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 side effects, including 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 that offer improved efficacy and tolerability in the treatment of symptoms associated with overactive bladder, above and beyond the currently available therapies.

SUMMARY ~~OF THE INVENTION~~

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 ~~invention~~ present disclosure comprises a beta-3 adrenergic receptor agonist and a muscarinic receptor antagonist. The inventors have shown that this combination has unexpectedly increased potency and efficacy, and is useful for the treatment of one or more symptoms associated with OAB.

Accordingly, the ~~invention~~ present 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 combination being useful for relieving one or more symptoms associated with overactive bladder (OAB) in a synergistic manner, versus the individual components (i) and (ii). In an aspect, there is provided a synergistic combination for relieving one or more symptoms associated with overactive bladder (OAB) 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. In another aspect, there is provided a synergistic combination for relieving one or more symptoms associated with overactive bladder (OAB) comprising: (i) a therapeutically effective amount of solabegron, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof; and (ii) a therapeutically effective amount, or a sub-therapeutically effective amount of tolterodine, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof. The symptoms associated with overactive bladder are selected from the group consisting of frequency of urgency, frequency of mictruitions, nocturia, and urinary incontinence. The ~~invention~~ present 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 for the treatment of one or more symptoms associated with overactive bladder, 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.

The beta-3 adrenergic receptor agonist can comprise a compound selected from the group consisting of solabegron, CL-316,243, mirabegron, pharmaceutically acceptable salts thereof, pharmaceutically acceptable solvates thereof, and pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

The muscarinic receptor antagonist can comprise a compound selected from the group consisting of oxybutynin, tolterodine, solifenacin, pharmaceutically acceptable salts thereof, pharmaceutically acceptable solvates thereof, and pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

In a preferred embodiment the combination comprises (i) a therapeutically effective amount of solabegron, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof; and (ii) a therapeutically effective amount, or a sub-therapeutically effective amount of tolterodine, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof, the combination being useful for relieving one or more symptoms associated with overactive bladder (OAB) in a synergistic manner, versus the individual components (i) and (ii).

Another ~~aspect~~ embodiment of the ~~invention~~ present disclosure is directed to a method of treating one or more symptoms associated with overactive bladder in a mammal, comprising administering to the mammal (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.

In one embodiment of the method, the beta-3 adrenergic receptor agonist comprises a compound selected from the group consisting of solabegron, CL-316,243, mirabegron, pharmaceutically acceptable salts thereof, pharmaceutically acceptable solvates thereof, and pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

In a further embodiment of the method, the muscarinic receptor antagonist comprises oxybutynin, tolterodine, solifenacin, pharmaceutically acceptable sails thereof, pharmaceutically acceptable solvates thereof, and pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

In a preferred embodiment, the method of treating one or more symptoms associated with overactive bladder in a mammal, comprises administering to the mammal (i) a therapeutically effective amount of solabegron, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof; and (ii) a therapeutically effective amount, or a sub-therapeutically effective amount of tolterodine, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

The method can comprise co-administration of components (i) and (ii). In one embodiment, components (i) and (ii) are contained in a single dosage form. In another embodiment, co-administration comprises administering together the separately formulated components (i) and (ii).

The method can also comprise separate administration of components (i) and (ii). When administered separately there can be a time delay between the administration of components (i) and (ii).

In a preferred embodiment, the salt of solabegron comprises the hydrochloride salt.

In another aspect, there is provided the use of (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, in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder in a mammal.

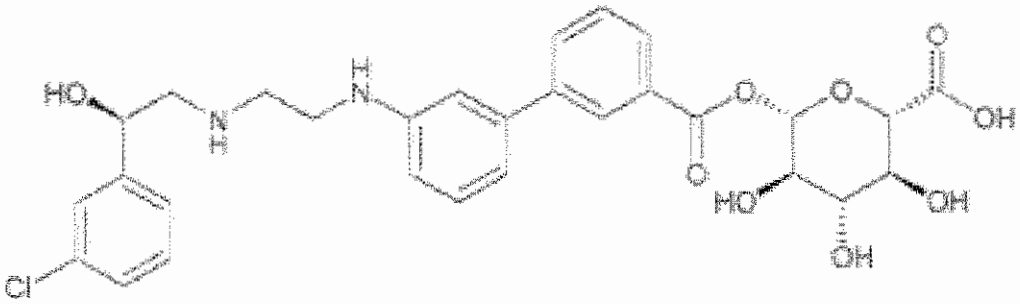
In another aspect, there is provided the use of (i) a therapeutically effective amount of solabegron, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof; and (ii) a therapeutically effective amount, or a sub-therapeutically effective amount of tolterodine, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof, in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder in a mammal.

In ~~A~~another aspect, there is provided ~~embodiment is directed to~~ a pharmaceutical composition comprising the combination of components (i) and (ii) as disclosed herein, and further comprising one or more pharmaceutically acceptable carriers, diluents, or excipients.

A further embodiment is directed to a method of treating one or more symptoms associated with overactive bladder in a mammal, comprising the step of administering to a mammal in need thereof, a therapeutically effective amount of the above-identified combination of components (i)

and (ii). In another aspect, there is provided the use of the combination as disclosed herein, in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder. In another aspect, there is provided the use of a therapeutically effective amount of the pharmaceutical composition as disclosed herein in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder in a mammal.

Another embodiment is directed to a method in which component (i) comprises solabegron, wherein component (i) further comprises the compound of Formula (III)



acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

8. The combination of claim 6, wherein said muscarinic receptor antagonist comprises tolterodine, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

9. The combination of claim 6, wherein said muscarinic receptor antagonist comprises solifenacin, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

10. A synergistic combination for relieving one or more symptoms associated with overactive bladder (OAB) comprising:

(i) a therapeutically effective amount of solabegron, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of tolterodine, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

11. ~~A method of treating one or more symptoms associated with overactive bladder in a mammal, comprising administering to said mammal:~~

Use of (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, in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder in a mammal.

12. The ~~method~~ use of claim 11, wherein said one or more symptoms associated with overactive bladder are selected from the group consisting of frequency of urgency, frequency of mictruitions, nocturia, and urinary incontinence.

13. The ~~method~~ use of claim 11 or 12, wherein said beta-3 adrenergic receptor agonist comprises a compound selected from the group consisting of solabegron,

CL-316,243, mirabegron, pharmaceutically acceptable salts thereof, pharmaceutically acceptable solvates thereof, and pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

14. The ~~method~~ use of claim 13, wherein said beta-3 adrenergic receptor agonist comprises solabegron, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

15. The ~~method~~ use of claim 13, wherein said beta-3 adrenergic receptor agonist comprises mirabegron, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

16. The ~~method~~ use of any one of claims 11-15, wherein said muscarinic receptor antagonist comprises oxybutynin, tolterodine, solifenacin, pharmaceutically acceptable salts thereof, pharmaceutically acceptable solvates thereof, and pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

17. The ~~method~~ use of claim 16, wherein said muscarinic receptor antagonist comprises oxybutynin, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

18. The ~~method~~ use of claim 16, wherein said muscarinic receptor antagonist comprises tolterodine, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

19. The ~~method~~ use of claim 16, wherein said muscarinic receptor antagonist comprises solifenacin, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

~~20. A method of treating one or more symptoms associated with overactive bladder in a mammal, comprising administering to said mammal:~~

20. Use of (i) a therapeutically effective amount of solabegron, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of tolterodine, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof, in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder in a mammal.

21. The ~~method~~ use of any one of claims 11-20, wherein components (i) and (ii) are co-administered.

22. The use ~~method~~ of any one of claims 11-21, wherein components (i) and (ii) are contained in a single dosage form.

23. The use ~~method~~ of any one of claims 11-20, wherein components (i) and (ii) are administered separately.

24. The use ~~method~~ of any one of claims 11-20 or 23, wherein there is a time delay between the administration of components (i) and (ii).

25. The combination according to claim 4, wherein the salt of solabegron comprises the hydrochloride salt.

26. The use ~~method~~ according to claim 14, wherein the salt of solabegron comprises the hydrochloride salt.

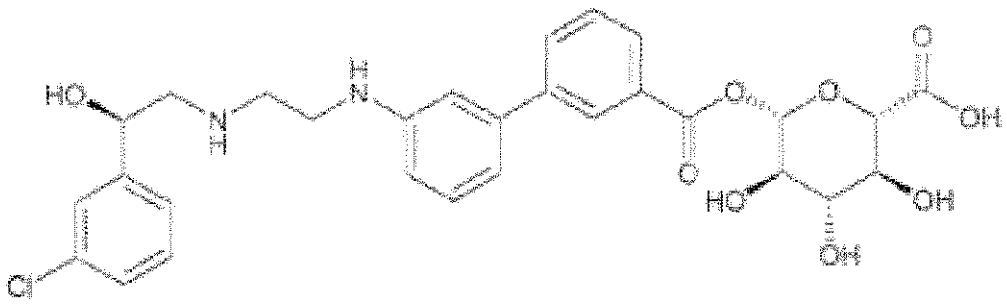
27. A pharmaceutical composition comprising the combination of any one of claims 1-10 or 25, further comprising one or more pharmaceutically acceptable carriers, diluents, or excipients.

28. Use of the combination of any one of claims 1-10 or 25, in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder.

~~29. A method of treating one or more symptoms associated with overactive bladder in a mammal, comprising the step of administering to a mammal in need thereof, a therapeutically effective amount of the combination of any one of claims 1-10 or 25.~~

~~3029~~. ~~A method of treating one or more symptoms associated with overactive bladder in a mammal, comprising the step of administering to a mammal in need thereof,~~ Use of a therapeutically effective amount of the pharmaceutical composition of claim 27 in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder in a mammal.

~~3130~~. The method of claim 14 or 26, wherein component (i) further comprises the compound of Formula (III)



Formula (III).

~~3231~~. The combination of any one of claims 1-10 or 25 for the treatment of overactive bladder (OAB).