

**SUMMARY OF PRODUCT CHARACTERISTICS,  
LABELLING AND PACKAGE LEAFLET**

Version: May 19, 2015

## **1. NAME OF THE MEDICINAL PRODUCT**

Spiolto Respimat 2.5 microgram/2.5 microgram, inhalation solution

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

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.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Inhalation solution

Clear, colourless, inhalation solution

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Spiolto Respimat is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

### **4.2 Posology and method of administration**

#### Posology

The medicinal product is intended for inhalation use only. The cartridge can only be inserted and used in the Respimat inhaler.

Two puffs from the Respimat inhaler comprise one medicinal dose.

#### Adults

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.

The recommended dose should not be exceeded.

#### 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 metabolized 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.

For patients with moderate to severe impairment (creatinine clearance  $\leq 50$  ml/min) see 4.4 and 5.2.

Spiolto Respimat contains olodaterol. There is limited experience with the use of olodaterol in patients with severe renal impairment.

Paediatric population

There is no relevant use of Spiolto Respimat in the paediatric population (under 18 years).

Method of administration

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


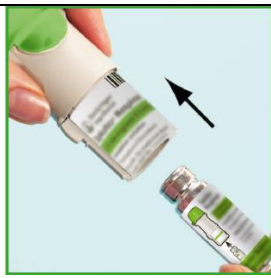
Patient's instructions for use and handling





**Spiolto Respimat inhaler and the Spiolto Respimat cartridge**




**1) Inserting the cartridge**

The following steps 1-6 are necessary before first use:

 <p>1</p>	<p><b>1</b> With the light-green cap (A) closed, press the safety catch (E) while pulling off the clear base (G).</p>
 <p>2a</p>	<p><b>2</b> Take the cartridge (H) out of the box. Push the <b>narrow</b> end of the cartridge into the inhaler until it <b>clicks</b> into place. The cartridge should be pushed <b>firmly</b> against a firm surface to ensure that it has gone all the way in (2b). <b>The cartridge will not be flush with the inhaler, you will still see the silver ring of the lower end of the cartridge.</b></p> <p>Do not remove the cartridge once it has been inserted into the inhaler.</p>



	<p>2b</p>
	<p>3 Replace the clear base (G).</p> <p>Do not remove the clear base again.</p>

**2) To prepare the Spiolto Respimat inhaler for first-time use**

	<p>4 Hold the Spiolto Respimat inhaler upright, with the light-green cap (A) closed. Turn the base (G) in the direction of the black arrows on the label until it <b>clicks</b> (half a turn).</p>
	<p>5 Open the light-green cap (A) until it snaps fully open.</p>
	<p>6 Point the Spiolto Respimat inhaler towards the ground. Press the dose release button (D). Close the light-green cap (A).</p> <p><b>Repeat steps 4, 5 and 6 until a cloud is visible.</b></p> <p><b>Then repeat steps 4, 5 and 6 three more times to ensure the inhaler is prepared for use.</b></p> <p><b>Your Spiolto Respimat inhaler is now ready to use.</b></p> <p>These steps will not affect the number of doses available. After preparation your Spiolto Respimat inhaler will be able to deliver your 60 puffs (30 medicinal doses).</p>

## Daily use of your Spiolto Respimat inhaler

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

 <p>I</p>	<p><b>I</b> Hold the Spiolto Respimat inhaler upright, with the light-green cap (A) closed, to avoid accidental release of dose. Turn the base (G) in the direction of the black arrows on the label until it clicks (half a turn).</p>
 <p>II</p>	<p><b>II</b> Open the light-green cap (A) until it snaps fully open. Breathe out slowly and fully, and then close your lips around the end of the mouthpiece without covering the air vents (C). Point your Spiolto Respimat inhaler to the back of your throat.</p> <p>While taking in a slow, deep breath through your mouth, press the dose release button (D) and continue to breathe in slowly for as long as you can. Hold your breath for 10 seconds or for as long as comfortable.</p> <p><b>III Repeat steps I and II so that you get the full dose.</b></p> <p><b>You will need to use this inhaler only ONCE A DAY.</b></p> <p><b>Close the light-green cap until you use your Spiolto Respimat inhaler again.</b></p> <p>If Spiolto Respimat inhaler has not been used for more than 7 days release one puff towards the ground. If Spiolto Respimat inhaler has 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.</p>

## When to get a new Spiolto Respimat inhaler



The Spiolto Respimat inhaler contains 60 puffs (30 medicinal doses). The dose indicator shows approximately how much medication is left. When the pointer enters the red area of the scale, there is, approximately, medication for 7 days left (14 puffs). This is when you need to get a new Spiolto Respimat inhaler prescription.

Once the dose indicator has reached the end of the red scale (i.e. all 30 doses have been used), the Spiolto Respimat inhaler locks automatically – no more doses can be released. At this point, the base cannot be turned any further.

At the latest, three months after use the Spiolto Respimat inhaler should be discarded even if not all medication has been used.

## How to care for your inhaler

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 the performance of your Spiolto Respimat inhaler.

If necessary, wipe the outside of your Spiolto Respimat inhaler with a damp cloth.

### **4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

History of hypersensitivity to atropine or its derivatives, e.g. ipratropium or oxitropium.

### **4.4 Special warnings and precautions for use**

#### Asthma

Spiolto Respimat should not be used in asthma. The efficacy and safety of Spiolto Respimat in asthma have not been studied.

#### Not for acute use

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

#### 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.

### Anticholinergic effects related to tiotropium

#### 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.

#### Eye symptoms

Patients should be cautioned to avoid getting the spray into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema. Should any combination of these eye symptoms develop, patients should stop using Spiolto Respimat and consult a specialist immediately.

#### Dental caries

Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental caries.

#### Patients with renal impairment

As plasma concentration of tiotropium increases with decreased renal function in patients with moderate to severe renal impairment (creatinine clearance  $\leq 50$  ml/min) Spiolto Respimat should be used only if the expected benefit outweighs the potential risk. There is no long term experience in patients with severe renal impairment (see 5.2).

#### Cardiovascular effects

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

Like other beta<sub>2</sub>-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.

Long acting beta<sub>2</sub>-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially ischaemic heart disease, severe cardiac decompensation, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, hypertension, and aneurysm, in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval (e.g. QT  $> 0.44$  s), and in patients who are unusually responsive to sympathomimetic amines.

#### Hypokalaemia

Beta<sub>2</sub>-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<sub>2</sub>-adrenergic agonists may produce increases in plasma glucose.

#### Anaesthesia

Caution needs to be taken in case of a planned operation with halogenated hydrocarbon anaesthetics due to an increased susceptibility to the adverse cardiac effects of beta agonist bronchodilators.

Spiolto Respimat should not be used in conjunction with any other medications containing long-acting beta<sub>2</sub>-adrenergic agonists.

Patients who have been taking inhaled, short-acting beta<sub>2</sub>-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.

Spiolto Respimat should not be used more frequently than once daily.

#### Hypersensitivity

As with all medications, immediate hypersensitivity reactions may occur after administration of Spiolto Respimat.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Although no formal *in vivo* drug interaction studies have been performed between Spiolto Respimat and other drugs, inhaled Spiolto Respimat has been used concomitantly with other COPD medicinal products, including short acting sympathomimetic bronchodilators and inhaled corticosteroids without clinical evidence of drug interactions.

#### Anticholinergic agents

The co-administration of tiotropium bromide, one component of Spiolto Respimat, with other anticholinergic containing drugs has not been studied and therefore is not recommended.

#### Adrenergic agents

Concomitant administration of other adrenergic agents (alone or as part of combination therapy) 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 hypokalemic 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 and tricyclic antidepressants, QTc Prolonging drugs

Monamine 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

No relevant effect on systemic exposure to olodaterol has been observed in drug-drug interaction studies with co-administration of fluconazole, used as model inhibitor of CYP2C9.

Co-administration of ketoconazole as potent P-gp and CYP3A4 inhibitor increased systemic exposure to olodaterol by approximately 70%. No dose adjustment of Spiolto Respimat is necessary.

*In vitro* investigations have shown that olodaterol does not inhibit CYP enzymes or drug transporters at the plasma concentrations achieved in clinical practice.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

###### Tiotropium

There is a very limited amount of data from the use of tiotropium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (see 5.3).

###### Olodaterol

For olodaterol no clinical data on exposed pregnancies are available. 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.

Like other beta<sub>2</sub>-adrenergic agonists, olodaterol a component of Spiolto Respimat may inhibit labour due to a relaxant effect on uterine smooth muscle.

##### Breast-feeding

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

In animal 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.

A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Spiolto Respimat should be made taking into account the benefit of breast-feeding to the child and the benefit of Spiolto Respimat therapy to the woman.

##### 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 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

Many of the listed undesirable effects can be assigned to the anticholinergic properties of tiotropium bromide or to the β<sub>2</sub>-adrenergic properties of olodaterol, the components of Spiolto Respimat

b. Tabulated summary of adverse reactions

The frequencies assigned to the undesirable effects listed below are based on the crude incidence rates of adverse drug reactions (i.e. events attributed to Spiolto Respimat) observed in the tiotropium 5 microgram/olodaterol 5 microgram dose group (1302 patients), pooled from 5 active or placebo-controlled, parallel group clinical trials in COPD patients with treatment periods ranging between 4 and 52 weeks.

Adverse reactions reported in all clinical trials with Spiolto Respimat 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data)*

<b>System Organ Class</b>	<b>Adverse reaction</b>	<b>Frequency</b>
<b>Infections and infestations</b>	Nasopharyngitis	rare
<b>Metabolism and nutrition disorders</b>	Dehydration	not known
<b>Nervous system disorders</b>	Dizziness	uncommon
	Insomnia	uncommon
	Headache	uncommon
<b>Eye disorders</b>	Vision blurred	rare
	Glaucoma	not known
	Intraocular pressure increased	not known
<b>Cardiac disorders</b>	Atrial fibrillation	uncommon
	Palpitations	uncommon
	Tachycardia	uncommon
	Supraventricular tachycardia	rare
<b>Vascular disorders</b>	Hypertension	uncommon
<b>Respiratory, thoracic and mediastinal disorders</b>	Cough	uncommon
	Dysphonia	rare
	Epistaxis	rare
	Laryngitis	rare
	Pharyngitis	rare
	Bronchospasm	not known

	Sinusitis	not known
<b>Gastrointestinal disorders</b>	Dry mouth	common
	Constipation	uncommon
	Gingivitis	rare
	Nausea	rare
	Oropharyngeal candidiasis	rare
	Intestinal obstruction Ileus paralytic	not known
	Dental caries	not known
	Dysphagia	not known
	Gastroesophageal reflux disease	not known
	Glossitis	not known
	Stomatitis	not known
<b>Skin and subcutaneous tissue disorders, Immune system disorders</b>	Angioedema	rare
	Urticaria	rare
	Hypersensitivity	rare
	Pruritus	rare
	Anaphylactic reaction	not known
	Rash	not known
	Dry skin	not known
	Skin infection and skin ulcer	not known
<b>Musculoskeletal and connective tissue disorders</b>	Back pain <sup>1</sup>	rare
	Arthralgia	rare
	Joint swelling	not known
<b>Renal and urinary disorders</b>	Urinary retention	rare
	Dysuria	rare
	Urinary tract infection	not known

1 undesirable effects reported with Spiolto Respimat, but not with the individual components

c. Description of selected adverse reactions

Spiolto Respimat combines anticholinergic and  $\beta_2$ -adrenergic properties due to its components tiotropium and olodaterol.

Anticholinergic adverse reaction profile

In the long term 52-weeks clinical trials with Spiolto Respimat, the most frequently observed undesirable anticholinergic effect was dry mouth which occurred in approximately 1.7% of patients treated with Spiolto Respimat and in 2.7% and 1% in the tiotropium 5 microgram and olodaterol 5

microgram arms, respectively. Dry mouth led to discontinuation in 1 of 1,029 patients (0.1 %) treated with Spiolto Respimat.

Serious undesirable effects consistent with anticholinergic effects include glaucoma, constipation, intestinal obstruction including ileus paralytic and urinary retention.

#### β-adrenergic adverse reaction profile

In the long term 52-weeks clinical trials with Spiolto Respimat, the most frequently observed β-adrenergic undesirable effects were palpitations, tachycardia and hypertension.

Olodaterol, one component of Spiolto Respimat is a member of the therapeutic class of long-acting beta<sub>2</sub>-adrenergic agonists. Therefore 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, nervousness, muscle spasms, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis.

#### d. Other special populations

An increase in anticholinergic effect may occur with increasing age.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via **the national reporting system listed in Appendix V\***.

## **4.9 Overdose**

There is limited information on overdosing with Spiolto Respimat. Spiolto Respimat has been studied up to 5 microgram / 10 microgram (tiotropium/olodaterol) in COPD patients and up to 10 microgram / 40 microgram (tiotropium/olodaterol) in healthy subjects; no clinically relevant effects were observed. An overdose could lead to exaggerated anti-muscarinic effects of tiotropium and/or exaggerated β<sub>2</sub> agonists effects of olodaterol.

#### Symptoms

##### *Overdose of anticholinergic tiotropium*

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

However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 microgram tiotropium bromide in healthy volunteers. Additionally, no relevant adverse events, beyond dry mouth/throat and dry nasal mucosa were observed following 14-day dosing of up to 40 microgram tiotropium inhalation solution in healthy volunteers with the exception of pronounced reduction in salivary flow from day 7 onwards.

##### *Overdose of β<sub>2</sub>-agonist olodaterol*

An overdose of olodaterol is likely to lead to exaggerated effects typical of beta<sub>2</sub>-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 of overdose

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*

Spiolto Respimat is a fixed dose combination inhalation solution containing a long acting muscarinic receptor antagonist, tiotropium and a long acting beta<sub>2</sub>-adrenergic agonist, olodaterol (LAMA/LABA) which is delivered via the Spiolto Respimat soft mist inhaler device.

The two active ingredients provide additive bronchodilation due to their different mode of action. Since muscarinic receptors appear to be more prominent in the central airways while  $\beta_2$  adrenoceptors have a higher expression level in the peripheral airways, a combination of tiotropium and olodaterol should provide optimal bronchodilatation in all regions of the lungs.

##### *Tiotropium*

Tiotropium bromide is a long-acting, specific antagonist at muscarinic receptors. It has similar affinity to the subtypes, M<sub>1</sub> to M<sub>5</sub>. In the airways, tiotropium bromide competitively and reversibly binds to the M<sub>3</sub> receptors in the bronchial smooth musculature, antagonising the cholinergic (bronchoconstrictive) effects of acetylcholine, resulting in bronchial smooth muscle relaxation. The effect was dose dependent and lasted longer than 24h. As an N-quaternary anticholinergic, tiotropium bromide is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before systemic anticholinergic effects may occur.

##### *Olodaterol*

Olodaterol has a high affinity and high selectivity to the human beta<sub>2</sub>-adrenoceptor.

*In vitro* studies have shown that olodaterol has 241-fold greater agonist activity at beta<sub>2</sub>-adrenoceptors compared to beta<sub>1</sub>-adrenoceptors and 2299-fold greater agonist activity compared to beta<sub>3</sub>-adrenoceptors.

The compound exerts its pharmacological effects by binding and activation of beta<sub>2</sub>-adrenoceptors after topical administration by inhalation.

Activation of these receptors in the airways results in a stimulation of intracellular adenylyl 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<sub>2</sub>-adrenoceptor agonist (LABA) with a fast onset of action and a duration of action of at least 24 hours.

Beta-adrenoceptors are divided into three subtypes, beta<sub>1</sub>-adrenoceptors predominantly expressed on cardiac muscle, beta<sub>2</sub>-adrenoceptors predominantly expressed on airway smooth muscle and beta<sub>3</sub>-adrenoceptors predominantly expressed on adipose tissue. Beta<sub>2</sub>-agonists cause bronchodilation.

Although the beta<sub>2</sub>-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<sub>2</sub>-receptors in the heart is not known, but their presence raises the possibility that even highly selective beta<sub>2</sub>-adrenergic agonists may have cardiac effects.

#### Effects on cardiac electrophysiology

##### *Tiotropium*

In a dedicated QT study involving 53 healthy volunteers, tiotropium inhalation powder 18 microgram and 54 microgram (i.e. three times the therapeutic dose) over 12 days did not significantly prolong QT intervals of the 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 for individually corrected QT (QTcI).

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*

Two 52-week randomized, double-blind trials using Spiolto Respimat enrolled 5162 patients with COPD. In a pooled analysis the number of subjects with changes from baseline-corrected QTcF (Fridericia correction) interval of >30 msec at 40 minutes post-dose on day 85, 169, and 365, ranged from 3.1%, 4.7%, and 3.6% for the Spiolto Respimat group compared to 4.1%, 4.4%, and 3.6% for olodaterol 5 microgram and 3.4%, 2.3%, and 4.6% for the tiotropium 5 microgram group, respectively.

#### Clinical efficacy and safety

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 (1029 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.

#### 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<sub>1</sub> was 1.37 L (GOLD 2 [50%], GOLD 3 [39%], 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<sub>1</sub> 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%].

#### Effects on 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<sub>1</sub> 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<sub>1</sub> AUC<sub>0-3h</sub> response and trough FEV<sub>1</sub> response after 24 weeks (lung function primary endpoints) for Spiolto Respimat compared to tiotropium 5 microgram and olodaterol 5 microgram (Table 1).

**Table 1** Difference in FEV<sub>1</sub> AUC<sub>0-3h</sub> and trough FEV<sub>1</sub> response for Spiolto Respimat compared to tiotropium 5 microgram, olodaterol 5 microgram after 24 weeks (Trials 1 and 2)

	FEV <sub>1</sub> AUC <sub>0-3h</sub> response				Trough FEV <sub>1</sub> response			
	Trial 1		Trial 2		Trial 1		Trial 2	
	n	Mean	n	Mean	n	Mean	n	Mean
<b>Spiolto Respimat versus</b>	522	--	502	--	521	--	497	--
<b>Tiotropium 5 microgram</b>	526	0.117 L	500	0.103 L	520	0.071 L	498	0.050 L
<b>Olodaterol 5 microgram</b>	525	0.123 L	507	0.132 L	519	0.082 L	503	0.088 L

pre-treatment baseline FEV<sub>1</sub>: Trial 1 = 1.16 L; Trial 2 = 1.15 L

p<0.0001 for all comparisons

n= number of patients

Patients with a higher degree of reversibility at baseline generally exhibited a higher bronchodilator response with Spiolto Respimat than patients with a lower degree of reversibility at baseline.

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 6 week trial, Spiolto Respimat showed a significantly greater FEV<sub>1</sub> response compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo (p<0.0001) over the full 24 hour dosing interval (Table 2).

**Table 2** Average difference in FEV<sub>1</sub> (L) over 3 hr, 12 hr and 24 hr and difference in trough FEV<sub>1</sub> (L) for Spiolto Respimat compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo after 6 weeks (Trial 3)

	n	3 hr average	n	12 hr average	24 hr average <sup>1</sup>	Trough
<b>Spiolto Respimat versus</b>	138		138			
<b>Tiotropium 5 microgram</b>	137	0.109	135	0.119	0.110	0.079
<b>Olodaterol 5 microgram</b>	138	0.109	136	0.126	0.115	0.092
<b>Placebo</b>	135	0.325	132	0.319	0.280	0.207

pre-treatment baseline FEV<sub>1</sub> = 1.30 L

<sup>1</sup> primary endpoint

p<0.0001 for all comparisons

n= number of patients



### Health-related Quality of Life

Spiolto Respimat showed improvement in health-related quality of life as indicated by a reduction in St. George Respiratory Questionnaire (SGRQ) total score. After 24 weeks, there was a statistically significant improvement in mean SGRQ total score for Spiolto Respimat compared to tiotropium 5 microgram and olodaterol 5 microgram (Table 3); 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 3: SGRQ total score after 24 weeks of treatment**

		n	Treatment Mean (change from baseline)	Difference to 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 ( $p=0.002$ )

n= number of patients

### Dyspnea

After 24 weeks, mean TDI focal score was 1.98 units for Spiolto Respimat, with a significant improvement compared to tiotropium 5 microgram (mean difference 0.36,  $p=0.008$ ) and olodaterol 5 microgram (mean difference 0.42 ( $p=0.002$ )).

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%,  $p=0.0026$ ).

### Rescue Medication Use

Patients treated with Spiolto Respimat used less daytime and nighttime rescue salbutamol compared to patients treated with tiotropium 5 microgram and olodaterol 5 microgram (mean daytime rescue use for Spiolto Respimat of 0.76 occasions per day compared to 0.97 occasions per day for tiotropium 5 microgram and 0.87 occasions per day for olodaterol 5 microgram,  $p<0.0001$ ; mean nighttime rescue use for Spiolto Respimat of 1.24 occasions per day compared to 1.69 occasions per day for tiotropium 5 microgram and 1.52 occasions per day for olodaterol 5 microgram,  $p<0.0001$ ).

### 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.

### 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 at least one moderate/severe COPD exacerbation was 27.7% for Spiolto Respimat and 28.8% for tiotropium 5 microgram ( $p=0.39$ ). These studies were not specifically designed to evaluate the effect of treatments on COPD exacerbations.

### 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 at rest two hours post-dose compared to tiotropium 5 microgram (0.114 L,  $p < 0.0001$ ; Trial 4, 0.088 L,  $p = 0.0005$ ; Trial 5), olodaterol 5 microgram (0.119 L,  $p < 0.0001$ ; Trial 4, 0.080 L,  $p = 0.0015$ ; Trial 5) and placebo (0.244 L,  $p < 0.0001$ ; Trial 4, 0.265 L,  $p < 0.0001$ ; Trial 5) after 6 weeks.

In Trials 4 and 5, Spiolto Respimat significantly improved endurance time during constant work rate cycling compared to placebo after 6 weeks (Trial 4: geometric mean endurance time of 454 s for Spiolto Respimat compared to 375 seconds for placebo (20.9% improvement,  $p < 0.0001$ ); Trial 5: geometric mean endurance time of 466 seconds for Spiolto Respimat compared to 411 seconds for placebo (13.4% improvement,  $p < 0.0001$ ).

In Trial 6, Spiolto Respimat significantly improved endurance time during constant work rate cycling compared to placebo after 12 weeks (geometric endurance time of 528 seconds for Spiolto Respimat compared to 464 seconds for placebo (13.8% improvement,  $p = 0.021$ ).

#### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Spiolto Respimat in all subsets of the paediatric population in chronic obstructive pulmonary disease (COPD) as per decision on class waivers (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### a. General Introduction

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.

### b. General Characteristics of the Active Substance after Administration of the Medicinal Product

#### 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. Olodaterol is a substrate for the P-gp, OAT1, OAT3 and OCT1 transporter. Olodaterol is not a substrate for the following transporters: BCRP, MRP, OATP2, OATP8, OATP-B, OCT2 and OCT3.

#### 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 metabolised by cytochrome P450 (CYP) 2D6 and 3A4 dependent oxidation and subsequent glutathion 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 binds 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. 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*: The total clearance in healthy volunteers is 880 mL/min. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). 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. Following intravenous administration of [<sup>14</sup>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 (0.7% unchanged olodaterol) 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. Olodaterol plasma concentrations after inhalation decline in a multiphasic manner with a terminal half-life of approximately 45 hours.

#### c. 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  $\geq$ 65 years. This did not result in a corresponding increase in AUC<sub>0-6,ss</sub> or C<sub>max,ss</sub> 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.

### Race

*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 Respimat at 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*: There were no clinically relevant increases of systemic exposure in patients with renal impairment.

### 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*: There was no evidence for differences in elimination of olodaterol, nor did protein binding differ, between subjects with mild or moderate hepatic impairment and their healthy controls. A study in subjects with severe hepatic impairment was not performed.

## **5.3 Preclinical safety data**

### *Tiotropium + olodaterol*

Effects in non-clinical studies with the combination tiotropium/olodaterol were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

### *Tiotropium*

Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans.

Harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. Tiotropium bromide was not teratogenic in rats or rabbits. The respiratory (irritation) and urogenital (prostatitis) changes and reproductive toxicity were observed at local or systemic exposures more than five-fold the therapeutic exposure.

### *Olodaterol*

Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans.

Increased incidences were observed of mesovarian leiomyoma in rats and of uterus leiomyoma and leiomyosarcoma in mice. This is considered a class effect which is observed in rodents after long-term exposure to high doses of  $\beta_2$ -agonists. Up to now,  $\beta_2$ -agonists have not been associated with cancer in humans.

In rats, no teratogenic effects occurred after inhalation at doses of 1054 microgram/kg/day (> 2600 times the human exposure ( $AUC_{(0-24h)}$ ) at the dose of 5 mcg). 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 beta-adrenoceptor stimulation; these included patchy ossifications, short/bent bones, partially open eye, cleft palate,

cardiovascular abnormalities. No significant effects occurred at an inhalation dose of 974 microgram/kg/day (approximately 1353 times the 5 microgram dose based on AUC<sub>(0-24h)</sub>).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Benzalkonium chloride  
Disodium edetate  
Water, purified  
1M Hydrochloric acid (for pH adjustment)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years  
In-use shelf life: 3 months

### **6.4 Special precautions for storage**

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.  
Each cartridge contains 4 ml inhalation solution.

Pack sizes and devices supplied:

Single pack: 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Double pack: 2 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Triple pack: 3 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Eight pack: 8 single packages, each containing 1 Respimat inhaler and one 1 cartridge, providing 60 puffs (30 medicinal doses)

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

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

**7. MARKETING AUTHORISATION HOLDER**

Boehringer Ingelheim International GmbH  
Binger Strasse 173  
D-55216 Ingelheim am Rhein  
Germany

**8. MARKETING AUTHORISATION NUMBER(S)**

<[To be completed nationally]>

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

**10. DATE OF REVISION OF THE TEXT**

{MM/YYYY}

<[To be completed nationally]>

## **LABELLING**

Version: May 19, 2015

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**FOLDING BOX**

**1. NAME OF THE MEDICINAL PRODUCT**

Spiolto Respimat 2.5 microgram/2.5 microgram, inhalation solution

tiotropium/olodaterol

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

The delivered dose is 2.5 microgram tiotropium (as bromide monohydrate) and 2.5 microgram olodaterol (as hydrochloride) per puff

**3. LIST OF EXCIPIENTS**

List of excipients:

Benzalkonium chloride

Disodium edetate

Purified water

1M Hydrochloric acid for pH adjustment

**4. PHARMACEUTICAL FORM AND CONTENTS**

Inhalation solution

One cartridge contains 4.0 ml providing 60 puffs (30 medicinal doses)

Single pack: 1 Respimat Inhaler and 1 cartridge

Double pack: 2 single packages, each containing 1 Respimat Inhaler and 1 cartridge

Triple pack: 3 single packages, each containing 1 Respimat Inhaler and 1 cartridge

Eight pack: 8 single packages, each containing 1 Respimat Inhaler and 1 cartridge

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Inhalation use

Read the package leaflet before use

Insert cartridge in the Respimat inhaler before first use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**



**8. EXPIRY DATE**

EXP

In-use shelf life: 3 months

**9. SPECIAL STORAGE CONDITIONS**

Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Boehringer Ingelheim International GmbH  
D-55216 Ingelheim am Rhein  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

To be completed nationally

**13. BATCH NUMBER**

Batch:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Spiolto Respimat

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**DEVICE – Front label**

**1. NAME OF THE MEDICINAL PRODUCT**

Spiolto Respimat  
2.5 microgram/2.5 microgram inhalation solution  
tiotropium/olodaterol

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Boehringer Ingelheim

**3. EXPIRY DATE**

(See device back label)  
In-use shelf life: 3 months

**4. BATCH NUMBER**

(See device back label)

**5. OTHER**

60 puffs (30 medicinal doses)

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**DEVICE – BACK LABEL (Requirements according to Medical Device Directive)**

**1. NAME OF THE MEDICINAL PRODUCT**

Spiolto Respimat Inhaler

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Batch:

**5. OTHER**

Scale for dose indicator

▷ ▷ Turn ▷ ▷

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**CARTRIDGE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Spiolto Respimat  
2.5 microgram/ 2.5 microgram inhalation solution  
tiotropium/olodaterol

**2. METHOD OF ADMINISTRATION**

Inhalation use

**3. EXPIRY DATE**

EXP  
In-use shelf life: 3 months

**4. BATCH NUMBER**

Batch:

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

One cartridge contains 4.0 ml providing 60 puffs (30 medicinal doses)

**6. OTHER**

**PACKAGE LEAFLET**

Version: May 19, 2015

## **Package leaflet: Information for the user**

### **Spiolto Respimat 2.5 microgram/2.5 microgram, inhalation solution** tiotropium/olodaterol

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Spiolto Respimat is and what it is used for
2. What you need to know before you take Spiolto Respimat
3. How to take Spiolto Respimat
4. Possible side effects
5. How to store Spiolto Respimat
6. Contents of the pack and other information

## **1. What Spiolto Respimat is and what it is used for**

### **What Spiolto Respimat is**

Spiolto Respimat contains two active substances called tiotropium and olodaterol. These belong to a group of medicines called long-acting bronchodilators. Tiotropium belongs to the subgroup of anticholinergics; olodaterol belongs to the subgroup of long acting beta<sub>2</sub> agonists.

### **What Spiolto Respimat is used for**

Spiolto Respimat helps adult patients who have chronic obstructive pulmonary disease (COPD) to breathe more easily. COPD is a long-term lung disease that causes shortness of breath and coughing. The term COPD is associated with the conditions chronic bronchitis and emphysema.

Spiolto Respimat helps to open your airways and make it easier to get air in and out of the lungs. Regular use of Spiolto Respimat can also help you when you have on-going shortness of breath related to your disease, and will help to minimise the effects of the disease on your everyday life. As COPD is a long-term disease you should take Spiolto Respimat every day and not only when you have breathing problems or other symptoms of COPD.

## **2. What you need to know before you take Spiolto Respimat**

### **Do not use Spiolto Respimat**

- if you are allergic to tiotropium or olodaterol or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to atropine or substances related to it, e.g. ipratropium or oxitropium

## Warnings and precautions

### Talk to your doctor or pharmacist before using Spiolto Respimat

- if you have asthma (you should not use Spiolto Respimat for the treatment of asthma).
- if you have diseases of the heart.
- if you have high blood pressure.
- if you have epilepsy.
- if you have a specific thyroid gland problem called thyrotoxicosis.
- if you have an abnormal widening of an artery called aneurysm.
- if you have diabetes.
- if you have severe hepatic impairment.
- if you have renal impairment.
- in case of a planned surgery.
- if you have an eye problem called narrow-angle glaucoma.
- if you have prostate problems or have difficulty passing urine.

### During treatment with Spiolto Respimat

- **Stop using the medicine and tell your doctor immediately** if you get tightness of the chest, coughing, wheezing or breathlessness immediately after using the medicine. These may be signs of a condition called bronchospasm (see section 4).
- If your breathing has got worse or if you experience rash, swelling or itching directly after using your inhaler, stop using it and tell your doctor immediately (see section 4).
- If you experience any side effects affecting your heart (increase in pulse rate, increase in blood pressure and/or increase in symptoms like chest pain), tell your doctor immediately (see section 4).
- If you experience muscle spasm, muscle weakness or abnormal heart rhythm, consult your doctor as these may be related to low blood levels of potassium (see section 4).

When taking Spiolto Respimat take care not to let any spray enter your eyes. This may result in eye pain or discomfort, blurred vision, seeing halos around lights or coloured images in association with red eyes (i.e. narrow angle glaucoma). Eye symptoms may be accompanied by headache, nausea or vomiting. Wash your eyes in warm water, stop using Spiolto Respimat and immediately consult your doctor for further advice.

Spiolto Respimat is indicated for the maintenance treatment of your chronic obstructive pulmonary disease. **It should not be used to treat a sudden attack of breathlessness or wheezing.**

Do not use Spiolto Respimat together with certain medicines containing long-acting  $\beta$ -adrenergic agonists, like salmeterol or formoterol.

If you regularly take certain medicines called short-acting  $\beta$ -adrenergic agents, like salbutamol, continue to use these only to relieve acute symptoms like breathlessness.

Dry mouth which has been observed with anti-cholinergic treatment may in the long term be associated with dental caries. Therefore, please remember to pay attention to oral hygiene.

Do not take Spiolto Respimat more frequently than once daily.

### **Children and adolescents**

Spiolto Respimat **should not** be given to **children or adolescents (below the age of 18 years)**.

### **Other medicines and Spiolto Respimat**

Please tell your doctor or pharmacist if you are taking, or have recently taken any other medicines.

In particular, please tell your doctor if you are using:

- any medicines that may be similar to Spiolto Respimat (contain similar active substances, such as anticholinergic drugs or  $\beta$ -adrenergic agents). You may be more likely to get side effects.
- medicines called beta blockers that are used for high blood pressure or other heart problems (such as propranolol), or for the eye problem called glaucoma (such as timolol). This may result in loss of the effect of Spiolto Respimat
- medicines that lower the amount of potassium in your blood. These include:
  - o steroids (e.g. prednisolone),
  - o diuretics (water tablets),
  - o medicines for breathing problems such as theophylline.If you use these medicines together with Spiolto Respimat you may experience symptoms of muscle spasm, muscle weakness or abnormal heart rhythm.
- medicines called tricyclic antidepressants or monoamine oxidase (MAO) inhibitors (like selegiline or moclobemide), that are used to treat neurological or psychiatric disorders like Parkinson's disease or depression; the use of these drugs will increase the likelihood that you get side effects affecting your heart.

### **Pregnancy, breast-feeding and fertility**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not use this medicine unless specifically recommended by your doctor.

### **Driving and using machines**

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

If you feel dizzy or if blurred vision occurs while taking Spiolto Respimat, do not drive or use any tools or machines.

## **3. How to take Spiolto Respimat**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Spiolto Respimat is for inhalation use only.

### **Dosage**

The recommended dose is:



Spiolto Respimat is effective for 24 hours so you will need to use Spiolto Respimat only **ONCE A DAY**, if possible at the same time of the day. Each time you use it take **TWO PUFFS**.

As COPD is a long-term disease take Spiolto Respimat every day and not only when you experience breathing problems. Do not take more than the recommended dose.

#### **Use in children and adolescents**

There is no relevant use of Spiolto Respimat in the paediatric population (under 18 years).

Make sure that you know how to use your Spiolto Respimat inhaler properly. The instructions for use of the Spiolto Respimat inhaler are provided on the other side of this leaflet.

#### **If you take more Spiolto Respimat than you should**

You may be at a higher risk of experiencing a side effect such as dry mouth, constipation, difficulties passing urine, blurred vision, chest pain, high or low blood pressure, faster or irregular heartbeat or feeling of heart beat, dizziness, nervousness, difficulty in sleeping, anxiety, headache, shaking, muscle cramps, nausea, fatigue, malaise, low blood levels of potassium (which may cause symptoms of muscle spasm, muscle weakness or abnormal heart rhythm), high blood sugar, or too much acid in your blood (which may cause symptoms of nausea, vomiting, weakness, muscle cramps and more rapid breathing).

#### **If you forget to take Spiolto Respimat**

If you forget to inhale a dose, inhale just one dose at the usual time the next day. Do not take a double dose to make up for a forgotten dose.

#### **If you stop using Spiolto Respimat**

Before you stop taking Spiolto Respimat, you should talk to your doctor or your pharmacist. If you stop taking Spiolto Respimat the signs and symptoms of COPD may worsen.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Immediate allergic reactions such as rash, nettle rash (urticaria), swelling of the mouth and face or sudden difficulties in breathing (angioneurotic oedema) or other hypersensitivity reactions (such as sudden reduction of your blood pressure or dizziness) may occur individually or as part of severe allergic reaction (anaphylactic reaction) after administration of Spiolto Respimat. If any of these occur, **please stop using this medicine** and consult your doctor immediately.

The side effects described below have been experienced by people taking this medicine and they are listed according to frequency.

#### **Common (may affect up to 1 in 10 people)**

- dry mouth

#### **Uncommon (may affect up to 1 in 100 people)**

- dizziness

- difficulty in sleeping (insomnia)
- headache
- hypertension
- irregular heart beat (atrial fibrillation)
- feeling your heartbeat (palpitations)
- faster heart beat (tachycardia)
- cough
- constipation

**Rare (may affect up to 1 in 1,000 people)**

- nasopharyngitis
- sore throat (pharyngitis)
- inflammation of the larynx (laryngitis)
- inflammation of the gums (gingivitis)
- hoarseness (dysphonia)
- nosebleed (epistaxis)
- fungal infections of the oral cavity and throat (oropharyngeal candidiasis)
- blurred vision
- rapid heartbeat (supraventricular tachycardia)
- feeling sick (nausea)
- joint pain (arthralgia)
- back pain
- difficulties passing urine (urinary retention)
- painful urination (dysuria)
- hypersensitivity, including immediate reactions
- serious allergic reaction which causes swelling of the mouth and face or throat (angioneurotic oedema)
- itching (pruritus)
- nettle rash (urticaria)

**Not known (frequency cannot be estimated from the available data)**

- seeing halos around lights or coloured images in association with red eyes (glaucoma)
- increase of the measured eye pressure
- tightness of the chest, associated with coughing, wheezing or breathlessness immediately after inhalation (bronchospasm)
- inflammation of the tongue (glossitis)
- dental caries
- inflammation in sinuses (sinusitis)
- inflammation of the mouth (stomatitis)
- difficulties swallowing (dysphagia)
- heart burn (gastrooesophageal reflux disease)
- blockage of intestines or absence of bowel movements (intestinal obstruction, including ileus paralytic)
- rash
- severe allergic reaction (anaphylactic reaction)
- dryness of the skin
- infections or ulcerations of the skin
- depletion of body water (dehydration)
- infections of the urinary tract
- swelling of joint

You may also experience side effects which are known to occur with certain medicines for breathing problems similar to Spiolto Respimat (beta-adrenergic agents). These may be irregular heartbeat, chest pain, low blood pressure, shaking, nervousness, muscle cramps, fatigue, malaise, low blood levels of potassium (which may cause symptoms of muscle spasm, muscle weakness or abnormal heart rhythm),

high blood sugar, or too much acid in your blood (which may cause symptoms of nausea, vomiting, weakness, muscle cramps and more rapid breathing).

In addition, in common with all inhaled medicines, some patients may experience an unexpected tightness of the chest, coughing, wheezing or breathlessness immediately after inhalation (bronchospasm).

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Spiolto Respimat**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the inhaler label after EXP. The expiry date refers to the last day of the month.

Do not freeze.

Spiolto Respimat inhaler should be discarded at the latest 3 months after first use.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Spiolto Respimat contains**

The active substances are tiotropium and olodaterol. 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.

The other ingredients are:

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

### **What Spiolto Respimat looks like and contents of the pack**

Spiolto Respimat is composed of one cartridge with inhalation solution and one Respimat inhaler. The cartridge has to be inserted into the inhaler before the first use.

Single pack: 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Double pack: 2 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Triple pack: 3 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Eight pack: 8 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder and Manufacturer**

The marketing authorisation holder for Spiolto Respimat is:

Boehringer Ingelheim International GmbH  
Binger Straße 173  
D-55216 Ingelheim am Rhein  
Germany

The manufacturer for Spiolto Respimat is:

Boehringer Ingelheim Pharma GmbH & Co. KG  
Binger Straße 173  
D-55216 Ingelheim am Rhein  
Germany

**This medicinal product is authorised in the Member States of the EEA under the following names:**

<b>Austria, Liechtenstein:</b>	Spiolto Respimat 2,5 Mikrogramm/2,5 Mikrogramm – Lösung zur Inhalation
<b>Belgium, Luxembourg:</b>	Spiolto Respimat 2,5 microgrammes/2,5 microgrammes/inhalation, solution à inhaler
<b>Bulgaria:</b>	Spiolto Respimat СПИОЛТО РЕСПИМАТ
<b>Cyprus, Greece:</b>	Spiolto Respimat
<b>Croatia</b>	Spiolto Respimat 2,5 mikrograma/ 2,5 mikrograma, otopina inhalata
<b>Czech Republic:</b>	Spiolto Respimat 2,5 mikrogramů/2,5 mikrogramů
<b>Denmark:</b>	Spiolto Respimat
<b>Estonia:</b>	Spiolto Respimat
<b>France:</b>	Spiolto Respimat 2,5 microgrammes/2,5 microgrammes/dose, solution à inhaler
<b>Germany:</b>	Spiolto Respimat 2,5 Mikrogramm/2,5 Mikrogramm pro Hub, Lösung zur Inhalation
<b>Hungary:</b>	Spiolto Respimat 2,5 mikrogramm/2,5 mikrogramm inhalációs oldat
<b>Iceland:</b>	Spiolto Respimat
<b>Ireland, Malta, UK:</b>	Spiolto Respimat
<b>Italy:</b>	Spiolto Respimat 2,5 microgrammi/2,5 microgrammi, soluzione per inalazione
<b>Latvia:</b>	Spiolto Respimat 2,5 mikrogrami/2,5 mikrogrami šķīdums inhalācijām
<b>Lithuania:</b>	Spiolto Respimat 2,5 mikrogramo/2,5 mikrogramo/išpurškime įkvepiamasis tirpalas
<b>Netherlands:</b>	Spiolto Respimat 2,5 microgram/2,5 microgram, inhalatieoplossing
<b>Norway:</b>	Spiolto Respimat
<b>Poland:</b>	Spiolto Respimat

<b>Portugal:</b>	Spiolto Respimat
<b>Romania:</b>	Spiolto Respimat 2,5 micrograme/2,5 micrograme soluție de inhalat
<b>Slovakia:</b>	Spiolto Respimat
<b>Slovenia:</b>	Spiolto Respimat 2,5 mikrogramov/2,5 mikrogramov/vdih raztopina za inhaliranje
<b>Spain:</b>	Spiolto Respimat 2,5 microgramos/2,5 microgramos solución para inhalación
<b>Sweden:</b>	Spiolto Respimat

**This leaflet was last revised in {MM/YYYY}.**

To be completed nationally

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## Instructions for Use

### Spiolto Respimat inhaler

#### How to use your Spiolto Respimat inhaler

This leaflet explains how to use and care for your Spiolto Respimat inhaler. **Please read and carefully follow these instructions.** See also section 3. How to take Spiolto Respimat on the other side of this leaflet.

The Spiolto Respimat inhaler releases medication slowly and gently, making it easy to inhale it into your lungs.





The Spiolto Respimat inhaler enables you to inhale the medicine contained in a cartridge. The full cartridge provides 60 puffs (30 medicinal doses). **You will need to use this inhaler only ONCE A DAY**, if possible at the same time of the day. **Each time you use it take TWO PUFFS.** There is enough medicine for 30 days when it is used according to the directions for use. In the box you will find the Spiolto Respimat inhaler and the Spiolto Respimat cartridge. Before the Spiolto Respimat inhaler is used for the first time, the cartridge provided must be inserted.




**Spiolto Respimat inhaler and the Spiolto Respimat cartridge**

## 1) Inserting the cartridge

The following steps 1-6 are necessary before first use:

 <p>1</p>	<p>1 With the light-green cap (A) closed, press the safety catch (E) while pulling off the clear base (G).</p>
 <p>2a</p>  <p>2b</p>	<p>2 Take the cartridge (H) out of the box. Push the <b>narrow</b> end of the cartridge into the inhaler until it <b>clicks</b> into place. The cartridge should be pushed <b>firmly</b> against a firm surface to ensure that it has gone all the way in (2b). <b>The cartridge will not be flush with the inhaler, you will still see the silver ring of the lower end of the cartridge .</b></p> <p>Do not remove the cartridge once it has been inserted into the inhaler.</p>
 <p>3</p>	<p>3 Replace the clear base (G).</p> <p>Do not remove the clear base again.</p>

## 2) To prepare the Spiolto Respimat inhaler for first-time use

 <p>4</p>	<p>4 Hold the Spiolto Respimat inhaler upright, with the light-green cap (A) closed. Turn the base (G) in the direction of the black arrows on the label until it <b>clicks</b> (half a turn).</p>
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**5** Open the light-green cap (A) until it snaps fully open.



**6** Point the Spiolto Respimat inhaler towards the ground. Press the dose release button (D). Close the light-green cap (A).

**Repeat steps 4, 5 and 6 until a cloud is visible.**

**Then repeat steps 4, 5 and 6 three more times to ensure the inhaler is prepared for use.**



**Your Spiolto Respimat inhaler is now ready to use.**

These steps will not affect the number of doses available. After preparation your Spiolto Respimat inhaler will be able to deliver your 60 puffs (30 medicinal doses).



## Daily use of your Spiolto Respimat inhaler

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

	<p><b>I</b> Hold the Spiolto Respimat inhaler upright, with the light-green cap (A) closed, to avoid accidental release of dose. Turn the base (G) in the direction of the black arrows on the label until it clicks (half a turn).</p>
	<p><b>II</b> Open the light-green cap (A) until it snaps fully open. Breathe out slowly and fully, and then close your lips around the end of the mouthpiece without covering the air vents (C). Point your Spiolto Respimat inhaler to the back of your throat.</p> <p>While taking in a slow, deep breath through your mouth, press the dose release button (D) and continue to breathe in slowly for as long as you can. Hold your breath for 10 seconds or for as long as comfortable.</p> <p><b>III Repeat steps I and II so that you get the full dose.</b></p> <p><b>You will need to use this inhaler only ONCE A DAY.</b></p> <p><b>Close the light-green cap until you use your Spiolto Respimat inhaler again.</b></p> <p>If Spiolto Respimat inhaler has not been used for more than 7 days release one puff towards the ground. If Spiolto Respimat inhaler has 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.</p>

## When to get a new Spiolto Respimat inhaler

	<p>The Spiolto Respimat inhaler contains 60 puffs (30 medicinal doses). The dose indicator shows approximately how much medication is left. When the pointer enters the red area of the scale, there is, approximately, medication for 7 days left (14 puffs). This is when you need to get a new Spiolto Respimat inhaler prescription.</p> <p>Once the dose indicator has reached the end of the red scale (i.e. all 30 doses have been used), the Spiolto Respimat inhaler locks automatically – no more doses can be released. At this point, the base cannot be turned any further.</p> <p>At the latest, three months after use the Spiolto Respimat inhaler should be discarded even if not all medication has been used.</p>
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## What if...

What if...	Reason	What to do
I can't turn the base easily.	a) The Spiolto Respimat inhaler is already prepared and ready to use. b) The Spiolto Respimat inhaler is locked after 60 puffs (30 medicinal doses).	a) The Spiolto Respimat inhaler can be used as it is. b) Prepare and use your new Spiolto Respimat inhaler.
The cap is fully pulled off and apart from the inhaler.	While opening the cap it was pulled too hard.	The cap can easily be attached again.
I can't press the dose release button.	The clear base has not been turned.	Turn the clear base until it <b>clicks</b> . (half a turn)
The clear base springs back after I have turned it.	The clear base was not turned far enough.	Prepare the Spiolto Respimat inhaler for use by turning the clear base until it <b>clicks</b> . (half a turn)
I can turn the clear base past the point where it clicks.	Either the dose release button has been pressed, or the clear base has been turned too far.	With the light-green cap <b>closed</b> , turn the base until it <b>clicks</b> . (half a turn)

## How to care for your inhaler

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 the performance of your Spiolto Respimat inhaler.

If necessary, wipe the outside of your Spiolto Respimat inhaler with a damp cloth.

### **Further Information**

The Spiolto Respimat inhaler must not be disassembled after inserting the cartridge and replacing the clear base.

Do not touch the piercing element inside the base.