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(54) Title: COMPOSITIONS CONTAINING PROSTAGLANDIN E1 AND/OR TROXERUTINE COMPLEXED WITH PHOSPHATIDYLCHOLINE FOR TOPICAL TREATMENT OF ERECTILE IMPOTENCE

(57) Abstract

Description of pharmaceutical or cosmetic compositions aimed at improving the local microcirculation of the penis for chronic topical treatment of vascular impotence due to vascular causes, with main impairment of the arterial-arteriolar afferents of the cavernous bodies. The new pharmacological properties of the complex between PGE1 and/or Troxerutine with Phosphatidylcholine are administered locally on the skin of the penis; the activity is obtained using the T.E.B. system according to Curri.

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# COMPOSITIONS CONTAINING PROSTAGLANDIN E1 AND/OR TROXERUTINE COMPLEXED WITH PHOSPHATIDYLCHOLINE FOR TOPICAL TREATMENT OF ERECTILE IMPOTENCE

This invention refers in general to pharmaceutical or cosmetic compositions aimed at improving local microcirculation of the penis in conditions such as erectile impotence of vascular origin in which the cause of the dysfunction is attributable to a deficiency in blood flow to the cavernous bodies.

The invention more specifically refers to pharmaceutical and/or cosmetic compositions able to increase the volume and speed of blood flow in the capillary network of the skin that covers the penis and of the mucosa of the glans penis.

It is known that during the last few years the pathogenetic question as to the real cause of erectile impotence has continued to place ever increasing emphasis on the vascular origin of the problem rather than on the psychological causes. This is due to the continuous improvement of the instrumental techniques available for diagnosis. In a consistent number of cases of impotence it is, therefore, now possible to identify the organic (and not simply functional) origin of the affection.

This obviously means that medical treatment of impotence reverts less to psychotherapy, favouring drugs or methods that enable adequate treatment of local vascular deficiencies.

It is also known that the various types of impotence due to vascular problems are presently classified in the two following forms:

1. arterial forms, in which there is impairment of the arterial afferents to the penile cavernous bodies;
2. venous forms, in which there is impairment of the venular-venous efferents of the cavernous bodies and the system's collector veins.

Whilst it is possible to treat the latter types of impotence, also referred to as "from venous leakage", with fine vascular surgery to reduce the quantity of blood that flows away from the cavernous bodies, therapeutical measures for the former types are scarce and restricted to provoking a pharmacological erection by intracavernous injection of vasodilators such as papaverine and, more recently, prostaglandins or prostacyclins. Intracavernous injection of these substances causes a temporary erection by blocking the efferent routes of exit for the blood that flows into the cavernous bodies. This approach achieves the desired effect, but does not treat the primary causes of the erectile deficiency. It, therefore, represents a temporary therapeutical measure, to be adopted as required, but which is not followed by a progressive improvement of the underlying pathological erectile condition that is at the basis of the problem. The results are, therefore, partial, of limited duration and, as such, unsatisfactory.

Topical medications, containing papaverine, in the form of ointments or gels for local application on the penis in cases of erectile impotence, have recently been proposed. The results are disappointing, since papaverine administered topically does not, in any of the cases, cross the tunica albuginea of the penis nor penetrate directly into the cavernous bodies. The use of nitrates and nitrites also, as such in the form of ointments, gels, or transdermal plasters, has not led to the expected results.

The problem at the basis of this invention, therefore, is to find and make available a pharmaceutical or cosmetic composition able to increase the speed and volume of blood flow in the small arteries and pre-capillary arterioles, especially the small terminal branches of the helicine arteries which lead into the penile cavernous bodies, as well as into the capillaries of the penis skin and the mucosa of the glans penis.

According to this invention, this problem is resolved by topical administration, instead of prostacyclins or vasodilators which paralyze the sphygmic activity and the intrinsic tone of the smooth muscle cells of the small arteries, of a composition containing a drug with microvasculo-kinetic activity and, therefore, able to strengthen the sphygmic activity of the small arteries and consequently the blood volume that reaches the cavernous bodies and the capillaries of the penis within a unit of time. In this manner, opposition is made to the pathological deficiency of the "pumping function" of the small arteries that is present in arterial hypertension and in diabetic and arteriolosclerotic micro-angiopathy, which are the main causes of penile erectile impotence and/or rapid detumescence of the erected penis.

It is widely known from the data reported in worldwide literature on the subject, that Prostaglandin E1 (PGE1) is an endogenous substance that exerts a wide spectrum of pharmacological activities, among which: increased blood flow due to vasodilation, improved microcirculation due to increased erythrocyte deformability, inhibition of platelet activation and aggregation, inhibition of neutrophil leukocyte activity, increased fibrinolytic activity. Its main indications regard treatment by intra-arterial or intravenous infusion of obliterating peripheral arteriopathies in which the vasodilating action of PGE1 is mainly exploited.

More recently, the relaxing effetcts of PGE1 on the smooth muscles were exploited in the treatment of erectile impotence of vascular origin, by intracavernous administration of doses varying between 5 to 20 mcg and over, which induce an erection within 2-15 minutes (mean 7.5), lasting between 30 minutes and 7 hours (mean 2.3 h), according to data reported by R. Hasun and W. Stackl *("Prostaglandin E1 test in the diagnosis of vascular impotence", 1er Symposium Int. sur l'Erection Pharmacologique, Paris, 17-18 Nov. 1989)*. The most widespread opinion on the mechanism of action of PGE1 is reported by M. Sohn, R. Sikora and D. Albrecht in: *"Comparative study of papaverine and Prostaglandin E1 in diagnosis of venous leakage in erectile dysfunction", Artéres et Veines 1991, Vol. X, nr. 4, 263-265:* "In contrast

to Papaverine or Phentolamin, Prostaglandin E1 has a dualistic action: it effects a direct smooth muscle relaxation of the corpus cavernosum and at the same time inhibits adrenergic activity". This opinion, unanimously shared in international andrological environments, is based on observations made by H. Hedlund and K. E. Anderson, who were the first to describe such effect *("Contraction and relaxation induced by some prostanoids in isolated human penile erectile tissue and cavernous artery", J. Urol. 1985, 184, 1245).*

The vasodilating effect can be demonstrated also after intraurethral administration *("Medicated Urethral System for Erection", MUSE)*: administration of high doses of PGE1 (500 mcg) through this route, *"effectively produced intracorporal smooth muscle relaxation comparable to intracavernosal injection of PGE1 (10 mcg) ... furthermore, arterial dilation appeared to be more diffused compared to ICI (H. Padma-Nathan et al., "Hemodynamic effects of intraurethral alprostadil: the medicated urethral system for erection (MUSE)", Int. J. Impotence Res., 1994, 6, Suppl. 1).*

It has also been observed that a drug normally used for oral treatment of chronic venous insufficiency of the lower limbs, 3-0-beta-hydroxyethylrutine (Troxerutine), applied locally on the penis and glans penis, through appropriate methods and at suitable doses, in patients affected by erectile impotence of vascular genesis, is able to significantly increase the volume and speed of blood flow in the capillary networks of the dorsal and ventral penile areas and of the glans penis, subjected to treatment.

In particular it is believed that Troxerutine - in the form indicated by this invention, i.e.: a physical-chemical complex with Phosphatidylcholine microdispersed in water and, therefore, "liposomal-like" - is able to penetrate deeply and with unique efficacy in every minimum interstice of penile skin and mucosa, involving and significantly increasing the sphygmic function of the small arteries and pre-capillary arterioles of the penis.

In fact, in subjects affected by erectile impotence of vascular origin, it has been observed that the pharmacological stimulus achievable with the compositions

of this invention is followed by a statistically significant increase in vasomotility of the small penile arteries and by a rapid and intense increase in the number of perfused capillaries.

For the purposes of this invention, preference is given to the 3-0-beta-hydroxyethyl-rutoside, of vegetable extractive origin that appears as a very fine, yellow-greenish powder with a characteristic odour.

Furthermore, in accordance with this invention, Troxerutine and Phosphatidylcholine purified from Soya are complexed in a molar ratio of 2:1, giving place to a pharmaceutical or cosmetic composition according to known methods.

The compositions of the invention are specified in the claims listed below. Phosphatidylcholine is a complex defined in EP-B 0 369 105.

Topical application on penile skin of a complex of highly purified Phosphatidylcholine (PC) and PGE1 has surprisingly demonstrated the existence of a pharmacological activity to date not described in the literature available on PGE1. It consists of a microvasculokinetic action, characterized by marked and significant potentiation of the sphygmic activity of the small arteries and pre-capillary arterioles.

This effect appears with criteria that are instrumentally observable within 15-30 minutes from the topical T.E.B. *("Trans-Epidermal Barrier" according to Curri)* application of the PC/PGE1 complex. The complexed PGE1 dose that is active on the arterial-arteriolar inotropy, strengthening the sphygmicity of the small arteries and pre-capillary arterioles *(see S. B. Curri: "Vasomotility, Sphygmicity and Vasomotion", Progr. in Appl. Microcirculation, Karger (Basle) 1993, 20, 8-13; "Vasomotion and Vasomotility: two different concepts", 16th World Congr. Int. Union of Angiology, Paris, Sept. 13-18, 1992, Abstr. Book IL091-1010:226),* is between 5 and 100 mcg of the complex that is the subject matter of this invention.

The difference, which is determinant with the knowledge acquired to-date, consists in the fact that the PC/PGE1 complex does not exert a vasodilating effect, but surprisingly activates and strengthens sphygmic contractility of the small arteries and pre-capillary arterioles, thus inducing an increase in the speed and volume of flow in the affluent capillary networks.

The method adopted in order to demonstrate the new activity which is the subject of this invention involves the instrumental evaluation of sphygmic contractility of the small penile arteries and pre-capillary arterioles through computerized calculation of the extension of the sphygmic waves (HFRV = "High Frequency Rhythmic Variations"), recorded with a laser-Doppler device (Pf2b, Perimed, Linkoeping, Sweden). Before recording the measurements a calibration was carried out towards the "motility standard" supplied by the manufacturer for a signal between 240 -260 PU; the gains of the device were regulated so as to make 1 PU correspond with 10 mV. The values were obtained using "Perisoft" software (Perimed, Linkoeping, Sweden) and statistically analyzed with the two route variance analysis ("Statgraphics Plus") using a computer connected to the recording system.

The material used consisted of 15 male subjects aged between 29 and 64 years, affected by impotence of vascular origin, with significantly impaired microcirculation (see Table 1). The recordings were carried out in a controlled temperature environment, at baseline and 15 - 30 minutes after topical T.E.B. administration of the PC/PGE1 complex.

The results summarized in Table 1 indicate that the effect on arterial-arteriolar sphygmicity occurred in 100% of the cases observed, with a significant (P = 0,005) increase in the mean values related to increased sphygmic motility which passed from 54.33 ± 37.89 mV at baseline to 153 ± 121.6 after application of the PC/PGE1 complex, which is the subject matter of this invention.

**Table 1** Values of the Laser-Doppler signal (LDF) expressed in mV before and after treatment with PGE1 complexed with Phosphatidylcholine and administered through the T.E.B. route on penile areas for the treatment of impotence of vascular origin.

| Pat. No. | Initials | Age | Diagnosis | LDF Before | LDF After |
|---|---|---|---|---|---|
| 1 | S.F. | 53 | Cavernous arteriovenous macro-microangiosclerosis | 60.55 | 225.03 |
| 2 | I.P. | 51 | Cavernous arterial macro-microvasculopathy | 17.55 | 136.2 |
| 3 | F.S. | 32 | Erectile dysfunction due to diabetic microangiopathy | 97.27 | 207.25 |
| 4 | F.G. | 55 | Arterial and cavernous macro-microangiopathy | 56.96 | 160.51 |
| 5 | B.G. | 40 | Cavernous arterial microangiopathy | 11.64 | 111.31 |
| 6 | C.G. | 29 | Microangiosclerotic tabagic erectile dysfunction | 30.94 | 103.57 |
| 7 | F.M. | 48 | Initial arterial hypertensive angiosclerosis | 53.16 | 80.21 |
| 8 | B.R. | 64 | Cavernous arterial macro- and microangiosclerosis | 13.11 | 43.12 |
| 9 | S.L. | 56 | Cavernous arterial microangiosclerosis | 48.22 | 58.88 |
| 10 | C.G. | 51 | Cavernous hypertensive arterial-sclerotic microangiopathy | 139.66 | 324.74 |
| 11 | G.A. | 49 | Cavernous veno-occlusive dysfunction | 116.63 | 453 |
| 12 | M.A. | 59 | Cavernous arterial microangiopathy | 42 | 81.16 |
| 13 | P.R. | 30 | Cavernous arterial microangiopathy | 22.09 | 52.01 |
| 14 | S.G. | 36 | Cavernous arterial microangiopathy | 37.62 | 78.8 |
| 15 | N.M. | 43 | Hypertensive cavernous arterial microangiopathy | 67.2 | 152.1 |
| Mean values ± S.D. | | | | 54.33 ± 37.69 | 153 ± 121.60 |
| Statistical significance | | | | P = 0.005 | |

A series of pharmacological tests clearly evidenced, with high statistical significance, the positive effects of the Troxerutine/Phosphatidylcholine complex on skin microcirculation.

Demonstration of the microvasculokinetic activity of the Phosphatidylcholine/Troxerutine complex in man is given in Table 2 that regards the contraction strength of the smooth muscle cells of the arteriolar media (sphygmicity, vasomotility: see Curri, S.B.: "Vasomotility, Sphygmicity and Vasomotion", Int. Symp. on Microcirculation, Rome, 10th Oct., 1991).

**Table 2** Modification of the area of the sphygmic waves, expressed in mm2, in a group of untreated controls and after 20, 40 and 60 minutes from topical application of a Phosphatidylcholine/Troxerutine complex at the dose of 5 ml (30 mg/ml)

| Groups | Area mm2 | Significance |
|---|---|---|
| Controls | 50.87 ± 11.5 | . |
| after 20 min. | 79.71 ± 17 | P< 0.001 |
| after 40 min. | 106.6 ± 24.4 | P< 0.0001 |
| after 60 min. | 106.9 ± 23 | P< 0.0001 |

(from Curri et al. Art. Vein. XI, Oct. 1992, mod.)

The pharmaceutical or cosmetic composition referred to in this invention preferably include quantities between 01 and 20% in weight of the active principle having microvasculo-kinetic activity.

Advantageously and preferably, such compositions also include de-ionized sterile water, which by suitable stirring using appropriate mechanical devices give place to an aqueous liposomal microdispersion. Furthermore, such compositions include a pharmacologically inert excipient and are prepared in any administration form that is suitable for topical and epimucosal application on any surface of the body and on skin that is particularly thin and sensitive,

such as that of the penis, i.e.: in the form of cream, ointment, gel, emulsion and similar forms, prepared with traditional methods; and also urethral suppositories.

For the purposes of the invention, the pharmacologically inert excipients preferred are those reported in the "Remington Pharmaceutical Sciences Handbook", Hack Publ. Co., N.Y., USA.

The compositions of this invention are mainly used in the following areas:

1. In the pharmaceutical field: for the topical treatment of pathological conditions deriving from insufficient local penile microcirculatory flow, such as erectile impotence or excessively short duration of erection, especially in subjects with early physiological senile involution of the arteries and arterioles; in patients with hypertension, particularly those undergoing treatment with beta-blockers; in diabetic patients, even in the absence of clinically evident manifestations of diabetic microangiopathy; in patients affected by vasculopathies of arterial-arteriolosclerotic origin, even in the absence of evident symptoms of central or peripheral vascular insufficiency; in patients affected by rheumatoid arthritis, with rheumatic microangiopathy, in whom among the symptoms related to the main disease there is a clinical condition of erectile impotence.
2. In cosmetology: for the treatment of penile areas that are considered "at risk", in which despite the absence of a clinically evident condition of impotence due to vascular causes, it is deemed appropriate to carry out prevention therapy to avoid the presumable evolution of the previously ascertained basic clinical condition. Furthermore, in the cases where occasional episodes of erectile impotence appear to indicate a possible deterioration in time of the contingent situations leading to permanent erectile impotence: this is the case of senile physiological involution of the macro and microvasculo-tissue system of erection.

Further characteristics and advantages of the invention are more evident in the following description of certain unrestrictive examples of pharmaceutical or cosmetic compositions according to the invention, whose microvasculo-kinetic effects and activity in increasing the speed and volume of penile blood flow directed towards the cavernous bodies can be observed by using suitable instrumental techniques.

## EXAMPLE 2.1

A formulation with microvasculokinetic activity in the form of a "liposomal-like" aqueous microdispersion was prepared with known methods, having the following composition:

each 10 ml vial contains:

| | | |
|---|---|---|
| Complex of hydrodispersible Phosphatidylcholine purified from soya / Troxerutine | | 100 mg |
| De-ionized sterile water | q.s. to: | 10 ml |

Vials prepared in a sterile environment

## EXAMPLE 2.2

A formulation with penile microvasculokinetic activity in the form of a gel was prepared with known methods, having the following composition:

100 g of gel contain:

| | |
|---|---|
| Troxerutine complexed with Phosphatidylcholine purified from Soya | 5.0 g |
| Polyacrylamide | 5.0 g |
| Isoparaffin | 5.0 g |
| Laureth 7 | 5.0 g |
| Methyldibromo-glutaronitrile | 0.2 g |
| Phenoxyethanol | 0.2 g |
| Fragrance Cerizza 25670 | 0.2 g |
| De-ionized water q.s. to: | 100.0 g |

## EXAMPLE 2.3

A formulation with penile microvasculokinetic activity in the form of a gel was prepared with known methods, having the following composition:

| | |
|---|---|
| 100 g of gel contain: | |
| Troxerutine complexed with Phosphatidylcholine | 10.0 g |
| Eichosapentaenoic acid 60% | 1.0 g |
| Volpo 20 (ethoxylated triglycerides C8-C12) | 7.5 g |
| Propyleneglycol | 20.0 g |
| Softigen 767 (polyoxyethylene-20-oleilether) | 20.0 g |
| Carboxyvinylpolymer | 1.5 g |
| Triethanolamine | 2.0 g |
| Imidazolidinylurea | 0.3 g |
| Methylparahydroxybenzoate | 0.1 g |
| De-ionized water q.s. to: | 100.0 g |

## EXAMPLE 2.4

Experimental comparative data

In order to carry out an in vivo verification of the effects on cutaneous and glans penis microcirculation recently developed capillaroscopic techniques were used based on the Optic Probe Video-Capillaroscope, which for the first time enabled examination of the microvessels of the penis in normal and in pathological conditions, as well as other cutaneous or mucosal regions that to-date could not be reached for biomicroscopic exploration *(S. B. Curri: Min. Angiol. 1992, 17, suppl. 4, nr. 3, 43-51; ibid. 1993, 18. suppl.2, n. 4, 38-43 and ibid. 159-165; S. B. Curri, Artéres et Veines 1994, vol. XIII, nr. special, 16-22; S. B. Curri, Progr. Appl. Microcirc., Basel, Karger 1993, Vol. 20, 8-13; S. B. Curri, Flebologia 1992, 3/3, 247-259).*

Visualization of the local microcirculatory system of penile skin and of the glans penis in vivo was carried out with a Video-Capillaroscope "Video-Microscope System, Scopeman MS 204, Japan", equipped with 200 x (field depth: 1.6 mm) and 400 x (field depth: 0.28 mm) contact lenses, devices for the automatic

control of lighting (cold halogen light from a 100 W lamp), automatic calibration of the whiteness, for continuous regulation of brightness and selection of the filters. This Video-Capillaroscope elaborates an image captured through a lens placed in direct contact with the skin of the penis or with the glans penis, appropriately diaphanized with an immersion oil for microscopy, which is transmitted to a monitor through an optical fibre cable. The resulting capillaroscopic image is recorded on a videorecorder (Sony Video 8 Hi-Fi, Stereo Video GV-USE PAL) and then printed on special photographic paper with a video-printer having an image-holding function (Color-Video Printer VY-SS50, Hitachi, Japan), according to the description reported in: S. B. Curri, V Nat. Congress and IV Int. Congr., It. Soc. of Phlebology, Siena 27-30 Sept. 1993, Abstr. in Min. Angiol., 1993, 18,36.

For the quantification of the area occupied by the capillaries of the dorsal and ventral areas of the penis and the glans penis, the Video-Capillaroscope was connected through a cable to a computerized image analysis system (EIZO-FLEXSCAN System, TTL Analog Multiple Scan, 15.5-38.5 Khz, Accorn Ltd., Cambridge, U.K.), equipped with suitable software from Foster-Findlay Ass., Ltd., Cambridge, U.K.

The capillaroscopic image of the microvessels of the penis (we repeat, for the first time in the history of microangiology and microcirculation) was in this way digitalized, thus enabling expression in numbers of pixels of both the total surface of the capillaroscopic field ("Total field Area" = TFA) and the area occupied by the microvessels of the penis ("Total Object Area" = TOA) - See Table 3.

Through this novel capillaroscopic technique it was therefore possible, by calculating the TFA/TOA ratio, to discover the "capillary density" (CD), corresponding to the area in pixels occupied by the microvessels perfused by blood flow present in the penile skin and the glans penis mucosa (see "%" column in Table 3).

The trial was performed on a group of 10 patients affected by impotence of vascular origin, aged between 34 and 62 years (mean 49 ± 7.97), in whom the clinical condition was investigated also with instrumental methods (Eco-Color Doppler technique) able to indicate the anatomic-functional status of the left and right dorsal arteries of the penis.

The Video-Capillaroscopic observations were performed in the dorsal region of the penis, at baseline and after application of a preparation according to example No. 1.

Statistical analysis of the data was carried out with "Statgraphics Plus" software (Manugistic Inc., Bitstream Inc., Cambride, MA, USA).

In a second group of 5 patients, affected by impotence of vascular origin due to diastolic arterial hypertension, who were undergoing treatment with beta-blockers, after having performed the baseline controls and ascertained the degree of microcirculatory damage in the dorsal penile region using the Optic Probe Video-Capillaroscope, a long term treatment was undertaken for a minimum of two months with the formulation described under Example No. 1.

The admission criteria were the following:

1. no active erections during the last six months;
2. not more than 3-4 partial, incomplete erections during sleep at night or upon awakening, per month.

Treatment at the dose of 10 ml twice per day, mornings and evenings, was carried out as follows:

keeping the left hand cupped beneath the penis, with the glans penis uncovered, approximately 0.5 ml of the hydrodispersible complex are

dripped on to the penile skin and the mucosa of the glans penis and massaged delicately with the right hand until the liquid is completely absorbed. This procedure is repeated until the whole contents of the 10 ml vial are used. The time required is approximately 4-6 minutes.

The clinical evaluation parameters were the following:

A. number of active erections per month
B. number of erections after night rest or upon awakening per month

**TABLE 3**

| | | | NO. | TFA | TOA | % |
|---|---|---|---|---|---|---|
| Z.P.A. | BEFORE | no. 1 | 237 | 45793 | 2754.75 | 5.99 |
| | | no. 2 | 129 | 44693 | 3658.5 | 8.18 |
| | | no. 3 | 158 | 43232 | 2057.25 | 4.76 |
| | | no. 4 | 122 | 42147 | 2184.75 | 5.18 |
| | | no. 5 | 189 | 38986 | 3309 | 8.49 |
| | AFTER | no. 1 | 179 | 45120 | 2372.25 | 5.26 |
| | | no. 2 | 262 | 48555 | 4617.75 | 9.5 |
| | | no. 3 | 195 | 49276 | 3407.25 | 6.9 |
| | | no. 4 | 268 | 45360 | 2898.75 | 6.39 |
| | | no. 5 | 101 | 40309 | 1583.25 | 3.93 |
| P.G. | BEFORE | no. 1 | 217 | 38304 | 3405 | 8.89 |
| | | no. 2 | 53 | 30816 | 1238.25 | 4.01 |
| | | no. 3 | 248 | 36240 | 2333.25 | 6.44 |
| | | no. 4 | 177 | 27178 | 1942.5 | 7.14 |
| | | no. 5 | 197 | 31605 | 2036.25 | 6.44 |
| | AFTER | no. 1 | 285 | 36792 | 3515.25 | 9.55 |
| | | no. 2 | 239 | 34808 | 2613 | 7.5 |
| | | no. 3 | 190 | 33516 | 3707.25 | 11.06 |
| | | no. 4 | 234 | 33810 | 4011 | 11.86 |
| | | no. 5 | 263 | 36058 | 3105 | 8.61 |
| P.A. | BEFORE | no. 1 | 278 | 36456 | 1301.25 | 3.57 |
| | | no. 2 | 118 | 26607 | 2000.25 | 7.5 |
| | | no. 3 | 212 | 39215 | 1638 | 4.18 |
| | | no. 4 | 214 | 50547 | 1693.5 | 3.35 |
| | | no. 5 | 223 | 34368 | 1734.75 | 5.05 |
| | AFTER | no. 1 | 230 | 47188 | 3189 | 6.75 |
| | | no. 2 | 401 | 48694 | 5054.25 | 10.37 |
| | | no. 3 | 294 | 46376 | 2333.25 | 5.03 |
| | | no. 4 | 222 | 50094 | 2217.75 | 4.42 |
| | | no. 5 | 216 | 45974 | 2529 | 5.5 |
| A.U. | BEFORE | no. 1 | 187 | 49530 | 2262 | 4.5 |
| | | no. 2 | 309 | 46552 | 2658 | 5.7 |
| | | no. 3 | 293 | 47058 | 2656.5 | 5.64 |
| | | no. 4 | 356 | 34119 | 2784.75 | 8.16 |
| | | no. 5 | 277 | 46872 | 3723 | 7.94 |
| | AFTER | no. 1 | 159 | 44704 | 2640 | 5.9 |
| | | no. 2 | 207 | 47244 | 3670.5 | 7.76 |
| | | no. 3 | 194 | 45825 | 4259.25 | 9.29 |
| | | no. 4 | 321 | 48006 | 3605.25 | 7.5 |
| | | no. 5 | 177 | 46366 | 4182 | 9.02 |
| T.R. | BEFORE | no. 1 | 97 | 31652 | 1761.75 | 5.56 |
| | | no. 2 | 339 | 48514 | 3939.75 | 8.12 |
| | | no. 3 | 217 | 47250 | 4473.75 | 9.46 |
| | | no. 4 | 89 | 37636 | 3365.25 | 8.94 |
| | | no. 5 | 202 | 47564 | 3783.75 | 7.95 |
| | AFTER | no. 1 | 261 | 46228 | 3957 | 8.55 |
| | | no. 2 | 255 | 46872 | 4350.75 | 9.28 |
| | | no. 3 | 272 | 48514 | 6675.75 | 13.76 |
| | | no. 4 | 202 | 44750 | 6319.5 | 14.12 |
| | | no. 5 | 158 | 40584 | 5554.5 | 6.68 |

| | | | NO. | TFA | TOA | % |
|---|---|---|---|---|---|---|
| T.M. | BEFORE | no. 1 | 277 | 45980 | 4787.25 | 10.41 |
| | | no. 2 | 187 | 32308 | 2405.25 | 7.44 |
| | | no. 3 | 160 | 35126 | 3748.5 | 10.67 |
| | | no. 4 | 237 | 33033 | 3805.5 | 11.52 |
| | | no. 5 | 191 | 36660 | 4643.25 | 12.66 |
| | AFTER | no. 1 | 376 | 46624 | 5859 | 12.56 |
| | | no. 2 | 191 | 41904 | 4407 | 10.51 |
| | | no. 3 | 280 | 47970 | 3944.25 | 8.22 |
| | | no. 4 | 292 | 34104 | 5533.5 | 16.22 |
| | | no. 5 | 237 | 42423 | 3752.25 | 8.84 |
| T.R. 2 | BEFORE | no. 1 | 229 | 40950 | 3196.5 | 7.8 |
| | | no. 2 | 202 | 38793 | 2434.5 | 6.27 |
| | | no. 3 | 233 | 26469 | 1907.25 | 7.2 |
| | | no. 4 | 172 | 25800 | 2094 | 8.12 |
| | | no. 5 | 144 | 16932 | 1982.25 | 11.7 |
| | AFTER | no. 1 | 461 | 45741 | 3686.25 | 8.05 |
| | | no. 2 | 551 | 47752 | 3684 | 7.71 |
| | | no. 3 | 466 | 48250 | 5974.5 | 12.38 |
| | | no. 4 | 189 | 40132 | 2938.5 | 7.32 |
| | | no. 5 | 405 | 46046 | 4771.5 | 10.36 |
| G.G. | BEFORE | no. 1 | 337 | 46299 | 3200.25 | 6.91 |
| | | no. 2 | 298 | 46470 | 3981 | 8.56 |
| | | no. 3 | 339 | 45682 | 2749.5 | 6.01 |
| | | no. 4 | 372 | 48006 | 3546 | 7.38 |
| | | no. 5 | 407 | 47564 | 5610 | 11.79 |
| | AFTER | no. 1 | 356 | 46314 | 3729 | 8.05 |
| | | no. 2 | 331 | 46000 | 4418.25 | 9.6 |
| | | no. 3 | 192 | 32697 | 3581.25 | 10.95 |
| | | no. 4 | 295 | 40608 | 3531 | 8.69 |
| | | no. 5 | 207 | 36480 | 3255.75 | 8.92 |
| C.V. | BEFORE | no. 1 | 341 | 34944 | 2715 | 7.76 |
| | | no. 2 | 377 | 42846 | 3345 | 7.8 |
| | | no. 3 | 364 | 44652 | 3462.75 | 7.75 |
| | | no. 4 | 286 | 44454 | 2997.75 | 6.74 |
| | | no. 5 | 105 | 47058 | 2278.5 | 4.84 |
| | AFTER | no. 1 | 318 | 37636 | 2261.25 | 6 |
| | | no. 2 | 443 | 41860 | 4405.5 | 10.52 |
| | | no. 3 | 324 | 44196 | 5125.5 | 11.59 |
| | | no. 4 | 392 | 45162 | 4861.5 | 10.76 |
| | | no. 5 | 311 | 28028 | 4314.75 | 15.39 |
| P.M. | BEFORE | no. 1 | 343 | 42672 | 3577.5 | 8.38 |
| | | no. 2 | 431 | 45684 | 4317 | 9.45 |
| | | no. 3 | 213 | 28028 | 2628 | 9.38 |
| | | no. 4 | 303 | 32754 | 3358.5 | 10.25 |
| | | no. 5 | 193 | 27722 | 2786.25 | 10.05 |
| | AFTER | no. 1 | 158 | 32130 | 4122 | 12.83 |
| | | no. 2 | 291 | 41109 | 5451 | 13.26 |
| | | no. 3 | 138 | 31313 | 3706.5 | 11.84 |
| | | no. 4 | 269 | 34692 | 4332 | 12.49 |
| | | no. 5 | 293 | 38592 | 6508.5 | 16.86 |

## RESULTS

Table 3 reports the results obtained at baseline and 60 minutes after application of 5 ml of the preparation described under Example No. 1, on the penile skin and on the glans penis.

The data indicate that topical and epimucosal administration of the invention directly onto the skin of the penis and the glans penis, causes a statistically significant increase of microcirculatory flow in the penis, that is very evident in patients affected by erectile impotence in whom there is a constant deficiency of arterial-arteriolar blood flow at baseline.

Chronic topical treatment, for not less than two-three months, with 10 ml twice per day of the invention described under Example No. 1, applied in small quantities and massaged until completely absorbed by the penile skin, results in a substantial improvement of the clinical baseline condition.

In particular, there was a substantial increase in the frequency of spontaneous morning erections, which in many patients had been almost non-existent at baseline; a longer duration of the erections to enable normal and satisfactory sexual intercourse; and a remarkable increase in the number of monthly erections from libido. Upon pathogenetic evaluation of the causes, these clinical aspects appear strictly correlated with the improved penile microcirculation induced by administration of the microvasculo-kinetic drug applied topically.

The following table reports the trend of the clinical parameters registered after long term treatment (2 months) with the formulation described under Example No. 1, in the second group of patients (see Example No. 4, "Experimental Comparative Data"):

TABLE 4 Trend of the clinical parameters after two months' treatment with the formulation under Example 2.1, at the dose of 10 ml twice per day, in patients with erectile impotence of vascular origin due to hypertensive penile microangiopathy.

| PAT. NO. | INITIALS | AGE | NO. OF ERECTIONS AFTER NIGHT REST AND UPON AWAKENING | | NUMBER OF ACTIVE ERECTIONS PER MONTH | |
|---|---|---|---|---|---|---|
| | | | Before | After | Before | After |
| 1 | S.G. | 55 | 0 | 8 | 0 | 6 |
| 2 | M.B. | 57 | 0 | 10 | 0 | 13 |
| 3 | C.G. | 50 | 2 | 20 | 0 | 18 |
| 4 | A.A. | 52 | 6 | 14 | 0 | 12 |
| 5 | M.G. | 50 | 0 | 4 | 0 | 4 |

Table 4 clearly indicates the efficacy of the treatment.

The novelty, therefore, consists in the opportunity to adopt a different therapeutical approach from normal andrological practice which, as is known, involves intracavernous injection of active principles and/or vasodilators, in order to handle the complex microvascular-tissue condition that is at the basis of erectile impotence caused by insufficient arterial-arteriolar blood flow, particularly as regards the evident and ubiquitous microvascular pathologies such as for example, arterial hypertension, diabetes, arteriolosclerosis.

Markedly, one of the unrecognized and unreported problems among the undesired side effects of treatment with beta-blockers for arterial hypertension, is the appearance, after approximately 1-3 years from starting treatment, of a progressive decrease of erections, in some cases up to complete disappearance, both spontaneous and from libido. As far as the application termed "cosmetic" is concerned (see above), the novelty of the invention assumes remarkable practical interest with basically preventive objectives in patients who are defined "at risk", such as those who suffer from hypertension.

## CLAIMS

1. Pharmaceutical composition to increase the volume and speed of microcirculatory blood flow of the penis, characterized by the fact that it includes Prostaglandin E1 and/or 3-o-β-hydroxyethylrutoside (Troxerutine), both in the form of a physical-chemical complex with purified Phosphatidylcholine.

2. Pharmaceutical composition according to claim 1, characterized by the fact that it includes from 1 to 15% in weight of the above compounds complexed with Phosphatidylcholine.

3. Pharmaceutical composition according to claim 1 or 2, characterized by the fact that it includes the above active principles together with at least one further excipient that is pharmacologically acceptable.

4. Pharmaceutical composition according to claim 1, 2 or 3, characterized by the fact that it is in the form of an aqueous liposomal microdispersion, gel, cream, ointment, emulsion, or similar form.

5. Cosmetic composition, especially for the topical preventive treatment of conditions caused by a deficiency in microcirculatory flow in the penis, characterized by the fact that it includes Prostaglandin E1 and/or 3-o-β-hydroxyethylrutoside (Troxerutine), both complexed with purified Phosphatidylcholine having microvasculokinetic activity.

6. Cosmetic composition according to claim 5, characterized by the fact that it includes from 1 to 15% in weight of the above compounds complexed with Phosphatidylcholine.

7. Cosmetic composition according to claim 6, characterized by the fact that it is in the form of an aqueous liposomal microdispersion, gel, ointment, cream, emulsion or similar forms.

8. Method for the treatment of penile erection deficiencies due to local penile microcirculatory impairment of the penis, characterized by the fact that it includes topical administration on the penile skin and glans penis of a pharmaceutical and/or cosmetic composition according to any of the claims from 1 to 7 included.

# INTERNATIONAL SEARCH REPORT

Interna. ..al Application No
PCT/IB 95/00584

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557 A61K31/70 A61K47/24 //(A61K31/70,31:557)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | LYMPHOLOGY (UNITED STATES), MAR 1993, VOL. 26, NO. 1, PAGE(S) 25-7, Casley-Smith JR et al 'Topical treatment of acute hindlimb lymphedema of the rat using a troxerutin-phosphatidylcholine complex in liposomal-like microdispersion.' | 1-7 |
| Y | see the whole document | 1-8 |
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| | --- | |
| | -/-- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 28 August 1995 | 11. 09. 95 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: ( + 31-70) 340-3016 | Stierman, B |

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 95/00584

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | DRUGS (NEW ZEALAND), 1992 , VOL. 44, NO. 6, PAGE(S) 1013-1032, 'Hydroxyethylrutosides: A review of its pharmacology, and therapeutic efficacy in venous insufficiency and related disorders' see abstract | 1-8 |
| Y | DRUGS EXP CLIN RES (SWITZERLAND), 1985, VOL. 11, NO. 9, PAGE(S) 627-31, Otomo S et al 'Prostaglandin E1 incorporated in lipid microspheres (lipo PGE1).' see the whole document | 1-8 |
| Y | UROLOGY (UNITED STATES), JUL 1993, VOL. 42, NO. 1, PAGE(S) 73-5, Wolfson B et al 'Intraurethral prostaglandin E-2 cream: a possible alternative treatment for erectile dysfunction.' see the whole document | 1-8 |
| Y | EP,A,0 459 377 (REALE A.) 4 December 1991 see the whole document | 1-8 |
| Y | DATABASE WPI Week 8606, Derwent Publications Ltd., London, GB; AN 86-039687 & JP,A,60 260 524 (NAKANASHI M.) 23 December 1985 see abstract | 1-8 |
| Y | DE,A,41 25 255 (KNOLL AG) 4 February 1993 see the whole document | 1-8 |
| P,Y | J. OF UROLOGY, vol.153, April 1995 page 474A Canning J R et al 'Prostaglandin E1 as a topical agent for treatment of erectile dysfunction' see abstract | 1-8 |
| P,Y | J UROL (UNITED STATES), JUN 1995, VOL. 153, NO. 6, PAGE(S) 1828-30, dysfunction [see comments] 'Topical prostaglandin-E1 for the treatment of erectile' see the whole document | 1-8 |

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1

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 95/00584

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,Y | WO,A,95 03787 (UNIV. OF SASKATCHEWAN) 9 February 1995<br>see the whole document<br>see claims 29,35,61,62 | 1-8 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 95/00584

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 8 is directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/IB 95/00584

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
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| DE-A-4125255 | 04-02-93 | CA-A- | 2113443 | 18-02-93 |
| | | WO-A- | 9302681 | 18-02-93 |
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