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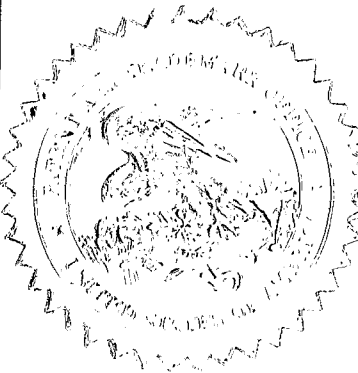
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**APPLICATION NUMBER: 60/123,244  
FILING DATE: March 08, 1999  
PCT APPLICATION NUMBER: PCT/US00/05711**



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# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (C).

03/08/99  
c490 U.S. PTO

|             |         |
|-------------|---------|
| CASE NUMBER | 20315PV |
|-------------|---------|

55/90/10  
JCS41 U.S. PTO  
477627/60/123144

| INVENTOR(S)                            |                        |  |
|--|------------------------|--|
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| Elizabeth Joanne                       | Stoner Waldstreicher   | Westfield, New Jersey<br>Scotch Plains, New Jersey   |

Additional inventors are being named on the \_\_ separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

METHODS AND COMPOSITONS FOR TREATING ERECTILE DYSFUNCTION

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|       |            |          |       |         |        |
|-------|------------|----------|-------|---------|--------|
| STATE | New Jersey | ZIP CODE | 07065 | COUNTRY | U.S.A. |
|-------|------------|----------|-------|---------|--------|

ENCLOSED APPLICATION PARTS (check all that apply)

|   |                  |    |   |
|---|------------------|----|---|
| <input checked="" type="checkbox"/> Specification | Number of Pages  | 27 | <input type="checkbox"/> Small Entity Statement |
| <input type="checkbox"/> Drawing(s)               | Number of Sheets |    | <input type="checkbox"/> Other (specify)        |

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

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| <input type="checkbox"/> A check or money order is enclosed to cover the filing fees   | FILING FEE AMOUNT (\$) | \$150.00 |
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government

No.

Yes, the name of the U.S. Government agency and the Government contract number are: \_\_\_\_\_

Respectfully submitted,

SIGNATURE Philippe L. Durette

Date 3/8/99

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TITLE OF THE INVENTION  
METHODS AND COMPOSITIONS FOR TREATING ERECTILE  
DYSFUNCTION

5 FIELD OF THE INVENTION

The present invention provides for novel methods for the treatment of erectile dysfunction comprising a drug combination. More particularly, the drug combination of the present invention comprises an agonist of the melanocortin receptor with a cyclic-GMP-specific  
10 phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. The present invention also provides for pharmaceutical compositions comprising such drug combinations useful in the methods to treat erectile dysfunction. Moreover, the present invention provides for a method of manufacture of a medicament useful in the treatment of  
15 erectile dysfunction.

BACKGROUND OF THE INVENTION

Erectile dysfunction denotes the medical condition of inability to achieve penile erection sufficient for successful sexual  
20 intercourse. The term "impotence" is oftentimes employed to describe this prevalent condition. Approximately 140 million men worldwide, and, according to a National Institutes of Health study, about 30 million American men suffer from impotency or erectile dysfunction. It has been estimated that the latter number could rise to 47 million men by the  
25 year 2000. Erectile dysfunction can arise from either organic or psychogenic causes, with about 20% of such cases being purely psychogenic in origin. Erectile dysfunction increases from 40% at age 40, to 67% at age 75, with over 75% occurring in men over the age of 50. In spite of the frequent occurrence of this condition, only a small  
30 number of patients have received treatment because existing treatment alternatives, such as injection therapies, penile prosthesis implantation, and vacuum pumps, have been uniformly disagreeable [for a discussion, see "ABC of sexual health - erectile dysfunction," Brit. Med. J. 318: 387-390 (1999)]. Only more recently have more viable treatment modalities  
35 become available, in particular orally active agents, such as sildenafil

citrate, marketed by Pfizer under the brand name of Viagra®. Sildenafil is a selective inhibitor of type V phosphodiesterase (PDE-V), a cyclic-GMP-specific phosphodiesterase isozyme [see R.B. Moreland et al., "Sildenafil: A Novel Inhibitor of Phosphodiesterase Type 5 in Human Corpus Cavernosum Smooth Muscle Cells," Life Sci., 62: 309-318 (1998)]. Prior to the introduction of Viagra on the market, less than 10% of patients suffering from erectile dysfunction received treatment. Sildenafil is also being evaluated in the clinic for the treatment of female sexual dysfunction.

10           The regulatory approval of Viagra® for the oral treatment of erectile dysfunction has invigorated efforts to discover even more effective methods to treat erectile dysfunction. Several additional selective PDE-V inhibitors are in clinical trials. UK-114542 is a sildenafil backup from Pfizer with supposedly improved properties. IC-351 (ICOS Corp.) is claimed to have greater selectivity for PDE-V over PDE-VI than 15 sildenafil. Other PDE-V inhibitors include M-54033 and M-54018 from Mochida Pharmaceutical Co. and E-4010 from Eisai Co., Ltd.

          Other pharmacological approaches to the treatment of erectile dysfunction have been described [see, e.g., "Latest Findings on the Diagnosis and Treatment of Erectile Dysfunction," Drug News & Perspectives, 9: 572-575 (1996); "Oral Pharmacotherapy in Erectile Dysfunction," Current Opinion in Urology, 7: 349-353 (1997)]. A product 20 under clinical development by Zonagen is an oral formulation of the alpha-adrenoceptor antagonist phentolamine mesylate under the brand name of Vasomax®. Vasomax® is also being evaluated for the 25 treatment of female sexual dysfunction.

          Drugs to treat erectile dysfunction act either peripherally or centrally. They are also classified according to whether they "initiate" a sexual response or "facilitate" a sexual response to prior stimulation [for 30 a discussion, see "A Therapeutic Taxonomy of Treatments for Erectile Dysfunction: An Evolutionary Imperative," Int. J. Impotence Res., 9: 115-121 (1997)]. While sildenafil and phentolamine act peripherally and are considered to be "enhancers" or "facilitators" of the sexual response to erotic stimulation, sildenafil appears to be efficacious in both mild

organic and psychogenic erectile dysfunction. Sildenafil has an onset of action of 30-60 minutes after an oral dose with the effect lasting about 4 hours, whereas phentolamine requires 5-30 minutes for onset with a duration of 2 hours. Although sildenafil is effective in a majority of patients, it takes a relatively long time for the compound to show the desired effects. The faster-acting phentolamine appears to be less effective and to have a shorter duration of action than sildenafil. Oral sildenafil is effective in about 70% of men who take it, whereas an adequate response with phentolamine is observed in only 35-40% of patients. Both compounds require erotic stimulation for efficacy. Since sildenafil indirectly increases blood flow in the systemic circulation by enhancing the smooth muscle relaxation effects of nitric oxide, it is contraindicated for patients with unstable heart conditions or cardiovascular disease, in particular patients taking nitrates, such as nitroglycerin, to treat angina. Other adverse effects associated with the clinical use of sildenafil include headache, flushing, dyspepsia, and "abnormal vision," the latter the result of inhibition of the type VI phosphodiesterase isozyme (PDE-VI), a cyclic-GMP-specific phosphodiesterase that is concentrated in the retina. "Abnormal vision" is defined as a mild and transient "bluish" tinge to vision, but also an increased sensitivity to light or blurred vision. Moreover, since some patients have developed a tolerance to prior phosphodiesterase inhibitors, sildenafil may prove to have a similar outcome in some percentage of patients when used over a long period of time.

Synthetic melanocortin receptor agonists (melanotropic peptides) have been found to initiate erections in men with psychogenic erectile dysfunction [See H. Wessells *et al.*, "Synthetic Melanotropic Peptide Initiates Erections in Men With Psychogenic Erectile Dysfunction: Double-Blind, Placebo Controlled Crossover Study," *J. Urol.*, 160: 389-393 (1998); *Fifteenth American Peptide Symposium*, June 14-19, 1997 (Nashville TN)]. Activation of melanocortin receptors of the brain appears to cause normal stimulation of sexual arousal. In the above study, the centrally acting  $\alpha$ -melanocyte-stimulating hormone analog, melanotan-II (MT-II), exhibited a 75% response rate, similar to results obtained with apomorphine, when injected intramuscularly or

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