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(54) THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE

THERAPEUTISCHE FORMULIERUNG ZUR VERABREICHUNG VON TOLTERODIN MIT KONTROLLIERTER FREISETZUNG

FORMULATION DE TOLTERODINE THERAPEUTIQUE A LIBERATION CONTROLEE

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Description

[0001] The present invention relates to an improved method of treating unstable or overactive urinary bladder as well as a formulation therefor.

[0002] A substantial part (5-10%) of the adult population suffers from urinary incontinence, and the prevalence, particularly of so-called urge incontinence, increases with age. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has been based on muscarinic receptor antagonists. The drug of choice has for a long time been oxybutynin.

[0003] Oxybutynin, which chemically is the DL-racemic form of 4-diethylamino-2-butynyl-phenylcyclohexylglycolate, is given orally, usually as a tablet or syrup. Oxybutynin, usually administered as the chloride salt, is metabolized to an active metabolite, N-desethyl-oxybutynin. The drug is rapidly absorbed from the gastrointestinal tract following administration and has a duration of from three to six hours. While the effectiveness of oxybutynin has been well documented, its usefulness is limited by classical antimuscarinic side-effects, particularly dry mouth, which often leads to discontinuation of treatment.

[0004] WO 96/12477 discloses a controlled release delivery system for oxybutynin, which delivery system is said not only to be of convenience to the patient by reducing the administration to a once daily regimen, but also to reduce adverse side-effects by limiting the initial peak concentrations of oxybutynin and active metabolite in the blood of the patient.

[0005] The alleged relief of side-effects by reducing or eliminating peak concentrations through administration of the controlled release delivery system is, however, contradicted by a later published clinical report, Nilsson, C. G., et al., Neurourology and Urodynamics 16 (1997) 533-542, which describes clinical tests performed with the controlled release delivery system disclosed in WO 96/12477 above. In the clinical tests reported, a 10 mg controlled release oxybutynin tablet was compared with the administration of a conventional (immediate release) 5 mg tablet given twice daily to urge incontinent patients. While high peak levels of the drug obviously were eliminated with the controlled release oxybutynin tablet, no difference in side-effects between the controlled release tablet and the conventional tablet was observed. The advantage of the controlled release tablet thus resided merely in enhancing treatment compliance by its once-a-day dosage rather than also reducing side-effects as stated in WO 96/12477.

[0006] Recently, an improved muscarinic receptor antagonist, tolterodine, (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, has been marketed for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder. Both tolterodine and its major, active metabolite, the 5-hydroxymethyl derivative of tolterodine, which significantly contributes to the therapeutic effect, have considerably less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195-207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647-655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287-295.

[0007] The currently marketed administration form of tolterodine is filmcoated tablets containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract, the recommended dosage usually being 2 mg twice a day. While, as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

[0008] According to the present invention it has now surprisingly been found that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

[0009] In one aspect, the present invention therefore provides the use of tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of unstable or overactive urinary bladder, wherein the medicament is in the form of an oral controlled release formulation capable of maintaining a substantially constant serum level of the active moiety or

moieties for at least 24 hours, such that the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than 2.0, said fluctuation index, FI, being defined as FI = (Cmax - Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

[0010] Overactive urinary bladder encompasses detrusor instability, detrusor hyperreflexia, urge incontinence, urgency and urinary frequency.

[0011] As mentioned above, the chemical name of tolterodine is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine. The major, active metabolite of tolterodine is (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine is (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer is (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; and the corresponding racemate to tolterodine is (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine.

[0012] By the term "active moiety or moities" is meant the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine is administered.

[0013] The term "substantially constant" with respect to the serum level of active moiety or moieties means that the release profile of the controlled release formulation should essentially not exhibit any peak values. This is expressed by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI = (Cmax - Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve) for dosage interval τ, and τ is the length of the dosage interval. The controlled release formulation should provide a mean fluctuation index (for n being at least 30) preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

[0014] For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

[0015] Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average (blood) serum or plasma levels are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

[0016] Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. WO 89/06644. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to WO 94/11337. The (S)-enantiomer and its use in the treatment of urinary and gastrointestinal disorders is described in WO 98/03067.

[0017] In another aspect, the present invention provides a pharmaceutical oral controlled release formulation containing tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours, whereby it provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than 2.0, said fluctuation index, FI, being defined as FI = (Cmax - Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

[0018] An exemplary type of oral controlled release formulation, a specific embodiment of which is described in Example 1 below, is a multi-unit formulation comprising controlled-release beads. Each bead comprises (i) a core unit of a water-soluble, water-swellable or water-insoluble inert material (having a size of about 0.05 to 2 about 2 mm), such as e.g. a sucrose sphere; (ii) a first layer on the core of a substantially water-insoluble (often hydrophilic) polymer (this layer may be omitted in the case of an insoluble core, such as e.g. of silicon dioxide), (iii) a second layer of a water-soluble polymer having an active ingredient dissolved or dispersed therein, and (iv) a third polymer layer effective for controlled release of the active ingredient (e.g. a water-insoluble polymer in combination with a water-soluble polymer).

[0019] In the case of an oral controlled release formulation for once-daily administration, the dosage of tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt

thereof is, for example, 4 mg or 6 mg.

[0020] With the guidance of the disclosure herein, the skilled person may either adapt controlled release administration forms, such as tablets, capsules etc, known in the art, to obtain the objectives of the present invention, or design modified or new controlled release administration forms.

[0021] The invention is illustrated by the following Examples.

[0022] Percentages are by weight, unless otherwise stated. Reference will be made to the accompnaying drawings, in which:

Figure 1 is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a predetermined total dosage of tolterodine (4 mg) through (i) an immediate release tablet (2 mg) twice daily as in the prior art, and (ii) a controlled release capsule (4 mg) once daily in accordance with the present invention;

Figure 2 is a diagram showing the variation of the basal salivation (g/min) with time (hours) during 4 hours after administration of (i) a 4 mg tolterodine controlled release capsule in accordance with the present invention, (ii) a prior art tolterodine immediate release tablet, and (iii) placebo; and

Figure 3 is is a bar chart diagram showing patients' individual estimates of experienced dry mouth side effect (no dry mouth, mild, moderate, severe) after administration of tolterodine through (i) a conventional 2 mg immediate release tablet, (ii) controlled release capsules of 4, 6 and 8 mg, respectively, according to the present invention, and (iii) placebo.

EXAMPLE 1

TOLTERODINE ORAL CR CAPSULE AND IR TABLET

Preparation of tolterodine CR capsules 2 mg and 4 mg

[0023] A controlled release (CR) capsule containing nonpareil beads coated by (i) an ethylcellulose layer, (ii) a tolterodine/HPMC layer, and (iii) a sustained release ethylcellulose/HPMC layer was prepared as follows:

1200 g of (starch-containing) sugar spheres, 20-25 mesh, were charged into a Wurster fluid bed and sequentially coated with the following three coating solutions:

- (1) a Surelease® sealcoating solution prepared by mixing 788 g of Surelease® with 563 g of purified water (Surelease® is an aqueous filmcoating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil; manufactured by Colorcon, Inc., West Point, PA, U.S.A.);
- (2) a suspension prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of Hypromellose, 5cP (hydroxypropylmethyl cellulose (HPMC)); and
- (3) a sustained release coating solution prepared by mixing 29 g of Hypromellose, 5 cP, with 375 g of purified water, and then mixing with 695 g of Surelease®.

[0024] After drying, the coated spheres were filled into hard gelatin capsule shells (size 3, white/white) to obtain 2 mg and 4 mg capsules, respectively, of the composition (filling mass for 2 mg capsule, 169-207 mg/capsule):

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20-25 mesh	69 mg	137 mg
Surelease®	21 mg	42 mg
Hypromellose, 5cP	2.0 mg	4.1 mg

Tolterodine L-tartrate IR tablets 2 mg

[0025] Commercially available tolterodine L-tartrate 2 mg tablets for immediate release (IR) (Detrusitol®, Pharmacia & Upjohn AB, Sweden) were used. The tablets had the following composition:

Core

[0026]

Tolterodine L-tartrate	2.0 mg
cellulose, microcrystalline	53.4 mg
calcium hydrogen phosphate dihydrate	18.0 mg
sodium starch glycollate	6.0 mg
magnesium stearate	0.4 mg
colloidal anhydrous silica	0.2 mg

Coasting

[0027]

Methylhydroxypropyl cellulose	1.5 mg
cellulose, microcrystalline	0.3 mg
stearic acid	0.6 mg
titanum dioxide E 171	0.6 mg

PHARMACODYNAMIC AND PHARMACOKINETIC STUDIES

[0028] A clinical trial was performed in patients with overactive bladder to determine the pharmacodynamic and pharmacokinetic effects of different daily doses of (i) the above described tolterodine controlled release capsule (below referred to as TOD), compared with (ii) the above described tolterodine immediate release tablet (below referred to as TIR), and (iii) a placebo capsule (containing sugar spheres only). The trial was performed as a double-blind, double dummy, cross-over trial in 60 patients for three one week periods and six treatments (2, 4, 6 and 8 mg TOD once daily, 2 mg TIR twice daily, and placebo). All patients were randomised to three out of six treatments, meaning that 30 patients were subjected to each of the treatments. Pharmacodynamic and pharmacokinetic measurements were performed on day seven in each treatment period. The determinations included measurements of (i) serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time, (ii) salivation (dry mouth), and (iii) residual urine volumes.

Serum concentrations of tolterodine and main metabolite

[0029] Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136). Figure 1 shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily, and, on the other hand, the administration of a 2 mg TIR tablet twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

[0030] The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as FI = (Cmax - Cmin)/$AUC\tau/\tau$, where τ is the length of the dosage interval and $AUC\tau$ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index for the active moiety was 2.40 (95% CI 1.95-2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59-0.78) for the TOD capsule.

Salivation (dry mouth)

[0031] Salivation was measured using dental cotton rolls applied in the mouth for 3 x 2 minutes. Measurements were performed before breakfast and thereafter after each blood sample on day seven in each treatment period. Based on all measurements after dosing, the mean salivation during 12 hours was calculated. The basal salivation at steady state

was measured after treatment with (i) 4 mg TOD capsule, (ii) 2 mg TIR tablet, and (iii) placebo. The results are presented in Figure 2. As can be seen in the Figure, the salivation is substantially constant during the period shown for the TOD capsule, whereas a considerable reduction in salivation (i.e. drier mouth) is obtained with the TIR tablet.

[0032] While Fig. 2 shows the total salivation as measured, the degree of salivation, or dry mouth, was also determined, based on the patient's estimate of experienced intensity of the phenomenon. The results for 2 mg TIR tablet b.i.d., 4 mg TOD capsule, 6 mg TOD capsule and 8 mg TOD capsule, are presented in bar chart form in Figure 3. The four bars for each dosage represent, from left to right in the figure, no dry mouth, mild, moderate, and severe, respectively.

[0033] As apparent from Fig. 3, the dry mouth intensity for the TIR 2 mg b.i.d. tablet is clearly higher than that of the TOD 4 mg capsule, and about twice that dosage, i.e. TOD 8 mg, is required to match the adverse dry mouth effects of the TIR 2 mg b.i.d. tablet.

[0034] The results from the salivation determinations thus show that flattening of the concentration peaks of the "active moiety" (i.e. tolterodine plus 5-HM) leads to a substantial reduction of the undesired dry mouth effect.

Residual urine volume

[0035] Residual volume is the volume of urine left in the bladder immediately after voiding. Measuring residual volume offers a method of assessing the effect of antimuscarinic treatment on the bladder. In fact, it offers a measure of efficacy (change in residual volume) as well as safety (urinary retention, i.e. inability to pass urine). Efficacy may thus be measured as the mean residual volume per unit of time, and safety as any case where the residual urine exceeds a fixed level. The mean residual volume per micturition was measured by a non-invasive (ultrasonic) method for placebo, TIR tablet 2 mg b.i.d., and for capsules TOD 2 mg, TOD 4 mg, TOD 6 mg, and TOD 8 mg.

[0036] The results are presented in Tables 1 and 2 below. Table 1 shows the mean residual volume per micturition, and Table 2 shows the maximum residual volume during 12 hours.

[0037] The results presented clearly demonstrate that the TOD capsule dosages are as efficacious as the corresponding TIR b.i.d dosages, and also that the TOD dose may be increased up to 8 mg daily and still be safe with regard to urinary retention.

Table 1

Mean Residual Volume per micturition (ml)						
	Placebo	TIR 2mg b.i.d	TOD 2mg	TOD 4mg	TOD 6mg	TOD 8mg
Estimated mean	29	62	40	59	69	77
95% confidence interval	12 to 46	45 to 79	26 to 55	51 to 66	60 to 78	65 to 89
Estimated difference vs. IR			-22	-4	7	14
			-44 to 1	-23 to 15	-13 to 26	-7 to 36

Table 2

Maximum Residual Volume during 12 hours						
	Placebo	TIR 2mg b.i.d	TOD 2mg	TOD 4mg	TOD 6mg	TOD 8mg
Median value (ml)	46	72	45	55	87	77
min-max	5-267	10-316	0-192	0-349	0-360	0-390

[0038] The results from the clinical trial described above demonstrate that a flatter serum concentration of active moiety (tolterodine plus 5-HM) not only does not lead to a loss of efficacy or to untoward side-effects, primarily urinary retention, but, importantly, also provides for a reduced dry mouth effect (unaffected or less reduced salivation).

Claims

1. Use of tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of unstable or overactive urinary bladder, wherein the medicament is in the form of an oral controlled release formulation capable of maintaining a substantially constant serum level of the active moiety or moieties for at least 24 hours, such that the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than 2.0, said fluctuation index, FI, being defined as FI = (Cmax - Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

2. The use according to claim 1, wherein the fluctuation index is not higher than 1.0.

3. The use according to claim 1 or claim 2, wherein the medicament provides a 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, which is from 5 to 150 nM*h.

4. The use according to claim 1, 2 or 3, wherein the medicament provides a serum level of unbound tolterodine and 5-hydroxymethyl metabolite which is in the range of 0.2 to 6.3 nM.

5. The use according to any one of claims 1 to 4, wherein the controlled release formulation is a capsule or tablet for oral administration once daily.

6. The use according to any one of claims 1 to 5, wherein the medicament contains tolterodine, or a pharmaceutically acceptable salt thereof.

7. The use according to any one of claims 1 to 6 wherein the medicament is for the treatment of urinary incontinence.

8. A pharmaceutical oral controlled release formulation containing tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours, whereby it provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than 2.0, said fluctuation index, FI, being defined as FI = (Cmax - Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

9. The formulation according to claim 8, which provides a fluctuation index of not higher than 1.0.

10. The formulation according to claim 8 or 9, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to 150 nM*h.

11. The formulation according to claim 8, 9 or 10, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of 0.2 to 6.3 nM.

12. The formulation according to any one of claims 8 to 11, which is a capsule or tablet for oral administration once daily.

13. The formulation according to any one of claims 8 to 12, which provides controlled release of tolterodine, or a pharmaceutically acceptable salt thereof.

Patentansprüche

1. Verwendung von Tolterodin, seinem 5-Hydroxymethyl-Metaboliten oder des Racemats, das Tolterodin entspricht, oder eines pharmazeutisch verträglichen Salzes davon bei der Herstellung eines Medikaments für die Behandlung von instabiler oder überaktiver Harnblase, wobei das Medikament in der Form einer oralen Formulierung mit kontrollierter Freisetzung ist, das fähig ist, einen im Wesentlichen konstanten Serumlevel der aktiven Komponente oder Komponenten für wenigsten 24 Stunden aufrecht zu erhalten, so dass die Formulierung mit kontrollierter Freisetzung

einen mittleren Fluktuationsindex des Serumlevels der aktiven Komponente oder Komponenten bereitstellt, der nicht höher als 2,0 ist, wobei der Fluktuationsindex, FI, als FI=(Cmax - Cmin)/AUCτ/τ definiert ist, worin Cmax und Cmin die maximale bzw. minimale Konzentration der aktiven Komponenten ist, AUCτ die Fläche unter dem Serum-Konzentrationsprofil ist und τ die Länge des Dosierungsintervalls ist.

2. Verwendung nach Anspruch 1, wobei der Fluktuationsindex nicht höher als 1,0 ist.

3. Verwendung nach Anspruch 1 oder Anspruch 2, wobei das Medikament ein 24-Stunden-Serumprofil, ausgedrückt als die AUC von ungebundenem Tolterodin und 5-Hydroxymethyl-Metabolit, bereitstellt, das von 5-150 nM*h ist.

4. Verwendung nach Anspruch 1, 2 oder 3, wobei das Medikament einen Serumlevel von ungebundenem Tolterodin und 5-Hydroxymethyl-Metabolit bereitstellt, der im Bereich von 0,2 bis 6,3 nM ist.

5. Verwendung nach einem der Ansprüche 1-4, wobei die Formulierung mit kontrollierter Freisetzung eine Kapsel oder Tablette zur oralen Verabreichung einmal täglich ist.

6. Verwendung nach einem der Ansprüche 1-5, wobei das Medikament Tolterodin oder ein pharmazeutisch verträgliches Salz davon enthält.

7. Verwendung nach einem der Ansprüche 1-6, wobei das Medikament für die Behandlung von Harninkontinenz bestimmt ist.

8. Orale pharmazeutische Formulierung mit kontrollierter Freisetzung, die Tolterodin, seinen 5-Hydroxymethyl-Metaboliten oder das Racemat, das Tolterodin entspricht, oder ein pharmazeutisch verträgliches Salz davon enthält, wobei die Formulierung, wenn sie an einen Patienten verabreicht wird, eine kontrollierte Freisetzung von Tolterodin, seinem 5-Hydroxymethyl-Metaboliten oder dem Racemat, das Tolterodin entspricht, oder einem pharmazeutisch verträglichen Salz davon bereitstellt, sodass ein im Wesentlichen konstanter Serumlevel der aktiven Komponente oder Komponenten für wenigsten 24 Stunden aufrecht erhalten wird, wobei sie einen mittleren Fluktuationsindex des Serumlevels der aktiven Komponente oder Komponenten bereitstellt, der nicht höher als 2,0 ist, wobei der Fluktuationsindex, FI, als FI=(Cmax - Cmin)/AUCτ/τ definiert ist, worin Cmax und Cmin die maximale bzw. minimale Konzentration der aktiven Komponenten ist, AUCτ die Fläche unter dem Serum-Konzentrationsprofil ist und τ die Länge des Dosierungsintervalls ist.

9. Formulierung nach Anspruch 8, die einen Fluktuationsindex von nicht höher als 1,0 bereitstellt.

10. Formulierung nach Anspruch 8 oder 9, wobei das 24-Stunden-Serumprofil, ausgedrückt als die AUC von ungebundenem Tolterodin und 5-Hydroxymethyl-Metabolit, von 5 bis 150 nM*h ist.

11. Formulierung nach Anspruch 8, 9 oder 10, wobei der Serumlevel von ungebundenem Tolterodin und 5-Hydroxymethyl-Metabolit im Bereich von 0,2 bis 6,3 nM ist.

12. Formulierung nach einem der Ansprüche 8-11, die eine Kapsel oder Tablette zur oralen Verabreichung einmal täglich ist.

13. Formulierung nach einem der Ansprüche 8-12, die eine kontrollierte Freisetzung von Tolterodin oder einem pharmazeutisch verträglichen Salz davon bereitstellt.

Revendications

1. Utilisation de la toltérodine, de son métabolite 5-hydroxyméthyle ou du racémate correspondant à la toltérodine, ou d'un sel pharmaceutiquement acceptable de ceux-ci, dans la fabrication d'un médicament pour le traitement de la vessie instable ou hyperactive, ce médicament étant sous la forme d'une formulation orale à libération contrôlée capable de maintenir un taux sérique sensiblement constant du ou des groupe(s) fonctionnel(s) actif(s) pendant au moins 24 heures, de telle sorte que la formulation à libération contrôlée offre un indice de fluctuation moyen dudit taux sérique du ou des groupe(s) fonctionnel(s) actif(s) qui n'est pas supérieur à 2,0, ledit indice de fluctuation, FI, étant défini comme étant FI = (Cmax - Cmin)/AUCτ/τ, Cmax et Cmin étant respectivement les concentrations maximale et minimale des groupes fonctionnels actifs, AUCτ étant l'aire sous la courbe de concentration sérique

et τ étant la longueur de l'intervalle entre administrations.

2. Utilisation selon la revendication 1, dans laquelle l'indice de fluctuation n'est pas supérieur à 1,0.

3. Utilisation selon la revendication 1 ou la revendication 2, dans laquelle le médicament offre une courbe sérique sur 24 heures, exprimée en tant que AUC de la toltérodine non-liée et du métabolite 5-hydroxyméthyle, qui est comprise entre 5 et 150 nM*h.

4. Utilisation selon la revendication 1, 2 ou 3, dans laquelle le médicament offre un taux sérique de la toltérodine non-liée et du métabolite 5-hydroxyméthyle qui est situé dans la gamme allant de 0,2 à 6,3 nM.

5. Utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle la formulation à libération contrôlée est une gélule ou un comprimé devant être administré(e) par voie orale une fois par jour.

6. Utilisation selon l'une quelconque des revendications 1 à 5, dans laquelle le médicament contient de la toltérodine ou un sel pharmaceutiquement acceptable de celle-ci.

7. Utilisation selon l'une quelconque des revendications 1 à 6, dans laquelle le médicament est destiné au traitement de l'incontinence urinaire.

8. Formulation pharmaceutique orale à libération contrôlée contenant de la toltérodine, son métabolite 5-hydroxyméthyle ou le racémate correspondant à la toltérodine, ou un sel pharmaceutiquement acceptable de ceux-ci, cette formulation, lorsqu'elle est administrée à un patient, offrant une libération contrôlée de la toltérodine, de son métabolite 5-hydroxyméthyle ou du racémate correspondant à la toltérodine, ou d'un sel pharmaceutiquement acceptable de ceux-ci, de telle sorte qu'il est maintenu un taux sérique sensiblement constant du ou des groupe(s) fonctionnel(s) actif(s) pendant au moins 24 heures, grâce à quoi elle offre un indice de fluctuation moyen dudit taux sérique du ou des groupe(s) fonctionnel(s) actif(s) qui n'est pas supérieur à 2,0, ledit indice de fluctuation, FI, étant défini comme étant FI = (Cmax - Cmin)/AUCτ/τ, Cmax et Cmin étant respectivement les concentrations maximale et minimale du ou des groupe(s) fonctionnel(s) actif(s), AUCτ étant l'aire sous la courbe de concentration sérique et τ étant la longueur de l'intervalle entre administrations.

9. Formulation selon la revendication 8, qui offre un indice de fluctuation qui n'est pas supérieur à 1,0.

10. Formulation selon la revendication 8 ou 9, dans laquelle la courbe sérique sur 24 heures, exprimée en tant que AUC de la toltérodine non-liée et du métabolite 5-hydroxyméthyle, est comprise entre 5 et 150 nM*h.

11. Formulation selon la revendication 8, 9 ou 10, dans laquelle le taux sérique de la toltérodine non-liée et du métabolite 5-hydroxyméthyle est situé dans la gamme allant de 0,2 à 6,3 nM.

12. Formulation selon l'une quelconque des revendications 8 à 11, qui est une gélule ou un comprimé devant être administré(e) par voie orale une fois par jour.

13. Formulation selon l'une quelconque des revendications 8 à 12, qui offre une libération contrôlée de toltérodine ou d'un sel pharmaceutiquement acceptable de celle-ci.

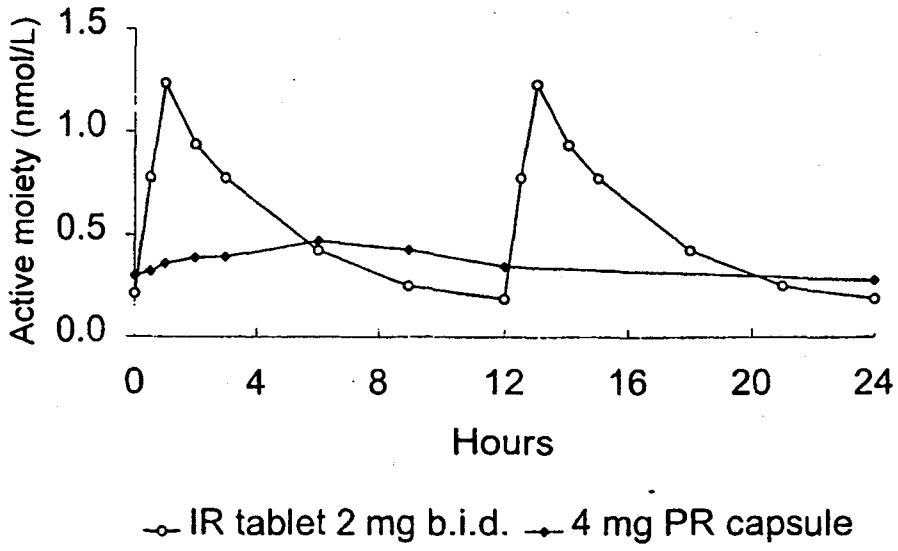
Active moiety (nmol/L)
1.5
1.0
0.5
0.0
0
4
8
12
16
20
24
Hours
IR tablet 2 mg b.i.d.
4 mg PR capsule

FIG. 1

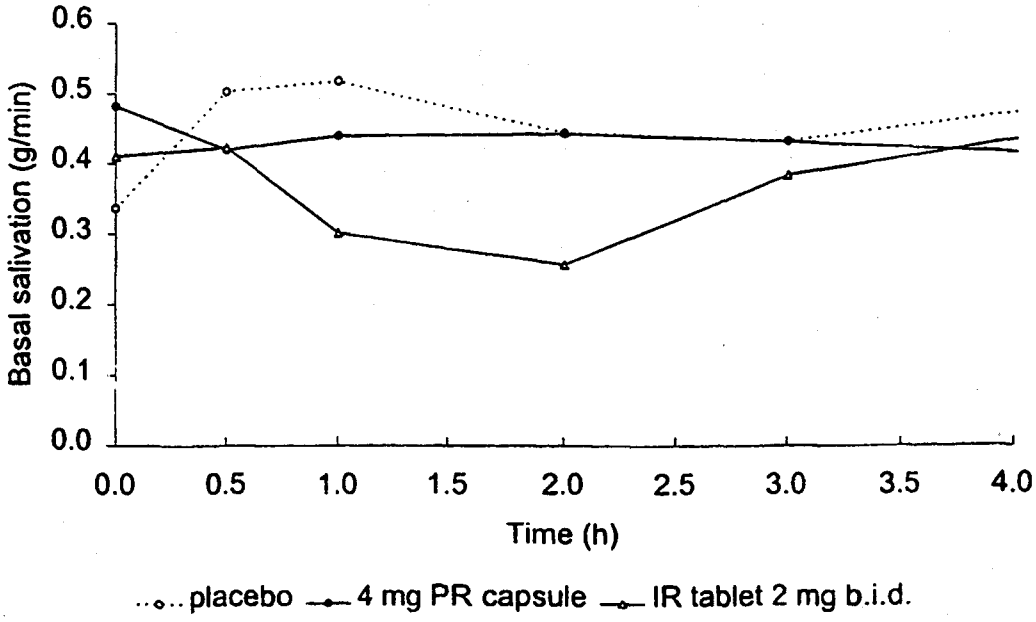
Basal salivation (g/min)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (h)
placebo
4 mg PR capsule
IR tablet 2 mg b.i.d.

FIG. 2

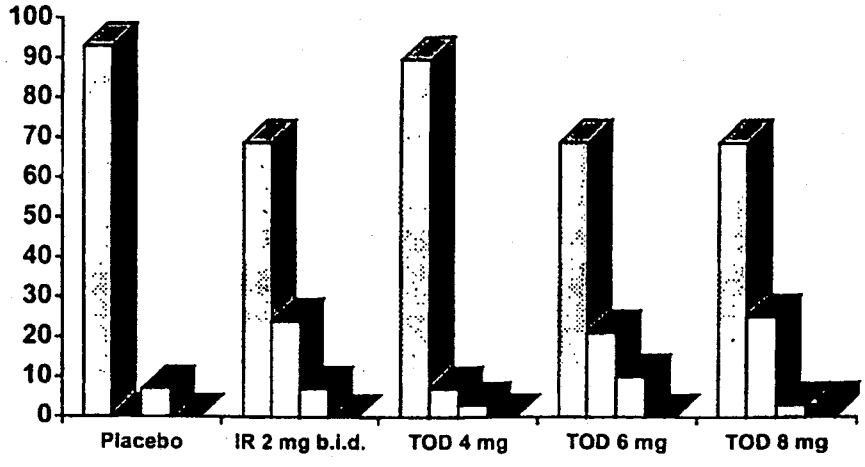
100
90
80
70
60
50
40
30
20
10
0
Placebo
IR 2 mg b.i.d.
TOD 4 mg
TOD 6 mg
TOD 8 mg

FIG. 3

REFERENCES CITED IN THE DESCRIPTION

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