(51) International Patent Classification  
A61K 31/00

(11) International Publication Number:  
WO 00/44363

(43) International Publication Date:  
3 August 2000 (03.08.00)

(21) International Application Number:  
PCT/US00/001470

(22) International Filing Date:  
21 January 2000 (21.01.00)

(30) Priority Data:  
60/117,611 28 January 1999 (28.01.99) US

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(81) Designated States:  

Published  
Without international search report and to be republished upon receipt of that report.

(54) Title:  
DESMETHYLSILDENAFIL COMPOSITIONS AND METHODS

(57) Abstract

Methods and compositions are disclosed utilizing desmethyilsildenafil for the treatment of sexual dysfunction in humans. Desmethyilsildenafil exhibits a lessened liability toward drug-drug interactions than sildenafil and a more predictable dosing regimen than sildenafil. Desmethyilsildenafil is also useful for the treatment of angina, hypertension, heart failure or atherosclerosis.
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DESMEHYLSILDENAFIL COMPOSITIONS AND METHODS

FIELD OF THE INVENTION

This invention relates to compositions of matter containing desmethylsildenafil. The invention also relates to methods of treating sexual dysfunction and various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

BACKGROUND OF THE INVENTION

Sildenafil, 5-[2-ethoxy-5-(4-methylpiperazinyl)sulfonyl]phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, I, is an orally active, potent and selective inhibitor of cGMP-phosphodiesterase. Sildenafil is available from Pfizer, Inc., as Viagra®.

![Chemical Structure of Sildenafil (I)]
The main serum metabolite of sildenafil is II, 5-[2-ethoxy-5-(1-piperazinylsulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one hereinafter referred to as "desmethylsildenafil."

![Chemical Structure](image)

Formation of desmethylsildenafil occurs in the liver through the enzymes of the P450 system, specifically CYP3A4 (major route) and CYP2D9 (minor route). Other drugs which inhibit the CYP3A4 or CYP2D9 isozymes may interfere with the formation of this metabolite. In addition, coadministration of another drug metabolized by CYP3A4 or CYP2D9 may lead to elevated blood concentrations of one or both drugs through competitive inhibition. For example, known inhibitors of CYP3A4, such as erythromycin, ketoconazole, and cimetidine, and known inhibitors of CYP2D9, such as tolbutamide and warfarin, may interfere with demethylation of sildenafil. Compounds which are inducers of CYP3A4 or CYP2D9 may cause faster metabolism of sildenafil when coadministered.
It would be desirable to find a compound with the advantages of sildenafil which would provide a more predictable dosage regimen in the patient population and that would decrease the chances for drug-drug interactions.

SUMMARY OF THE INVENTION

The present invention relates to use of desmethylsildenafil for treating sexual dysfunction (e.g., erectile dysfunction and female sexual dysfunction) and angina, hypertension, heart failure and atherosclerosis. It provides this effective treatment while exhibiting a lessened liability toward adverse effects than sildenafil, a lessened liability toward drug interactions than sildenafil and a more predictable dosing regimen than sildenafil.

DETAILED DESCRIPTION OF THE INVENTION

The active compound of these compositions and methods is desmethylsildenafil. The compound may be prepared as described in U.S. Patent No. 5,250,534, the disclosure of which is incorporated herein by reference. It has now been discovered that desmethylsildenafil is a superior agent for treating sexual dysfunction, and cardiovascular disorders including angina, hypertension, heart failure and atherosclerosis in that it provides this effective treatment while exhibiting fewer or milder adverse effects than sildenafil, a lessened liability toward drug-drug interactions than sildenafil and a more predictable dosing regimen than sildenafil. Reported adverse effects include headache, flushing, dyspepsia, nasal congestion urinary tract infection, abnormal vision, diarrhea, dizziness, and rash. As a result of sidespread use of sildenafil concern has arisen about cardiovascular side effects. These include: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal
electrocardiogram, and cardiomyopathy. Other adverse events are:

**Body as a whole**: face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

**Digestive**: vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.

**Hemic and Lymphatic**: anemia and leukopenia.

**Metabolic and Nutritional**: Thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.

**Musculoskeletal**: arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

**Nervous**: ataxia hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia somnolence, abnormal dreams, reflexes decreased, hypesthesia.

**Respiratory**: asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

**Skin and appendages**: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

**Special senses**: mydriasis, conjunctivitis, photophobia, tinnitus, eye pain,
deafness, ear pain, eye hemorrhage, cataract, dry eyes.

Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

The present method encompasses a method of treating sexual dysfunction, which comprises administering to a human in need of such therapy, an amount of desmethylsildenafil, or a pharmaceutically acceptable salt thereof, said amount being sufficient to alleviate the symptoms of sexual dysfunction. In particular, the sexual dysfunction may be erectile dysfunction.

The present invention also encompasses an oral composition for the treatment of a human in need of therapy for sexual dysfunction, which comprises a pharmaceutically acceptable carrier for oral administration and a therapeutically effective amount of desmethylsildenafil or a pharmaceutically acceptable salt thereof. Preferably the composition is in the form of a tablet or capsule and the amount of desmethylsildenafil in the tablet or capsule is preferably about 3-150 mg. The present invention further encompasses a method of treating angina, hypertension, heart failure or atherosclerosis.

Utilizing desmethylsildenafil results in enhanced dosage predictability and in improved therapeutic index. In particular, desmethylsildenafil exhibits less potential for drug-drug interaction than does sildenafil, where CYP3A4 or CYP2D9 inhibitors or inducers are coadministered. Desmethylsildenafil may also be used to treat various conditions or disorders while minimizing or avoiding adverse cardiac events associated with administration of sildenafil. Furthermore, desmethylsildenafil can be administered to treat various conditions or disorders while minimizing or avoiding impact on hepatic function (e.g., liver enzyme abnormalities).
The term "cardiovascular disorders" as used herein includes, but is not limited to stable, unstable and variant angina, hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency (post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, and stroke.

The term "sexual dysfunction" encompasses male sexual dysfunction, or erectile dysfunction, and female sexual dysfunction, including orgasmic dysfunction related to clitoral disturbances.

The term "erectile dysfunction" as used herein means an inability to achieve penile erection or ejaculation or both, or an inability to obtain or sustain an erection adequate for intercourse.

The magnitude of a prophylactic or therapeutic dose of desmethylsildenafil in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose and perhaps the dose frequency will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range for desmethylsildenafil for the conditions described herein is from about 3 mg to about 150 mg in single or divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps at about 5 mg and increased up to about 100 mg or higher depending on the patient's global response. It is further recommended that patients over 65 years old and those with impaired renal or hepatic function, initially receive low doses and that they be titrated based on individual response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.
The relative activity, potency and specificity of desmethylsildenafil in the treatment of sexual dysfunction and cardiovascular disorders can be assessed by determination of an IC\textsubscript{50} value, as described in U.S. Patent 5,656,629. Briefly, the cGMP-PDE and other PDE isozymes are isolated from cardiovascular tissues (heart and aorta) of various animal species and man by anion-exchange and affinity chromatography as described by Silver et al., *See. Messeng. Phos.*, 13: 13-25, 1991; PDE activity, in the presence and absence of test compounds is determined essentially as described by Thompson et al., *Adv. Cyclic Nucleotide Res.*, 10:69-92. To determine the potency and selectivity of compounds as PDE inhibitors, compounds are screened for their effect on cyclic nucleotide hydrolysis at 10 μM. If ≥50% inhibition of PDE activity is observed, an IC\textsubscript{50} value is calculated (concentration-response curves as described by Tallarida and Murray, *Manual of Pharmacologic Calculations with Computer Programs*, Procedure 8, Graded Dose-response, pp. 14-19, Springer-Verlag, New York, 1981. The test provides an estimate of relative activity, potency and, through a measure of specificity, an estimate of the therapeutic index.

Any suitable route of administration may be employed for providing the patient with an effective dosage of desmethylsildenafil. Oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, and like forms of administration are possible, but oral administration is preferred. Oral dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, and the like.

The pharmaceutical compositions of the present invention comprise desmethylsildenafil as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients. The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable nontoxic acids. Since the compound of the present
invention is basic, salts may be prepared from pharmaceutically acceptable nontoxic acids including inorganic and organic acids. Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic (mesylate), mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like.

The compositions of the present invention include suspensions, solutions, elixirs or solid dosage forms. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred to the oral liquid preparations.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release formulations, which are well known in the art. Compositions suitable for rectal administration are described in European Application 645140, the disclosure of which is incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more necessary ingredients. In general, the compositions
are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet or capsule contains about 3-150 mg of the active ingredient.

An enteric coating, such as the polyacrylate Eudragit L® and Eudragit S® series, may be applied, preferably with an aqueous dispersion of the coating polymer. Tablets of other strengths may be prepared by altering the ratio of active ingredient to the excipients or to the final weight of the tablet.

The invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the invention.
EXAMPLES

Example 1 - 20 mg Tablets

<table>
<thead>
<tr>
<th>Composition per tablet:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmethylsildenafil</td>
<td>20 mg</td>
</tr>
<tr>
<td>croscarmellose</td>
<td>60 mg</td>
</tr>
<tr>
<td>colloidal silicon dioxide</td>
<td>8 mg</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>1 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>190 mg</td>
</tr>
<tr>
<td>croscarmellose</td>
<td>15 mg</td>
</tr>
<tr>
<td>talc</td>
<td>10 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>304 mg</strong></td>
</tr>
</tbody>
</table>

EXAMPLE 1

Desmethylsildenafil and silicon dioxide are dry mixed, the first portion of croscarmellose is added and the mixture is further dry mixed. The magnesium stearate is added, dry mixed and the mixture is run through a roller compactor and mill. The resulting dry granulate is mixed with the remaining three ingredients and compressed into tablets.
Example 2 - 10 mg Tablets

<table>
<thead>
<tr>
<th>Composition per unit dosage:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmethylsildenafil</td>
<td>10 mg</td>
</tr>
<tr>
<td>pregelatinized starch</td>
<td>200 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>25 mg</td>
</tr>
<tr>
<td>povidone</td>
<td>15 mg</td>
</tr>
<tr>
<td>croscarmellose</td>
<td>10 mg</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>3.75 mg</td>
</tr>
<tr>
<td>FD&amp;C yellow #2 lake</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Water</td>
<td>(5 mL)</td>
</tr>
<tr>
<td></td>
<td>Total 266.25 mg</td>
</tr>
</tbody>
</table>

**EXAMPLE 2**

The ingredients above are mixed well in the proportions shown in a high shear mixer until uniform granules result. The mixture is tray-dried at 40°C under vacuum until the desired consistency is reached. The granules are milled to less than 60 mesh using a screen mill and compressed into tablets.
What is claimed is:

1. A method of treating angina, hypertension, heart failure or atherosclerosis which comprises administering to a human a therapeutically effective amount of desmethylsildenafil or a pharmaceutically acceptable salt thereof.

2. A method of treating sexual dysfunction which comprises administering to a human a therapeutically effective amount of desmethylsildenafil or a pharmaceutically acceptable salt thereof.

3. The method of claim 2, wherein the sexual dysfunction is erectile dysfunction.

4. The method of claim 1 or 2 wherein desmethylsildenafil is administered orally.

5. The method of claim 4 wherein the amount of desmethylsildenafil or a pharmaceutically acceptable salt thereof administered is from about 3 mg to about 150 mg per day.

6. A method of treating angina, hypertension, heart failure or atherosclerosis and avoiding drug-drug interactions associated with the administration of sildenafil which comprises administering to a human a therapeutically effective amount of desmethylsildenafil or a pharmaceutically acceptable salt thereof.
7. A method of treating sexual dysfunction and avoiding drug-drug interactions associated with the administration of sildenafil which comprises administering to a human male a therapeutically effective amount of desmethylsildenafil or a pharmaceutically acceptable salt thereof.

8. The method of claim 7, wherein the sexual dysfunction is erectile dysfunction.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier for oral therapy and a therapeutically effective amount of desmethylsildenafil or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition according to claim 7 in the form of a tablet or capsule.

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