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(54) **METHOD OF TREATMENT**

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(57) **ABSTRACT**

The invention provides the use of darifenacin, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the reduction of urgency in patients suffering from overactive bladder.

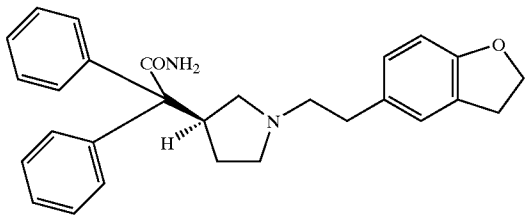
METHOD OF TREATMENT

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 60/347,456 filed Jan. 11, 2002, and U.K. Provisional Application No. 0129962.7 filed Dec. 14, 2001.

[0002] This invention relates to a new use of darifenacin, and its pharmaceutically acceptable derivatives.

[0003] Darifenacin is (S)-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenyl-acetamide and is disclosed in European Patent No 0388054, Examples 1B and 8. It is referred to therein as 3-(S)-(−)-(1-carbamoyl-1, 1-diphenylmethyl)-1-[2-(2,3-dihydro-benzofuran-5-yl) ethyl]pyrrolidine. It is indicated in the treatment of urinary incontinence and irritable bowel syndrome and has the following structure:



[0004] The symptoms of overactive bladder (OAB) include urinary frequency and urgency, with or without incontinence in the absence of local pathological or systemic condition. Urgency is described in the draft ICS Terminology Report [Terminology Report of the International Continence Society; Draft 6, Aug. 15, 2001] as the sudden compelling desire to pass urine, which is difficult to control.

[0005] Recently, the terms OAB Wet and OAB Dry have been proposed to describe OAB patients with or without incontinence respectively. Overall prevalence of OAB Wet and Dry is similar in men and women with a prevalence rate in the US of 16.6% [Stewart et al, Prevalence of Overactive Bladder in the United States: Results from the NOBLE Program; Abstract Presented at the 2nd International Consultation on Incontinence, July 2001, Paris, France]. Until recently, the cardinal symptom of OAB was believed to be incontinence. However, with the advent of the new terms this is clearly not meaningful for the large number of sufferers who are not incontinent (i.e. OAB Dry patients). Thus, a recent study from Liberman et al [Health Related Quality of Life Among Adults with Symptoms of Overactive Bladder: Results From A US Community-Based Survey; Urology 57(6), 1044-1050, 2001] examined the impact of all OAB symptoms on the quality of life of a community-based sample of the US population. This study demonstrated that individuals suffering from OAB without any demonstrable loss of urine have an impaired quality of life when compared with controls. Additionally, individuals with urgency alone have an impaired quality of life compared with controls.

[0006] Thus, urgency is now believed to be the primary symptom of OAB, but to date it has not been evaluated in a quantified way in clinical studies.

[0007] It has now been found that darifenacin, and its pharmaceutically acceptable derivatives, is useful in the reduction of urgency in patients suffering from overactive bladder.

[0008] This finding is surprising because it could not have been predicted that a compound known to be useful in the treatment of incontinence (i.e. the unwanted and often unconscious leaking of urine) would be able to reduce the feeling of urgency (i.e. the sudden compelling desire to pass urine). It is even more surprising that darifenacin, and its pharmaceutically acceptable derivatives, is able to reduce the feeling of urgency in patients who are not incontinent (i.e. OAB Dry patients).

[0009] Thus, according to the present invention, there is provided the use of darifenacin, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the reduction of urgency in patients suffering from overactive bladder (OAB).

[0010] Pharmaceutically acceptable derivatives of darifenacin include solvates and salts, particularly acid addition salts such as the hydrobromide salt.

[0011] The patients to be treated may be suffering from wet overactive bladder (OAB Wet) or dry overactive bladder (OAB Dry). The darifenacin, or a pharmaceutically acceptable derivative thereof, can be administered alone or in any convenient pharmaceutical presentation, including those mentioned in European Patent No 388054. Oral administration is preferred. In the present indication, a suitable dosage of darifenacin, or of the active darifenacin moiety in a pharmaceutically acceptable derivative thereof, for a 70 kg person, is in the range 3.75-40 mg daily, for example 7.5-30 mg daily. The dosage may be administered in, say, 3 divided doses or in a single controlled release formulation.

[0012] However, it is preferred that the darifenacin, or a pharmaceutically acceptable derivative thereof, is administered in a dosage form that is adapted to release at least 10% of the darifenacin, or a pharmaceutically acceptable derivative thereof, in the lower gastrointestinal tract of the patient. Such formulations are described in U.S. Pat. No. 6,106,864 (the teaching of which is incorporated herein by reference). The preferred such formulation is a slow release matrix tablet (see particularly Example 3 of U.S. Pat. No. 6,106, 864).

[0013] The invention further provides darifenacin, or a pharmaceutically acceptable derivative thereof, for use in the reduction of urgency in patients suffering from overactive bladder.

[0014] The invention further provides a method of reducing urgency in patients suffering from overactive bladder, which comprises administering darifenacin, or a pharmaceutically acceptable derivative thereof, to a patient in need of such treatment.

[0015] The invention is illustrated by the following examples.

EXAMPLES

[0016] Clinical Investigations of Urgency in Subjects with Overactive Bladder

[0017] Two novel methods for the assessment of urgency were used. The first was for use in a large scale clinical trial, and the second was for use in clinical laboratory studies.

[0018] In both of these studies, darifenacin was administered as its hydrobromide salt. It was presented in slow release matrix tablets of the type described in U.S. Pat. No. 6,106,864, particularly Example 3. Tablets were administered once daily (o.d.).

[0019] Clinical Study 1

[0020] In this study, OAB Wet patients recorded each episode of urgency per day and the overall severity of urgency for each day in a diary. The severity of urgency was recorded by the use of a visual analogue scale (VAS) where the anchor points were mild and severe.

[0021] Darifenacin (as hydrobromide salt; 7.5 mg, 15 mg and 30 mg of the active moiety, o.d.) and placebo were evaluated in subjects with a diagnosis of overactive bladder in a multicentre trial and symptoms of urgency were assessed using the VAS at baseline and at the end of the study (12 weeks of treatment).

[0022] 108 patients (14 male, 94 female) received 7.5 mg; 107 patients (15 male, 92 female) received 15 mg; 114 patients (16 male, 98 female) received 30 mg; and 108 patients (18 male, 90 female) received placebo.

[0023] Results

[0024] Darifenacin (7.5-30 mg) produced a dose-related reduction in both the number of episodes of urgency and the overall severity of urgency experienced by the OAB subject in the clinical study. The effect was significantly greater than that produced by placebo. The data is presented below in Table 1 and 2.

TABLE 1

Effect of Darifenacin and Placebo on Frequency and Severity of Urgency in OAB Subjects

	Placebo	7.5 mg	15 mg	30 mg
	No of episodes of urgency/day			
Baseline	8.1	8.5	8.6	8.4
Median change from baseline	−1.2	−1.8	−2.3*	−3***
Median % Change from baseline	−15.7	−29.2	−26.9	−33.1
	Severity of urgency/day			
Baseline	53.5	53.2	56.2	53.5
Median change from baseline	−3.9	−7	−7*	−9.4*

*P < 0.05,
**P < 0.01,
***P < 0.001

[0025]

TABLE 2

Effect of Darifenacin on Frequency & Severity of Urgency in OAB subjects corrected for placebo

	7.5 mg	15 mg	30 mg
	No of episodes of urgency/day		
Baseline	8.5	8.6	8.4
Median difference from placebo	−0.5	−1.1*	−1.4***

TABLE 2-continued

Effect of Darifenacin on Frequency & Severity of Urgency in OAB subjects corrected for placebo

	7.5 mg	15 mg	30 mg
	Severity of urgency/day		
Baseline	53.2	56.2	53.5
Median difference from placebo	−2.5	−3.8*	−5.5*

*P < 0.05,
**P < 0.01,
***P < 0.001

[0026] Clinical Study 2

[0027] This study used a novel method for measuring the time between the first onset of the urgency and the need to micturate, which is known as the 'warning time'. A modified stop-watch was used which required the subject to press a button at the onset of urge and a second button when they felt they needed to micturate. Darifenacin (as the hydrobromide salt; 30 mg o.d.) and placebo were evaluated in subjects with symptoms of urgency. The subjects were a mixture of OAB Wet and OAB Dry sufferers. The 'warning time' was assessed at baseline and following 2 weeks of treatment using the modified stop watch.

[0028] 36 patients (29 female, 7 male) received darifenacin; and 36 patients (22 female, 14 male) received placebo.

[0029] Results

[0030] Treatment with darifenacin of subjects with urgency produced a significant increase in the warning time when compared with subjects treated with placebo. The data are displayed in Table 3.

[0031] It should be noted that both OAB Wet and OAB Dry subjects responded to treatment.

TABLE 3

Effect of Darifenacin and Placebo on Warning Time in Subjects with Urgency and Frequency

Warning Time (Min)	Darifenacin	Placebo
Baseline (Median)	4.7	9.4
Week 2 (Median)	8.4**	4.1

*P < 0.05,
**P <0.01,
***P <0.001

[0032] Median difference from placebo 4.3 minutes

[0033] Conclusions

[0034] The results show darifenacin produced a clinically significant attenuation of the symptom of urgency in subjects with overactive bladder.

1. The use of darifenacin, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the reduction of urgency in patients suffering from overactive bladder.

2. The use as claimed in claim 1, wherein the darifenacin is in the form of a pharmaceutically acceptable acid addition salt.

3. The use as claimed in claim 1, wherein the darifenacin is in the form of its hydrobromide salt.

4. The use as claimed in any one of the preceding claims, wherein the patients to be treated are suffering from wet overactive bladder.

5. The method in any one of claims 1 to 3, wherein the patients to be treated are suffering from dry overactive bladder.

6. The use as claimed in any one of the preceding claims, wherein the darifenacin, or a pharmaceutically acceptable derivative thereof, is administered in a dosage form that is adapted to release at least 10% of said darifenacin, or a pharmaceutically acceptable derivative thereof, in the lower gastrointestinal tract of the patients.

7. The use as claimed in claim 6, wherein the dosage form is a slow release matrix tablet.

8. Darifenacin, or a pharmaceutically acceptable derivative thereof, for use in the reduction of urgency in patients suffering from overactive bladder.

9. A method of reducing urgency in patients suffering from overactive bladder, which comprises administering darifenacin, or a pharmaceutically acceptable derivative thereof, to a patient in need of such treatment.

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