**AUSTRALIAN PRODUCT INFORMATION - SPIOLTO® RESPIMAT® 2.5 micrograms/ 2.5 micrograms tiotropium/olodaterol solution for inhalation (with dose indicator)**

## 1 NAME OF THE MEDICINE

tiotropium (as bromide monohydrate) and olodaterol (as hydrochloride)

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SPIOLTO RESPIMAT is a soft mist inhaler delivering tiotropium + olodaterol solution for inhalation. The SPIOLTO RESPIMAT cartridge containing the solution for inhalation is only for use with the SPIOLTO RESPIMAT re-usable inhaler. The delivered dose is 2.5 microgram tiotropium and 2.5 microgram olodaterol per puff (2 puffs comprise one medicinal dose) and is equivalent to 3.124 micrograms tiotropium bromide monohydrate and 2.7 micrograms olodaterol hydrochloride. Two puffs equal one dose of 5 micrograms/5 micrograms. The delivered dose is the dose which is available for the patient after passing the mouthpiece.

Excipients with known effect:

SPIOLTO RESPIMAT contains 0.0011 mg benzalkonium chloride in each actuation.

For the full list of excipients, see Section 6.1 List of excipients.

## 3 PHARMACEUTICAL FORM

SPIOLTO RESPIMAT solution for inhalation is a clear, colourless solution contained in a plastic container crimped into an aluminium cylinder (cartridge) with a dose counter, for use with the SPIOLTO RESPIMAT re-usable inhaler. The SPIOLTO RESPIMAT re-usable inhaler has a light-green coloured cap. The SPIOLTO RESPIMAT cartridge is only intended for use with the SPIOLTO RESPIMAT re-usable inhaler.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

SPIOLTO RESPIMAT is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

### 4.2 DOSE AND METHOD OF ADMINISTRATION

SPIOLTO RESPIMAT is for oral inhalation only.

**Adults**

The recommended dose for adults is 5 microgram tiotropium and 5 microgram olodaterol given as two puffs from the SPIOLTO RESPIMAT inhaler once daily, at the same time of the day (see Section 4.2 Dose and Method of Administration, Instructions for Use and Handling).

**Children**

COPD does not normally occur in children. The safety and effectiveness of SPIOLTO RESPIMAT in the paediatric population have not been established.

**Elderly**

Elderly patients can use SPIOLTO RESPIMAT at the recommended dose.

**Patients with hepatic impairment**

SPIOLTO RESPIMAT contains olodaterol, which is predominantly metabolised in the liver.

Patients with mild and moderate hepatic impairment can use SPIOLTO RESPIMAT at the recommended dose.

There are no data available for use of SPIOLTO RESPIMAT in patients with severe hepatic impairment.

**Patients with renal impairment**

Renally impaired patients can use SPIOLTO RESPIMAT at the recommended dose.

SPIOLTO RESPIMAT contains tiotropium, which is a predominantly renally excreted drug. Therefore, SPIOLTO RESPIMAT use should be monitored closely in patients with moderate to severe renal impairment.

**Instructions for Use and Handling**

To ensure proper administration of SPIOLTO RESPIMAT, the patient should be shown how to use the SPIOLTO RESPIMAT re-usable inhaler by a physician or other health professional.

(see RESPIMAT re-usable inhaler Instructions for Use)

## 4.3 CONTRAINDICATIONS

SPIOLTO RESPIMAT is contraindicated in patients with hypersensitivity to tiotropium or olodaterol or to any of the excipients.

SPIOLTO RESPIMAT is also contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, e.g. ipratropium or oxitropium.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**General warnings**

SPIOLTO RESPIMAT should not be used more frequently than once daily.

SPIOLTO RESPIMAT contains 0.0011 mg benzalkonium chloride in each actuation.

Benzalkonium chloride may cause wheezing and breathing difficulties. Patients with asthma are at an increased risk for these adverse events.

**Asthma**

SPIOLTO RESPIMAT should not be used in the treatment of asthma as the efficacy and safety have not been studied in this indication.

The long-term efficacy and safety of olodaterol in the treatment of asthma have not been studied. LABAs may increase the risk of asthma-related hospitalisations and death. Data from a large placebo-controlled study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABAs, including olodaterol, one of the active ingredients in SPIOLTO RESPIMAT.

**Acute bronchospasm**

SPIOLTO RESPIMAT is not indicated for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy.

**Deterioration of disease and acute episodes**

SPIOLTO RESPIMAT should not be initiated in patients with acutely deteriorating COPD. In this case, the patient's COPD management plan should direct the patient to seek medical advice immediately, and a re-evaluation of the patient and the COPD treatment regimen should be undertaken. Increasing the daily dosage of SPIOLTO RESPIMAT beyond the recommended dose is not appropriate.

**Hypersensitivity**

As with all medications, immediate hypersensitivity reactions may occur after administration of SPIOLTO RESPIMAT.

**Paradoxical bronchospasm**

As with other inhaled medicines SPIOLTO RESPIMAT may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs SPIOLTO RESPIMAT should be discontinued immediately and alternative therapy substituted.

**Narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction**

Consistent with the anticholinergic activity of tiotropium, SPIOLTO RESPIMAT should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

In a meta-analysis of placebo-controlled trials, tiotropium was associated with a non-significant increase in the risk of urinary retention, and a significant increase in the risk of micturition difficulties.

**Eye symptoms**

Patients must be instructed in the correct administration of SPIOLTO RESPIMAT. Care must be taken not to allow the solution or mist to enter into the eyes. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop specialist advice should be sought immediately.

Miotic eye drops are not considered to be effective treatment.

**Systemic effects**

SPIOLTO RESPIMAT contains a long acting beta$_2$-adrenergic agonist. LABAs should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy and hypertension; in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval; and in patients who are unusually responsive to sympathomimetic amines.

**Cardiovascular effects**

Like other beta$_2$-adrenergic agonists, olodaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, treatment may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce ECG changes, such as flattening of the T wave and ST segment depression, although the clinical significance of these observations is unknown.

Patients with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalised for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (>100 beats per minute) were excluded from the clinical trials. Therefore the experience in these patient groups is limited. SPIOLTO RESPIMAT should be used with caution in these patient groups.

**Hypokalaemia**

Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions), which may increase the susceptibility to cardiac arrhythmias.

**Hyperglycaemia**

Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose.

**Use in hepatic impairment**

Based on pharmacokinetic data of the tiotropium and olodaterol monotherapies, patients with mild and moderate hepatic impairment can use SPIOLTO RESPIMAT at the recommended dose.

There are no data available for use of SPIOLTO RESPIMAT in patients with severe hepatic impairment. These patients should be closely monitored.

**Use in renal impairment**

Because tiotropium is a predominantly renally excreted drug, SPIOLTO RESPIMAT use should be monitored closely in patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min) (see Section 4.2 Dose and Method of Administration).

**Use in the elderly**

Elderly patients can use SPIOLTO RESPIMAT at the recommended dose.

**Paediatric use**

COPD does not normally occur in children. The safety and effectiveness of SPIOLTO RESPIMAT in the paediatric population have not been established.

**Effects on laboratory tests**

No data available

**Other**

SPIOLTO RESPIMAT should not be used in conjunction with any other medication containing LABAs or LAMAs (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Patients who have been taking inhaled, short acting beta$_2$-adrenergic agonists on a regular basis (e.g. four times a day) should be instructed to use them only for symptomatic relief of acute respiratory symptoms.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

**Tiotropium**

Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs which are commonly used in the treatment of COPD, methylxanthines, oral and inhaled steroids, without clinical evidence of drug interactions.

The chronic co-administration of tiotropium bromide with other anticholinergic medicines has not been studied. Therefore, the chronic co-administration of other anticholinergic drugs with SPIOLTO RESPIMAT is not recommended.

**Olodaterol**

*In vitro* studies indicated pharmacokinetic drug interactions involving CYP450 enzymes are not expected. Inhibitors of P-glycoprotein, OAT1, OAT3 or OCT1 may alter the systemic exposure to or disposition of olodaterol. Olodaterol was not an inhibitor of these transporters at clinically-relevant concentrations.

**Adrenergic agents**

Concomitant administration of other adrenergic agents may potentiate the undesirable effects of SPIOLTO RESPIMAT.

**Xanthine derivatives, steroids or diuretics**

Concomitant treatment with xanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate any hypokalaemic effect of adrenergic agonists (see Section 4.4 Special Warnings and Precautions for Use).

**Beta-blockers**

Beta-adrenergic blockers may weaken or antagonise the effect of olodaterol. Cardioselective beta-blockers could be considered, although they should be administered with caution.

**MAO inhibitors, tricyclic antidepressants, QTc prolonging drugs**

Monoamine oxidase inhibitors, or tricyclic antidepressants or other drugs known to prolong the QTc interval may potentiate the action of SPIOLTO RESPIMAT on the cardiovascular system.

**Pharmacokinetic drug-drug interactions**

In a drug interaction study with olodaterol using the strong dual CYP and P-gp inhibitor ketoconazole, a 1.7-fold increase of systemic exposure was observed (see Section 5.2 Pharmacokinetic Properties). No safety concerns were identified in clinical studies of up to one year with olodaterol at doses up to twice the recommended therapeutic dose. No dose adjustment of SPIOLTO RESPIMAT is necessary.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**

Clinical data on fertility are not available for tiotropium and olodaterol or the combination of both components. Nonclinical studies performed with the individual components tiotropium and olodaterol showed no adverse effect on fertility.

No reproduction toxicity studies for the combination were performed.

Tiotropium

Tiotropium (as bromide) did not affect the fertility of male or female rats when administered by inhalation at doses up to 2 mg/kg (750x the maximum recommended human daily dose of the drug, based on body surface area).

Olodaterol

Decreased epididymal and testicular weights were seen in rats at inhalational doses greater than or equal to 55 microgram/kg/day; however there was no effect on sperm count, concentration or motility. No impairment of male or female fertility or early embryonic development was seen in the rat at inhalational doses up to approximately 3,000 microgram/kg/day (plasma AUC more than 2,000 times the anticipated AUC in adults from a 5 microgram dose basis).

**Use in pregnancy (Category B3)**

There is a limited amount of data from the use of tiotropium in pregnant women. For olodaterol no clinical data on exposed pregnancies is available.

Tiotropium

Reproductive toxicity studies with tiotropium bromide administered by inhalation to rats and rabbits at doses up to 2.0 and 0.5 mg/kg/day, respectively, produced no evidence of fetal malformations. These doses correspond to 750x and 400x the maximum recommended human daily dose of the drug based on body surface area. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses.

Olodaterol

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures.

Olodaterol and/or its metabolites crossed the placenta in rats. In the rat, no teratogenic effects occurred after inhalation of doses up to 1,054 microgram/kg/day (plasma AUC approximately 3,000 times the anticipated AUC in adults). In pregnant rabbits, the administered inhalational dose of 2,489 microgram/kg/day olodaterol exhibited foetal toxicity characteristic of beta-adrenoceptor stimulation; these included patchy ossifications, short/bent bones, partially open eye, cleft palate, and cardiovascular abnormalities. No significant effects occurred at an inhalational dose of 974 microgram/kg/day (approximately 1,300 times the anticipated AUC in adults).

As a precautionary measure, it is preferable to avoid the use of SPIOLTO RESPIMAT during pregnancy.

The inhibitory effect of beta-adrenergic agonists, like olodaterol a component of SPIOLTO RESPIMAT, on uterine contraction should be taken into account.

**Use in lactation**

Clinical data from lactating women exposed to tiotropium and/or olodaterol are not available.

In preclinical studies for both tiotropium and olodaterol the substances and/or its metabolites have been detected in the milk of lactating rats, but it is not known whether tiotropium and/or olodaterol pass into human breast milk.

Therefore, SPIOLTO RESPIMAT should not be used in lactating women unless the expected benefit outweighs any possible risk to the infant.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that dizziness and blurred vision have been reported with the use of SPIOLTO RESPIMAT. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience such symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

The clinical development program of SPIOLTO RESPIMAT encompassed more than 19,000 patients with COPD, of which more than 5,900 COPD patients received a dose of 5 microgram tiotropium and 5 microgram olodaterol.

Side effects of SPIOLTO RESPIMAT were primarily identified from data obtained in 2 active-controlled, parallel-group, long-term treatment (52 weeks) clinical trials in COPD patients comparing SPIOLTO RESPIMAT with tiotropium and olodaterol. Additionally, a third active-controlled, parallel-group, long-term treatment (52 weeks) clinical trial in COPD patients comparing SPIOLTO RESPIMAT with tiotropium was conducted (Trial 9).

In the two pivotal trials (Trials 1 and 2) the overall incidence of adverse events in patients treated with SPIOLTO RESPIMAT was comparable to patients treated with the mono compound olodaterol at a dose of 5 microgram (74% and 76.6%, respectively). In the pooled analysis of all three long-term clinical trials (Trial 1, Trial 2 and Trial 9) the overall incidence

of adverse events in patients treated with SPIOLTO RESPIMAT was comparable to patients treated with the mono components tiotropium at a dose of 5 microgram (74.1% and 74.3% respectively). All undesirable effects previously reported with one of the individual components are considered undesirable effects with SPIOLTO RESPIMAT and are included in the adverse reactions listed below. In Trial 9, no new side effects were identified contributing more than 3,900 COPD patients treated with SPIOLTO RESPIMAT; furthermore the safety profile was consistent with that documented in the pivotal trials.

Table 1 shows all adverse events from Trials 1 and 2 that occurred with an incidence of >2% with SPIOLTO RESPIMAT treatment group and a higher incidence rate than the active comparator groups listed. The rates are derived from all reported adverse events of that type, regardless if considered drug-related or not by the clinical investigator.

**Table 1 Number and frequency of adverse events greater than 2% (and higher than any of the active comparator groups) in COPD patients exposed to SPIOLTO RESPIMAT: Pooled data from the two 52-week, double-blind, active-controlled clinical trials in COPD patients 40 years of age and older [Trials 1 and 2]**

| **Treatment** | **SPIOLTO RESPIMAT 5 µg/5 µg once daily** | **Tiotropium 5 µg once daily** | **Olodaterol 5 µg once daily** |
|---|---|---|---|
| ***System Organ Class*** **Adverse event** | **n = 1029 n (%)** | **n = 1033 n (%)** | **n = 1038 n (%)** |
| *Infections and infestations* | | | |
| Nasopharyngitis | 128 (12.4) | 121 (11.7) | 131 (12.6) |
| Pneumonia | 34 (3.3) | 26 (2.5) | 36 (3.5) |
| Bronchitis | 31 (3.0) | 23 (2.2) | 33 (3.2) |
| Influenza | 31 (3.0) | 22 (2.1) | 25 (2.4) |
| Urinary tract infection | 22 (2.1) | 30 (2.9) | 13 (1.3) |
| Sinusitis | 21 (2.0) | 13 (1.3) | 18 (1.7) |
| *Respiratory, thoracic and mediastinal disorders* | | | |
| Cough | 40 (3.9) | 45 (4.4) | 31 (3.0) |
| Dyspnoea | 39 (3.8) | 51 (4.9) | 38 (3.7) |
| *Musculoskeletal and connective tissue disorders* | | | |
| Back pain | 37 (3.6) | 19 (1.8) | 35 (3.4) |

Table 2 shows all adverse events from Trial 9 that occurred with an incidence of >2% with SPIOLTO RESPIMAT treatment group and a higher incidence rate than the active comparator group listed. The rates are derived from all reported adverse events of that type, regardless if considered drug-related or not by the clinical investigator.

**Table 2 Number and frequency of adverse events greater than 2% (and higher than the active comparator group) in COPD patients exposed to SPIOLTO RESPIMAT: Data from one 52-week, double-blind, active-controlled clinical trial in COPD patients 40 years of age and older [Trial 9]**

| **Treatment** | **SPIOLTO RESPIMAT 5 µg/5 µg once daily** | **Tiotropium 5 µg once daily** |
|---|---|---|
| ***System Organ Class*** **Adverse event** | **n = 3939 n (%)** | **n = 3941 n (%)** |
| *Infections and infestations* | | |
| Bronchitis | 123(3.1) | 122(3.1) |
| *Musculoskeletal and connective tissue disorders* | | |
| Back pain | 96(2.4) | 91(2.3) |
| *Injury, poisoning and procedural complications* | | |
| Overdose | 87(2.2) | 61(1.5) |
| *Nervous system disorders* | | |
| Headache | 113(2.9) | 99(2.5) |

Adverse reactions reported in all clinical trials with SPIOLTO RESPIMAT with a frequency of less than 2% are shown below according to system organ class. These also include all adverse reactions previously reported with one of the individual components.

Frequency is defined using the following convention:

| | |
|---|---|
| Very common | ≥ 1/10 |
| Common | ≥ 1/100 < 1/10 |
| Uncommon | ≥ 1/1,000 < 1/100 |
| Rare | ≥ 1/10,000 < 1/1,000 |
| Very rare | < 1/10,000 |
| Not known | cannot be estimated from the available data |

**Table 3 Adverse Drug Reaction frequencies**

| **System Organ Class** | **MedDRA term (Preferred Terms)** | **Frequency categories** |
|---|---|---|
| Infections and infestations | Nasopharyngitis | not known |
| Metabolism and nutrition disorders | Dehydration | not known |
| Nervous system disorders | Dizziness | uncommon |
| | Insomnia | rare |
| Eye disorders | Vision blurred | rare |
| | Glaucoma | not known |
| | Intraocular pressure increased | not known |

| System Organ Class | MedDRA term (Preferred Terms) | Frequency categories |
|---|---|---|
| Cardiac disorders | Atrial fibrillation | rare |
| | Tachycardia | uncommon |
| | Palpitations | rare |
| | Supraventricular tachycardia | rare |
| Vascular disorders | Hypertension | rare |
| Respiratory, thoracic and mediastinal disorders | Cough | uncommon |
| | Dysphonia | uncommon |
| | Laryngitis | rare |
| | Pharyngitis | rare |
| | Epistaxis | rare |
| | Bronchospasm | rare |
| | Sinusitis | not known |
| Gastrointestinal disorders | Dry mouth | uncommon |
| | Constipation | rare |
| | Oropharyngeal candidiasis | rare |
| | Gingivitis | rare |
| | Intestinal obstruction incl. ileus paralytic | not known |
| | Gastrooesophageal reflux disease | not known |
| | Dysphagia | not known |
| | Glossitis | not known |
| | Stomatitis | rare |
| Skin and subcutaneous tissue disorders, Immune system disorders | Hypersensitivity (including immediate reactions) | rare |
| | Angioneurotic oedema | rare |
| | Urticaria | rare |
| | Pruritus | rare |
| | Rash | rare |
| | Skin infection and skin ulcer | not known |
| | Dry skin | not known |
| Musculoskeletal and connective tissue disorders | Arthralgia | rare |
| | Back pain[1] | rare |
| | Joint swelling | rare |

| System Organ Class | MedDRA term (Preferred Terms) | Frequency categories |
|---|---|---|
| Renal and urinary disorders | Urinary retention (usually in men with predisposing factors) | rare |
| | Urinary tract infection | rare |
| | Dysuria | rare |

[1] undesirable effects reported with SPIOLTO RESPIMAT, but not with the individual components.

Many of the listed adverse effects can be assigned to either the anticholinergic properties of tiotropium or to the β-adrenergic properties of olodaterol, the components of SPIOLTO RESPIMAT.

In addition the occurrence of other undesirable effects related to the beta-adrenergic agonist class, which are not listed above, should be taken into consideration, such as arrhythmia, myocardial ischaemia, angina pectoris, hypotension, tremor, headache, nervousness, nausea, muscle spasms, fatigue, malaise, hypokalaemia, hyperglycaemia, and metabolic acidosis.

### 4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

**Symptoms**

High doses of tiotropium may lead to anticholinergic signs and symptoms.

No relevant adverse events, beyond dry mouth/throat and dry nasal mucosa in a dose-dependent [10-40 µg daily] incidence, were observed following 14 day dosing of up to 40 µg tiotropium inhalation solution in healthy subjects with the exception of pronounced reduction in salivary flow from day 7 onwards. No significant undesirable effects have been observed in six long-term studies in COPD patients when a daily dose of 10 µg tiotropium inhalation solution was given over 4-48 weeks.

An overdose of olodaterol is likely to lead to exaggerated effects typical of beta$_2$-adrenergic agonists, i.e. myocardial ischemia, hypertension or hypotension, tachycardia, arrhythmias, palpitation, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasms, nausea, fatigue, malaise, hypokalaemia, hyperglycaemia and metabolic acidosis.

**Treatment**

Treatment with SPIOLTO RESPIMAT should be discontinued. Supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardioselective beta-blockers may be considered, but only subject to extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics

ATC code: RO3AL06

**Mechanism of action**

SPIOLTO RESPIMAT

Tiotropium, a long acting muscarinic antagonist and olodaterol a long acting beta$_2$-adrenergic are administered together in the SPIOLTO RESPIMAT soft mist inhaler. These two active ingredients are intended to provide additive bronchodilation due to their different mode of action and different locations of the target receptors in the lungs.

Tiotropium

Tiotropium is a long-acting, muscarinic receptor antagonist (LAMA) (anticholinergic). It has similar affinity to the muscarinic receptor subtypes $M_1$ to $M_5$ ($K_D$ 5-41 pM). In the airways, inhibition by tiotropium of $M_3$-receptors at the smooth muscle results in relaxation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors. In non-clinical *in vitro* as well as *in vivo* studies, bronchoprotective effects were dose-dependent. Bronchoprotective effects lasting at least 24 hours in some of the *in vivo* studies. The long duration of effect of tiotropium is likely to be due to its slow dissociation from $M_3$-receptors. Tiotropium exhibited a significantly longer dissociation half-life from $M_3$ receptors than ipratropium.

Tiotropium, a N-quaternary anticholinergic agent, is topically (broncho-) selective when administered by inhalation. The high potency ($IC_{50}$ approximately 0.4 nM for $M_3$) and slow receptor dissociation is associated with a significant and long-acting bronchodilation in patients with chronic obstructive pulmonary disease (COPD).

The bronchodilation following inhalation of tiotropium is primarily a local effect on the airways, not a systemic one.

Olodaterol

Functional *in vitro* assays indicate greater activity of olodaterol at human beta$_2$-adrenoceptors than beta$_1$- or beta$_3$-adrenoceptors. The compound exerts its pharmacological effects by binding and activation of beta$_2$-adrenoceptors after topical administration by inhalation.

Activation of these receptors in the airways results in a stimulation of intracellular adenyl cyclase, an enzyme that mediates the synthesis of cyclic-3',5' adenosine monophosphate (cAMP). Elevated levels of cAMP induce bronchodilation by relaxation of airway smooth muscle cells.

Olodaterol has the pre-clinical profile of a long-acting selective beta$_2$-adrenoceptor agonist (LABA) with a fast onset of action and duration of action of at least 24 hours.

Beta-adrenoceptors are divided into three subtypes, beta$_1$-adrenoceptors predominantly expressed on cardiac muscle, beta$_2$-adrenoceptors predominantly expressed on airway smooth muscle and beta$_3$-adrenoceptors predominantly expressed on adipose tissue. Beta$_2$-agonists cause bronchodilation. Although the beta$_2$-adrenoceptor is the predominant adrenergic receptor in the airway smooth muscle it is also present on the surface of a variety of other cells, including lung epithelial and endothelial cells and in the heart. The precise function of beta$_2$-receptors in the heart is not known, but their presence raises the possibility that even highly selective beta$_2$-adrenergic agonists may have cardiac effects.

Effects on cardiac electrophysiology

*Tiotropium*

In a dedicated QT study involving 53 healthy volunteers, SPIRIVA 18 µg and 54 µg (i.e. three times the therapeutic dose) over 12 days did not significantly prolong QT intervals of the electrocardiogram (ECG).

*Olodaterol*

The effect of olodaterol on the QT/QTc interval of the ECG was investigated in 24 healthy male and female volunteers in a double-blind, randomised, placebo- and active (moxifloxacin) controlled study. Olodaterol at single doses of 10, 20, 30 and 50 microgram, demonstrated that compared with placebo, the mean changes from baseline in QT interval over 20 minutes to 2 hours after dosing increased dose-dependently from 1.6 (10 microgram olodaterol) to 6.5 ms (50 microgram olodaterol), with the upper limit of the two-sided 90% confidence intervals being less than 10 ms at all dose levels.

The effect of 5 microgram and 10 microgram olodaterol on heart rate and rhythm was assessed using continuous 24-hour ECG recording (Holter monitoring) in a subset of 772 patients in the 48-week, placebo-controlled Phase 3 Trials. There were no dose- or time-related trends or patterns observed for the magnitudes of mean changes in heart rate or premature beats. Shifts from baseline to the end of treatment in premature beats did not indicate meaningful differences between olodaterol 5 microgram, 10 microgram and placebo.

*SPIOLTO RESPIMAT*

In two 52-week randomised, double-blind trials using SPIOLTO RESPIMAT that enrolled 5,162 patients with COPD, ECG assessments were performed post-dose on days 1, 85, 169, and 365. In a pooled analysis the number of subjects with changes from baseline-corrected QT interval of >30 ms using both the Bazett (QTcB) and Fredericia (QTcF), corrections of QT for heart rate ranged from 4.9-6.4% (QTcB) and 1.3-4.7% (QTcF) for the SPIOLTO RESPIMAT group compared to 5.0-6.0% (QTcB) and 1.3-4.4% (QTcF) for olodaterol 5 microgram and 5.3-6.5% (QTcB) and 2.1-4.6% (QTcF) for tiotropium 5 microgram across the assessments conducted.

**Clinical trials**

The Phase III clinical development program for SPIOLTO RESPIMAT included three randomised, double-blind trials:

(i) two replicate, 52 week parallel group trials comparing SPIOLTO RESPIMAT with tiotropium 5 microgram and olodaterol 5 microgram (1,029 received SPIOLTO RESPIMAT) [Trials 1 and 2]
(ii) one 6 week cross-over trial comparing SPIOLTO RESPIMAT with tiotropium 5 microgram and olodaterol 5 microgram and placebo (139 received SPIOLTO RESPIMAT) [Trial 3].

In these trials, the comparator products, tiotropium 5 microgram, olodaterol 5 microgram and placebo, were administered via the RESPIMAT inhaler.

All studies included lung function measurements (forced expiratory volume in one second, $FEV_1$). In the 52 week studies, lung function was measured up to 3 hours post-dose (12 hours post-dose in a subset of patients) and at 23-24 hours post-dose; the primary lung function efficacy endpoints were change from pre-treatment baseline (response) in $FEV_1$ $AUC_{0-3h}$ and trough $FEV_1$ after 24 weeks. In the 6 week study, lung function was measured up to 12 hours post-dose and at 22-24 hours post-dose; the primary efficacy endpoint was $FEV_1$ $AUC_{0-24h}$ response after 6 weeks. The 52 week trials also included the St. George's Respiratory Questionnaire (SGRQ) as a primary endpoint as a measure of health-related quality of life and the Mahler Transition Dyspnoea Index (TDI) as a key secondary endpoint as a measure of dyspnoea.

Patients enrolled into the Phase III program were 40 years of age or older with a clinical diagnosis of COPD, had a smoking history of more than 10 pack years and had moderate to very severe pulmonary impairment (post-bronchodilator $FEV_1$ less than 80% predicted normal (GOLD Stage 2-4); post-bronchodilator $FEV_1$ to FVC ratio of less than 70%).

Patient characteristics

The majority of the 5,162 patients recruited in the global, 52 week trials [Trials 1 and 2] were male (73%), white (71%) or Asian (25%), with a mean age of 64.0 years. Mean post-bronchodilator $FEV_1$ was 1.37 L (GOLD 2 (50%), GOLD 3 (39%), and GOLD 4 (11%)). Mean $\beta_2$-agonist responsiveness was 16.6% of baseline (0.171 L). Pulmonary medications allowed as concomitant therapy included inhaled steroids (47%) and xanthines (10%).

The 6 week trial [Trial 3] was conducted in Europe and North America. The majority of the 219 recruited patients were male (59%) and white (99%), with a mean age of 61.1 years. Mean post-bronchodilator $FEV_1$ was 1.55 L (GOLD 2 (64%), GOLD 3 (34%), GOLD 4 (2%)). Mean $\beta_2$-agonist responsiveness was 15.9% of baseline (0.193 L). Pulmonary medications allowed as concomitant therapy included inhaled steroids (41%) and xanthines (4%).

Lung function

In the 52 week trials, SPIOLTO RESPIMAT, administered once daily in the morning, provided clear improvement in lung function within 5 minutes after the first dose compared to tiotropium 5 microgram (mean increase in $FEV_1$ of 0.137 L for SPIOLTO RESPIMAT vs. 0.058 L for tiotropium 5 microgram [p<0.0001] and 0.125 L for olodaterol 5 microgram [p=0.16]). In both studies, significant improvements were observed in $FEV_1$ $AUC_{0-3h}$ response and trough $FEV_1$ response after 24 weeks (lung function primary endpoints) for SPIOLTO RESPIMAT compared to tiotropium 5 microgram and olodaterol 5 microgram (Table 4).

**Table 4 Difference in $FEV_1$ $AUC_{0-3h}$ and trough $FEV_1$ response for SPIOLTO RESPIMAT compared to tiotropium 5 microgram, olodaterol 5 microgram after 24 weeks [Trials 1 and 2]**

| | **$FEV_1$ $AUC_{0-3h}$ response** | | | | **Trough $FEV_1$ response** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Trial 1** | | **Trial 2** | | **Trial 1** | | **Trial 2** | |
| | **n** | **Mean (95% CI)** | **n** | **Mean (95% CI)** | **n** | **Mean (95% CI)** | **n** | **Mean (95% CI)** |
| **SPIOLTO RESPIMAT versus** | 522 | -- | 502 | -- | 521 | -- | 497 | -- |
| **Tiotropium 5 microgram** | 526 | 0.117 L (0.094, 0.140) | 500 | 0.103 L (0.078, 0.127) | 520 | 0.071 L (0.047, 0.094) | 498 | 0.050 L (0.024, 0.075) |
| **Olodaterol 5 microgram** | 525 | 0.123 L (0.100, 0.146) | 507 | 0.132 L (0.108, 0.157) | 519 | 0.082 L (0.059, 0.106) | 503 | 0.088 L (0.063, 0.113) |

Pre-treatment baseline $FEV_1$: Trial 1 = 1.16 L; Trial 2 = 1.15 L
p≤0.0001 for all comparisons

The increased bronchodilator effects of SPIOLTO RESPIMAT compared to tiotropium 5 microgram and olodaterol 5 microgram were maintained throughout the 52 week treatment period. SPIOLTO RESPIMAT also improved morning and evening PEFR (peak expiratory flow rate) compared to tiotropium 5 microgram and olodaterol 5 microgram as measured by patient's daily recordings.

In the subset of patients who completed extended lung function measurements up to 12 hours post-dose, SPIOLTO RESPIMAT showed a significantly greater $FEV_1$ response compared to tiotropium 5 microgram and olodaterol 5 microgram over the full 24 hour dosing interval (Figure 1, Table 5).

**Figure 1 $FEV_1$ profile for SPIOLTO RESPIMAT, tiotropium 5 microgram and olodaterol 5 microgram over a continuous 24 hour dosing interval after 24 weeks (12 hr pulmonary function testing (PFT) subset from Trials 1 and 2; combined dataset)**

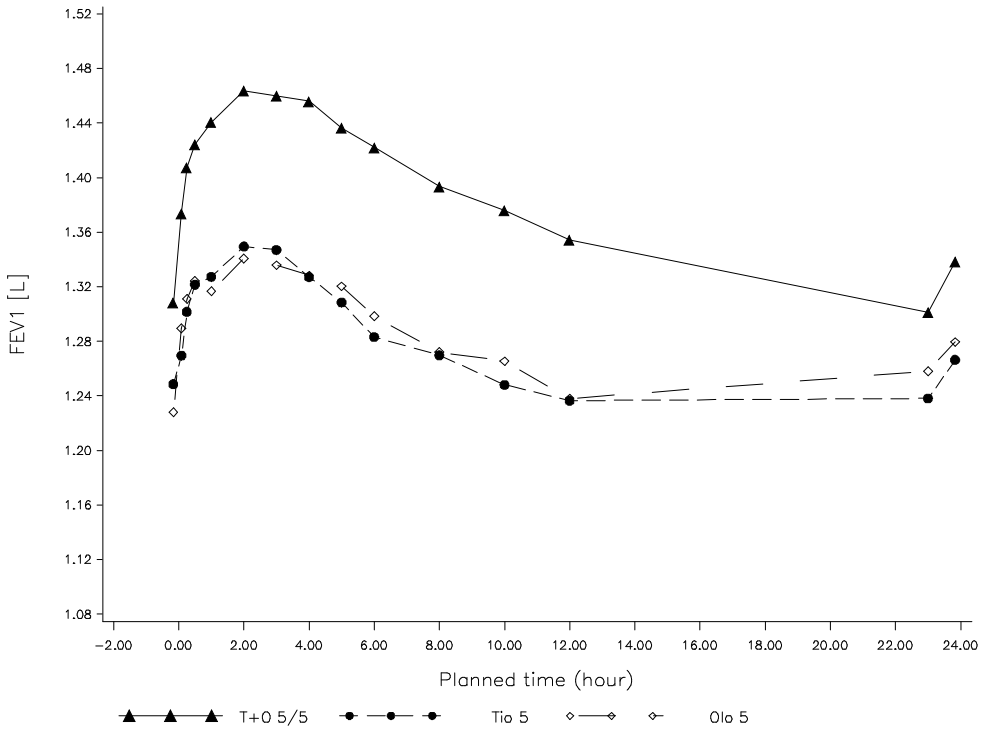



**Table 5 Difference in $FEV_1$ for SPIOLTO RESPIMAT compared to tiotropium 5 microgram and olodaterol 5 microgram over a continuous 24 hour dosing interval after 24 weeks (12 hr PFT subset from Trials 1 and 2; combined dataset)**

| | n | 12 hr mean (95% CI) | 24 hr mean (95% CI) |
|---|---|---|---|
| **SPIOLTO RESPIMAT versus** | 167 | | |
| **Tiotropium 5 microgram** | 160 | 0.123 (0.077, 0.169) | 0.106 (0.063, 0.149) |
| **Olodaterol 5 microgram** | 194 | 0.118 (0.074, 0.162) | 0.098 (0.057, 0.139) |

[1] Pre-treatment baseline $FEV_1$ = 1.17 L
p<0.0001 for all comparisons

In the 6 week trial, SPIOLTO RESPIMAT showed a significantly greater $FEV_1$ response compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo over the full 24 hour dosing interval (Figure 2, Table 6).

**Figure 2 $FEV_1$ profile for SPIOLTO RESPIMAT, tiotropium 5 microgram, olodaterol 5 microgram and placebo over a continuous 24 hour dosing interval after 6 weeks (Trial 3)**

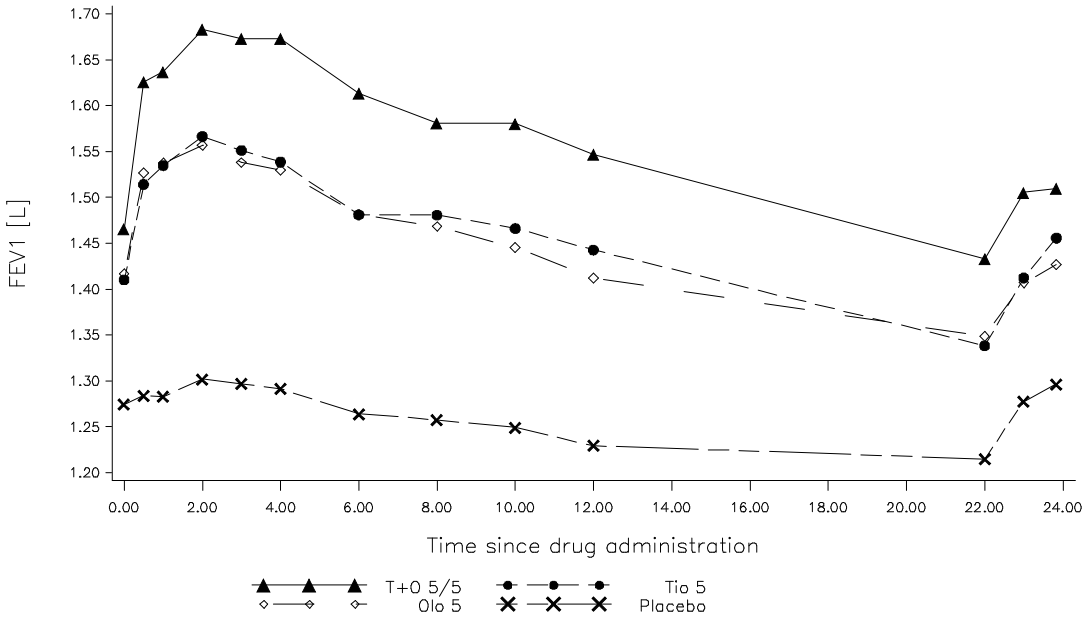



**Table 6 Difference in $FEV_1$ (L) for SPIOLTO RESPIMAT compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo over a continuous 24 hour dosing interval after 6 weeks (Trial 3)**

| | n | 3 hr mean (95% CI) | n | 12 hr mean (95% CI) | 24 hr mean[1] (95% CI) | Trough (95% CI) |
|---|---|---|---|---|---|---|
| **SPIOLTO RESPIMAT versus** | 138 | | 138 | | | |
| **Tiotropium 5 microgram** | 137 | 0.109 (0.077, 0.141) | 135 | 0.119 (0.089, 0.149) | 0.110 (0.082, 0.139) | 0.079 (0.045, 0.113) |
| **Olodaterol 5 microgram** | 138 | 0.109 (0.078, 0.141) | 136 | 0.126 (0.096, 0.156) | 0.115 (0.087, 0.143) | 0.092 (0.059, 0.126) |
| **Placebo** | 135 | 0.325 (0.293, 0.357) | 132 | 0.319 (0.289, 0.349) | 0.280 (0.252, 0.309) | 0.207 (0.173, 0.241) |

Pre-treatment baseline $FEV_1$ = 1.30 L
[1] Primary endpoint
p<0.0001 for all comparisons

Dyspnoea

After 24 weeks (Trials 1 and 2), SPIOLTO RESPIMAT significantly improved mean TDI focal score compared to tiotropium 5 microgram and olodaterol 5 microgram (Table 7). More patients treated with SPIOLTO RESPIMAT had a clinically meaningful improvement in TDI focal score (MCID, defined as a value of at least 1 unit) compared to tiotropium 5 microgram (54.9% vs. 50.6%, p=0.0546) and olodaterol 5 microgram (54.9% vs. 48.2%, p=0.0026).

**Table 7 TDI focal score after 24 weeks of treatment (Trials 1 and 2)**

| | n | Treatment Mean | Difference to SPIOLTO RESPIMAT |
|---|---|---|---|
| | | | Mean (p-value) (95% CI) |
| SPIOLTO RESPIMAT | 992 | 1.98 | |
| Tiotropium 5 microgram | 978 | 1.63 | 0.36 (p=0.008) (0.09, 0.62) |
| Olodaterol 5 microgram | 984 | 1.56 | 0.42 (p=0.002) (0.16, 0.68) |

Rescue Medication Use

Patients treated with SPIOLTO RESPIMAT used less daytime and night-time rescue salbutamol compared to patients treated with tiotropium 5 microgram and olodaterol 5 microgram (Trials 1 and 2).

Exacerbations

Tiotropium 5 microgram has previously demonstrated a statistically significant reduction in risk of a COPD exacerbation compared to placebo. COPD exacerbations was included as an additional endpoint in the 52 week pivotal trials [Trials 1 and 2]. In the combined dataset, the proportion of patients experiencing a moderate/severe COPD exacerbation was 27.7% for SPIOLTO RESPIMAT, 28.8% for tiotropium 5 microgram and 31.9% for olodaterol 5 microgram.

In a one-year, randomised, double-blind, active-controlled parallel group clinical trial (Trial 9) SPIOLTO Respimat was compared with tiotropium 5 microgram on COPD exacerbations. All respiratory medications except anticholinergics, long-acting beta-agonists and combinations thereof were allowed as concomitant treatment, i.e. rapidly acting beta-agonists, inhaled corticosteroids and xanthines. The primary endpoint was the annualised rate of moderate to severe COPD exacerbations (3939 patients received SPIOLTO RESPIMAT and 3941 patients received tiotropium 5 microgram).

The majority of patients were male (71.4%) and Caucasian (79.3%). The mean age was 66.4 years, mean post-bronchodilator $FEV_1$ was 1.187 L (SD 0.381), and 29.4% of patients had a history of clinically important cardiovascular disease.

Exacerbations of COPD were defined as “a complex of lower respiratory events / symptoms (increase or new onset) related to the underlying COPD, with duration of three days or more, requiring a prescription of antibiotics and/or systemic steroids and/or hospitalisation”.

SPIOLTO RESPIMAT treatment resulted in an additional 7% reduction in the annualised rate of moderate to severe COPD exacerbations in comparison to tiotropium 5 microgram (rate ratio (RR) 0.93, 99% Confidence Interval (CI), 0.85-1.02, p=0.0498). The study was designed to reach a significance level of 1%. A post hoc analysis using a multiple covariate adjustment model, as done in other exacerbation studies, resulted in an additional 11% reduction in the annualised rate of moderate to severe COPD exacerbation in comparison to tiotropium 5 microgram (RR 0.89, 95% CI, 0.84-0.96, nominal p-value <0.01).

There was no significant difference in the risk of all-cause mortality between SPIOLTO RESPIMAT and tiotropium 5 microgram. During the planned study period (381 days), 107 deaths were observed for SPIOLTO RESPIMAT compared with 121 for tiotropium 5 microgram (HR 0.88, 95% CI, 0.68, 1.15, p=0.3485).

The analysis of the additional exacerbation trial (Trial 9) is displayed in Table 8.

**Table 8 Effect of SPIOLTO RESPIMAT on exacerbations (Trial 9)**

| **Study ($N_{Spiolto}$, $N_{tio\ 5}$)** | **Endpoints** | **SPIOLTO RESPIMAT** | **Tiotropium 5 microgram** | **Ratio** |
|---|---|---|---|---|
| **1-year Ph IIIb exacerbation study**<br><br>**(treated set: 3939, 3941)** | **Annualised rate of COPD exacerbation**<br><br>**Moderate to severe** | 0.90 | 0.97 | RR 0.93 (0.85, 1.02) 99% CI |
| | **Time to first COPD exacerbation**<br><br>**Moderate to severe** | Number of patients with event: 1746 | Number of patients with event: 1777 | HR 0.95 (0.87, 1.03) 99% CI |
| | **Annualised rate of hospitalised exacerbations** | 0.18 | 0.20 | RR 0.89 (0.76, 1.03) 95% CI |
| | **Time to first hospitalised COPD exacerbation** | Number of patients with event: 450 | Number of patients with event: 469 | HR 0.93 (0.82, 1.06) 95% CI |

Health-related Quality of Life

After 24 weeks (Trials 1 and 2), SPIOLTO RESPIMAT significantly improved mean SGRQ total score compared to tiotropium 5 microgram and olodaterol 5 microgram (Table 9); improvements were seen in all SGRQ domains. More patients treated with SPIOLTO RESPIMAT had a clinically meaningful improvement in SGRQ total score (MCID, defined as a decrease of at least 4 units from baseline) compared to tiotropium 5 microgram (57.5% vs. 48.7%, p=0.0001) and olodaterol 5 microgram (57.5% vs. 44.8%, p<0.0001).

**Table 9 SGRQ total and domain scores after 24 weeks of treatment (Trials 1 and 2)**

| | | n | Treatment Mean (change from baseline) | Difference from SPIOLTO RESPIMAT |
|---|---|---|---|---|
| | | | | Mean (p-value) (95% CI) |
| **Total score** | Baseline | | 43.5 | |
| | SPIOLTO RESPIMAT | 979 | 36.7 (-6.8) | |
| | Tiotropium 5 microgram | 954 | 37.9 (-5.6) | -1.23 (p=0.025) (-2.31, -0.15) |
| | Olodaterol 5 microgram | 954 | 38.4 (-5.1) | -1.69 (p=0.002) (-2.78, -0.61) |
| **Symptoms** | Baseline | | 51.9 | |
| | SPIOLTO RESPIMAT | 982 | 42.6 | |
| | Tiotropium 5 microgram | 957 | 45.5 | -2.94 (p=0.0008) (-4.65, -1.23) |
| | Olodaterol 5 microgram | 958 | 45.0 | -2.48 (p=0.0046) (-4.19, -0.76) |
| **Activities** | Baseline | | 58.0 | |
| | SPIOLTO RESPIMAT | 981 | 51.9 | |
| | Tiotropium 5 microgram | 959 | 53.2 | -1.34 (p=0.052) (-2.69, 0.01) |
| | Olodaterol 5 microgram | 958 | 54.0 | -2.11 (p=0.002) (-3.47, -0.76) |
| **Impact** | Baseline | | 32.6 | |
| | SPIOLTO RESPIMAT | 983 | 26.1 | |
| | Tiotropium 5 microgram | 960 | 26.8 | -0.67 (p=0.283) (-1.89, 0.55) |
| | Olodaterol 5 microgram | 959 | 27.2 | -1.11 (p=0.075) (-2.33, 0.11) |

In two additional 12 week (Trials 7 and 8), placebo-controlled clinical trials, SGRQ total score at 12 weeks was also included as primary endpoint as a measure of health-related quality of life.

In the 12 week trials, SPIOLTO RESPIMAT demonstrated an improvement compared with placebo at week 12 in mean SGRQ total score (primary endpoint) of -4.9 (95%CI: −6.9, −2.9; p<0.0001) and -4.6 (95%CI: −6.5, −2.6; p<0.0001). In a pooled supportive analysis of the 12-week trials, the proportion of patients with a clinically meaningful decrease in SGRQ total score (defined as a decrease of at least 4 units from baseline) at week 12 was greater for SPIOLTO RESPIMAT (52% [206/393]) compared with tiotropium 5 microgram (41% [159/384]; odds ratio: 1.56 (95%CI: 1.17, 2.07), p = 0.0022) and placebo (32% [118/370]; odds ratio: 2.35 (95%CI: 1.75, 3.16), p < 0.0001).

Inspiratory capacity, breathing discomfort and exercise endurance

The effect of SPIOLTO RESPIMAT on inspiratory capacity, breathing discomfort and symptom-limited exercise endurance was investigated in three randomised, double-blind trials in COPD patients:

(i) two replicate, 6 week cross-over trials comparing SPIOLTO RESPIMAT with tiotropium 5 microgram, olodaterol 5 microgram and placebo during constant work rate cycling (450 received SPIOLTO RESPIMAT) [Trials 4 and 5]

(ii) one 12 week parallel group trial comparing SPIOLTO RESPIMAT with placebo during constant work rate cycling (139 received SPIOLTO RESPIMAT) and constant speed walking (subset of patients) [Trial 6].

SPIOLTO RESPIMAT significantly improved inspiratory capacity compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo after 6 weeks (Trials 4 and 5; Table 10) and compared to placebo after 12 weeks (0.234 L, p<0.0001; 95% CI: 0.133, 0.336; Trial 6).

**Table 10 Difference in inspiratory capacity at rest (IC) (L) for SPIOLTO RESPIMAT compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo after 6 weeks [Trials 4 and 5]**

| | n | Trial 4[1] (95% CI) | n | Trial 5[2] (95% CI) |
|---|---|---|---|---|
| **SPIOLTO RESPIMAT versus** | 219 | | 218 | |
| **Tiotropium 5 microgram** | 213 | 0.114 (p<0.0001) (0.061, 0.167) | 208 | 0.088 (p=0.0005) (0.039, 0.137) |
| **Olodaterol 5 microgram** | 214 | 0.119 (p<0.0001) (0.065, 0.172) | 208 | 0.080 (p=0.0015) (0.031, 0.129) |
| **Placebo** | 211 | 0.244 (p<0.0001) (0.191, 0.298) | 202 | 0.265 (p<0.0001) (0.215, 0.315) |

[1] Pre-treatment baseline: 2.53 L
[2] Pre-treatment baseline: 2.59 L

In Trials 4 and 5, SPIOLTO RESPIMAT improved endurance time during constant work rate cycling by 20.9% and 13.4% compared to placebo (Table 11). In Trial 6, SPIOLTO RESPIMAT improved endurance time during constant work rate cycling by 12.6% after the first dose (in a subset of patients), by 22.9% after 6 weeks and by 13.8% after 12 weeks compared to placebo. The endurance time during constant speed-walking (in a subset of patients) increased by 20.6% after 6 weeks and by 20.9% after 12 weeks compared to placebo, although the result was not statistically significant (Table 12).

**Table 11 Geometric mean endurance time(s) during constant work rate cycle ergometry for SPIOLTO RESPIMAT compared to placebo after 6 weeks [Trials 4 and 5]**

| | n | Trial 4[1] (95% CI) | n | Trial 5[2] (95% CI) |
|---|---|---|---|---|
| **SPIOLTO RESPIMAT** | 212 | 454.1 | 216 | 465.7 |
| **Placebo** | 209 | 375.5 | 205 | 410.8 |
| **Ratio** | | 1.209 (p<0.0001) (1.132, 1.292) | | 1.134 (p<0.0001) (1.065, 1.206) |

[1] Pre-treatment baseline: 460.0 s
[2] Pre-treatment baseline: 434.3 s

**Table 12 Geometric mean endurance time(s) during constant work rate cycling and constant speed walking for SPIOLTO RESPIMAT compared to placebo after first dose, and after 6 and 12 weeks [Trial 6]**

| | Cycling | | | | | Walking | | |
|---|---|---|---|---|---|---|---|---|
| | n | First dose[1] (95% CI) | n | 6 weeks[2] | 12 weeks[2,3] (95% CI) | n | 6 weeks[4] | 12 weeks[4,5] (95% CI) |
| **SPIOLTO RESPIMAT** | 80 | 538.8 | 135 | 525.6 | 527.5 | 59 | 376.2 | 376.4 |
| **Placebo** | 77 | 478.6 | 121 | 427.7 | 463.6 | 50 | 312.0 | 311.4 |
| **Ratio** | | 1.126 (p=0.025) (1.015, 1.248) | | 1.229 (p=0.0002) (1.103, 1.370) | 1.138 (p=0.021) (1.020, 1.269) | | 1.206 (p=0.058) (0.994, 1.462) | 1.209 (p=0.055) (0.996, 1.467) |

[1] Pre-treatment baseline: 461.5 s
[2] Pre-treatment baseline: 443.0 s
[3] Primary endpoint
[4] Pre-treatment baseline: 311.2 s
[5] Key secondary endpoint

In Trials 4 and 5, SPIOLTO RESPIMAT decreased the slope of breathing discomfort during constant work rate cycling compared to placebo (nominal p<0.0005; Table 13).

**Table 13 Slope of breathing discomfort (Borg units/s) during constant work rate cycle ergometry for SPIOLTO RESPIMAT compared to placebo after 6 weeks [Trials 4 and 5]**

| | n | Trial 4[1] (95% CI) | n | Trial 5[2] (95% CI) |
|---|---|---|---|---|
| **SPIOLTO RESPIMAT** | 212 | 0.016 | 216 | 0.015 |
| **Placebo** | 209 | 0.018 | 205 | 0.018 |
| **Difference** | | -0.003 (p=0.0004) (-0.004, -0.001)* | | -0.003 (p<0.0001) (-0.004, -0.002)* |

[1] Pre-treatment baseline: 0.015 Borg units/s
[2] Pre-treatment baseline: 0.016 Borg units/s
*nominal p-value

## 5.2 PHARMACOKINETIC PROPERTIES

When tiotropium and olodaterol were administered in combination by the inhaled route, the pharmacokinetic parameters for each component were similar to those observed when each active substance was administered separately.

Tiotropium and olodaterol demonstrate linear pharmacokinetics in the therapeutic range. On repeated once-daily inhalation administration, steady-state of tiotropium is reached by day 7. Steady state of olodaterol is achieved after 8 days of once-daily inhalation, and accumulation is up to 1.8-fold as compared to a single dose.

### Absorption

*Tiotropium*:

Following inhalation by young healthy volunteers, urinary excretion data suggest that approximately 33% of the dose inhaled via the RESPIMAT inhaler reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Food is

not expected to influence the absorption of tiotropium. Maximum tiotropium plasma concentrations were observed 5-7 minutes after the inhalation *via* RESPIMAT. At steady state, peak tiotropium plasma concentrations of 10.5 pg/mL were achieved in COPD patients and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.60 pg/mL.

*Olodaterol*:

Olodaterol is rapidly absorbed, reaching maximum plasma concentrations generally within 10 to 20 minutes following drug inhalation. In healthy volunteers, the absolute bioavailability of olodaterol following inhalation was estimated to be approximately 30%, whereas the absolute bioavailability was below 1% when given as an oral solution. Thus, the systemic availability of olodaterol after inhalation is mainly determined by lung absorption, while any swallowed portion of the dose only negligibly contributes to systemic exposure.

**Distribution**

*Tiotropium:*

Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier to any relevant extent.

*Olodaterol:*

Olodaterol exhibits multi-compartmental disposition kinetics after inhalation as well as after intravenous administration. The volume of distribution is high (1,110 L), suggesting extensive distribution into tissue. *In vitro* binding of [$^{14}$C] olodaterol to human plasma proteins is independent of concentration and is approximately 60%.

**Metabolism**

*Tiotropium*:

Metabolism does not occur to any great extent, as indicated by 74% renal excretion of unchanged drug after an intravenous dose in young healthy volunteers. The major metabolic pathway is non-enzymatic ester cleavage to the alcohol N-methylscopine and dithienylglycolic acid that are inactive on muscarinic receptors. *In vitro* metabolism: In studies in animals and *in vitro* experiments with human liver microsomes and hepatocytes, minor amounts of a variety of glutathione conjugates after oxidation of the thiophene rings were observed.

*In vitro* studies in human liver microsomes revealed that the enzymatic pathway, relevant for only a small amount of tiotropium metabolism, can be inhibited by cytochrome P450 (CYP) 2D6 inhibitor quinidine and CYP 3A4 inhibitors ketoconazole and gestodene.

Tiotropium, even in supra-therapeutic concentrations, does not inhibit CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

*Olodaterol:*

Olodaterol is substantially metabolised by direct glucuronidation and by O-demethylation at the methoxy moiety followed by conjugation. Of the six metabolites identified, only the unconjugated demethylation product (SOM 1522) binds significantly to beta$_2$-receptors. This metabolite however is not detectable in plasma after chronic inhalation of the recommended therapeutic dose or doses of up to 4-fold higher.

Olodaterol thus is considered the only compound relevant for pharmacological action.

Cytochrome P450 isozymes CYP2C9 and CYP2C8, with negligible contribution of CYP3A4, are involved in the O-demethylation of olodaterol, while uridine diphosphate glycosyl transferase isoforms UGT2B7, UGT1A1, 1A7 and 1A9 were shown to be involved in the formation of olodaterol glucuronides.

**Excretion**

*Tiotropium*:

The effective half-life of tiotropium ranges between 27 and 45 hours following inhalation by COPD patients. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. Urinary excretion of unchanged substance in young healthy volunteers is 74% of an intravenous dose. After inhalation of the solution for inhalation by COPD patients, urinary excretion is 18.6% (0.93 µg) of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated *via* the faeces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic, once daily inhalation, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter. Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

*Olodaterol*:

Total clearance of olodaterol in healthy volunteers is 872 mL/min, and renal clearance is 173 mL/min. The terminal half-life following intravenous administration is 22 hours. The terminal half-life following inhalation in contrast is about 45 hours, indicating that the latter is determined by absorption rather than by elimination processes.

Following intravenous administration of [$^{14}$C]-labelled olodaterol, 38% of the radioactive dose was recovered in the urine and 53% was recovered in faeces. The amount of unchanged olodaterol recovered in the urine after intravenous administration was 19%. Following oral administration, only 9% of the radioactivity was recovered in urine, while the major portion was recovered in faeces (84%). More than 90% of the dose was excreted within 6 and 5 days following intravenous and oral administration, respectively. Following inhalation, excretion of unchanged olodaterol in urine within the dosing interval in healthy volunteers at steady state accounted for 5-7% of the dose.

**Pharmacokinetics in special patient groups**

*Tiotropium:*

As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance from 347 mL/min in COPD patients <65 years to 275 mL/min in COPD patients ≥65 years. Exposure to tiotropium was not found to differ with age in patients with asthma.

*Olodaterol*:

A pharmacokinetic meta-analysis was performed utilising data from 2 controlled clinical trials that included 405 patients with COPD and 296 patients with asthma who received treatment with olodaterol RESPIMAT. The analysis showed that no dose adjustment is necessary based on the effect of age, gender and weight on systemic exposure in COPD patients after inhalation of olodaterol RESPIMAT.

<u>Renal insufficiency</u>

*Tiotropium:*

Following once daily inhaled administration of tiotropium to steady-state in COPD patients with mild renal impairment ($CL_{CR}$ 50-80 mL/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 1.8 to 30% higher) and similar $C_{max,ss}$ compared to patients with normal renal function ($CL_{CR}$ >80 mL/min). In COPD patients with moderate to severe renal impairment ($CL_{CR}$ <50 mL/min) intravenous administration of tiotropium resulted in a doubling of the total exposure (82% higher $AUC_{0-4h}$ and 52% higher $C_{max}$) compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.

*Olodaterol:*

In subjects with severe renal impairment ($CL_{CR}$ <30 mL/min), systemic exposure to olodaterol was on average 1.4-fold increased. This magnitude of exposure increase does not raise any safety concerns given the safety experience of treatment with olodaterol in clinical studies of up to one year at doses up to twice the recommended therapeutic dose.

Hepatic insufficiency

*Tiotropium:*

Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

*Olodaterol*:

In subjects with mild and moderate hepatic impairment, systemic exposure to olodaterol was not affected. The effect of severe hepatic impairment on systemic exposure to olodaterol was not investigated.

Race

Comparison of pharmacokinetic data within and across studies with olodaterol revealed a trend for higher systemic exposure in Japanese and other Asians than in Caucasians.

No safety concerns were identified in clinical studies with olodaterol in Caucasians and Asians of up to one year with olodaterol doses up to twice the recommended therapeutic dose.

**Drug-drug interactions**

Olodaterol:

Drug-drug interaction studies were carried out using fluconazole as model inhibitor of CYP 2C9 and ketoconazole as potent P-gp and CYP inhibitor.

*Fluconazole*: Co-administration of 400 mg fluconazole once daily for 14 days had no relevant effect on systemic exposure to olodaterol.

*Ketoconazole*: Co-administration of 400 mg ketoconazole once daily for 14 days increased olodaterol $C_{max}$ by 66% and $AUC_{0-1}$ by 68%.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

*In vitro* mutagenicity for tiotropium or olodaterol alone did not show any genotoxic potential. In the *in vivo* rat bone marrow micronucleus assay, after inhalational doses up to 2,266+2,174 microgram/kg/day tiotropium+olodaterol for 4 weeks (dose ratio 1:1), the combination was free of genotoxic potential.

Tiotropium

Tiotropium (as bromide) did not exhibit any genotoxic effects in assays for gene mutation (bacteria and mammalian cells *in vitro* and *in vivo* mouse micronucleus test) or DNA damage (rat hepatocytes *in vitro*).

Olodaterol

There was no evidence for genotoxicity for olodaterol in standard *in vitro* (bacterial reverse mutation, mammalian forward mutation) and *in vivo* rat bone marrow micronucleus assay after inhalational doses up to 1,360 microgram/kg/day for 4 weeks (plasma AUC 1,100 times the anticipated clinical exposure). An increased frequency of micronuclei in rats after single

intravenous doses of 10 mg/kg or greater was likely related to drug enhanced (compensatory) erythropoiesis, and is unlikely to be relevant at clinical exposures.

**Carcinogenicity**

No carcinogenicity studies for the combination were performed.

Tiotropium

Long-term carcinogenicity studies in mice and rats, with tiotropium (as bromide) administered by inhalation, showed no evidence of neoplastic responses. The highest doses studied were approximately 0.8x (male mouse), 38x (female mouse) and 16x (rat) greater than the maximum recommended human daily dose of the drug, based on body surface area.

Olodaterol

Lifetime treatment of rats induced class- and rodent-specific leiomyomas of the mesovarium at exposures approximately 213-fold the anticipated plasma AUC in adults at the dose of 5 microgram once daily. Lifetime treatment of mice induced class- and rodent-specific smooth muscle tumours (leiomyomas, leiomyosarcomas) of the uterus and incidences of sex cord stromal focal hyperplasia and luteal focal hyperplasia in the ovary at exposures approximately 40- to 400-fold the AUC in adults at the dose of 5 microgram once daily. These findings are not considered to indicate a carcinogenic hazard to patients.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Benzalkonium chloride, disodium edetate, purified water, and hydrochloric acid for pH adjustment.

### 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

SPIOLTO RESPIMAT cartridge should be used within 3 months after inserting in the SPIOLTO RESPIMAT re-usable inhaler.

The in-use shelf-life of the re-usable inhaler is 1 year.

Recommended use per re-usable inhaler is 6 cartridges.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Do not freeze.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Type and material of the container in contact with the medicinal product:

Solution filled into a polyethylene/polypropylene cartridge with a polypropylene cap with integrated silicone sealing ring. The cartridge is enclosed within an aluminium cylinder.

Pack sizes and devices supplied:

Single pack: 1 SPIOLTO RESPIMAT re-usable inhaler and 1 SPIOLTO RESPIMAT cartridge, providing 60 puffs (30 doses).

Double pack: 1 SPIOLTO RESPIMAT re-usable inhaler and 2 SPIOLTO RESPIMAT cartridges, providing 60 puffs (30 doses) each.

Triple pack: 1 SPIOLTO RESPIMAT re-usable inhaler and 3 SPIOLTO RESPIMAT cartridges, providing 60 puffs (30 doses) each.

Single refill pack: 1 SPIOLTO RESPIMAT cartridge, providing 60 puffs (30 doses).

Triple refill pack: 3 SPIOLTO RESPIMAT cartridges, providing 60 puffs (30 doses) each.

Not all pack sizes may be marketed.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

Tiotropium bromide is a white to yellowish-white, odourless crystalline powder. It exists as a quaternary ammonium salt, and there are no ionisable functional groups on the molecule. The active substance is not optically active.

Tiotropium bromide is freely soluble in dimethyl sulphoxide, soluble in methanol, sparingly soluble in water and practically insoluble in methylene chloride. The solubility in aqueous solutions at room temperature is approx. 2.5%, independent of pH. At pH 7.4, the apparent partition coefficient (log $P_{app}$) is -2.25.

A monohydrate form of tiotropium bromide is produced by the synthetic process. The compound melts with decomposition between 225°C and 235°C, when determined by differential scanning calorimetry at a heating rate of 10 K per minute.

Olodaterol hydrochloride is a white to off-white powder. It is freely soluble in methanol, soluble in ethanol, sparingly soluble in acetone and slightly soluble in 2-propanol. Dissociation constants: $pK_{a1}$ = 9.3; $pK_{a2}$ = 10.1. Partition coefficient: Log $P_{ow}$ (free base) = 3.0; Log D (pH 7.4) = 1.2.

**Chemical Structure**

Tiotropium bromide monohydrate

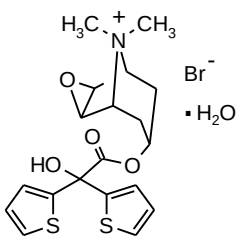
Chemical name*:* 3-Oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane, 7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide, monohydrate, (1$\alpha$, 2$\beta$, 4$\beta$, 5$\alpha$, 7$\beta$)-

Molecular formula*:* Free base anhydrous: $C_{19}H_{22}NO_4S_2Br$
Monohydrate: $C_{19}H_{22}NO_4S_2Br.H_2O$

Molecular weight: Free base anhydrous: 472.4

Monohydrate: 490.4

Chemical Structure:



Olodaterol hydrochloride

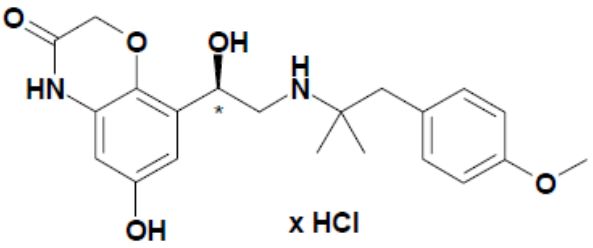
Chemical name*:* 2H-1,4-Benzoxazin-3H(4H)-one, 6-hydroxy-8-[(1R)-1-hydroxy-2-[[2-(4-methoxyphenyl)-1,1-dimethylethyl]amino]ethyl]-,monohydrochloride

Molecular formula*:* Free base anhydrous: $C_{21}H_{26}N_2O_5$
Hydrochloride salt: $C_{21}H_{26}N_2O_5xHCl$

Molecular weight*:* Free base anhydrous: 386.45
Hydrochloride salt: 422.91

Stereochemistry*:* (R) enantiomer

Chemical Structure:




**CAS number**

Tiotropium bromide monohydrate: 139404-48-1

Olodaterol hydrochloride: 869477-96-3

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

## 8 SPONSOR

Boehringer Ingelheim Pty Limited
ABN 52 000 452 308
78 Waterloo Road
North Ryde NSW 2113

www.boehringer-ingelheim.com.au

## 9 DATE OF FIRST APPROVAL

4 March 2020

## 10 DATE OF REVISION

17 May 2024

**Summary table of changes**

| Section changed | Summary of new information |
|---|---|
| 6.5 | Update to include new double pack size |