NEW ZEALAND DATASHEET

1. PRODUCT NAME

SPIOLTO RESPIMAT 2.5 microgram/2.5 microgram solution for inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SPIOLTO RESPIMAT cartridge contains 4 mL inhalation solution. The delivered dose is 2.5 microgram tiotropium (as bromide monohydrate) and 2.5 microgram olodaterol (as hydrochloride) per puff.

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.

3. PHARMACEUTICAL FORM

SPIOLTO RESPIMAT is a clear, colourless, inhalation solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SPIOLTO RESPIMAT is indicated for the long term, once-daily maintenance treatment in patients with COPD (including chronic bronchitis and emphysema), to reduce airflow obstruction, to improve quality of life and to reduce associated dyspnoea.

4.2 Dose and method of administration

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

The recommended dose should not be exceeded.

Special populations
Elderly population
Elderly patients can use SPIOLTO RESPIMAT at the recommended dose.

Hepatic impairment and renal impairment
SPIOLTO RESPIMAT contains tiotropium which is a predominantly renally excreted drug and olodaterol, which is predominantly metabolised in the liver.

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

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

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.

Paediatric population
There is no relevant use of SPIOLTO RESPIMAT in the paediatric population in COPD. The safety and effectiveness of SPIOLTO RESPIMAT in the paediatric population have not been established.

Method of administration
To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler by a doctor or other health care professional.

Instructions for Use

Read these Instructions for Use before you start using SPIOLTO RESPIMAT.

You will need to use this inhaler only ONCE A DAY. Each time you use it take TWO PUFFS.

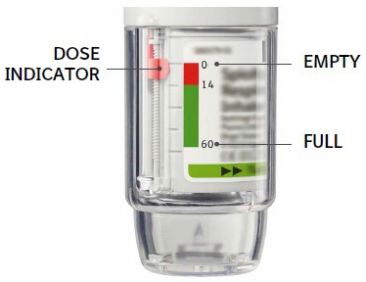
- If not been used for more than 7 days release one puff towards the ground.
- If not been used for more than 21 days repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

How to care for your SPIOLTO RESPIMAT

- Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.

- Any minor discoloration in the mouthpiece does not affect your SPIOLTO RESPIMAT inhaler performance.

When to get a new SPIOLTO RESPIMAT



- Your SPIOLTO RESPIMAT inhaler contains 60 puffs (30 doses) if used as indicated (two puffs/Once daily).
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale you need to get a new prescription; there is approximately medication for 7 days left (14 puffs).
- Once the dose indicator reaches the end of the red scale, your SPIOLTO RESPIMAT locks automatically – no more doses can be released. At this point, the clear base cannot be turned any further.
- Three months after first use, the SPIOLTO RESPIMAT should be discarded even if it has not been used.

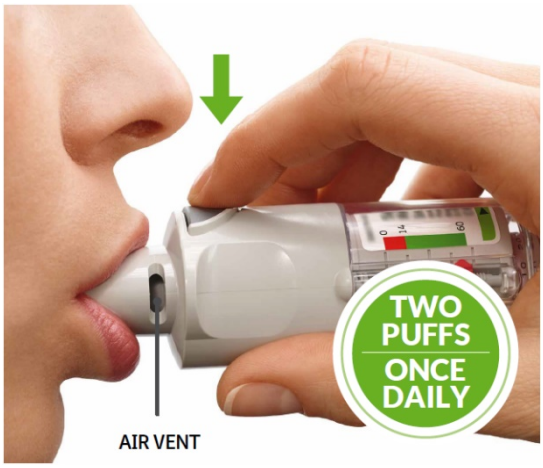
Prepare for first use

1. Remove clear base • **Keep the cap closed.** • **Press the safety catch while firmly pulling off the clear base with your other hand.**	
2. Insert cartridge • **Insert the narrow end of the cartridge into the inhaler.** • **Place the inhaler on a firm surface and push down firmly until it snaps into place.**	
3. Replace clear base • **Put the clear base back into place until it clicks.**	
4. Turn • **Keep the cap closed.** • **Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).**	

5. <u>Open</u> • **Open the cap until it snaps fully open.**	
6. <u>Press</u> • **Point the inhaler toward the ground** • **Press the dose-release button.** • **Close the cap.** • **Repeat steps 4-6 until a cloud is visible.** • **<u>After a cloud is visible</u>, repeat steps 4-6 three more times.**	

<u>Daily use</u>

<u>TURN</u> • **Keep the cap closed.** • **<u>TURN</u> the clear base in the direction of the arrows on the label until it clicks (half a turn).**	
<u>OPEN</u> • **<u>OPEN</u> the cap until it snaps fully open.**	

PRESS • **Breathe out slowly and fully.** • **Close your lips around the mouthpiece without covering the air vents.** • **While taking a slow, deep breath through your mouth, PRESS the dose-release button and continue to breathe in.** • **Hold your breath for 10 seconds or for as long as comfortable.** • **Repeat TURN, OPEN, PRESS for a total of 2 puffs.** • **Close the cap until you use your inhaler again.**	

4.3 Contraindications

SPIOLTO RESPIMAT is contraindicated in patients with hypersensitivity to tiotropium or olodaterol or to any of the excipients listed in Section 6.1.

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

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

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 asthma. The efficacy and safety of SPIOLTO RESPIMAT in asthma have not been studied.

Acute bronchospasm

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

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.

Patients with 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).

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. Long acting $beta_2$-adrenergic agonists 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 electrocardiogram (ECG) changes, such as flattening of the T wave and ST segment depression, although the clinical significance of these observations is unknown.

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), which may increase the susceptibility to cardiac arrhythmias.

Hyperglycaemia
Inhalation of high doses of $beta_2$-adrenergic agonists may produce increases in plasma glucose.

SPIOLTO RESPIMAT should not be used in conjunction with any other medication containing long-acting $beta_2$-adrenergic agonists. 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 Interaction with other medicines and other forms of interaction

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

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

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).

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). 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

Pregnancy

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

Preclinical studies with tiotropium do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (see Section 5.3).

Preclinical data for olodaterol revealed effects typical for beta-adrenergic agonists at high multiples of the therapeutic doses (see Section 5.3).

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.

Breast-feeding

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

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

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

Fertility

Clinical data on fertility are not available for tiotropium and olodaterol or the combination of both components. Preclinical studies performed with the individual components tiotropium and olodaterol showed no indication of any adverse effect on fertility (see Section 5.3).

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 Undesirable effects

a. Summary of the safety profile

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 (AEs) 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 (Trials 1, 2 and 9) the overall incidence of AEs in patients treated with SPIOLTO RESPIMAT was comparable to patients treated with the mono component 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.

b. Tabulated summary of adverse reactions

Adverse reactions reported in all clinical trials with SPIOLTO RESPIMAT are shown below in Table 1 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 1: Summary of Adverse Drug Reactions (ADRs) per frequency category

System Organ Class	Adverse reaction	Frequency
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	Adverse reaction	Frequency
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	Adverse reaction	Frequency
Renal and urinary disorders	Urinary retention	Rare
	Urinary tract infection	Rare
	Dysuria	Rare

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

Many of the listed undesirable effects can be assigned to either the anticholinergic properties of tiotropium or to the ß-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 ischemia, angina pectoris, hypotension, tremor, headache, nervousness, nausea, muscle spasms, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

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, e.g. myocardial ischaemia, hypertension or hypotension, tachycardia, arrhythmias, palpitation, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasms, nausea, fatigue, malaise, hypokalemia, hyperglycemia, 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: R03AL06

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 provide additive bronchodilation due to their different mode of action and different locations of the target receptors in the lungs.

Tiotropium

Tiotropium bromide is a long-acting, muscarinic receptor antagonist (LAMA), in clinical medicine often called an anticholinergic. It has a similar affinity to the subtypes of muscarinic receptors M_1 to M_5. In the airways, inhibition 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 and isolated organ preparations. In pre-clinical *in vitro* as well as *in vivo* studies bronchoprotective effects were dose-dependent and lasted longer than 24 hours. The long duration of the effect is likely to be due to its very slow dissociation from M_3-receptors, exhibiting a significantly longer dissociation half-life than that seen with ipratropium. As an N-quaternary anticholinergic tiotropium is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before giving rise to systemic anti-cholinergic effects. Dissociation from M_2-receptors is faster than from M_3, which in functional *in vitro* studies, elicited (kinetically controlled) receptor subtype selectivity of M_3 over M_2.

The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD.

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

Olodaterol

Olodaterol has a high affinity and high selectivity to the human $beta_2$-adrenoceptor. *In vitro* studies have shown that olodaterol has 241-fold greater agonist activity at $beta_2$-adrenoceptors compared to $beta_1$-adrenoceptors and 2299-fold greater agonist activity compared to $beta_3$-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

The effect of tiotropium (inhalation powder 18 and 54 microgram once daily) on the QT/QTc interval of the ECG was investigated in 56 healthy male and female volunteers in a double-blind, randomised, placebo- and active (moxifloxacin) controlled study. The mean changes

from baseline in QT interval over 5 minutes to 2 hours after dosing on day 12 was -1.4 ms for placebo, +0.6 ms for 18 microgram tiotropium and -2.1 ms for 54 microgram tiotropium; the upper limit of the one-sided 95% confidence intervals of the placebo-adjusted difference from baseline was less than 10 ms for both tiotropium doses (+4.9 ms for 18 microgram tiotropium, +2.2 ms for 54 microgram tiotropium).

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 msec 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.

<u>Clinical efficacy and safety</u>
The Phase III clinical development program for SPIOLTO RESPIMAT included three randomised, double-blind trials:

1. 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]
2. 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, FEV1). In the 52 week studies, lung function was measured up to 3 hrs post-dose and at 23-24 hrs post-dose; the primary lung function efficacy endpoints were change from pre-treatment baseline (response) in FEV1 AUC0-3h and trough FEV1 after 24 weeks. In the 6 week study, lung function was measured up to 12 hrs post-dose and at 22-24 hrs post-dose; the primary efficacy endpoint was FEV1 AUC0-24h 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 Dyspea Index (TDI) as a key secondary endpoint as a measure of dyspnea.

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 FEV1 less than 80% predicted normal (GOLD Stage 2-4); post-bronchodilator FEV1 to FVC ratio of less than 70%).

Patient characteristics
The majority of the 5162 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%], GOLD 4 [11%]). Mean β_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 β_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 2).

Table 2: 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**	**n**	**Mean**	**n**	**Mean**	**n**	**Mean**
SPIOLTO RESPIMAT versus	522	--	502	--	521	--	497	--
Tiotropium 5 microgram	526	0.117 L	500	0.103 L	520	0.071 L	498	0.050 L
Olodaterol 5 microgram	525	0.123 L	507	0.132 L	519	0.082 L	503	0.088 L

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 sub-set of patients who completed extended lung function measurements up to 12 hrs 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 3).

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 PFT sub-set from Trials 1 and 2; combined dataset)

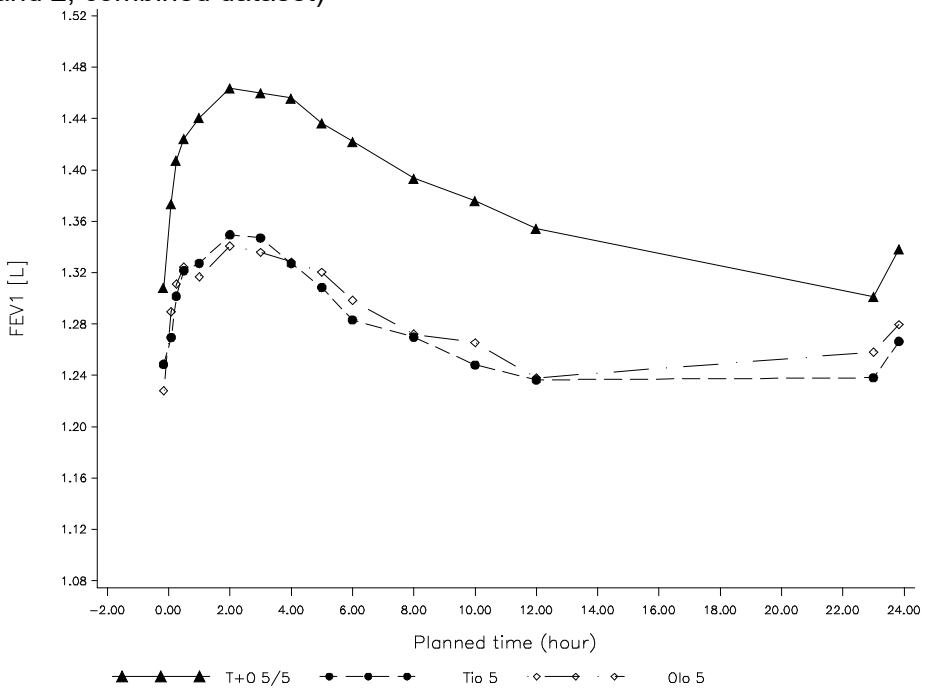


Table 3: Difference in FEV_1 for SPIOLTO RESPIMAT compared to tiotropium 5 microgram and olodaterol 5 microgram over a continuous 24 hour dosing interval after 24 weeks (12 hr PFT sub-set from Trials 1 and 2; combined dataset)

	n	12 hr average	24 hr average
SPIOLTO RESPIMAT versus	167		
Tiotropium 5 microgram	160	0.123	0.106
Olodaterol 5 microgram	194	0.118	0.098

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 4).

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]

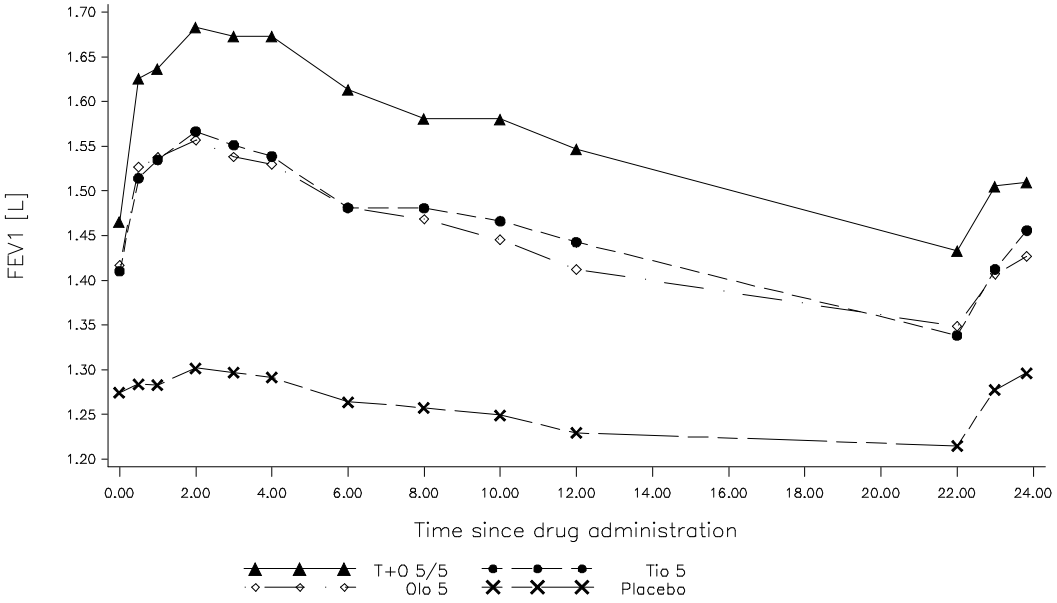


Table 4: Difference in FEV_1 (L) for SPIOLTO RESPIMAT compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo over a continuous 24 hour dosing interval after 6 weeks [Trial 3]

	n	3 hr average	N	12 hr average	24 hr average[1]	Trough
SPIOLTO RESPIMAT versus	138		138			
Tiotropium 5 microgram	137	0.109	135	0.119	0.110	0.079
Olodaterol 5 microgram	138	0.109	136	0.126	0.115	0.092
Placebo	135	0.325	132	0.319	0.280	0.207

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 5). 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 5: TDI focal score after 24 weeks of treatment (Trials 1 and 2)

	n	Treatment Mean	Difference to SPIOLTO RESPIMAT
			Mean (p-value)
SPIOLTO RESPIMAT	992	1.98	
Tiotropium 5 microgram	978	1.63	0.36 (p=0.008)
Olodaterol 5 microgram	984	1.56	0.42 (p=0.002)

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).

Patient Global Rating
Patients treated with SPIOLTO RESPIMAT perceived a greater improvement in their respiratory condition compared to tiotropium 5 microgram and olodaterol 5 microgram, as measured by a Patient´s Global Rating (PGR) scale (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 (3,939 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 did not reach the pre-specified significance level of 0.01. 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).

SPIOLTO RESPIMAT treatment resulted in an 11% lower annualised rate of hospitalisations due to a COPD exacerbation (RR 0.89, 95% CI 0.76-1.03, p=0.1265). Beyond this SPIOLTO

RESPIMAT treatment resulted in a 20% lower annualised rate of moderate to severe exacerbations that required treatment with systemic corticosteroids (RR 0.80, 95% CI 0.68-0.94, p=0.0068) and in a 9% lower annualised rate of moderate to severe exacerbations that required treatment with systemic corticosteroids and antibiotics (RR 0.91, 95% CI 0.83-1.00, p=0.0447). Treatment with SPIOLTO RESPIMAT did not result in a reduction in the rate of moderate to severe exacerbations treated with antibiotics only (RR 1.07, 95% CI 0.96-1.20, p=0.2062).

Time to all-cause mortality was included as a secondary endpoint in this trial. There was no significant difference in the risk of all-cause mortality between SPIOLTO RESPIMAT and tiotropium 5 microgram. During the actual treatment period (i.e. on-treatment plus one day) 36 versus 32 deaths were observed (Hazard Ratio (HR) 1.09, 95% CI, 0.67, 1.75, p=0.7357), while during the planned study period (381 days) 107 versus 121 deaths were observed (HR 0.88, 95% CI, 0.68, 1.15, p=0.3485) for SPIOLTO RESPIMAT and tiotropium 5 microgram, respectively.

The analysis of the additional exacerbation trial (Trial 9) is displayed in Table 6.

Table 6: Effect of SPIOLTO RESPIMAT on exacerbations [Trial 9]

Study ($N_{Spiolto}$, $N_{tio\ 5}$)	**Endpoints**	**SPIOLTO RESPIMAT**	**Tiotropium 5 microgram**	**Ratio**	**p-value**
1-year Ph IIIb exacerbation study **(treated set: 3939, 3941)**	**Annualised rate of COPD exacerbation** **Moderate to severe**	0.90	0.97	RR 0.93 (0.85, 1.02) 99% CI	0.0498
	Time to first COPD exacerbation **Moderate to severe**	Number of patients with event: 1746	Number of patients with event: 1777	HR 0.95 (0.87, 1.03) 99% CI	0.1188
	Annualised rate of hospitalised exacerbations	0.18	0.20	RR 0.89 (0.76, 1.03) 95% CI	0.1265
	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	0.2773

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 7); 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 7: 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)
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)
	Olodaterol 5 microgram	954	38.4 (-5.1)	-1.69 (p=0.002)
Symptoms	Baseline		51.9	
	SPIOLTO RESPIMAT	982	42.6	
	Tiotropium 5 microgram	957	45.5	-2.94 (p=0.0008)
	Olodaterol 5 microgram	958	45.0	-2.48 (p=0.0046)
Activities	Baseline		58.0	
	SPIOLTO RESPIMAT	981	51.9	
	Tiotropium 5 microgram	959	53.2	-1.34 (p=0.052)
	Olodaterol 5 microgram	958	54.0	-2.11 (p=0.002)
Impact	Baseline		32.6	
	SPIOLTO RESPIMAT	983	26.1	
	Tiotropium 5 microgram	960	26.8	-0.67 (p=0.283)
	Olodaterol 5 microgram	959	27.2	-1.11 (p=0.075)

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 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%) compared with tiotropium 5 microgram (41%; odds ratio: 1.56 (95%CI: 1.17, 2.07), p = 0.0022) and placebo (32%; odds ratio: 2.35 (95%CI: 1.75, 3.16), p < 0.0001).

In Trial 9, treatment with SPIOLTO RESPIMAT provided improvements in the COPD Assessment Test score (CAT, a measure of health-related quality of life) versus tiotropium 5 microgram at all study visits (adjusted mean difference versus tiotropium from -0.7 (95% CI (-1.0, -0.5)) at day 90 to -0.4 (95% CI (-0.7,-0.1)) at day 360, all p<0.01). In a responder analysis the proportion of patients experiencing a clinically meaningful improvement in CAT (defined as a reduction of 2 points or more) was larger with SPIOLTO RESPIMAT versus tiotropium 5 microgram (44.51% vs 40.77% respectively, odds ratio 1.17, 95% CI 1.06-1.28 p<0.001).

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 (sub-set 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 8) and compared to placebo after 12 weeks (0.234 L, p<0.0001; Trial 6).

Table 8: 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]	n	Trial 5[2]
SPIOLTO RESPIMAT versus	219		218	
Tiotropium 5 microgram	213	0.114 (p<0.0001)	208	0.088 (p=0.0005)
Olodaterol 5 microgram	214	0.119 (p<0.0001)	208	0.080 (p=0.0015)
Placebo	211	0.244 (p<0.0001)	202	0.265 (p<0.0001)

[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 9). In Trial 6, SPIOLTO RESPIMAT improved endurance time during constant work rate cycling by 12.6% after the first dose (in a sub-set of patients), by 22.9% after 6 weeks and by 13.8% after 12 weeks compared to placebo and increased endurance time during constant speed walking (in a sub-set of patients) by 20.6% after 6 weeks and by 20.9% after 12 weeks compared to placebo (Table 10).

Improvements in exercise endurance were not demonstrated for SPIOLTO RESPIMAT compared to equivalent monotherapies.

Table 9: 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]	n	Trial 5[2]
SPIOLTO RESPIMAT	212	454.1	216	465.7
Placebo	209	375.5	205	410.8
Ratio		1.209 (p<0.0001)		1.134 (p<0.0001)

[1] pre-treatment baseline: 460.0 sec
[2] pre-treatment baseline: 434.3 sec

Table 10: 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]**	**n**	**6 weeks[2]**	**12 weeks[2,3]**	**n**	**6 weeks[4]**	**12 weeks[4,5]**
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)		1.229 (p=0.0002)	1.138 (p=0.021)		1.206 (p=0.058)	1.209 (p=0.055)

[1] pre-treatment baseline: 461.5 sec
[2] pre-treatment baseline: 443.0 sec; [3] primary endpoint
[4] pre-treatment baseline: 311.2 sec; [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 (p<0.0005; Table 11).

Table 11: 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]**	**n**	**Trial 5[2]**
SPIOLTO RESPIMAT	212	0.016	216	0.015
Placebo	209	0.018	205	0.018
Difference		-0.003 (p=0.0004)		-0.003 (p<0.0001)

[1] pre-treatment baseline: 0.015 Borg units/sec
[2] pre-treatment baseline: 0.016 Borg units/sec

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: Urinary excretion data from young healthy volunteers suggests that approximately 33% of the dose inhaled via the RESPIMAT inhaler reaches the systemic circulation. The absolute bioavailability from an orally administered solution was found to be 2–3%. Maximum tiotropium plasma concentrations are observed 5-7 minutes after the inhalation via RESPIMAT.

Olodaterol: 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. Maximum olodaterol plasma concentrations generally are reached within 10 to 20 minutes following drug inhalation via RESPIMAT.

Distribution

Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier to any relevant extent.

Olodaterol has a plasma protein binding of approximately 60% and shows a volume of distribution of 1110 L.

Biotransformation

Tiotropium: The extent of metabolism is small. This is evident from 74% of an intravenous dose being excreted in the urine as unchanged drug. The ester tiotropium is nonenzymatically cleaved into its alcohol and acid component (N-methylscopine and dithienylglycolic acid, respectively), both not binding to muscarinic receptors. *In vitro* experiments with human liver microsomes and human hepatocytes suggest that some further drug (<20% of the dose after intravenous administration) is metabolized by cytochrome P450 (CYP) 2D6 and 3A4 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-metabolites.

Olodaterol is substantially metabolized 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 to $ß_2$-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. 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.

Elimination

Tiotropium: Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). The total clearance in healthy volunteers is 880 mL/min. After inhalation by COPD patients to steady-state, urinary excretion is 18.6% 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 glomerular filtration rate, indicating active secretion into the urine. The effective half-life of tiotropium following inhalation by COPD patients ranges between 27 and 45 h.

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 hrs. The terminal half-life following inhalation in contrast is about 45 hrs, 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 feces. 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 feces (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.

Characteristics in Patients

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. This did not result in a corresponding increase in $AUC_{0-6,ss}$ or $C_{max,ss}$ values.

Olodaterol: A pharmacokinetic meta-analysis utilizing data from 2 controlled clinical trials that included 405 patients with COPD and 296 patients with asthma showed that no dose adjustment is necessary due to effects of age, gender and weight on systemic exposure to olodaterol.

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.

Renal Insufficiency

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 subjects with moderate to severe renal impairment (CL_{CR} <50 mL/min) intravenous administration of tiotropium resulted in twofold higher total exposure (82% higher AUC_{0-4h} and 52% higher C_{max}) compared to subjects with normal renal function, which was confirmed by observations 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 simple non-enzymatic ester cleavage to pharmacologically inactive products.

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.

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

Single-dose toxicity

For the combination tiotropium + olodaterol single-dose toxicity studies after inhalation administration have been performed for three dose ratios in mice and rats, revealing a low acute toxicity. In mice, the approximate lethal doses (ALD) were 34.8+36.6 mg/kg for tiotropium+olodaterol in the ratio 1:1. In rats, no deaths occurred, therefore the ALDs were >17.9+18.8 mg/kg for tiotropium/olodaterol in the ratio 1:1.

Repeat-dose toxicity

Inhalation repeat-dose toxicity studies for the combination tiotropium + olodaterol were performed in rats (4 weeks) and dogs (up to 13 weeks) at different dose ratios. In the 13-week studies in dogs, body weight development, clinical signs, changes of the cardiovascular system

and of respective enzyme activities as well as the macroscopical and microscopical pathology were characteristic β_2-agonistic and anticholinergic effects. In the 13-week toxicity studies with the dose ratio 1:1 for tiotropium/olodaterol, the no observed adverse effect levels (noael) were 14+16 microgram/kg/day.

Reproduction toxicity

No reproduction toxicity studies for the combination were performed.

Tiotropium: In the reproduction studies in rabbits and rats harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. In a general reproduction and fertility study in rats, there was no indication of any adverse effect on fertility or mating performance of either treated parents or their offspring at any dosage.

Olodaterol: In rats, no teratogenic effects occurred after inhalation at doses 1054 microgram/kg/day (> 2600 times the human exposure ($AUC_{(0-24h)}$) at the dose of 5 microgram). In pregnant NZW rabbits, an inhalation dose of 2489 microgram/kg/day (approximately 7130 times the human exposure at 5 microgram based on $AUC_{(0-24h)}$) of olodaterol exhibited fetal toxicity characteristically resulting from ß-adrenoceptor stimulation; these included patchy ossifications, short/bent bones, partially open eye, cleft palate, cardiovascular abnormalities. No significant effects occurred at a dose of 974 microgram/kg (approximately 1353 times the 5 microgram dose based on $AUC_{(0-24h)}$). No impairment of male or female fertility or early embryonic development was seen in the rat up to inhalation doses of 3068 microgram/kg (approximately 2332 times the 5 microgram dose based on $AUC_{(0-24h)}$).

No effects were observed on mating, fertility or bearing of live implants to Day 14/15/16 of gestation in the F1 animals in the rat up to inhalation doses of 3665 microgram/kg/day (approximately 2332 times the 5 microgram dose based on $AUC_{(0-24h)}$).

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 inhalation at dose levels of up to 2266 + 2174 microgram/kg/day tiotropium+olodaterol for 4 weeks (dose ratio 1:1), the combination was free of genotoxic potential.

Carcinogenicity

No carcinogenicity studies for the combination were performed.

Tiotropium: Tiotropium did not show any carcinogenic potential in the respective studies in mice and rats.

Olodaterol: Lifetime treatment of rats induced class- and rodent-specific leiomyomas of the mesovarium at exposures approximately 2235-fold and 715-fold the exposure at the dose of 5 microgram dose (on systemic exposure). 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 477- to 3596-fold the exposure at the dose of 5 microgram dose (on systemic exposure), again considered as class- and rodent specific (exposure multiples). Both studies revealed no evidence for an olodaterol-related human risk with regard to carcinogenicity or chronic toxicity.

In the *in vivo* rat bone marrow micronucleus assay after inhalation exposure (up to approximately 1092 times the 5 microgram dose based on $AUC_{(0-24h)}$) and the *in vitro* (Ames test, mouse lymphoma assay) mutagenicity assays, olodaterol was free of any genotoxic potential up to very high dose levels. An increased frequency of micronuclei was observed in

rats after i.v. exposure at doses of at least 5500-times the 5 microgram dose based on $AUC_{(0-24h)}$ may be related to drug enhanced (compensatory) erythropoiesis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Purified water
Hydrochloric acid for pH adjustment

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months from the date of manufacture.

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

6.4 Special precautions for storage

Store below 25ºC. Do not freeze.

6.5 Nature of contents of container

Type of 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.

The SPIOLTO RESPIMAT inhaler has a green-coloured cap.
The SPIOLTO RESPIMAT cartridge is only intended for use with the SPIOLTO RESPIMAT inhaler.

SPIOLTO RESPIMAT is available in a labelled carton containing one SPIOLTO RESPIMAT cartridge of solution for inhalation and one SPIOLTO RESPIMAT inhaler delivering 60 metered puffs after preparation for use (equivalent to 30 doses when used as two puffs once daily).

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Boehringer Ingelheim (N.Z.) Limited
P O Box 76-216
Manukau City
Auckland
New Zealand

Telephone: 0800 802 461

9. DATE OF FIRST APPROVAL

26 November 2015

10 DATE OF REVISION OF THE TEXT

26 July 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Update to instructions for use to include additional instructional text. Minor editorial changes.
4.4	Update to precautionary text for patients with renal impairment - Creatine clearance corrected.