how it works, then to combine it with alpha blocking products such as phenoxybenzamine and phentolamine (BRINDLEY GS—Cavernosal Alpha-blockade, a new techn[ique] for investigating and treating impotence—BRIT. J. P[S]YCHIATRY 143, 1983). Prior work by the applicant has also made possible the detailed study of isolated and/or potentiating activity of numerous vasoactive substances (cf. "Papaverine et Impuissance: la voie pharmacologique" [Papaverine and Impotence: the pharmacological way] Ronald Virag, EDITIONS DU CERI, Paris, 1987) primarily the combination of the two above alpha blockers and papaverine.

The clinical use of the discovery has developed at the same time, with the use of two methods, i.e., perfusion and self-injections by the patient immediately before the sexual act (see the above-cited work).

However, the study of the initial results observed leads to two findings:

1. That no more than 50% of all impotent patients could be treated with papaverine alone, with the combination of papaverine and alpha blocker or with prostaglandin alone (PGE<sub>1</sub>);
2. Regardless of the product, in 10 to 30% of the erections produced, there is a risk of blocking of the erection, which varies depending on the drug used, the dose injected and the etiology of the impotence, with the risk that this prolonged erection will lead to a real priapism.

Considering the data collected through experimental studies and clinical results, the ideal product to be injected would be able to trigger a complete erection in 100% of the patients with no risk of blocked erection, and with no general clinical effects: it was found that none of the products used or tested to date corresponds to such a description.

Considering the local conditions under which the erection occurs, the applicant indeed determined that, to have this maximum effectiveness, the ideal product should be active in the different phases of the erectile cycle, and consequently that such effectiveness could only be achieved in the current state of available products through a combination of several main active ingredients, with the specific effects of each product making it possible to extend and reinforce the effects of the others.

In accordance with the invention, the vasoactive medicine is primarily composed of papaverine, in combination with main active ingredients containing at least one alpha blocker and one phosphodiesterase inhibitor, as well as, advantageously, a PGE<sub>1</sub>-type prostaglandin, a dopaminergic agent and an atropinic agent, with the alpha blocker itself being composed of one part alpha<sub>1</sub> and one part alpha<sub>2</sub>, these ingredients representing a

total of 5 to 20% by weight of the papaverine in an injectable aqueous solution.

FIG. 1, the sole FIGURE, is a graph showing the results of clinical tests set forth in Example 2, below.

It is known that papaverine acts as a myorelaxer of the smooth musculature through direct action on cyclical AMP whose inactivation it prevents. Secondary pharmacological actions were noted but were not demonstrated in the erectile tissue: discrete alpha blocking action[,] positive ganglioplegic action.

Alpha<sub>1</sub> blockers act by inhibiting alpha-adrenergic transmission at the post-synaptic level;

Alpha<sub>2</sub> blockers act by inhibiting this transmission at the presynaptic level;

The local mechanism that controls the action of dopamine or dopaminergic drugs on the erectile tissue has not to date been clarified, but the applicant found clinically that the product acts positively on erections;

Atropine has no effects on healthy erectile tissue. The product works by potentiating the action of the other active products on pathological erectile tissue by interfering with the mechanisms that trigger the relaxation of smooth muscle, especially the EDRF (Endothelium Releasing Factor);

Phosphodiesterase (dipyridamol type) inhibitors work by prolonging the action of the other products as well as through their anti platelet aggregation action. Locally, they prevent the risk of intracavernous blood thrombosis when the erection is prolonged;

Prostaglandin PGE<sub>1</sub>, or a similar material, acts as a relaxant for the smooth musculature at an earlier stage than the papaverine, whose action it completes, the two products potentiating each other.

Consequently, each of the active products in the medicine according to the invention not only has its expected effects on a given stage of the erection mechanism, but, furthermore, due to this effect itself, it prepares and facilitates, even accentuates, the effects of the other active products, while inhibiting harmful side effects.

The following examples, provided solely on an illustrative and non-restrictive basis, demonstrate the above-mentioned effects and provide a clearer understanding of the advantage and scope of the invention.

### EXAMPLE 1

#### Compounds

The clinical studies described below were conducted based on the following three compounds, in comparison with known products.

a) Compound N, comprising the following per 1 ml of injectable solution:

papaverine 20 mg  
ifenprodil tartrate 0.75 mg (alpha<sub>1</sub> blocker)  
atropine 0.025 mg (anticholinergic)  
yohimbine 0.075 mg (alpha<sub>2</sub> blocker)  
dipyridamol 0.25 mg (phosphodiesterase inhibitor)  
piribedil 0.225 mg (dopaminergic)

b) Compound P comprising, in addition to the derivatives mentioned above for compound N, 33 µg of alprostitil (Prostaglandin PGE<sub>1</sub>) per ml of injectable solution;

c) Compound X containing the following per 1 ml of injectable solution:

papaverine 20 mg  
phentolamine 1 mg (alpha blocker)  
PGE<sub>1</sub> 33 µg (prostaglandin)

effecto  
de cpts  
dopamin  
ergics  
concord

Blocked  
α

dipyridamol 0.25 mg (phosphodiesterase inhibitor)

### EXAMPLE 2

#### Clinical Tests

The study to test the different products among themselves was conducted by injecting 0.2 ml of the product tested per 100 ml of flaccid penis, a volume calculated in a manner known in and of itself (cf. the above-cited work). Ten minutes after this injection, patients were exposed to visual sexual stimulation (VSS) for 10 minutes.

Each product was tested by series randomization of 23 to 30 patients.

The volume of the penis was measured every three minutes using a chart; rigidity was measured using a specialized device known as a rigidimeter, calibrated at 0 to 200 PR (Penrig) units, in which the most important values are as follows:

- up to 35 PR: no signification variation;
- 35 to 50 PR: significant tumescence with considerable change in volume;
- 55 to 75 PR: beginning of rigidity;
- 75 PR and above: limit of rigidity needed for penetration;
- 100 PR and above: normal rigidity corresponding to complete venous blockage.

The percentage of patients in whom a complete erection (rigidity of over 75 PR) was produced for more than half of the visual stimulation time and which lasted at least one minute after this stimulation ended is used as a comparative measurement.

The results of this study are illustrated in the accompanying synoptic graph which for each product shows blocks whose height is measured according to a graduated scale of 0 to 100% of total erection. Each block also shows the percentage of non-lasting complete erection after VSS (A) and lasting at least one minute after VSS (B), as well as the number n of subjects who underwent the test. All of the measurements were taken after a local intra-cavernous injection of 0.2 ml of product, namely: a control or placebo of physiological serum (1), 40 mg/ml of papaverine (2), 40 mg of papaverine combined with 0.5 mg of phentolamine per ml (3), 33 µg/ml of PGE<sub>1</sub> (4), and compounds N (5), P (6) and X (7) according to the invention.

In reference to this graph, the results demonstrate that the three compounds N, X and P respectively produced 82, 75 and 91% complete erections according to the identified criteria. Conversely, the placebo, papaverine, prostaglandin alone and the combination of papaverine and phentolamine respectively produced 7, 22, 52 and 54% complete erections. It can be noted that the compounds according to the invention yielded these results with half the content of papaverine.

Another factor that must be considered is the capacity of a product to trigger a prolonged erection, which is a risk when it lasts longer than three hours. The presence of atropine and the phosphodiesterase inhibitor allows the blocking power of compounds N and P to be lower than that of the other combinations most effective in this respect, namely, papaverine, phentolamine, which is an additional advantage over products already used in this field.

### EXAMPLE 3

#### Clinical Studies

A total of 264 impotent patients underwent self-injection treatment with the compounds according to the invention.

After preliminary tests, one or two intracavernous injections were performed per week, prior to the sexual act. 221 of these patients (4.12%) [sic] suffered from organic impotence; 136 (51.51%) would have been advised to have surgery without the medication; 64 (24%) were recommended for penile prosthesis implants.

Among the 230 patients regularly studied: 19 were classified as obtaining poor results, 5 were unclassifiable due to insufficient use of the method, 12 yielded average results (sex life resumed in a satisfactory manner), 176 were considered good and 17 as very good. For 205 of these 230 patients (i.e., 89.13%) normal sexual activities were resumed. In 8.69% of the patients, recovery was complete, treatment was discontinued; for 12.6% injections were not used in over 50% of the sexual acts; and finally, in 42.6% of the cases, the patient was entirely dependent on the treatment. These results were obtained with no general or local complications outside of 5.8% hematomas at the point of injection, considering that, unlike other injected products, a compound according to the invention is completely painless when entering the cavernous body.

Of course, this invention was described and represented only on an explanatory and non-restrictive basis, and any useful modification, primarily in the area of technical equivalencies, may be made without departing from its scope.

What is claimed is:

1. A pharmaceutical composition applicable to the treatment of impotence in men, composed of a combination of main active ingredients with papaverine, wherein said main active ingredients comprise

an alpha blocker selected from the group consisting of phentolamine, ifenprodil, yohimbine and mixtures thereof; dipyridamol as a phosphodiesterase inhibitor; atropine as an anticholinergic; and piribedil as a dopaminergic, or a prostaglandin selected from the group consisting of PGE<sub>1</sub> and alprostitil, or both said piribedil and said prostaglandin,

all of said main active ingredients representing a total of 5 to 20% by weight of the papaverine.

2. A composition according to claim 1, having per 1 ml of injectable solution: papaverine 20 mg; ifenprodil tartrate 0.75 mg as an alpha<sub>1</sub>-blocker; yohimbine 0.075 mg as an alpha<sub>2</sub>-blocker; atropine 0.025 mg as said anticholinergic; piribedil 0.225 mg as said dopaminergic.

3. A composition according to claim 1 having per 1 ml of injectable solution: papaverine 20 mg; ifenprodil tartrate 0.75 mg as an alpha<sub>1</sub>-blocker; yohimbine 0.075 mg as an alpha<sub>2</sub>-blocker; atropine 0.025 mg as anticholinergic; piribedil 0.225 mg as said dopaminergic; alprostitil 33 µg as said prostaglandin.

4. A composition according to claim 1, having per 1 ml of injectable solution: papaverine 20 mg; phentolamine 1 mg as said alpha blocker; dipyridamol 0.25 mg as said phosphodiesterase inhibitor; alprostitil 33 µg as said prostaglandin.

105-108

Blocker

Dopaminergic

5. A composition according to claim 1, wherein said alpha-blocker is a mixture of ifenprodil tartrate and yohimbine.

6. A composition according to claim 1, comprising papaverine, dipyridamol atropine, ifenprodil tartrate, yohimbine and piribedil.

7. In a pharmaceutical composition having a vasoactive effect applicable to the treatment of impotence in men, composed of a combination of main active ingredients with papaverine, the improvement consisting of:

an injectable solution having a composition for 1 ml of said solution of

papaverine approximately 20 mg; ifenprodil tartrate approximately 0.75 mg as an alpha<sub>1</sub> blocker; atropine approximately 0.025 mg as an anticholinergic; yohimbine approximately 0.075 mg as an alpha<sub>2</sub> blocker; dipyridamol approximately 0.25 mg as a phosphodiesterase inhibitor; piribedil approximately 0.225 mg as a dopaminergic; and alprostil approximately 33 µg as a prostaglandin.

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# United States Patent [19]

Naftchi

[11] Patent Number: 4,742,054

[45] Date of Patent: May 3, 1988

[54] TREATMENT OF MAMMALS SUFFERING FROM DAMAGE TO THE CENTRAL NERVOUS SYSTEM

[76] Inventor: Nosrat E. Naftchi, 389 Forest Ave., Teaneck, N.J. 07666

[21] Appl. No.: 691,830

[22] Filed: Jan. 16, 1985

## Related U.S. Application Data

[63] Continuation of Ser. No. 443,915, Nov. 23, 1982, abandoned.

[51] Int. Cl.<sup>4</sup> ..... A61K 31/55; A61K 31/495; A61K 31/52; A61K 505

[52] U.S. Cl. .... 514/215; 514/255; 514/263; 514/269; 514/284; 514/288; 514/401; 514/414; 514/634; 514/964; 424/449; 424/457; 424/468

[58] Field of Search ..... 514/183, 222, 263, 401, 514/282, 284, 288, 269, 414, 255, 964, 215, 45, 46, 634; 424/449, 457, 468

## [56] References Cited PUBLICATIONS

Goodman and Gilman, 6th ed., pp. 797-799, 632-639, 483-484.

Chem. Absts., 84:258z, 1976; 100:168888c, 1984; 101:2122u, 1984; 98:192204n, 1983.

Primary Examiner—J. R. Brown

Assistant Examiner—John W. Rollins, Jr.

Attorney, Agent, or Firm—Barry G. Magidoff

## [57] ABSTRACT

A method, and compositions, for treating an animal with an injured spinal cord, causing loss to sensory function and motor control, to regain such function and control. The method comprises the administration of at least 1  $\alpha_2$ -adrenergic receptor agonist or a serotonergic receptor agonist or a dopaminergic receptor agonist, and preferably a combination with an anti-desensitization agent, such as a xanthine, a  $\beta$ -adrenergic receptor agonist or a vascular skeletal muscle dilator. The composition comprises at least 1 receptor agonist and a second compound acting in conjunction therewith or preventing desensitization thereof.

23 Claims, No Drawings

agonists receptor neural feedback  
dopaminergic  
opener for

do

Agonistas:

dopaminérgico  
 $\alpha$  2 adrenérgico  
o serotoninérgico

como p. ej. APOMORFINA

} tienen efectos en

p. ej. clonidina tiene como efecto en  
la  $\downarrow$  de la P. sanguínea.

P' contrarrestar esos efectos en se  
admiran conjunta/:

— un antagonista de p. ej. el agonista del receptor

$\alpha$  adrenérgico

— agentes bloqueantes  $\alpha$  2 como p. ej. FENTOLAMINA

# TREATMENT OF MAMMALS SUFFERING FROM DAMAGE TO THE CENTRAL NERVOUS SYSTEM

This is a continuation of application Ser. No. 443,915, filed Nov. 23, 1982, now abandoned.

This application is directed to a treatment method for mammals suffering from traumatic injury to the spinal cord, or from certain central nervous system diseases, the treatment comprising the timely administration of an  $\alpha_2$ -adrenergic receptor agonist. More particularly, this invention provides a method of treatment for mammals utilizing a neural receptor agonist, such as clonidine in combination with other materials which are synergistic to the activity of, e.g., clonidine, or which counteract any tendency to sub-sensitivity or tolerance of the primary treatment material. This application is further directed to a therapeutic composition useful in such treatment.

In the past, clonidine has been known to have a variety of effects. Primarily, it was known to have pronounced blood pressure-lowering properties with side effects of sedation and depression. As such, the drug had been indicated for use as a hypertension remedy. However, previously published reports have also referred to the activity of clonidine to reduce plasma renin activity, to decrease insulin secretion, and to increase the plasma level of the growth hormone in mammals. Its therapeutic uses, in addition to the treatment of hypertension, includes the treatment of migraine, glaucoma, and, very recently, as an aid in the treatment of opiate addicts to avoid severe withdrawal symptoms. In the majority of these uses, it has previously been proposed that the mechanism for the activity of clonidine is based upon its activity as an  $\alpha$ -adrenoceptor agonist; see, for example, \*TIPS, Volume 2, No. 7, pages 194-6, July, 1981.

\*Trends in Pharmacological Sciences

Previously, it has generally been assumed that traumatic injury to the spinal cord, especially one which effectively neurologically severs the cord, is, in mammals, for all practical purposes, irreversible. Some useful effect has been obtained by the treatment of an injured mammal with methyl prednisolone sodium succinate (MP) or with naloxone, to provide some relief and to prevent more extensive damage as a result of the anti-oxidant properties of these materials. In addition, and perhaps more importantly, an increase of regional blood flow and perfusion pressure is caused by naloxone (an opiate antagonist), thyrotropic releasing hormone (TRH), and  $\epsilon$ -aminocaproic acid ( $\epsilon$ -ACA). Methyl prednisolone has an anti-inflammatory effect. Unfortunately, if these drugs are not administered almost immediately, i.e., within the first hour after the initial injury, their effect is substantially nil. Further, naloxone may have a hyperalgesic effect, and the methyl prednisolone may reduce immune reaction and thus increase the possibility of infection.

It has now been discovered that by the use of a neural receptor agonist, e.g., clonidine, many of the undesirable aftereffects of traumatic spinal injury can be alleviated or completely eliminated, and, if treatment is commenced sufficiently early, at least some restoration of normal neural function with the attendant control over muscle activity, is attainable.

In accordance with this, invention, a mammal having a major spinal cord injury is treated to control autonomic dysreflexia, clonus and spasticity, and to return at least partial neural function, by the administration to the

injured mammal of a neural receptor agonist, including an  $\alpha_2$ -adrenergic, or a dopaminergic, or a serotonergic receptor agonist. The, e.g.,  $\alpha_2$ -adrenoceptor, agonist is most preferably initially administered immediately, i.e., within one hour after the injury to the spinal cord occurs, or even prior to the injury. However, dramatic effectiveness is obtainable even when treatment is not commenced until as much as six years after the original traumatic injury occurred.

It is understood that many of the presently known  $\alpha_2$ -adrenergic, dopaminergic or serotonergic receptor agonists, have direct physiologic effects on the mammal being treated, usually during the early stages of treatment before tolerance develops. Such physiologic effects are often contraindicated for the mammal being treated, e.g., the hypotensive effect of clonidine. It is thus often necessary to also administer a physiologically active antagonist to counteract any such undesirable physiologic side effects. The antagonist can be administered simultaneously or sequentially, after the physiologic side effects become manifest.

When treatment commences promptly after an injury, for a better titration of the drug and control of blood pressure, the initial administration of the neural receptor agonist is preferably intravenously. An antagonist of, e.g. the  $\alpha_2$ -adrenergic receptor agonist, or  $\alpha_2$ -blocking agents, must be available to counteract any undesirable side effects of the  $\alpha_2$ -adrenergic receptor agonist, for example, the blood pressure decrease caused by clonidine. Such antagonists include, e.g., for clonidine, for example, phenolamine, yohimbine and tolazoline, and piperoxane. Angiotensin II, in addition to its blood pressure increasing activity, may have a synergistic effect in combination with clonidine with respect to its primary purpose of providing neural function return.

Compounds such as 5-fluorodeoxyuridine (FUDR) and 3,4 dehydroprolene may also be included as part of the therapy to prevent or reduce glial and fibroblastic scar formation, respectively. These compounds can be topically applied, for example, in combination with dimethylsulfoxide (DMSO).

It is preferred that the, e.g.,  $\alpha_2$ -adrenergic receptor agonist, not be administered until the vital signs have stabilized after the initial spinal trauma shock. In the early stages, within the first, e.g., three hours after the initial shock, the previously known therapeutic materials such as naloxone, methyl prednisolone, dopamine or other materials, which have antiinflammatory and blood-flow increasing effects, should also be carefully administered, together with, or immediately before or after the neural receptor agonist. In addition to their specific effects, they may also act to accelerate the effects of the primary agent. In addition, any mechanical obstruction or pressure in the region should be surgically eliminated or restructured.

Useful  $\alpha_2$ -adrenergic receptor agonists, include iminoimidazolines, such as tiamenidine and clonidine, and especially of the type:

111  
dopa

Blockade  
2

112 112

0.4 mg clonidine and 2.5 mg bromocriptine mesylate  
 0.5 mg clonidine and 3.5 mg bromocriptine mesylate  
 0.6 mg clonidine and 4.0 mg bromocriptine mesylate  
 0.9 mg clonidine and 6.0 mg bromocriptine mesylate  
 0.15 mg clonidine and 6.0 mg bromocriptine mesylate  
 0.9 mg clonidine and 1.25 mg bromocriptine mesylate

Such administered unit dosage forms can also include from 100 to 250 mg of a material, e.g. as theophylline; similar combinations can be prepared for transdermal use. At least 200 mg of theophylline is preferred if the mammal is able to tolerate that material in its digestive system. The latter problem is avoided in transdermal administration.

Where the injured mammal is initially unconscious, it is, of course, generally advisable to make the first administration intravenously, generally in either a saline or glucose solution. The  $\alpha_2$ -adrenergic, dopaminergic or serotonergic receptor agonist should be administered slowly over a one hour period, each period commencing at six-hour intervals, i.e., four administrations per day.

The preferred method of continuing administration of the active pharmacologic agents of this invention is transdermally or by oral ingestion of a sustained release form of medicament. The production of such sustained release forms is well known and need not constitute any part of this invention. For example, a common form of sustained release tablet is formed by admixing the pharmacologically active ingredients with a composition comprising a higher aliphatic alcohol, such as an 8-to-18 carbon atoms alkanol, with a selectively hydrated hydroxyalkyl cellulose compound.

It is of course possible to package the active pharmacologic agents of this invention into a capsule, or the like, wherein different portions of the active agents can be released at different, predetermined times.

Finally, it has been found that the primary therapeutic agents of this invention, including the  $\alpha_2$ -adrenergic receptor agonist and the serotonergic receptor agonist and the dopaminergic receptor agonist, can provide a certain degree of precautionary protection against subsequent injury, i.e., almost a prophylactic effect. It has been found that the administration of a dosage of the primary therapeutic agent, prior to the receiving of a traumatic injury, further increases the changes of ultimately recovering substantially complete function of the lower limbs, and also decreasing the time before such complete recovery is attained. Such precautionary administration could usefully be carried out before placing the mammal in a potentially dangerous situation.

It is also known that a problem affecting such traumatically injured mammals with spinal cord lesions is the loss of the normal ability had by warm-blooded animals to maintain a proper body temperature over a relatively wide range of ambient temperatures. There is apparently a loss of control and receptivity between the thermal receptors below the lesion and the hypothalamus. Mammals treated according to this invention regain this ability, including the ability to perspire below the lesion.

The patentable embodiments which are claimed are as follows:

1. A method for treating a mammal having an injured spinal cord with the resultant loss of motor and sensory function and the concomitant loss of muscular control, comprising administering to the mammal at least one neural receptor agonist as the primary therapeutic agent, in a dosage amount and at a dosage rate sufficient

to at least partially restore the lost motor and sensory function as evidenced by a return of motor and sensory functions.

2. The method of claim 1, wherein the receptor agonist is a serotonergic receptor agonist.

3. The method of claim 2 wherein the serotonergic receptor agonist is selected from the group consisting of 5-methoxy-N,N-dimethyl-tryptamine(5-MDT), quipazine, 1-(m-trifluoromethylphenyl)-piperazine, various indoleamines, and 6-chloro-2(1-piperazino) pyrazine.

4. The method of claim 1 wherein the receptor agonist is a D<sub>2</sub>-dopaminergic receptor agonist.

5. The method of claim 4 wherein the dopaminergic receptor agonist is selected from the group consisting of bromocriptine and its salts, apomorphine, piribedil, lergotril, and pergolide.

6. The method of claim 1 wherein the receptor agonist is an  $\alpha_2$ -adrenergic receptor agonist.

7. The method of claim 1 comprising in addition administering an anti-desensitization agent in a unit dosage amount sufficient to maintain the active effect of the primary therapy agent.

8. The method of claim 7 wherein the anti-desensitization agent is selected from the group consisting of xanthines,  $\beta$ -adrenergic receptor agonists and vascular-skeletal muscle dilators.

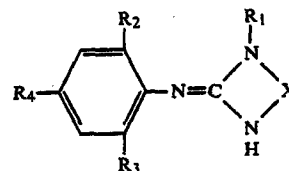
9. The method of claim 1 further comprising the administration of an antagonist to counteract any undesirable physiologic side effect of the primary therapeutic agent.

10. The method of claim 1 wherein there is administered in combination at least two different types of neural receptor agonists selected from the group of types consisting of serotonergic receptor agonists,  $\alpha_2$ -adrenergic receptor agonists, and D<sub>2</sub>-dopaminergic receptor agonists.

11. A pharmacologically active composition useful for treating a mammal having an injured spinal cord with a resultant loss of motor and sensory function, to restore at least partially the lost sensory-motor functions, the composition comprising a unit dosage amount of a primary therapeutic agent selected from the group consisting of an  $\alpha_2$ -adrenergic receptor agonist, a dopaminergic receptor agonist, and a serotonergic receptor agonist, and an anti-desensitization agent.

12. The composition of claim 11 wherein the primary therapeutic agent is an  $\alpha_2$ -adrenergic receptor agonist selected from the group consisting of iminoimidazoles, amino-dihydrothiazines, guanidines and azepines.

13. The composition of claim 12 wherein the  $\alpha_2$ -adrenergic receptor agonist is an iminoimidazoline having the formula:



wherein X is an alkylene group having 2-3 carbon atoms and forming a ring structure, R<sub>1</sub> is hydrogen or lower alkyl group, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, are selected from the group consisting of methyl, ethyl and chlorine; and their nontoxic, pharmacologically acceptable acid addition salts.

DOPAMINERGIC como APOMORFINA

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14. The composition of claim 11 wherein the primary agent is a serotonergic receptor agonist.

15. The composition of claim 11 wherein the primary agent is a dopaminergic receptor agonist.

16. The composition of claim 11 wherein the anti-desensitization agent is selected from the group consisting of xanthines,  $\beta$ -adrenergic receptor agonists and vascular-skeletal muscle dilators.

17. The composition of claim 16 comprising a clonidine and theophylline.

18. The composition of claim 11, in a form suitable for oral administration and comprising in addition a pharmacological carrier material to sustain release of the pharmacologically active agents over a prolonged period after oral ingestion.

19. The composition of claim 18 wherein the pharmacologically active compounds consist of clonidine and theophylline.

20. The composition of claim 11 comprising a unit dosage amount of an  $\alpha_2$  adrenergic receptor agonist having undesirable physiologic side effects and a unit

dosage amount of an antagonist to overcome the side effects.

21. The composition of claim 11 in a form suitable for transdermal administration and comprising in addition a pharmacological carrier material to sustain release of the pharmacologically active agents over a prolonged period after transdermal administration.

22. A pharmacologically active composition useful for treating a mammal having an injured spinal cord with a resultant loss of motor and sensory function, to restore at least partially the lost sensory-motor functions, the composition comprising a unit dosage amount of at least two different types of pharmacologically active neural receptor agonists selected from the group of types consisting of  $\alpha_2$ -adrenergic receptor agonists,  $D_2$ -dopaminergic receptor agonists and serotonergic receptor agonists.

23. The composition of claim 22 comprising clonidine and a hypertensive agent.

\* \* \* \* \*

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## SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

## DIVISION DE NUEVAS CREACIONES

2020

Bogotá, D.C., Septiembre 28 de 2006

Abogada

DILIA MARÍA RODRÍGUEZ D'ALEMÁN

|        |                |            |
|--------|----------------|------------|
| ASUNTO | Radicación No. | 02 102 954 |
|        | Trámite        | 002        |
|        | Evento         | 001        |
|        | Actuación      | 430        |
|        | Oficio No.     | 11197      |
|        | Folios         | 013        |

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

**Título de la solicitud:** "Terapia de Combinación para modular la respuesta sexual humana".

### 1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 4 - 78 y el capítulo reivindicatorio de los folios 79 - 84 de la solicitud.

### 2. Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 - 23 se refieren a una composición que comprende **fentolamina** y **apomorfina**.

La reivindicación 24 se refiere a un método de tratamiento que consiste en administrar una composición.

La reivindicación 25 se refiere a un método de manufactura.

El problema planteado en esta solicitud es la necesidad de una composición para el tratamiento de la disfunción eréctil masculina.

Para resolver este problema técnico la solicitud en estudio proporciona una composición que comprende **fentolamina** y **apomorfina**.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/505 // 45/06.

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No reivindica prioridad de una Solicitud de Patente anterior.

### 3. Excepciones a la Patentabilidad

El artículo 20 de la Decisión 486 establece: *"No serán patentables: d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

La reivindicación 24 se refiere a un método de tratamiento que consiste en administrar una composición.

Se observa que el método de tratamiento de la reivindicación 24 que comprende administrar una composición, no es patentable de acuerdo con la norma citada, que especifica que *los métodos terapéuticos para el tratamiento humano o animal* no son patentables.

En conclusión, el método de tratamiento de la reivindicación 24, que comprende administrar una composición, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486.

### 4. Con respecto a los Art. 28 y 30 de la D 486

El artículo 28 de la Decisión 486 establece: *"La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla. La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información:*

- a) el sector tecnológico al que se refiere o al cual se aplica la invención;*
- b) la tecnología anterior conocida por el solicitante que fuese útil para la comprensión y el examen de la invención, y las referencias a los documentos y publicaciones anteriores relativas a dicha tecnología;*
- c) una descripción de la invención en términos que permitan la comprensión del problema técnico y de la solución aportada por la invención, exponiendo las diferencias y eventuales ventajas con respecto a la tecnología anterior;*
- d) una reseña sobre los dibujos, cuando los hubiera;*
- e) una descripción de la mejor manera conocida por el solicitante para ejecutar o llevar a la práctica la invención, utilizando ejemplos y referencias a los dibujos, de ser éstos pertinentes; y,*
- f) una indicación de la manera en que la invención satisface la condición de ser susceptible de aplicación industrial, si ello no fuese evidente de la descripción o de la naturaleza de la invención.*

El artículo 30 de la Decisión 486 establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción.*

*Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple".*

La descripción divulga la invención de manera suficientemente clara y completa

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para su comprensión, tal como lo establece el Art 28 de la decisión 486 de la Comisión Andina. Menciona el sector tecnológico al que pertenece, los antecedentes de la técnica, la divulgación del problema técnico, la solución propuesta y la ventaja frente a la tecnología anterior.

Pero en cuanto a la reivindicación 25 que se refiere a un método de manufactura, se observa que no mencionan en forma clara y ordenada ninguno de los pasos que lo caracterizan. Debe hacerse claridad al respecto.

## 5. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*

*Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".*

Considerando que la fecha de presentación de la solicitud de patente de la cual es noviembre 13 de 2002, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

| No. | Documento    | Título                                                                   | Fecha de Publicación |
|-----|--------------|--------------------------------------------------------------------------|----------------------|
| D1  | US 5 145 852 | Vaso-active medicament to treat impotence                                | Sep 8, 1998          |
| D2  | US 4 742 054 | Treatment of mammals suffering from damage to the central nervous system | May 3, 1988          |

## 6. Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Las reivindicaciones 1 – 23 se refieren a una composición que comprende **fentolamina** y **apomorfina**.

D1 enseña composiciones que contienen bloqueadores alfa (tal como **fentolamina**) y agentes dopaminérgicos.

D2 enseña enseña composiciones que contienen bloqueadores alfa (tal como **fentolamina**) y agonistas del receptor dopaminérgico (tal como **apomorfina**).

## Evaluación de la Novedad

El Art. 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica."*

*El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente, o, en su caso, de la prioridad reconocida.*

*Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el Art 40".*

Se observa que los elementos característicos de las composiciones reivindicadas, es decir **fentolamina** y **apomorfina**, ya eran conocidos en D2; por lo cual las composiciones de las reivindicaciones 1 – 23 no pueden considerarse nuevas.

## Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

Se observa que:

- (a) debido a que los elementos característicos de las composiciones reivindicadas, es decir **fentolamina** y **apomorfina**, ya eran conocidos en las anterioridades D1 y D2, como bloqueadores alfa y agonistas del receptor dopaminérgico respectivamente, una persona de habilidades ordinarias en el arte adaptaría fácilmente estos compuestos a la preparación de la composición de esta solicitud;
- (b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a las composiciones reivindicadas, caracterizadas porque contienen **fentolamina** y **apomorfina**, que pueda considerarse como un aporte a la técnica, así que son obvias para una persona versada en la materia;
- (c) el problema planteado en esta solicitud que era la necesidad de una composición para el tratamiento de la disfunción eréctil masculina se resuelve proporcionando una composición que comprende **fentolamina** y **apomorfina**, es decir de la misma manera como se resolvía en las anterioridades;
- (d) el resultado obtenido: es decir la composición que contiene **fentolamina** y **apomorfina** no es inesperado.
- (e) no parece haberse superado un prejuicio técnico anterior, con la composición que contiene **fentolamina** y **apomorfina** propuesta de manera que el objeto reivindicado no tiene **nivel inventivo**.

## 7. Conclusión

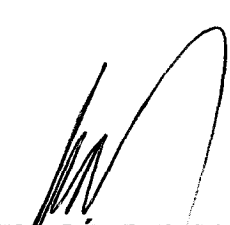
En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

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| Item | Documento    | Reivindicaciones afectadas | Requisito que afecta      |
|------|--------------|----------------------------|---------------------------|
| D1   | US 5 145 852 | 1 - 23                     | Nivel inventivo           |
| D2   | US 4 742 054 | 1 - 23                     | Novedad y 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 sesenta días contados a partir de la fecha de la 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 Unica No. 10 de 2001.



**ALIX CARMENZA CÉSPEDES DE VERGEL**  
Jefe de la División de Nuevas Creaciones.

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

05 OCT. 2006

|                              |                                     |
|------------------------------|-------------------------------------|
| CONCEPTO TÉCNICO<br>No. 1563 | EXAMINADOR TÉCNICO<br>Código 202007 |
|------------------------------|-------------------------------------|