Muscarinic receptor antagonists (also known as antimuscarinics or anticholinergics) such as Detrol® LA (tolterodine), Ditropan XL® (oxybutynin), and Vesicare® (solifenacin succinate) currently represent the major pharmacological options approved and marketed for the treatment of OAB. Antimuscarinics are believed to reduce bladder overactivity by inhibiting bladder smooth muscle contractility. Physicians and patients remain unsatisfied with the current therapies and desire medicines with improved efficacy and tolerability. In particular there is an unacceptably high incidence of dry mouth and constipation associated with these medications. Also, current medications do not adequately treat urgency, one of the most bothersome symptoms of OAB.

Accordingly, there remains a need for new medicines and methods of treatment which offer improved efficacy and tolerability in the treatment of symptoms associated with overactive bladder, above and beyond the currently available therapies.

SUMMARY

A method of treating one or more symptoms associated with overactive bladder using a new synergistic treatment combination has now been discovered. The treatment combination according to the disclosure comprises a beta-3 adrenergic receptor agonist and a muscarinic receptor antagonist. The inventors have shown that this combination has unexpectedly increased efficacy for the treatment of one or more symptoms associated with OAB.

Accordingly, the disclosure encompasses treatment combinations comprising (i) a therapeutically effective amount of a beta-3 adrenergic receptor agonist, and (ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a muscarinic receptor antagonist. The disclosure also encompasses methods of treating one or more symptoms associated with overactive bladder in a mammal using (i) and (ii), either in a single dosage form or separately. Use of the combinations in medical therapy and use of the combinations in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder, are also provided.

In one aspect, the present disclosure provides use of a combination comprising:

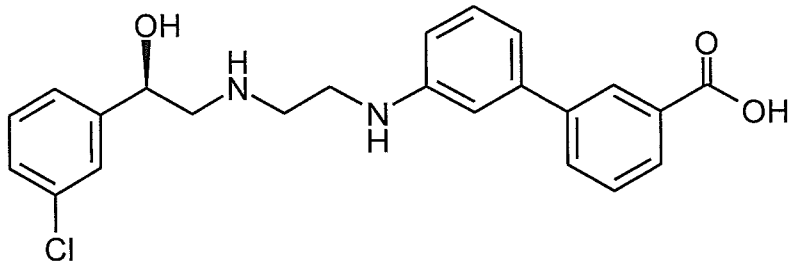
(i) a therapeutically effective amount of a beta-3 adrenergic receptor agonist selected from the group consisting of solabegron and pharmaceutically acceptable salts thereof; and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of a muscarinic receptor antagonist selected from the group consisting of tolterodine, oxybutynin, trospium, solifenacin, darifenacin, propiverine, fesoterodine, and pharmaceutically acceptable salts thereof,

in the manufacture of pharmaceutical composition for use in the treatment of one or more symptoms associated with overactive bladder.

In a one example of the present disclosure, there is provided a method of treating one or more symptoms associated overactive bladder in a mammal, comprising administering to said mammal:

(i) a therapeutically effective amount of a compound of Formula (I),

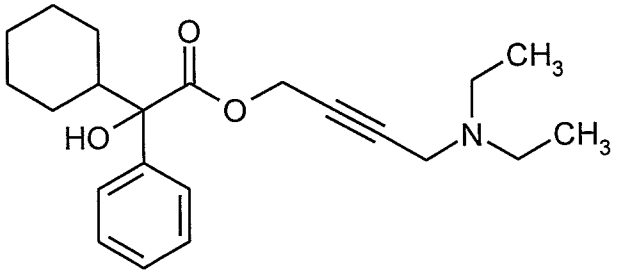


Formula (I)

or pharmaceutically acceptable salts (for example, the hydrochloride salt), pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a compound of Formula (II),

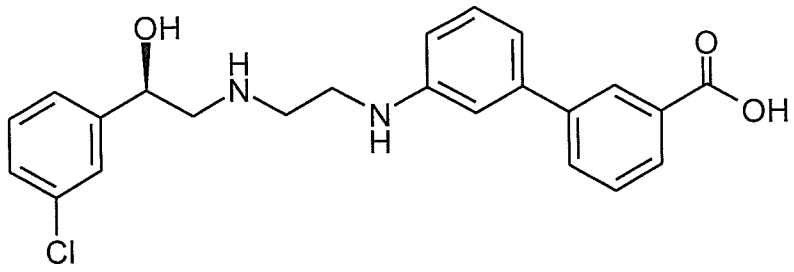


Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

In another example of the present disclosure, there is provided a combination comprising:

(i) a therapeutically effective amount of a compound of Formula (I),

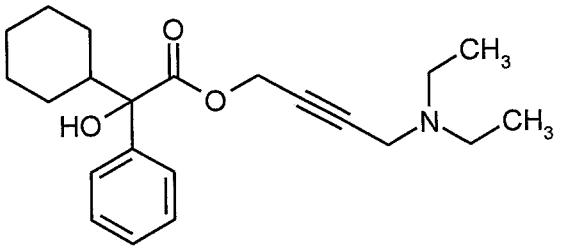


Formula (I)

or pharmaceutically acceptable salts (for example, the hydrochloride salt), pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a compound of Formula (II),

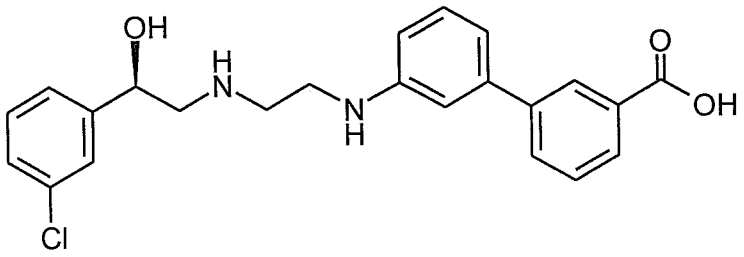


Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

In an additional example of the present disclosure, there is provided a combination comprising:

(i) a therapeutically effective amount of a compound of Formula (I),

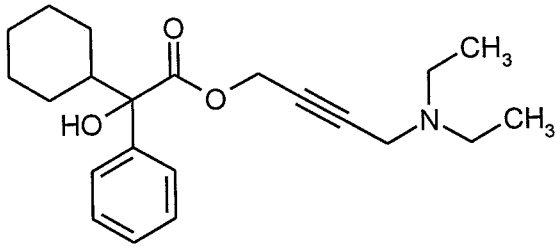


Formula (I)

or pharmaceutically acceptable salts (for example, the hydrochloride salt), pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a compound of Formula (II),

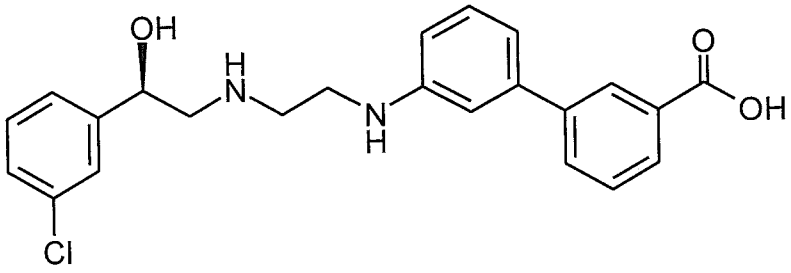


Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof, for use in medical therapy.

In an additional example of the present disclosure, there is provided a combination comprising:

(i) a therapeutically effective amount of a compound of Formula (I),

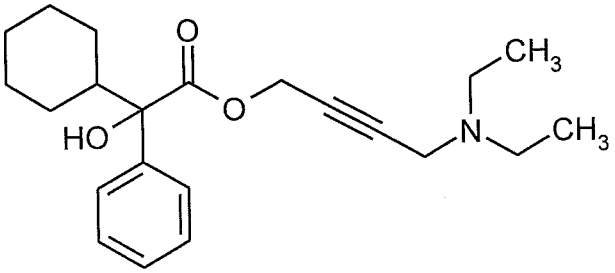


Formula (I)

or pharmaceutically acceptable salts (for example, the hydrochloride salt), pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a compound of Formula (II),

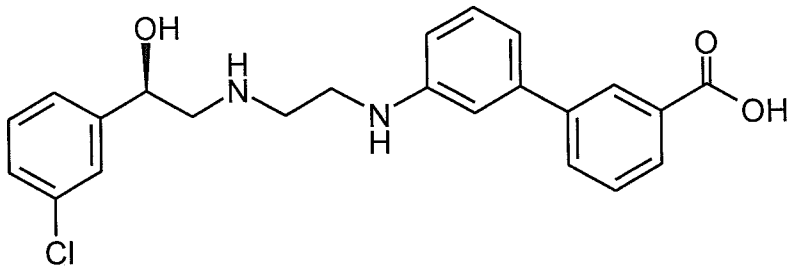


Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof, for use in the treatment of one or more symptoms associated with overactive bladder.

In another example of the present disclosure, there is provided the use of a combination comprising:

(i) a therapeutically effective amount of a compound of Formula (I),

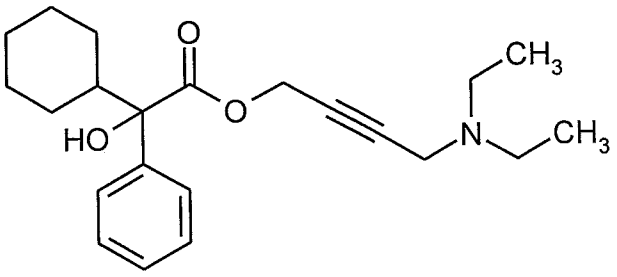


Formula (I)

or pharmaceutically acceptable salts (for example, the hydrochloride salt), solvates, or solvated pharmaceutically acceptable salts thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a compound of Formula (II),



Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof, in the preparation of a medicament useful in the treatment of one or more symptoms associated with overactive bladder.

DETAILED DESCRIPTION OF THE INVENTION

Unexpectedly, new synergistic drug combinations have been discovered which are useful in treating one or more symptoms associated with OAB. These combinations

What is claimed is:

1. Use of a combination comprising:

(i) a therapeutically effective amount of a beta-3 adrenergic receptor agonist selected from the group consisting of solabegron and pharmaceutically acceptable salts thereof; and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of a muscarinic receptor antagonist selected from the group consisting of tolterodine, oxybutynin, trospium, solifenacin, darifenacin, propiverine, fesoterodine, and pharmaceutically acceptable salts thereof,

in the manufacture of pharmaceutical composition for use in the treatment of one or more symptoms associated with overactive bladder.

2. The use of claim 1, wherein said one or more symptoms associated with overactive bladder are selected from the group consisting of frequency of urgency, nocturia, and urinary incontinence.

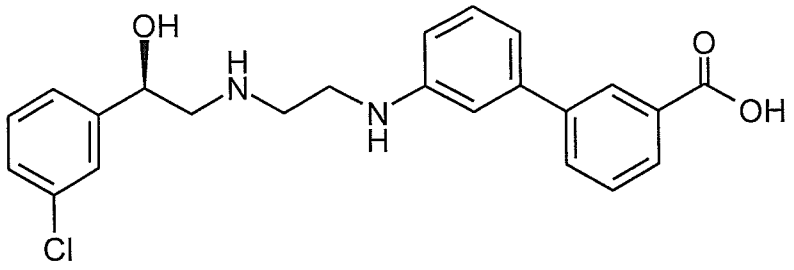
3. The use of claim 1 or 2, wherein components (i) and (ii) are to be co-administered.

4. The use of claim 1 or 2, wherein components (i) and (ii) are contained in a single dosage form.

5. The use of claim 1 or 2, wherein components (i) and (ii) are to be administered separately.

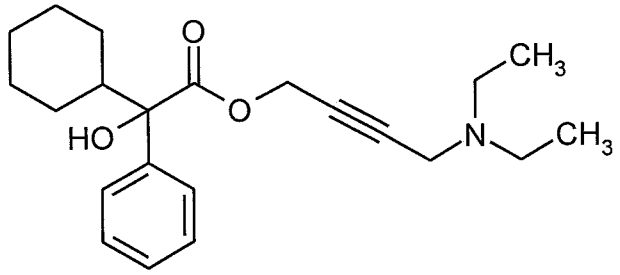
6. The use of claim 5, wherein there is a time delay between the administration of components (i) and (ii).

7. The use of any one of claims 1 to 6, wherein the beta-3 adrenergic receptor agonist is a compound of Formula (I):



Formula (I)

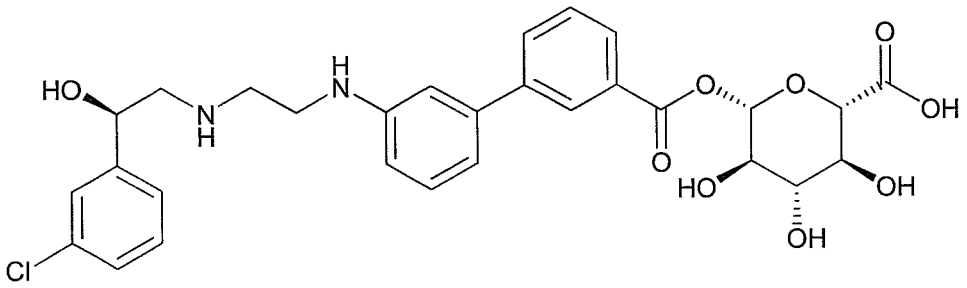
8. The use of any one of claims 1 to 7, wherein the muscarinic receptor antagonist is:



Formula (II)

9. The use of any one of claims 1 to 8, wherein the symptom associated with overactive bladder is increase in urinary micturition.

10. The use of any one of claims 1 to 9, wherein the pharmaceutical composition is to be administered with a compound of Formula (III):



Formula (III).