Abstract: The present invention refers to the combined use of antidepressant agents for the treatment of masculine sexual dysfunction, particularly premature ejaculation, considering that the combinations can comprise a Tricyclic Antidepressant (TCA), a Tetracyclic Antidepressant (TeCA), a Selective Serotonin Reuptake Inhibitor (SSRI), and optionally a Serotonin-Norepinephrine Reuptake Inhibitor (SNRI), in pharmaceutical forms offering bioavailability below the conventional doses used for these antidepressant agents, for the treatment of clinical settings of depression. These combinations allow the treatment of premature ejaculation, increasing the Intravaginal Ejaculation Latency Time for a time above 3 minutes, without the occurrence of adverse side effects.
The present invention comprises pharmaceutical forms to treat the masculine sexual dysfunction, particularly premature ejaculation, through the combined use of antidepressant agents.

"Premature ejaculation" refers to a dysfunction causing the intravaginal ejaculation of the man, along the copulative intercourse, in a time being substantially shorter than the average of the time considered as being normal, it means, few seconds after the vaginal penetration and before sexually satisfying his partner. It is the most prevalent form of masculine sexual dysfunction, with an estimated prevalence of 40%, according to Balon R., Antidepressants in the treatment of premature ejaculation, J Sex Marital Ther 1996; 22:85-96 and varying from 21% to 32.5%, according to other authors.

The text "Diagnostic and Statistical Manual of Mental Disorders", fourth edition, of the American Psychiatry Association, defines the premature ejaculation as "the persistence or recurrence of orgasm and ejaculation with minimum sexual stimulation, at the time or immediately after the penetration and before the desires of the patient".

The International Classification of Diseases and Health Related Problems, review 10 (ICD-10) of the World Health Organization, defines the premature ejaculation as the "incapacity to sufficiently control the ejaculation, impeding that both partners are able to be satisfied by the sexual intercourse".

The American Society of Urology, in the "Guideline on the Pharmacological Management of Premature Ejaculation" recently defined the premature ejaculation as "the ejaculation that happens before it is desired, or before, or immediately after the penetration, causing discomfort for one or both partners".
The Intravaginal Ejaculatory Latency Time (IELT) is used as scientific parameter of analysis, further to other subjective factors like the degree of sexual satisfaction, well-being of the partnership and others.

In a study of Patrick and colleagues (Premature ejaculation: an observational study of men and their partners. J.Sex Med., 2, 356-364, 2005), 207 men with premature ejaculation and 1,380 normal men were examined, all of them with stable heterosexual relationship of more than 6 months. The outcomes of this study demonstrated that men with premature ejaculation have a significant lower IELT than normal volunteers (average of 1.8 minutes versus average of 7.3 minutes). Other study by Wardinger and colleagues (A multinational population survey of intravaginal ejaculatory latency time. J.Sex Med., 2, 492-497, 2005) has demonstrated in 5 countries that a IELT of less than 1 minute is definitively a premature ejaculation and below 1.5 minutes it is probably a premature ejaculation setting.

The ejaculatory reflex is a complex process, with the participation of dopaminergic and serotonergic neurons, with secondary involvement of adrenergic, cholinergic, oxitonicergic neurons and also neurons related to GABA receptors. Under the aspect of the neural transmission, the ejaculatory process is exerted by the dopamine \( \text{H} \) and 5-hidroxytriptamine (5HT, serotonin), considering that the dopamine promotes the seminal emission whereas the serotonin has an inhibitory effect in the ejaculatory process (Gessa & Tagliamonte, Possible role of brain serotonin and dopamine in controlling male sexual behavior Adv. Biochem. Psychopharmacol., 11, 217, 1974) and, in this aspect, 14 subtypes of 5-HT receptors were identified.

Historically, the causes of premature ejaculation were considered as having a total psychological background.

In the group of behavioral therapies, or of counseling, there are the distraction techniques, as proposed by Seman, the Master-Johnson technique, of distraction combined with digital compression of the gland, and the "stop and start" technique of Kaplan. Usually, these techniques offer poorly satisfactory results at long-term, and require a large involvement of the partner.
Other techniques were proposed, without significant results, as topic anesthesia of the gland, through the use of a condom filled with lidocaine.

The pharmacotherapy for the treatment of premature ejaculation involves the use of antidepressants that can cause a delay of the ejaculation, as a side effect of the therapy.

The use of antidepressants has been a constant in the literature and there are evidences that certain drugs have a therapeutic effect on the premature ejaculation settings.

Several of those antidepressants are mentioned in the "Guideline on the Pharmacological Management of Premature Ejaculation" which may cause a modulation effect at the time of the ejaculation.

"Antidepressants", as mentioned herein, are related to medications indicated for the treatment or release of the clinical depression symptoms. Some of the antidepressants are used for the treatment of other alterations, like neuropathic pain, for instance. Many antidepressants are used for the treatment of anxiety disorders.

Some antidepressants classes that can be used as treatment of premature ejaculation are the following ones:

- Tricyclic antidepressants (TCA), like Amitripline, Amoxapine, Butriptline, Clomipramine, Desipramine, Dibenzepine, Dotiepine, Doxepine, Imipramine, Iprindole, Lofepramine, Melitracen, Nortripline, Opipramol, Protriptiline and Trimipramine
- Tetracyclic antidepressants (TeCA), like Maprotiline, Mianserine, Nefazodone and Trazodone.
- Serotonin selective reuptake inhibitors (SSRI), like Alaproclate, Etoperidine, Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline and Zimelidine.
- Serotonin-Norepinefrine reuptake inhibitors (SNRI), like Desipramine, Duloxetine, Milnacipran and Venlafaxine.

The overall therapeutic effects of the antidepressants are related to effects on the neurotransmitters, particularly by inhibiting the transportation of proteins, like serotonin and norepinefrine. The inhibitors of serotonin selective reuptake inhibitors (SSRI) prevent the reuptake of serotonin,
increasing the serotonin level in the brain synapses, whereas the trycyclic antidepressants (TCA) prevent the reuptake of several neurotransmitters including serotonin, norepinefrine and dopamine. Tetracyclic antidepressants can have an effect on the maintenance of the erectile function.

Fluoxetine is an antidepressant drug used to treat depression, obsessive-compulsive disorder, nervous bulimia and panic disturbance. Fluoxetine was derived from difenidramine, an antihistamine with capacity to inhibit the reuptake of the neurotransmitter serotonin. It is highly efficient in the treatment of clinical depression in cases of energy loss, being also used for a large variety of anxiety disorders. The known adverse effects include acathisia, aggressive behavior and anxiety, drowsiness, weight loss, weakness, anorgasmy and reduced sexual activity.

Clomipramine is a trichloride derived from Imipramine. It is a powerful serotonin reuptake inhibitor (SRI) and its main metabolite preferentially acts as noradrenaline reuptake inhibitor, and other metabolites are equally active. It exerts the blocking of sodium channels and NMDA receptors and can, as other trycyclic inhibitors, exert an effect on chronic pains, particularly the neuropathic ones. It also causes drowsiness as well as stroke, with higher prevalence than other trycyclic antidepressants.

On the other hand, it has important side effects, as on the central nervous system (headaches, fatigue, unrestlesness, drowsiness, nightmares, anxiety, schizophrenia induction and others). The anticholinergic effects are equally common, like dry mouth, constipation, rare paralysis of the large intestine, urination difficulties and precipitation of glaucoma. The antiadrenergic effects frequently occur due to the blocking of alpha receptors, like hypotension, postural collapse and arrhythmia. Usually, the drug causes impotence and ejaculation difficulties.

Trazodone is a psychoactive component with sedative, anxyolitics and antidepressant properties. Trazodone has less anticholinergic effects than other antidepressants (dry mouth, constipation, tachycardia), and it is associated to the occurrence of severe priapism, it means, undesirable extended erections that may cause permanent impotence or severe alterations of the erectile function.
The pharmacological methods to treat the premature ejaculation are widely known. The systemic administration of SRI (serotonin reuptake inhibitors) was formerly described (documents US 4507323, US 4940731, US 5151448 and US 5276042, PCT W095/13072). The use of Fluoxetine, commercially available with the name of Prozac, Eli Lilly & Company, that is a selective serotonin reuptake inhibitor (SSRI) was used to treat premature ejaculation, but with several undesired effects. Patients with altered renal function, for instance, due to its excretion way. Other secondary effects, like hair loss, nausea, vomit, dyspepsia, diarrhea, anorexia, anxiety, strokes, drowsiness, fatigue, headaches, tremors or skin alterations avoid it use for extended time periods, or decrease the compliance of the patients to the treatment protocol in a significant way. Further to this, Fluoxetine interacts with other drugs.

The document US 4940731 informs that Sertraline, from the same class of selective serotonin reuptake inhibitors, can be used to treat premature ejaculation. However, sertraline shares the same problems of Fluoxetine (Martindale, The Extra Pharmacopoeia, 31st edition, page 333). Further to these side effects, Sertraline can present other ones like gynecomasty, as consequence of the extended treatment.

The document US 5276042 informs that Paroxetine can be also be used to treat premature ejaculation, but it presents side effects like hyponatremia, asthenia, nausea, decreased appetite, drowsiness, tremors, anxiety, weakness and paresthesia.

The document US 6495154 informs that Clomipramine can be used to treat premature ejaculation, either for continuous use formulations or use immediately before the sexual intercourse, using additional agents, like Paroxetine or Trazodone. The dosing in accordance to the invention can vary between 1 and 300 mg for Clomipramine; therefore, it uses a widely extended range, with increased possibilities.

The document BR9806331-6 claims the isolated use of Fluoxetine in high doses and the document BR9806330-8 considers the Fluoxetine combined with sexual therapy, to delay the ejaculatory trigger.
The "Guideline on the Pharmacological Management of Premature Ejaculation" observed that the use of antidepressants requests a minimum time for it effectiveness, it means, the therapies of occasional doses, it means, immediately before the sexual intercourse, may be not effective. This same publication suggests the doses for each antidepressant, which are the doses suggested in the product's leaflets.

Considering that premature ejaculation is a highly prevalent phenomena, particularly in Young adults, and that a treatment form with proven efficacy is not available, it is important that the current therapeutic methods are improved, looking for the clinical improvement of sexual dysfunctions, particularly, of the premature ejaculation. Therefore, it is understood that the ejaculation phenomena is a complex neurotransmitter phenomena, being not associated to pure psychological alterations. The isolated use of antidepressants does not results in improvements of the patient's clinical conditions, requesting the association of antidepressants acting on the different mechanisms regulating the physiological ejaculatory process; it means, on adrenergic, cholinergic, serotonergic, dopaminergic, oxitonergic receptors and also on GABA receptors, further to other class of drugs having as side effect the maintenance of the blood flow to the penis, like Tetracyclic Antidepressants.

The applicant has developed a pharmaceutical composition comprising pharmaceutically acceptable active antidepressant agents of the classes and their salts:

(a) Tricyclic Antidepressants (TCA);
(b) Tetracyclic Antidepressants (TeCA);
(c) Selective Serotonin Reuptake Inhibitors (SSRI), and optionally,
(d) Serotonin - Norepinefrine Reuptake Inhibitors (SNRI).

The present innovative invention considers a pharmaceutical composition preferentially comprising the association of four or three antidepressants, of different classes, with subclinical doses, it means, preferably in doses not excelling the complete effect of the related drugs, therefore not causing the undesirable side effects of those drugs, for the treatment of masculine sexual dysfunctions, particularly premature
ejaculation, by the combined action on different neurotransmitter processes related to the sexual physiology further to the specific effects on the erectile function caused by agents of the Tetracyclic Antidepressants class.

As "treatment" it must be understood the continuous use or in alternated periods of the medication consisting of the combination of antidepressants with different actions, with daily doses preferably below the doses usually recommended for the therapy of depressive settings, reaching clinical results by improving the Intravaginal Ejaculation Latency Time from less than one minute to results above 3 minutes, preferentially above 5 minutes.

A daily dose preferably below the recommended doses for the treatment of depressive settings is related to doses that will not cause satisfactory clinical effects for the indication of treatment of clinically diagnosed depression settings.

The continuous use or in alternated periods of the medication composed by the combination of four or three antidepressants with different actions, preferably with daily doses below the doses recommended for the treatment of depressive settings, does not cause side actions usually associated to those drugs, it means, drowsiness, dry mouth, weakness among other symptoms, increasing the compliance of the patients to the treatment concerning the compliance indexes observed in the treatment with individual antidepressants, or in combinations of two drugs, with doses usually used for the treatment of clinical depression settings.

The present invention comprises pharmaceutical compositions for the treatment of premature ejaculation, a form of masculine sexual dysfunction. Among the Tricyclic Antidepressants (TCA) compounds being usable according to the invention, are those selected in the group consisting of: Amitripliline, Amoxapine, Butriptline, Clomipramine, Desipramine, Dibenzepine, Dotiepine, Doxepine, Imipramine, Iprindole, Lofepramine, Melitracen, Nortripline, Opipramol, Protriptiline, Trimipramine, or their mixtures, preferentially Clomipramine. Among the Tetracyclic Antidepressant (Teca) agents being usable according to the invention are those selected in the group consisting of: Maprotiline, Mianserine, Nefazodone or Trazodone,
or their mixtures, preferentially Trazodone. The Selective Serotonin Reuptake Inhibitors (SSRI) being usable according to the invention are those selected in the group consisting of: Alaproclate, Etoperidone, Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline or Zimelidine or their mixtures, but preferentially Fluoxetine. Optionally, Serotonin-Norepinefrine Reuptake Inhibitors (SNRI) can be used, like Desipramine, Duloxetine, Milnacipran, Venlafaxine, or also their mixtures. The invention can be preferentially executed through the combination of three antidepressant drugs, comprising Tricyclic Antidepressants (TCA), Tetracyclic Antidepressants (TeCA) and Selective Serotonin Reuptake Inhibitors (SSRI), but preferentially the combination of Clomipramine, Fluoxetine and Trazodone, all of them preferably in subclinical doses, it means, in lower doses than those usually indicated for the treatment of depressive settings, preferentially orally administered, preferentially in continuous way.

The drug for treatment of masculine sexual dysfunction, according to the invention, comprises the pharmaceutically acceptable agents mentioned below and their salts:

(a) Tricyclic Antidepressants (TCA);
(b) Tetracyclic Antidepressants (TeCA);
(c) Selective Serotonin Reuptake Inhibitor (SSRI); and optionally
(d) Serotonin-Norepinefrine Reuptake Inhibitor (SNRI).

The drug, comprising the pharmaceutical composition according to the invention, is characterized by presenting bioavailable release from 75% to 125% of the minimal recommended doses for the treatment of clinical depression settings. The drug may be presented in the form of capsules, tablets, for immediate release or slow release in up to 24 hours, preferentially orally administered to the patient.

According to one of the preferred embodiments, the invention comprises a method for the treatment of sexual dysfunction characterized by the administration of a therapeutically effective amount of a Tricyclic Antidepressant in a dose varying between approximately 1 mg to approximately 75 mg, preferable in a subclinical dose varying between
approximately 1 mg to approximately 10 mg; a Tetracyclic Antidepressant administered in an amount varying between approximately 1 mg to approximately 100 mg, preferable in a subclinical dose varying between approximately 1 mg to approximately 50 mg; a Selective Serotonin Reuptake Inhibitor administered in an amount varying between approximately 1 mg to approximately 50 mg, preferable in a subclinical dose varying between approximately 1 mg to approximately 25 mg and, optionally, a Serotonin-Noradrenaline Reuptake Inhibitor in an amount varying between approximately 1 mg to approximately 140 mg, preferable in a subclinical dose varying between approximately 1 mg to approximately 75 mg.

According to one embodiment of the invention, capsules or tablets for oral administration can contain 1 to 10 milligrams of Fluoxetine, 1 to 50 mg of Trazodone and 1 to 10 mg of Clomipramine, per unit.

According to another embodiment of the invention, capsules or tablets for oral administration can contain 1 to 20 milligrams of Paroxetine, 1 to 50 mg of Trazodone and 1 to 10 mg of Clomipramine, per unit.

Further, according to other embodiment of the invention, capsules or tablets for oral administration can contain 1 to 25 milligram of Sertraline, 1 to 50 mg of Trazodone and 1 to 10 mg of Clomipramine, per unit.

The tablets for immediate release can be obtained by direct compression process, or by granules compression, for instance. The continuous use of the association or of the drug according to the invention is recommended, by means of daily administration, along more than 7 days, being alternated with wash-out periods of, as maximum, 5 days each.

The composition of the main active ingredients can be released by several pharmaceutical forms, comprising the active ingredients, it means, antidepressant drugs, and other types of pharmaceutically acceptable ingredients, like excipients, surfactants, preservers, it means, antioxidants, stabilizers, chelants and other known by the man with the art to prepare pharmaceutical formulations to release the drugs. The pharmaceutical forms can be of any type promoting the systemic absorption of the drugs, it means, of the antidepressant agents, like tablets, by direct way of by wet way with the compression of granules, rapid disintegration tablets, effervescent
tablets, mouth release formulas, sublingual release formulas, nose and mouth sprays, inhalators, suspensions, powders, dry powders, dispersions, suppositories and chewing gum formulations.

The combination of antidepressant drugs can be also administered by means of transdermal patches, it means, a pharmaceutical form allowing the release of active ingredients through the skin, particularly in the scrotal sack region, as well as by means of lotions, creams, ointments and topical sprays.

The time of use of the claimed combination is determined by the clinical results obtained, it means, by the increase of the Intravaginal Ejaculation Latency Time, to values usually accepted as being satisfactory, preferentially above 3 minutes, and preferentially above 5 minutes. This time of use can be from one week to several months.

The active ingredients can be administered in the form of salt, ether, starch, pro-drugs, active metabolites, conjugated, in a form being pharmacologically active. These active agents, it means, the antidepressant drugs, can be prepared according to the art, as for instance through the ways described by J. March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, Fourth Edition, New York, Wiley-Interscience, 1992.

Additionally, the present invention comprises the active agents containing a chiral core, it means, in the form of isolated isomer or in the racemic mixture of the isomers. The aptive® agents can be administered in the form of pure isomers or in the form of racemic mixture of the isomers.

Other derivates and analogous of the active agents, it means, of the antidepressant drugs, can be prepared by the man of the art of the synthetic organic chemistry, or can be deduced from the proper literature.

The compounds can be administered by the oral, parenteral, rectal, mouth, sublingual and nasal ways, as well as by inhalation, topically, transdermal or by absorbable implants. The final release must allow the bioavailability, it means, the quantity effectively absorbed being equivalent to those obtained from the oral forms, it means, allowing the effective absorption similar to those obtained by oral pharmaceutical forms.
Preferentially, the active agents can be released by oral forms, commonly used as tablets, capsules, solutions, suspensions, syrups, powders, granules, prepared according to the techniques known by the man of the art, as those reported in Remington: The Science and Practice of Pharmacy, Twentieth Edition, Gennaro, A. R., Ed., Lippincott, Williams and Wilkins, 2000. Capsules and tablets represent the preferential release form due to the better convenience for the patient.

The tablets can be manufactured according to conventional techniques, in equipments like FETTE presses, for instance, for direct compression, containing further to the active agents, other excipients, dilution agents, stabilizers, surfactants, pigments and lubricants, like sugars, gelatin, polyethylene glycol, waxes, natural and synthetic gums, cellulose polymers, magnesium stearate, polyacrylic acid, corn starch, silicon dioxide, titanium dioxide, alumina, kaolin, talc and soluble materials, like urea, sucrose, lactose, dextrose, sodium chloride and sorbitol. The amount of the referred components may vary and the skilled in the art will know how to effect such alterations using no more than routine experimentation.

The capsules are the preferred forms of release of the claimed combinations, in which the active agents are encapsulated in the form of liquids or solids, including particulates like granules and micro-granules. The proper capsules can be hard or soft, usually manufactured of gelatin or cellulose derived material. In the present invention there are preferentially used hard capsules, in two sealed parts, as described in Remington: The Science and Practice of Pharmacy, Twentieth Edition, Gennaro, A. R., Ed., Lippincott, Williams and Wilkins, 2000.

The invention further considers devices for the administration of the drug or medical compound to the patients, like kit, or pack, or packing containing such drug, usually proper packing for each type of the pharmaceutical form and the use of the compound or drug for the treatment of the sexual dysfunction, particularly masculine, like premature ejaculation.

The example below is to better explain the scope of the invention, however, it must be not considered as a limitation effect of the invention.
Example

The manufacture of gelatin capsules was executed, filled in a ZANASI capsules filling machine, containing following composition:

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- Fluoxetine Hydrochloride - 5.60 mg - equivalent to 5.0 mg of Fluoxetine base
- Trazodone Hydrochloride - 25 mg
- Clomipramine Hydrochloride - 5 mg
- Corn Starch - 148.80 mg
- Colloidal Silicon Dioxide - 1.0 mg
- Magnesium stearate - 2.60 mg
- Monohydrated Lactose - 12.0 mg

Equipments:

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1. Glatt granulator, MGG - 01 or MGG 02 with a mesh of 1.0 mm; Capacity: 2,500 kg/hr;
2. Bin mixer; Capacity: 300 liters
3. Zanasi machine AZ 4OE; Capacity: 40,000 capsules/hr;
4. IMA machine for capsules selection: Capacity: 160,000 capsules/hr;
5. Blister envelope machine - MEB - 01, 02, 03 or 04; capacity: 7,200 blisters/hr

Production method

A) Powders mixture

1) Introduce the following raw materials into the mixer (Bin, U or Double cone), through a mesh size of 1.0 mm:

- Trazodone Hydrochloride - 25 mg
- Fluoxetine Hydrochloride - 5.60 mg
- Clomipramine Hydrochloride - 5 mg
Colloidal Silicon Dioxide - 1.0 mg
Super-Tab Lactose - 12.0 mg
Corn Starch -52.08 mg

Mix the above ingredients for 5 minutes.

2) Introduce the following raw materials into the mixer (Bin, U or Double cone), through a mesh size of 1.0 mm:
Corn starch 96.72 mg

Mix for 10 minutes.

3) Introduce the following raw materials into the mixer (Bin, U or Double cone), through a mesh size of 1.0 mm:
Magnesium stearate 2.60 mg

Mix for 3 minutes.

Theoric yield: 30,000 g of the powder mixture

B) Encapsulation

1) Specifications

Tools for filling the capsules (discs, matrixes)

Capsules:
Theoric mean weight of the empty capsule: 49 mg
Mean weight of the content: 190.0 - 210.0 mg (200mg +/- 5%)
Individual weight of the content: 185.0 - 215.0 mg (200mg +/- 7.5%)
Mean weight of the full capsule: 239.0 - 259.0 mg (249mg +/- 5%)
Individual weight of the full capsule: 234.0 - 264.0 mg (249mg +/- 7.5%)

Disintegration: maximum 10 minutes in water at 37°C
Powder humidity (PPS): maximum of 14%

2) Encapsulate
3) Theoric yield: 30,00 kg of the powder = 150,000 full capsules having 200 mg of powder each

C) Envelope/Blister Step

Clinical Tests

A group of patients was submitted to a daily treatment involving the administration of a daily dose of a capsule containing the composition mentioned above.

The study evaluated 32 men, with ages varying from 19 to 54 years old, having premature ejaculation. Each individual received a daily dose of a composition having 25 mg of Trazodone, 5 mg of Clomipramine and 5 mg of fluoxetine for a 6 month period. Patients were advised to administer the composition after dinner and to abstain from alcohol during the treatment. Each patient was assessed once a month and answered a questionnaire, so that it was possible to evaluate the treatment and possible side effects.

Results: 28 patients followed the protocol until its end. Between those patients, 20 (71.4%) said that they were able to adequate control of ejaculation during the treatment; 2 (7.1%) reported a partial benefit of ejaculation reflex and the 6 (21.4%) remaining patients said that there were no alteration in their condition. None of the patients related any kind of side effects.
CLAIMS

1. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION characterized by comprising pharmaceutically acceptable antidepressant active agents of the classes:
   (a) Tricyclic Antidepressants (TCA);
   (b) Tetracyclic Antidepressant (TeCA);
   (c) Selective Serotonin Reuptake Inhibitor (SSRI); and optionally
   (d) Serotonin-Norepinefrine Reuptake Inhibitor (SNRI)
   or their salts.

2. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 1 characterized by the fact that the Tricyclic Antidepressant (TCA) agents can be selected from the group consisting of: Amitripline, Amoxapine, Butriptline, Clomipramine, Desipramine, Dibenzepine, Dotiepine, Doxepine, Imipramine, Iprindole, Lofepramine, Melitracen, Nortripline, Opipramol, Protriptiline, Trimipramine, and their mixtures.

3. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 2 characterized by the fact that the Tricyclic Antidepressant is Clomipramine.

4. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 1 characterized by the fact that Tetracyclic Antidepressant (TeCA) agents can be selected from the group consisting of: Maprotiline, Mianserine, Nefazodone, Trazodone, and their mixtures.

5. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 4 characterized by the fact that the Tetracyclic Antidepressants is Trazodone.
6. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 1 characterized by the fact that the Selective Serotonin Reuptake Inhibitors (SSRI) agents can be selected from the group consisting of: Alaproclate, Etoperidone, Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Zimelidine, and their mixtures.

7. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 6 characterized by the fact that Selective Serotonin Reuptake Inhibitors (SSRI) are Fluoxetine, Paroxetine, Sertraline, or their mixtures.

8. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 7 characterized by the fact that the Selective Serotonin Reuptake Inhibitor is Fluoxetine.

9. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 1 characterized by the fact that Serotonin - Norepinefrine Reuptake Inhibitors (SNRI) agents can be selected from the group consisting of: Desipramine, Duloxetine, Milnacipran, Venlafaxine, and their mixtures.

10. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 1 characterized by the fact that it comprises fluoxetine, trazadone and clomipramide.

11. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 1 characterized by the fact that it comprises paroxetine, trazadone and clomipramine.
subclinical dose varying between approximately 1 mg to approximately 50 mg; approximately 1 to 50 mg of a Selective Serotonin Reuptake Inhibitor, preferable in a subclinical dose varying between approximately 1 mg to approximately 25 mg and, optionally, approximately 1 mg to 140 mg of a Serotonin-Norpinfrine Reuptake Inhibitor, preferable in a subclinical dose varying between approximately 1 mg to approximately 75 mg.

19. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 1 characterized by the fact that it contains 1 to 10 mg of Fluoxetine, 1 to 50 mg of Trazodone and 1 to 10 mg of Clomipramine, by unit.

20. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 1 characterized by the fact that it contains 1 to 20 mg of Paroxetine, 1 to 50 mg of Trazodone and 1 to 10 mg of Clomipramine, per unit.

21. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 1 characterized by the fact that it contains 1 to 25 mg of Sertraline, 1 to 50 mg of Trazodone and 1 to 10 mg of Clomipramine, per unit.

22. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SEXUAL DYSFUNCTION according to claim 1 characterized by the fact that its administration is made orally, by the parenteral, rectal, bucal, sublingual, nasal, transdermal way or by absorbable patches.

23. DEVICE CONTAINING THE PHARMACEUTICAL COMPOSITION according to any of claims 1 to 21, characterized by comprising a drug for the treatment of sexual dysfunction.
24. **USE OF THE PHARMACEUTICAL COMPOSITION** according to any of claims 1 to 21, characterized by being used in the treatment of masculine sexual dysfunction.

25. **METHOD FOR THE TREATMENT OF SEXUAL DYSFUNCTION** characterized by the fact that it comprises the administration to a patient of a therapeutically effective dose of pharmaceutically acceptable active antidepressant agents, of the classes:
   (a) Tricyclic Antidepressants (TCA);
   (b) Tetracyclic Antidepressant (TeCA);
   (c) Selective Serotonin Reuptake Inhibitor (SSRI); and optionally
   (d) Serotonin-Norepinefrin Reuptake Inhibitor (SNRI) or their salts.

26. **METHOD** according to claim 25 characterized by the fact that it is for the treatment of premature ejaculation.

27. **METHOD** according to claim 25 characterized by the fact that the Tricyclic Antidepressants are administered in an amount varying between approximately 1 mg to approximately 75 mg, the Tetracyclic Antidepressant is administered in an amount varying between approximately 1 mg to approximately 100 mg, the Selective Serotonin Reuptake Inhibitor is administered in an amount varying between approximately 1 mg to approximately 50 mg.

28. **METHOD** according to claim 25 characterized by the fact that the Tricyclic Antidepressants are administered in an amount varying between approximately 1 mg to approximately 75 mg, preferable in a subclinical dose between approximately 1 to 10 mg; the Tetracyclic Antidepressant is administered in an amount varying between approximately 1 mg to approximately 100 mg, preferable in a subclinical dose between approximately 1 to 50 mg; the Selective Serotonin Reuptake Inhibitor is administered in an amount varying between approximately 1 mg to
approximately 50 mg, preferable, in a subclinical dose between approximately 1 to 25 mg.

29. METHOD according to claim 25 characterized by the fact that it further comprises the administration of a Serotonin - Norepinefrine Reuptake Inhibitor in an amount varying between approximately 1 mg to approximately 140 mg, preferable in a subclinical dose between approximately 1 to 75 mg.