SPIOLTO® RESPIMAT®
Tiotropium bromide /Olodaterol

COMPOSITION

The SPIOLTO® RESPIMAT® is a soft mist inhaler delivering tiotropium + olodaterol inhalation solution.

The delivered dose is 2.5 microgram tiotropium and 2.5 microgram olodaterol per puff (2 puffs comprise one medicinal dose) and is equivalent to 3.124 microgram tiotropium bromide monohydrate and 2.7 microgram olodaterol hydrochloride.

The delivered dose is the dose which is available for the patient after passing the mouthpiece.

Excipients: Benzalkonium chloride, disodium edetate, purified water, 1 M hydrochloric acid (for pH adjustment)

Pharmaceutical Form
Inhalation Solution
Clear, colourless, inhalation solution

INDICATIONS

SPIOLTO® RESPIMAT® is indicated for the second line treatment in patients with COPD when tiotropium or olodaterol alone does not provide adequate responses to reduce airflow obstruction, to improve quality of life and to reduce associated dyspnoea.

DOSAGE AND ADMINISTRATION

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 (see Instructions for Use).
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.

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 (creatinine clearance ≤ 50 ml/min).

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) 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 physician or other health care professionals.

SPIOLTO® RESPIMAT®

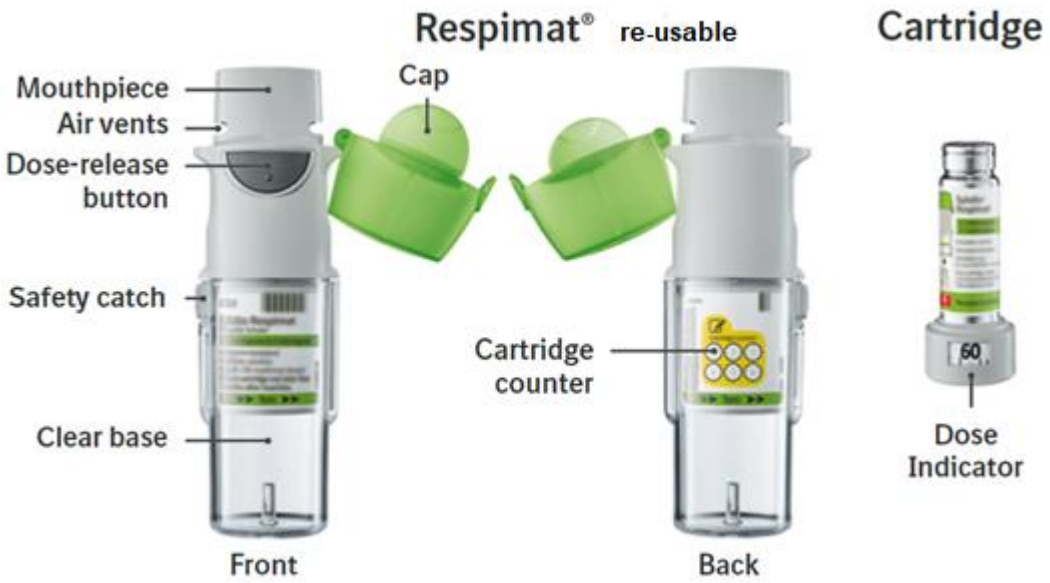
Tiotropium bromide /Olodaterol

HANDLING INSTRUCTIONS

Introduction

SPIOLTO® RESPIMAT® (tiotropium bromide and olodaterol).

Read these Instructions for Use before you start using SPIOLTO® RESPIMAT® re-usable.
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® re-usable

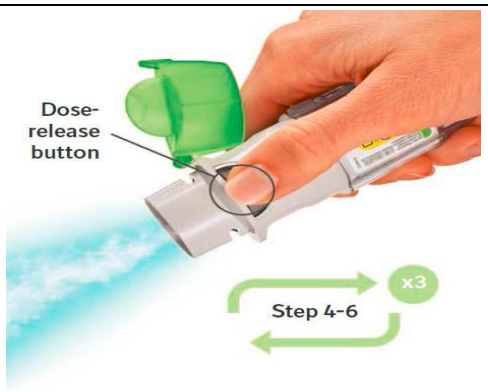
Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week. Any minor discoloration in the mouthpiece does not affect your SPIOLTO® RESPIMAT® re-usable inhaler performance. If necessary, wipe the outside of your SPIOLTO® RESPIMAT® re-usable inhaler with a damp cloth.

When to replace the inhaler

When you have used an inhaler with 6 cartridges, get a new SPIOLTO® RESPIMAT® re-usable pack containing an inhaler. Do not use the Respimat re-usable inhaler for more than one year, after having inserted the first cartridge.

Prepare for use

1. <u>Remove clear base</u> • Keep the cap closed. • Press the safety catch while pulling off the clear base with your other hand.	
2. <u>Insert cartridge</u> • Insert the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it snaps into place.	

3. Track cartridge and put clear base back • Mark the check-box on inhaler's label to track the number of cartridges. • 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. Open • Open the cap until it snaps fully open.	
6. Press • 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. Your inhaler is now ready to use and will deliver 60 puffs (30 doses).	

Daily use

TURN • Keep the cap closed. • **TURN** the clear base in the direction of the arrows on the label until it clicks (half a turn).	
OPEN • **OPEN** the cap until it snaps fully open.	
PRESS • Breathe out slowly and fully. • Close your lips around the mouthpiece without covering the air vents. Point your inhaler to the back of your throat. • While taking a slow, deep breath through your mouth, **PRESS** the dose-release button and continue to breathe in slowly for as long as comfortable. • Repeat Turn, Open, Press for a total of 2 puffs. • Close the cap until you use your inhaler again.	

When to replace the SPIOLTO® RESPIMAT® cartridge

The dose indicator shows how many puffs remain in the cartridge.

	60 puffs remaining

	Less than 10 puffs remaining. Obtain a new cartridge.
	Your cartridge is used up. Turn the clear base to loosen it. Your inhaler is now in a locked position. Pull off the cartridge from the inhaler. Insert a new cartridge until it clicks (refer to step 2). The new cartridge will stick out more than the very first cartridge (continue with step 3). Remember to put the clear base back to unlock the inhaler.

Answers to Common Questions

It is difficult to insert the cartridge deep enough.

Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.
Are you replacing the cartridge? The new cartridge will stick out more than the very first cartridge. Insert it until it clicks, then replace the clear base.

I cannot press the dose-release button.
Did you put the clear base back? If not, put the clear base back to unlock the inhaler. The Respimat re-usable only functions with the clear base in place.

Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).
Does the dose indicator on your cartridge display a white arrow on a red background? Your cartridge is used up. Insert a new cartridge.

It is difficult to remove the cartridge after it is used up.

Pull and turn the cartridge at the same time.

I cannot turn or put the clear base back.

Is the clear base loose and does the dose indicator on your cartridge display a white arrow on a red background? Your cartridge is used up. Insert a new cartridge.

Did you turn the clear base already?
If the clear base has already been turned, follow steps “OPEN” and “PRESS” under “Daily Use” to get your medicine.

My Respimat re-usable has been used up too early.

Did you use Respimat re-usable as indicated (two puffs/once daily)? Respimat will last 30 days if used at two puffs once daily.

Did you spray in the air often to check whether the Respimat re-usable is working? Once you have prepared Respimat **re-usable**, no test-spraying is required if used daily.

Did you take off and put the clear base multiple times back? Do not remove the clear base before the cartridge is used up. Each time you take off the clear base without cartridge exchange, the dose counter records one puff and the remaining doses are reduced.

My Respimat re-usable doesn’t spray.

Did you insert a cartridge? If not, insert a cartridge. Once your Respimat re-usable is assembled, do not remove the clear base or the cartridge until the cartridge is used up.
Did you repeat TURN, OPEN, PRESS less than three times after inserting the cartridge? Repeat TURN, OPEN, PRESS three times after inserting the cartridge as shown in the steps 4 to 6 under “Prepare for use”.
Does the dose indicator on your cartridge display a white arrow on a red background? Your cartridge is used up. Insert a new cartridge.

My Respimat re-usable sprays automatically.

Was the cap open when you turned the clear base? Close the cap, then turn the clear base.

Did you press the dose-release button when turning the clear base? Close the cap, so the dose-release button is covered, then turn the clear base.

Did you stop when turning the clear base before it clicked? Turn the clear base in a continuous movement until it clicks (half a turn). The dose counter will count each incomplete turn and the number of remaining doses is reduced.

Was the cap open when you replaced the cartridge? Close the cap, then replace the cartridge.

CONTRAINDICATIONS

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

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

SPECIAL WARNINGS AND PRECAUTIONS

General Warnings

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

Asthma

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

Acute bronchospasm

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

Deterioration of disease and acute episodes

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

Hypersensitivity

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

Paradoxical bronchospasm

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

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

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

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

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) (please refer to section Dosage and administration).

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 beta2-adrenergic agonist. Long acting beta2- 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 beta2-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.
Patients with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalised for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (>100 beats per minute) were excluded from the clinical trials. Therefore the experience in these patient groups is limited. SPIOLTO® RESPIMAT® should be used with caution in these patient groups.

Hypokalaemia

Beta2 -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 (please refer to section Interactions), which may increase the susceptibility to cardiac arrhythmias.

Hyperglycaemia

Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose.

Others

SPIOLTO® RESPIMAT® should not be used in conjunction with any other medication containing LABAs or LAMAs (please refer to section Interactions). Patients who have been taking inhaled, short acting beta2-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.

Benzalkonium chloride
This medicine contains 0.0011 mg benzalkonium chloride in each actuation.
Banzalkonium chloride may cause wheezing and breathing difficulties (bronchospasm), especially if you have asthma. Patients with asthma are at an increased risk for these adverse events.

USE IN SPECIFIC POPULATIONS

Pregnancy, Lactation and Fertility

Pregnancy
Tiotropium
There is a 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 (please refer to section Toxicology).

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 (please refer to section Toxicology).

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

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

Lactation
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 its metabolites have been detected in the milk of lactating rats, but it is not known whether tiotropium and/or olodaterol pass into human breast milk.
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 (please refer to section Toxicology).

Driving and Using 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.

INTERACTIONS

Tiotropium

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, methylxanthines, oral and inhaled steroids, without clinical evidence of drug interactions.
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.

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

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

Xanthine Derivatives,Steroids or Diuretics
Concomitant treatment with xanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate any hypokalemic effect of adrenergic agonists (see Special warnings and precautions).

Beta-blockers
Beta –adrenergic blockers may weaken or antagonize 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 Pharmacokinetics). 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.

SIDE EFFECTS

The safety of SPIOLTO® RESPIMAT® has been evaluated in active-controlled, parallel-group and cross-over clinical trials in overall 7,151 patients with COPD. A total of 1,988 patients with COPD received the target 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.

In the pooled analysis of these long-term clinical trials the overall incidence of adverse events in patients treated with SPIOLTO® RESPIMAT® was comparable to patients treated with the mono components tiotropium at a dose of 5 microgram or olodaterol at a dose of 5 microgram (74%, 73.3% and 76.6%, 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.

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

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

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

Adverse reactions reported in all clinical trials with SPIOLTO® RESPIMAT® with a frequency of less than 2% are shown below according to system organ class. These also include all adverse reactions previously reported with one of the individual components.
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

System Organ Class MedDRA terminology	Adverse Reaction	Frequency
Infection and infestations	Nasopharyngitis	Not known*
Metabolism system disorders	Dehydration	Not known*
Nervous system disorders	Dizziness	Uncommon
	Insomnia	Rare

Eye disorders	Vision blurred	Rare
	Glaucoma	Not known*
	Intraocular pressure increased	Not known*
Cardiac disorders	Atrial fibrilation	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	Rare
	Joint swelling	Rare
Renal and urinary disorders	Urinary retention	Rare
	Urinary tract infection	Rare
	Dysuria	Rare

*A precise frequency estimation is not possible as the adverse reaction has never been observed in clinical trials. The upper limit of the 95% confidence interval is not higher than 3/n with n representing the total sample size summed up across all relevant clinical trials (3/1,707 = 0.0017 = “uncommon”).

Many of the listed adverse effects can be assigned to either the anticholinergic properties of tiotropium or to the β-adrenergic properties of olodaterol, the components of SPIOLTO® RESPIMAT®.
In addition the occurrence of other undesirable effects related to the beta-adrenergic agonist class, which are not listed above, should be taken into consideration, such as arrhythmia, myocardial ischaemia, angina

pectoris, hypotension, tremor, headache, nervousness, nausea, muscle spasms, fatigue, malaise, hypokalaemia, hyperglycaemia, and metabolic acidosis.

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 following contact:
Telephone: +62 21 21684084 Or Email: IDsafety@zuelligpharma.com

OVERDOSE

Symptoms

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

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

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

Therapy

Treatment with SPIOLTO® RESPIMAT® should be discontinued. Supportive and symptomatic treatment is indicated. Serious cases should be hospitalized. 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.

PHARMACOLOGICAL PROPERTIES

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

ATC code: R03AL06

Mode of action

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 airways.

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.

Clinical Trials

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.

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 randomized, double-blind trials using SPIOLTO® RESPIMAT® that enrolled 5162 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.

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.

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

Patients enrolled into the Phase III program were 40 years of age or older with a clinical diagnosis of COPD,

had a smoking history of more than 10 pack years and had moderate to very severe pulmonary impairment (post-bronchodilator FEV_1 less than 80% predicted normal (GOLD Stage 2-4); post-bronchodilator FEV_1 to FVC ratio of less than 70%).

Patient characteristics

The majority of the 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%], and 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 xanthine´s [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 (95% CI)**	**n**	**Mean (95% CI)**	**n**	**Mean (95% CI)**	**n**	**Mean (95% CI)**
SPIOLTO® RESPIMAT® versus	522	--	502	--	521	--	497	--
Tiotropium 5 microgram	526	0.117 L (0.094, 0.140)	500	0.103 L (0.078, 0.127)	520	0.071 L (0.047, 0.094)	498	0.050 L (0.024, 0.075)
Olodaterol 5 microgram	525	0.123 L (0.100, 0.146)	507	0.132 L (0.108, 0.157)	519	0.082 L (0.059, 0.106)	503	0.088 L (0.063, 0.113)

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

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

In the 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)**

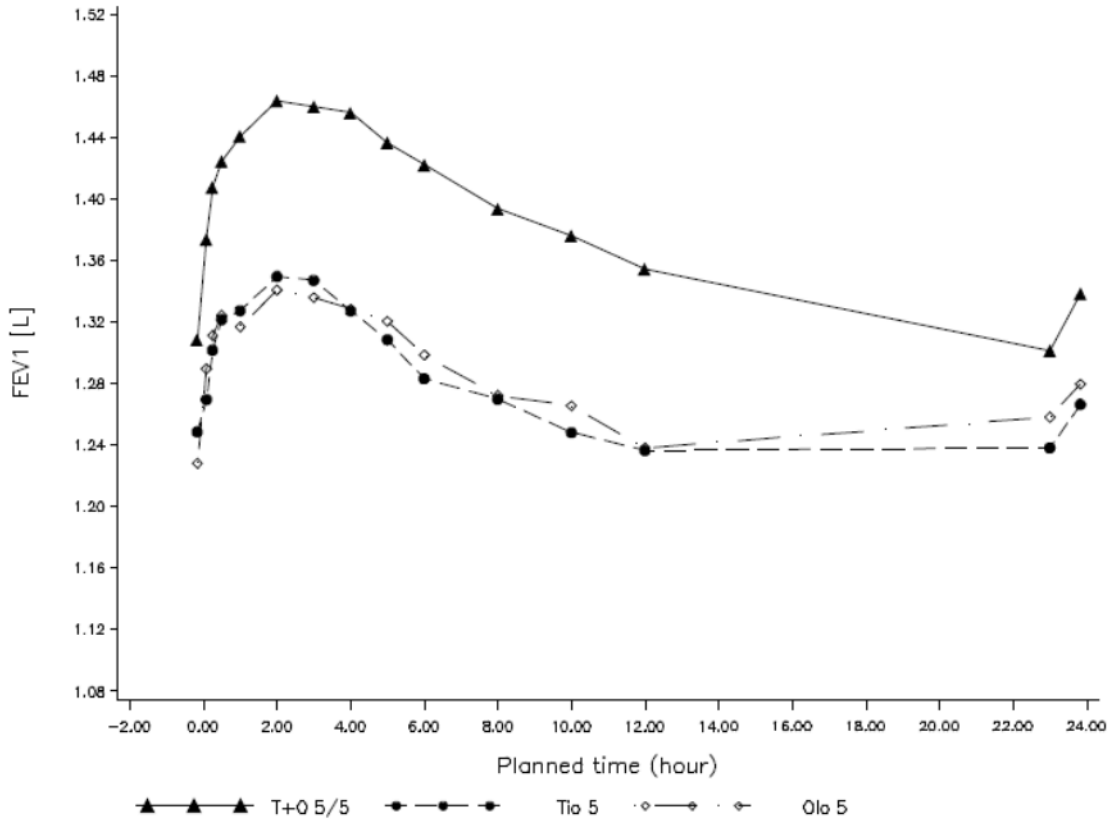


Table 3 **Difference in FEV_1 for SPIOLTO® RESPIMAT® compared to tiotropium 5 microgram and olodaterol 5 microgram over a continuous 24 hour dosing interval after 24 weeks (12 hr PFT sub-set from Trials 1 and 2; combined dataset)**

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

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

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

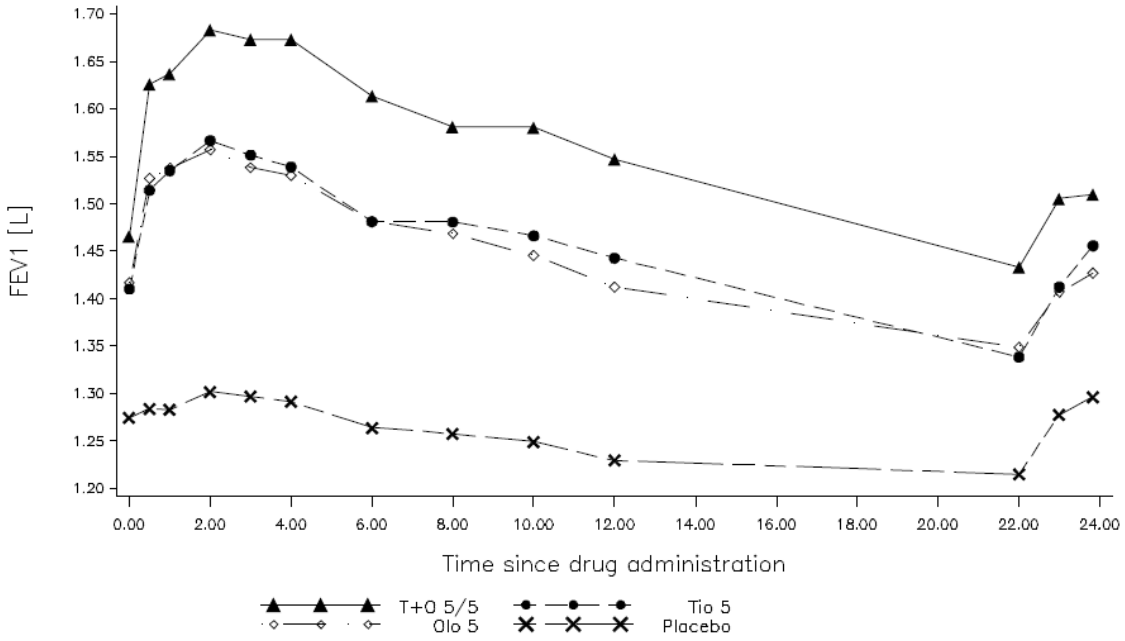


Table 4 **Difference in FEV_1 (L) for SPIOLTO® RESPIMAT® compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo over a continuous 24 hour dosing interval after 6 weeks (Trial 3)**

	n	3 hr average (95% CI)	n	12 hr average (95% CI)	24 hr average[1] (95% CI)	Trough (95% CI)

SPIOLTO® RESPIMAT® versus	138		138			
Tiotropium 5 microgram	137	0.109 (0.077, 0.141)	135	0.119 (0.089, 0.149)	0.110 (0.082, 0.139)	0.079 (0.045, 0.113)
Olodaterol 5 microgram	138	0.109 (0.078, 0.141)	136	0.126 (0.096, 0.156)	0.115 (0.087, 0.143)	0.092 (0.059, 0.126)
Placebo	135	0.325 (0.293, 0.357)	132	0.319 (0.289, 0.349)	0.280 (0.252, 0.309)	0.207 (0.173, 0.241)

pre-treatment baseline FEV_1 = 1.30 L

[1] primary endpoint

p<0.0001 for all comparisons

Health-related Quality of Life

After 24 weeks, SPIOLTO® RESPIMAT® significantly improved mean SGRQ total score compared to tiotropium 5 microgram and olodaterol 5 microgram (Table 5); 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 5 SGRQ total and domain scores after 24 weeks of treatment

		n	Treatment Mean (change from baseline)	Difference from SPIOLTO® RESPIMAT® Mean (p-value) (95% CI)
Total score	Baseline		43.5	
	SPIOLTO® RESPIMAT®	979	36.7 (-6.8)	
	Tiotropium 5 microgram	954	37.9 (-5.6)	-1.23 (p=0.025) (-2.31, -0.15)
	Olodaterol 5 microgram	954	38.4 (-5.1)	-1.69 (p=0.002) (-2.78, -0.61)
Symptoms	Baseline		51.9	
	SPIOLTO® RESPIMAT®	982	42.6	
	Tiotropium 5 microgram	957	45.5	-2.94 (p=0.0008) (-4.65, -1.23)
	Olodaterol 5 microgram	958	45.0	-2.48 (p=0.0046) (-4.19, -0.76)

Activities	Baseline		58.0	
	SPIOLTO® RESPIMAT®	981	51.9	
	Tiotropium 5 microgram	959	53.2	-1.34 (p=0.052) (-2.69, 0.01)
	Olodaterol 5 microgram	958	54.0	-2.11 (p=0.002) (-3.47, -0.76)
Impact	Baseline		32.6	
	SPIOLTO® RESPIMAT®	983	26.1	
	Tiotropium 5 microgram	960	26.8	-0.67 (p=0.283) (-1.89, 0.55)
	Olodaterol 5 microgram	959	27.2	-1.11 (p=0.075) (-2.33, 0.11)

In two additional 12-week, placebo-controlled clinical trials, SGRQ total score at 12 weeks was also included as primary endpoint as a measure of healthy-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 = 0022) and placebo (32%; odds ratio : 2.35 (95% CI: 1.75, 3.16), p < 0.0001).

Dyspnoea

After 24 weeks, SPIOLTO® RESPIMAT® significantly improved mean TDI focal score compared to tiotropium 5 microgram and olodaterol 5 microgram (Table 6). 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 6 TDI focal score after 24 weeks of treatment

	n	**Treatment Mean**	**Difference to SPIOLTO® RESPIMAT®**
			Mean (p-value) (95% CI)
SPIOLTO® RESPIMAT®	992	1.98	
Tiotropium 5 microgram	978	1.63	0.36 (p=0.008) (0.09, 0.62)

Olodaterol 5 microgram	984	1.56	0.42 (p=0.002) (0.16, 0.68)

Rescue Medication Use

Patients treated with SPIOLTO® RESPIMAT® used less daytime and night-time rescue salbutamol compared to patients treated with tiotropium 5 microgram and olodaterol 5 microgram.

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 a 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 compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo after 6 weeks (Trials 4 and 5; Table 7) and compared to placebo after 12 weeks (0.234 L, p<0.0001; 95% CI: 0.133, 0.336; Trial 6).

Table 7 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) (0.061, 0.167)	208	0.088 (p=0.0005) (0.039, 0.137)

Olodaterol 5 microgram	214	0.119 (p<0.0001) (0.065, 0.172)	208	0.080 (p=0.0015) (0.031, 0.129)
Placebo	211	0.244 (p<0.0001) (0.191, 0.298)	202	0.265 (p<0.0001) (0.215, 0.315)

[1] pre-treatment baseline: 2.53 L

[2] pre-treatment baseline: 2.59 L

In Trials 4 and 5, SPIOLTO® RESPIMAT® improved endurance time during constant work rate cycling by 20.9% and 13.4% compared to placebo (Table 8). 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. The endurance time during constant speed walking (in a sub- set of patients) increased by 20.6% after 6 weeks and by 20.9% after 12 weeks compared to placebo although the result was not statistically significant (Table 9).

Table 8 Geometric mean endurance time (s) during constant work rate cycle ergometry for SPIOLTO® RESPIMAT® compared to placebo after 6 weeks [Trials 4 and 5]

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

[1] pre-treatment baseline: 460.0 sec

[2] pre-treatment baseline: 434.3 sec

Table 9 Geometric mean endurance time (s) during constant work rate cycling and constant speed walking for SPIOLTO® RESPIMAT® compared to placebo after first dose, and after 6 and 12 weeks [Trial 6]

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

[1] pre-treatment baseline: 461.5 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 (nominal p<0.0005; Table 10).

Table 10 Slope of breathing discomfort (Borg units/s) during constant work rate cycle ergometry for SPIOLTO® RESPIMAT® compared to placebo after 6 weeks [Trials 4 and 5]

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

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

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

* nominal p-value

PHARMACOKINETICS

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 (CLcr >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

Pharmacokinetic drug interaction studies with SPIOLTO® RESPIMAT® have not been performed; however such studies have been conducted with individual components tiotropium and olodaterol.
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
An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once-daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC0-4h, a 28% decrease in the renal clearance of tiotropium and no significant change in the Cmax and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium.

Common concomitant medications (long-acting beta2-adrenergic agonists (LABA), inhaled corticosterioids (ICS)) used by patients with COPD were not found to alter the exposure to tiotropium.

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%.

Tiotropium: Co-administration of tiotropium bromide, delivered as a fixed-dose combination with olodaterol, for 21 days had no relevant effect on systemic exposure to olodaterol, and vice versa

TOXICOLOGY

Tiotropium+Olodaterol

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.

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.

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.

AVAILABILITY

Inhalation Solution
1 Respimat Reusable Inhaler and 1 cartridge Reg. No. DKIXXXXXXXXXX
1 Cartridge (single refill pack) Reg. No. DKIXXXXXXXXXX
One cartridge contains 4.0 ml providing 60 puffs (30 medicinal doses)

Only on doctor's prescription
Harus dengan resep dokter

Storage conditions:
Store below 30°C. Do not freeze.
Keep out of the sight and reach of children

Recommended use: 6 cartridges per inhaler
Exchange cartridge not later than 3 months after insertion.
Do not use the Respimat re-usable inhaler for more than one year, after having inserted the first cartridge.

Manufactured by:
Boehringer Ingelheim España, S.A.
c/ Prat de la Riba, 50
08174 Sant Cugat del Vallès
(Barcelona), Spain

For:
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

Registered by:
PT Tunggal Idaman Abdi
Jakarta, Indonesia

Version: 08-1025

Informasi Produk untuk Pasien

SPIOLTO® RESPIMAT®

TIOTROPIUM BROMIDE/ OLODATEROL
2.5 mikrogram / 2.5 mikrogram
Cairan Inhalasi

Bacalah seluruh leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisikan informasi penting untuk Anda.
- Simpanlah leaflet ini. Suatu saat Anda mungkin perlu membacanya kembali.
- Bila Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan berikan obat ini kepada orang lain. Hal ini dapat membahayakan mereka meskipun gejala penyakit mereka mirip dengan Anda.
- Bila Anda mengalami efek samping obat, bicarakan kepada dokter atau apoteker Anda, termasuk efek samping obat yang tidak terdaftar dalam leaflet ini. Lihat bagian 4.

Apa saja yang terdapat dalam leaflet ini

1. Apakah SPIOLTO® RESPIMAT®

SPIOLTO® RESPIMAT® mengandung dua senyawa aktif yang disebut Tiotropium dan Olodaterol. Keduanya merupakan obat dari golongan bronkodilator kerja-panjang. Tiotropium merupakan antikolinergik; Olodaterol merupakan beta$_2$ agonis kerja-panjang.

2. SPIOLTO® RESPIMAT® digunakan untuk apa

SPIOLTO® RESPIMAT® membantu pasien dewasa dengan Penyakit Paru Obstruktif Kronik (PPOK) untuk dapat bernapas lebih mudah. SPIOLTO® RESPIMAT® digunakan apabila pemberian Tiotropium dan Olodaterol tunggal tidak memberikan respon yang memadai untuk mengurangi obstruksi saluran pernapasan, untuk meningkatkan kualitas hidup dan mengurangi sesak napas yang menyertai PPOK. PPOK adalah penyakit paru jangka-panjang (bersifat kronik) yang menyebabkan sesak dan batuk. Istilah PPOK berhubungan dengan bronkitis kronik dan emfisema.

SPIOLTO® RESPIMAT® membantu membuka saluran napas Anda sehingga memudahkan udara masuk dan keluar dari paru-paru. Penggunaan secara teratur dapat membantu ketika Anda sedang mengalami sesak napas yang disebabkan oleh PPOK dan dapat meminimalkan pengaruh penyakit ini terhadap keseharian Anda. Karena PPOK merupakan penyakit jangka-panjang, Anda sebaiknya menggunakan SPIOLTO® RESPIMAT® setiap hari dan tidak hanya ketika Anda sedang mengalami masalah sesak napas atau gejala PPOK lainnya.

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2. Apakah yang perlu Anda ketahui sebelum Anda menggunakan SPIOLTO® RESPIMAT®

Jangan gunakan SPIOLTO® RESPIMAT®
- Bila Anda alergi (hipersensitif) terhadap Tiotropium atau Olodaterol atau bahan lainnya yang terkandung dalam obat ini (terdaftar dalam bagian 6)
- Bila Anda alergi (hipersensitf) terhadap Atropin atau zat yang berhubungan dengan Atropin, misalnya Ipratropium atau Oxitropium

Peringatan dan Perhatian

Bicarakan dengan dokter atau apoteker Anda sebelum menggunakan SPIOLTO® RESPIMAT®
- bila Anda memiliki asma (Anda tidak boleh menggunakan SPIOLTO® RESPIMAT® untuk mengobati asma)
- bila Anda memiliki penyakit jantung
- bila Anda memiliki tekanan darah tinggi
- bila Anda memiliki epilepsi
- bila Anda memiliki masalah kelenjar tiroid spesifik yang disebut tirotoksikosis
- bila Anda memiliki pelebaran arteri abnormal yang disebut aneurisma
- bila Anda memiliki diabetes
- bila Anda memiliki gangguan fungsi hepar berat
- bila Anda memiliki gangguan fungsi ginjal
- pada saat akan menjalani operasi
- bila Anda memiliki masalah mata yang disebut glaukoma sudut sempit
- bila Anda memiliki gangguan prostat atau sulit buang air kecil

Selama pengobatan dengan SPIOLTO® RESPIMAT®

- **Hentikan penggunaan obat dan beritahukan kepada pada dokter Anda segera,** bila Anda mengalami rasa berat di dada, batuk, mengi atau sesak napas segera setelah menggunakan obat. Keadaan ini mungkin gejala-gejala dari suatu kondisi yang disebut bronkospasm (lihat bagian 4).
- Bila napas Anda semakin terasa berat atau bila Anda mengalami ruam, bengkak atau gatal-gatal yang terjadi segera setelah menggunakan inhaler Anda, hentikan penggunaan obat ini dan beritahukan kepada dokter Anda segera (lihat bagian 4).
- Bila Anda mengalami efek samping yang berhubungan dengan jantung (peningkatan denyut nadi, peningkatan tekanan darah dan/atau peningkatan frekuensi gejala seperti nyeri dada), segera laporkan pada dokter Anda (lihat bagian 4).
- Bila Anda mengalami spasme otot, kelemahan otot atau irama jantung abnormal, konsultasi kepada dokter Anda karena hal ini dapat saja disebabkan oleh rendahnya kadar kalium dalam darah (lihat bagian 4).

Saat menggunakan SPIOLTO® RESPIMAT® pastikan semprotan tidak mengenai mata Anda. Hal tersebut dapat menyebabkan mata terasa nyeri atau tidak nyaman pandangan kabur, melihat lingkaran (halo) disekeliling cahaya atau objek berwarna, yang disertai dengan mata merah (glaukoma sudut sempit). Gejala pada mata dapat disertai dengan sakit kepala, mual atau muntah. Cuci mata Anda dengan air hangat, hentikan penggunaan SPIOLTO® RESPIMAT® dan segera konsultasikan dengan dokter Anda untuk tindakan selanjutnya.

SPIOLTO® RESPIMAT® diindikasikan untuk pengobatan penyakit paru obstruktif kronik Anda. **Obat ini tidak boleh digunakan untuk mengobati serangan sesak napas atau mengi yang terjadi secara tiba-tiba**.

Jangan menggunakan SPIOLTO® RESPIMAT® bersamaan dengan obat-obat yang mengandung agonis ß-adrenergik kerja panjang, seperti Salmeterol atau Formoterol.

Jika Anda mengkonsumsi secara teratur obat yang mengandung ß-adrenergik kerja pendek, seperti Salbutamol, lanjutkan penggunaan obat tersebut hanya untuk mengatasi gejala akut seperti sesak napas.

Mulut kering yang dapat ditemukan pada terapi anti-kolinergik jangka panjang dapat menyebabkan karies gigi. Oleh karena itu kebersihan gigi dan mulut harus diperhatikan.

Jangan menggunakan SPIOLTO® RESPIMAT® lebih dari sekali dalam satu hari.

Anak-anak dan Remaja
SPIOLTO® RESPIMAT® **tidak boleh** diberikan pada **anak-anak atau remaja (dibawah usia 18 tahun)**.

Obat lain dan SPIOLTO® RESPIMAT®
Beritahukan kepada dokter atau apoteker Anda bila Anda menggunakan atau akhir-akhir ini menggunakan obat-obatan lainnya.

Khususnya, beritahukan kepada dokter Anda bila Anda menggunakan:

- Obat-obatan untuk masalah pernapasan yang mirip dengan SPIOLTO® RESPIMAT® (mengandung zat aktif yang mirip, seperti obat antikolinergik atau agen β-adrenergik). Anda akan lebih cenderung untuk mengalami efek samping.

- Obat-obatan yang disebut beta bloker yang digunakan untuk tekanan darah tinggi atau masalah jantung lainnya (seperti Propanolol) atau untuk masalah mata yang disebut glaukoma (seperti Timolol). Obat-obat ini dapat menyebabkan hilangnya efek SPIOLTO® RESPIMAT®.

- Obat-obatan yang menurunkan jumlah kalium dalam darah Anda, diantaranya:
  - steroid (misalnya Prednisolone),
  - diuretik (tablet penarik air),
  - obat-obatan untuk masalah pernapasan seperti Teofilin.

  Bila Anda menggunakan obat-obatan ini bersama dengan SPIOLTO® RESPIMAT® maka Anda dapat mengalami gejala spasme otot, kelemahan otot atau irama jantung abnormal.

- Obat-obatan yang disebut antidepresan trisiklik atau penghambat monoamine oxidase (MAO) (seperti selegilin atau moklobemid), yang digunakan untuk mengobati gangguan neurologik atau psikiatrik seperti penyakit Parkinson atau depresi; penggunaan obat-obat ini akan meningkatkan kecenderungan terjadinya efek samping yang mempengaruhi jantung Anda.

Kehamilan, menyusui dan fertilitas
Bila Anda sedang hamil atau menyusui, berpikir bahwa Anda mungkin hamil atau merencanakan untuk hamil, mintalah saran kepada dokter atau apoteker Anda sebelum Anda menggunakan obat ini.

Berkendara dan mengoperasikan alat berat
Belum ada penelitian mengenai efek obat ini terhadap kemampuan dalam berkendara dan pengoperasian alat.
Bila Anda merasa pusing atau pandangan kabur terjadi saat mengkonsumsi SPIOLTO® RESPIMAT®, jangan berkendara atau mengoperasikan alat berat.

3. Bagaimana cara menggunakan SPIOLTO® RESPIMAT®

Selalu gunakan obat ini dengan tepat sesuai instruksi dokter Anda. Anda sebaiknya mengecek kepada dokter atau apoteker Anda bila Anda merasa tidak yakin.

SPIOLTO® RESPIMAT® hanya digunakan dengan cara inhalasi saja.

Dosis

Dosis yang dianjurkan adalah:

SPIOLTO® RESPIMAT® efektif untuk 24 jam oleh karena itu Anda hanya perlu menggunakan SPIOLTO® RESPIMAT® **SEKALI SEHARI**, bila memungkinkan gunakanlah pada waktu yang sama setiap harinya. Setiap kali Anda menggunakannya, lakukan DUA SEMPROT.

PPOK adalah penyakit jangka panjang oleh sebab itu gunakan SPIOLTO® RESPIMAT® Anda setiap hari dan tidak hanya ketika Anda mengalami masalah pernapasan. Jangan menggunakan lebih dari dosis yang disarankan.

Penggunaan pada anak dan remaja

SPIOLTO® RESPIMAT® tidak relevan untuk digunakan pada populasi pediatrik (usia dibawah 18 tahun).

Pastikan Anda mengetahui bagaimana menggunakan SPIOLTO® RESPIMAT® inhaler Anda dengan tepat. Instruksi untuk cara menggunakan SPIOLTO® RESPIMAT® inhaler disediakan pada bagian lain di leaflet ini.

Jika Anda menggunakan SPIOLTO® RESPIMAT® lebih dari yang seharusnya
Anda memiliki risiko lebih tinggi untuk mengalami efek samping seperti mulut kering, konstipasi, sulit buang air kecil, pandangan kabur, nyeri dada, tekanan darah tinggi atau rendah, denyut jantung lebih cepat atau lambat, pusing, gelisah, sulit tidur, kecemasan, sakit kepala, gemetar, keram otot, mual, fatigue, malaise, kekurangan kalium dalam darah (yang mengakibatkan kejang otot, kelemahan otot, atau irama jantung abnormal), peningkatan kadar gula darah, atau meningkatnya tingkat keasaman darah (yang menyebabkan mual, muntah, kelemahan, keram otot, dan napas cepat).

Bila Anda lupa mengkonsumsi SPIOLTO® RESPIMAT®
Bila Anda terlupa menghisap satu dosis maka hisaplah satu dosis sesuai jadwal yang biasa pada hari berikutnya. Jangan menggandakan dosis untuk menggantikan dosis yang terlupa.

Bila Anda berhenti menggunakan SPIOLTO® RESPIMAT®

Sebelum Anda berhenti menggunakan SPIOLTO® RESPIMAT®, Anda sebaiknya berbicara dengan dokter atau apoteker Anda. Bila Anda berhenti menggunakan SPIOLTO® RESPIMAT® maka tanda dan gejala PPOK dapat semakin berat.
Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan dokter atau apoteker Anda.

4. Kemungkinan efek samping

Sebagaimana semua obat lainnya, obat ini dapat menyebabkan efek samping meskipun tidak setiap orang mengalaminya.

Efek samping yang dipaparkan dibawah ini ditemukan pada orang yang mengkonsumsi obat ini dan daftarnya diurutkan berdasarkan frekuensi.

Tidak umum (ditemukan pada hampir 1 dari 100 orang)
- Pusing
- peningkatan denyut nadi (takikardia)
- batuk
- suara serak (disfonia)

- mulut kering

Jarang (ditemukan pada hampir 1 dari 1000 orang)
- sulit tidur (insomnia)
- denyut jantung irregular (atrial fibrilasi)
- berdebar-debar (palpitasi)
- hipertensi
- nyeri tenggorokan (faringitis)
- peradangan laring (laringitis)
- peradangan gusi (gingivitis)
- mimisan (epistaksis)
- infeksi jamur pada rongga mulut dan tenggorokan (orofaringeal candidiasis)
- pandangan kabur
- denyut jantung sangat cepat (supraventrikular takikardi)
- dada rasa terhimpit disertai batuk dan napas berbunyi (mengi) atau sesak segera setelah pemakaian obat tersebut (bronkospasme)
- konstipasi
- peradangan pada rongga mulut (stomatitis)
- nyeri sendi (artralgia)
- nyeri punggung
- pembengkakan sendi
- sulit buang air kecil (retensi urin)
- nyeri berkemih (disuria)
- hipersensitifitas, termasuk reaksi yang timbul segera
- reaksi alergi berat yang menyebabkan bengkak pada mulut dan wajah atau tenggorokan (angioneurotic edema)
- gatal-gatal (pruritus)
- biduran (urtikaria)
- ruam
- infeksi saluran kemih

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang ada)
- penampakan halo (lingkaran) disekeliling cahaya atau benda berwarna yang disertai mata merah (glaukoma)
- peningkatan tekanan bola mata
- peradangan lidah (glossitis)
- peradangan sinus (sinusitis)
- kesulitan menelan (disfagia)
- nyeri ulu hati (*gastrooesophageal reflux disease*)
- penyumbatan usus atau menghilangnya pergerakan usus (obstruksi usus, termasuk ileus paralitik)
- infeksi atau ulkus pada kulit
- berkurangnya cairan tubuh (dehidrasi)
- Nasofaringitis
- Kulit kering

Anda juga dapat mengalami efek samping yang diketahui terjadi pada obat-obatan untuk masalah pernapasan yang mirip dengan SPIOLTO® RESPIMAT® (agen beta adrenergik). Beberapa diantaranya adalah denyut jantung lebih cepat atau tidak teratur atau merasakan denyut jantung, nyeri dada, tekanan darah tinggi atau rendah, gemetar, sakit kepala, gugup, sulit tidur, pusing, mulut kering, mual, kram otot, fatigue, malaise, kadar kalium rendah dalam darah (yang dapat menyebabkan gejala spasme otot, lemah otot atau irama jantung abnormal), gula darah tinggi, terlalu banyak asam dalam darah Anda (yang dapat

menyebabkan gejala mual, muntah, lemah, kram otot dan napas lebih cepat).

Reaksi alergi langsung seperti ruam, biduran (urtikaria), bengkak pada mulut atau wajah atau tiba-tiba sulit bernapas (edema angioneurotik) atau reaksi hipersensitivitas lainnya (seperti penurunan tekanan darah tiba-tiba atau pusing) sebagai reaksi tunggal atau merupakan bagian dari reaksi alergi berat (reaksi anafilaksis) setelah penggunaan SPIOLTO® RESPIMAT®. Bila hal ini terjadi, harap hentikan penggunaan obat ini, dan segera konsultasikan kepada dokter Anda.

Disamping itu, seperti dengan obat-obatan inhalasi lainnya, beberapa pasien dapat mengalami rasa berat di dada yang tidak diduga, batuk, mengi atau sesak napas yang terjadi segera setelah inhalasi (bronkospasme).

Pelaporan efek samping
Jika Anda mengalami efek samping, beritahukan dokter atau apoteker Anda. Hal ini termasuk efek samping yang mungkin terjadi yang belum tercantum di leaflet ini. Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut:
Telepon: +62 21 21684084 atau Email IDsafety@zuelligpharma.com

Dengan melaporkan efek samping tersebut, Anda membantu mengumpulkan informasi mengenai keamanan dari obat ini.

5. Bagaimana cara menyimpan SPIOLTO® RESPIMAT®

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan disimpan pada suhu beku.

Jangan gunakan obat ini setelah tanggal kadaluarsa yang tertulis pada karton dan label inhaler. Tanggal kadaluarsa menunjukkan hari terakhir pada bulan tersebut. Respimat inhaler sebaiknya dibuang setelah 3 bulan sejak pertama kali digunakan (lihat Instruksi cara penggunaan pada halaman selanjutnya).

Jangan buang obat apapun ke pembuangan air kotor atau pembuangan limbah rumah tangga. Tanyakan apoteker Anda bagaimana cara membuang obat yang sudah tidak Anda gunakan lagi. Sikap ini akan membantu melindungi lingkungan.

6. Isi paket dan informasi lainnya

Apakah kandungan yang terdapat dalam SPIOLTO® RESPIMAT®

Bahan aktifnya terdiri dari Tiotropium dan Olodaterol. Dosis pemberiannya adalah 2,5 mikrogram Tiotropium (dalam bentuk bromide monohidrate) dan 2,5 mikrogram Olodaterol (dalam bentuk hidroklorid) dalam satu semprot.
Dosis pemberian adalah dosis yang diterima oleh pasien setelah melewati *mouthpiece*.

Bahan lainnya adalah:
Benzalkonium klorida, disodium edetate, air purifikasi and asam klorida untuk penyesuaian pH.

Seperti apa bentuk SPIOLTO® RESPIMAT® dan apa isi paketnya

SPIOLTO® RESPIMAT® terdiri dari satu cartridge yang berisi cairan inhalasi dan satu Respimat inhaler. *Cartridge* harus dimasukkan ke dalam inhaler sebelum pertama kali digunakan.

Single pack: 1 Respimat reusable inhaler dan 1 *cartridge*, menyediakan 60 semprot (30 dosis obat)
Refill pack: 1 cartridge

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Reg. No.

1 Respimat Reusable Inhaler and 1 cartridge	Reg. No. DKIXXXXXXXXXXX
1 Cartridge (single refill pack)	Reg. No. DKIXXXXXXXXXXX

Harus dengan resep dokter

Kondisi penyimpanan:
Simpan di bawah suhu 30°C. Jangan dibekukan.
Simpan di tempat yang aman, jauh dari jangkauan anak-anak.
Ganti *cartridge* dalam waktu tidak lebih dari 3 bulan setelah dimasukkan ke dalam alat.
Jangan gunakan inhaler *Respimat re-usable* lebih dari satu tahun, setelah memasukkan cartridge pertama.

Diproduksi oleh:
Boehringer Ingelheim España, S.A.
c/ Prat de la Riba, 50
08174 Sant Cugat del Vallès
(Barcelona), Spain

Untuk:
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Jerman

Diregistrasi oleh:
PT Tunggal Idaman Abdi
Jakarta, Indonesia

Version: 08-1025

Instruksi Cara Penggunaan

SPIOLTO® RESPIMAT®

Pendahuluan

SPIOLTO® RESPIMAT® (tiotropium bromide dan olodaterol). Bacalah Instruksi Cara Penggunaan ini sebelum Anda menggunakan SPIOLTO® RESPIMAT® *re-usable*.

Anda hanya perlu menggunakan inhaler ini SEKALI SEHARI. Setiap kali Anda menggunakannya, lakukan DUA SEMPROT.

Keterangan Gambar:

Respimat	
Cap	Penutup
Air vent	Lubang udara
Dose-release button	Tombol pelepas obat
Safety catch	Kunci pengaman
Clear base	Bagian dasar transparan
Cartridge	*Cartridge*
Cartridge *counter*	Penanda penggunaan *cartridge*
Mouthpiece	Corong
Dose indicator	Indikator dosis
Front	Bagian depan
Back	Bagian belakang
Re-usable	

- Jika SPIOLTO® RESPIMAT® tidak digunakan selama lebih dari 7 hari, maka Anda sebaiknya melepaskan satu semprotan ke arah bawah.

- Jika SPIOLTO® RESPIMAT® tidak digunakan selama lebih dari 21 hari, maka Anda harus mengulangi langkah 4 hingga 6 dalam bagian 'Persiapan untuk Penggunaan Pertama Kali' hingga kabut terlihat kembali. Kemudian ulangi langkah 4 hingga 6 sebanyak tiga kali

Bagaimana merawat inhaler Anda

Bersihkan *mouthpiece (corong)* termasuk bagian logam dalam *mouthpiece (corong)* dengan lap yang dibasahi atau tisu, paling sedikit sekali seminggu. Sedikit perubahan warna pada corong tidak mempengaruhi kinerja SPIRIVA RESPIMAT *re-usable* inhaler Anda. Jika diperlukan, bersihkan bagian luarnya menggunakan lap yang dibasahi.

Kapan dibutuhkan SPIOLTO® RESPIMAT® *re-usable* baru

Jika alat sudah digunakan sebanyak 6 kali, maka harus menggunakan SPIOLTO® RESPIMAT® *re-usable* (obat dan alat) baru. Jangan gunakan inhaler Respimat *re-usable* lebih dari satu tahun, setelah memasukkan cartridge pertama.

Persiapan untuk Penggunaan Pertama Kali

1. Lepas bagian dasar transparan • Biarkan penutup tetap tertutup. • Tekan kunci pengaman sambil menarik bagian dasar yang transparan.	
2. Memasukkan *cartridge* • Dorong ujung *cartridge* yang kecil ke dalam inhaler. • Letakkan inhaler di atas permukaan yang keras dan dorong dengan kuat pada permukaan yang rata untuk memastikan *cartridge* telah masuk seluruhnya.	

3. Tandai penanda penggunaan *cartridge* dan masukkan kembali bagian dasar transparan • Tandai lingkaran yang tersedia pada label *cartridge* • Pasang kembali dasar transparan hingga terdengar bunyi klik.	 
4. Putar • Pastikan penutup dalam posisi tertutup. • Putar bagian dasar sesuai arah panah yang terdapat pada label hingga terdengar bunyi klik (setengah putaran).	
5. Buka • Buka penutup hingga terbuka seluruhnya.	
6. Tekan • Arahkan inhaler ke bawah. • Tekan tombol pelepas obat. • Tutup penutup. • Ulangi langkah 4-6 hingga terlihat kabut. • **Setelah kabut terlihat**, kemudian ulangi langkah 4-6 sebanyak tiga kali. Sekarang alat inhalasi anda sudah siap digunakan untuk 60 semprot (30 dosis).	

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Penggunaan Sehari-hari

PUTAR • Pastikan penutup dalam posisi tertutup. • **PUTAR** bagian dasar sesuai arah panah yang terdapat pada label hingga terdengar bunyi klik (setengah putaran).	
BUKA • **BUKA** penutup hingga terbuka seluruhnya.	
TEKAN • Buang napas dengan lambat dan dalam. • Katupkan bibir Anda pada ujung corong tetapi jangan menutup lubang udara. • Kemudian tarik napas dengan lambat dan dalam sambil **TEKAN** tombol pelepas obat dan teruskan menarik napas perlahan atau selama waktu yang nyaman untuk Anda. • Ulangi PUTAR, BUKA, TEKAN untuk total 2 semprot. • Tutup alat setelah selesai digunakan sampai anda menggunakannya kembali.	

Kapan harus mengganti *cartridge* SPIOLTO® RESPIMAT®

Indikator dosis menunjukkan berapa semprot yang masih tersedia dalam *cartridge*

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	Sisa 60 semprot
	Kurang dari 10 semprot. Persiapkan cartridge baru.
	*Cartridge* anda sudah habis digunakan. Putar bagian transparan untuk dapat melepaskannya. Alat inhalasi anda sekarang dalam keadaan terkunci. Tarik *cartridge* dari alat inhalasi. Masukkan *cartridge* baru sampai terdengar bunyi 'klik' (lihat langkah 2). *Cartridge* baru akan lebih menempel daripada *cartridge* yang pertama kali digunakan (lanjutkan langkah 3). Ingatlah untuk selalu memasang kembali bagian dasar transparan supaya inhaler dalam posisi tidak terkunci.

Jawaban untuk Pertanyaan Umum

Sangat sulit untuk memasukkan *cartridge* sampai masuk seluruhnya.

Apakah Anda tidak sengaja memutar dasar transparan sebelum memasukkan *cartridge*? Buka penutup, tekan tombol pelepas obat, kemudian masukkan *cartridge*.

Apakah Anda akan mengganti *cartridge*? *Cartridge* baru akan lebih melekat dibandingkan dengan *cartridge* yang pertama. Masukkan sampai terdengar bunyi klik, kemudian lepaskan bagian dasar transparan.

Saya tidak dapat menekan tombol pelepas obat.

Apakah Anda sudah meletakkan dasar transparan ke tempat semula? Jika tidak, kembalikan dasar transparan untuk membuka inhaler. Respimat re-usable hanya berfungsi dengan dasar transparan kembali ke tempatnya.

Apakah Anda sudah memutar dasar transparan? Jika belum, putarlah dasar transparan secara berkelanjutan hingga terdengar bunyi klik (setengah putaran).

Apakah indikator dosis pada *cartridge* menunjukkan tanda panah putih dengan latar belakang merah? Obat telah habis. Silakan gunakan/masukkan *cartridge* baru Anda.

Sulit untuk melepaskan cartridge setelah habis digunakan.

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Tarik dan putar cartridge secara bersamaan.

Saya tidak dapat memutar dasar transparan.

Apakah bagian dasar transparan menjadi longgar dan indikator dosis pada *cartridge* menunjukkan tanda panah putih dengan latar belakang merah? Obat telah habis. Silakan gunakan/masukkan *cartridge* baru Anda.

Apakah sebelumnya Anda sudah memutar dasar yang transparan? Jika dasar transparan sudah diputar, silahkan ikuti langkah "BUKA" dan "TEKAN" pada bagian "Penggunaan Sehari-hari".

Indikator dosis pada RESPIMAT *re-usable* menunjukkan posisi kosong terlalu cepat.

Apakah Anda menggunakan RESPIMAT *re-usable* seperti yang dianjurkan (dua semprot/sekali sehari)? RESPIMAT akan bertahan sampai 30 hari jika digunakan untuk dua semprot sekali sehari.

Apakah Anda terlalu sering menyemprotkan di udara untuk mengecek apakah RESPIMAT *re-usable* berfungsi? Begitu Anda menyiapkan RESPIMAT *re-usable*, tidak perlu lagi dilakukan tes penyemprotan untuk penggunaan sehari-hari.

Apakah Anda melepas dasar transparan beberapa kali? Jangan lepas dasar transparan sebelum *cartridge* habis. Setiap kali Anda melepas dasar transparan tanpa penggantian *cartridge*, penghitung dosis menghitung satu isapan dan dosis yang tersisa dapat berkurang.

RESPIMAT *re-usable* saya tidak dapat menyemprot.

Apakah Anda sudah memasukkan *cartridge*? Jika belum, masukanlah *cartridge*. Ketika RESPIMAT re-usable siap digunakan, jangan lepaskan bagian dasar transparan sampai obat habis.

Apakah Anda mengulangi langkah Putar, Buka, Tekan kurang dari tiga kali setelah memasukkan *cartridge*? Ulangilah langkah Putar, Buka, Tekan sebanyak tiga kali setelah memasukkan *cartridge* seperti yang ditunjukkan pada langkah 4 sampai 6 pada bagian "Penggunaan Sehari-hari"

Apakah indikator dosis pada cartridge menunjukkan tanda panah putih dengan latar belakang merah? Obat telah habis. Silakan gunakan/masukkan *cartridge* baru Anda.

RESPIMAT *re-usable* saya menyemprot secara otomatis.

Apakah penutup terbuka ketika Anda memutar dasar transparan? Tutuplah penutup, baru kemudian memutar dasar transparan.

Apakah Anda menekan tombol pelepas obat ketika memutar dasar transparan? Tutuplah penutup sehingga tombol pelepas obat terlindungi, kemudian putarlah dasar transparan.

Apakah Anda berhenti memutar dasar transparan sebelum terdengar bunyi klik? Putarlah dasar transparan secara berkelanjutan hingga terdengar bunyi klik (setengah putaran).

Apakah penutup terbuka pada saat Anda memasukkan *cartridge* baru? Tutup penutup, kemudian masukkan *cartridge* baru.

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