SPIRIVA® RESPIMAT®

Tiotropium bromide

Composition

The delivered dose is 2.5 µg tiotropium per puff (2 puffs per dose).
2.5 µg tiotropium is equivalent to 3.124 µg tiotropium bromide monohydrate
(INN = tiotropium bromide)

Excipients: benzalkonium chloride, disodium edetate, purified water, hydrochloric acid for pH adjustment

Pharmaceutical Form

Inhalation solution
Clear, colourless, inhalation solution

Indications

COPD

SPIRIVA® RESPIMAT® is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, the maintenance treatment of associated dyspnoea and for prevention of exacerbations.

Asthma

SPIRIVA® RESPIMAT® is indicated as add-on maintenance bronchodilator treatment in patients aged 6 years and older with moderate to severe asthma who remain symptomatic on a combination of inhaled corticosteroid and a long acting β2 agonist and who experienced one or more severe exacerbations in the previous year.
SPIRIVA® RESPIMAT® is not indicated as rescue medication for the relief of acute bronchospasm in COPD or asthma.

Dosage and Administration

The recommended dosage of SPIRIVA® RESPIMAT® is inhalation of the spray of two puffs once daily from the RESPIMAT® inhaler at the same time of day (see Instructions for use).

In the treatment of asthma, the full benefits will be apparent after several doses of SPIRIVA® RESPIMAT®.

General considerations for Asthma

Use SPIRIVA® RESPIMAT® as add-on maintenance bronchodilator treatment in patients aged 6 years and older with moderate to severe asthma who remain symptomatic on a combination of inhaled corticosteroid and a long acting β2 agonist.

The need for continued therapy should be periodically reassessed based upon the patient's disease severity and level of asthma control.

Special populations:

Elderly patients can use SPIRIVA® RESPIMAT® at the recommended dose.

Renally impaired patients can use SPIRIVA® RESPIMAT® at the recommended dose. However, as with all predominantly renally excreted drugs, SPIRIVA® RESPIMAT® use should be monitored closely in patients with moderate to severe renal impairment.

Hepatically impaired patients can use SPIRIVA® RESPIMAT® at the recommended dose.

Paediatric population:

COPD does not normally occur in children.

In asthma, the recommended dosage of SPIRIVA® RESPIMAT® in patients 6 to 17 years of age is inhalation of the spray of two puffs once daily from the RESPIMAT® inhaler, at the same time of day (see Instructions for use).

The efficacy and safety of SPIRIVA® RESPIMAT® in paediatric patients below 1 year of age with asthma has not yet been established.

SPIRIVA® RESPIMAT®

Tiotropium bromide

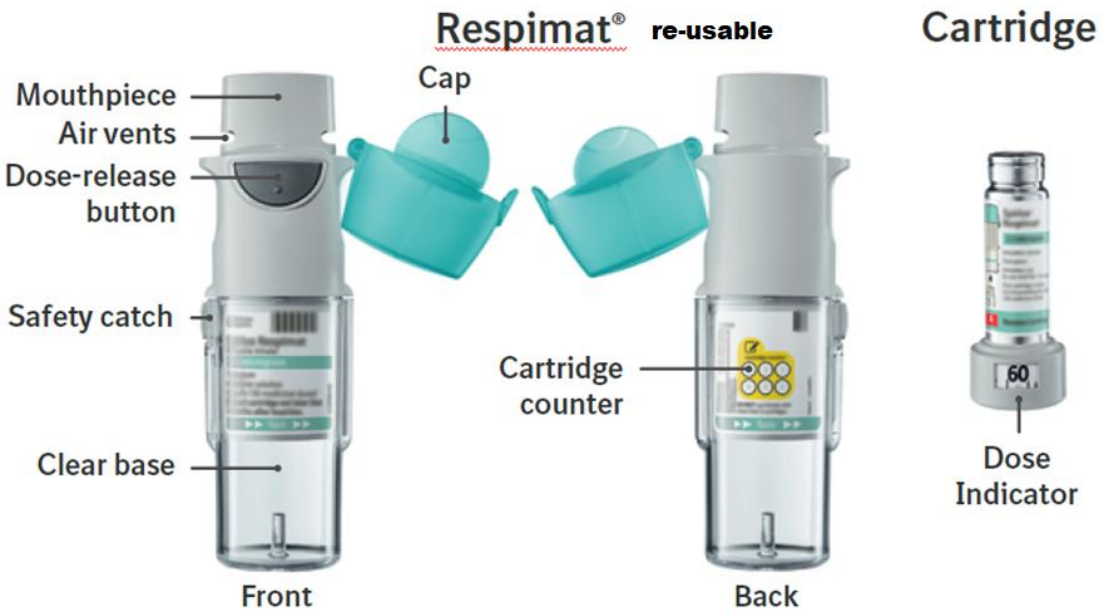
HANDLING INSTRUCTIONS

Introduction

SPIRIVA® RESPIMAT® (tiotropium bromide). Read these Instructions for Use before you start using SPIRIVA® RESPIMAT® re-usable.

Children should use SPIRIVA® RESPIMAT® with an adult's assistance.

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.

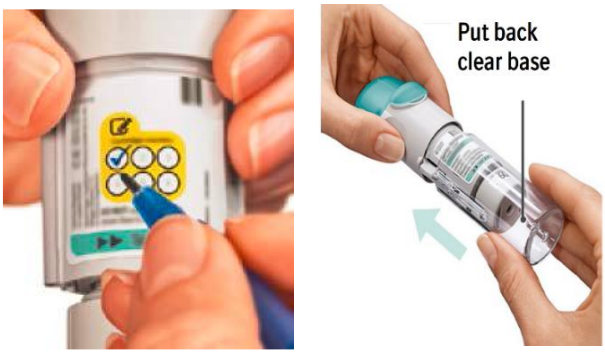
How to care for your SPIRIVA® RESPIMAT® re-usable

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 SPIRIVA® RESPIMAT® re-usable inhaler performance. If necessary, wipe the outside of SPIRIVA® 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 SPIRIVA® 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.

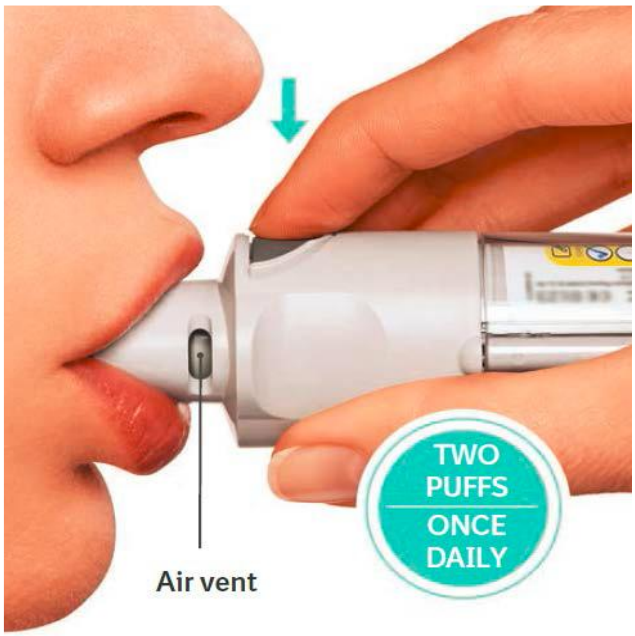
Prepare for first use

1. <u>Remove clear base</u> • Keep the cap closed. • Press the safety catch while firmly 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. <u>Track cartridge and put clear base back</u> • Mark the check-box on inhaler's label to track the number of cartridge • Put the clear base back into place until it clicks.	
4. <u>Turn</u> • Keep the cap closed. • Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	

5. <u>Open</u> • Open the cap until it snaps fully open.	
6. <u>Press</u> • Point the inhaler toward the ground • Press the dose-release button. • Close the cap. • Repeat steps 4-6 until a cloud is visible. • **<u>After a cloud is visible</u>**, repeat steps 4-6 three more times. Your inhaler is now ready to use and will deliver 60 puffs (30 doses).	

Daily use

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

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 inhale again.	

When to replace the SPIRIVA® 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. 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

SPIRIVA® RESPIMAT® is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, e.g. ipratropium or oxitropium or to any component of this product.

Special warnings and precautions

SPIRIVA® RESPIMAT®, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm or for the relief of acute symptoms. In the event of an acute attack, a rapid-acting beta-2-agonist should be used.

SPIRIVA® RESPIMAT® should not be used as a first-line treatment for asthma. Asthma patients must be advised to continue taking anti-inflammatory therapy, i.e. inhaled fluticasone, unchanged after the introduction of SPIRIVA® RESPIMAT®, even when their symptoms improve.

Immediate hypersensitivity reactions may occur after administration of SPIRIVA® RESPIMAT® inhalation solution.

As with other anticholinergic drugs, SPIRIVA® RESPIMAT® should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Inhaled medicines may cause inhalation-induced bronchospasm.

As with all predominantly renally excreted drugs, SPIRIVA® RESPIMAT® use should be monitored closely in patients with moderate to severe renal impairment (creatinine clearance of $\leq$ 50 ml/min).

Patients must be instructed in the correct administration of SPIRIVA® 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.

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

SPIRIVA® cartridges are to be used only with the RESPIMAT® inhaler.

Excipients

This medicine contains 0.0011 mg benzalkonium chloride in each actuation.
Benzalkonium chloride may cause wheezing and breathing difficulties. Patients with asthma are at an increased risk for these adverse events.

Interactions

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 and asthma, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leucotriene modifiers, cromones and anti-IgE treatment without clinical evidence of drug interactions.

Common concomitant medications (LABA, ICS and their combinations) used by patients with COPD were not found to alter the exposure to tiotropium.

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 SPIRIVA® RESPIMAT® is not recommended.

Pregnancy, Lactation and Fertility

Pregnancy

There is a limited amount of data from the use of tiotropium in pregnant women. Pre-clinical do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (please refer to section Toxicology).
As a precautionary measure, it is preferable to avoid the use of SPIRIVA® RESPIMAT® during pregnancy.

Lactation

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, a small amount of tiotropium is excreted into breast milk.
Therefore, SPIRIVA® RESPIMAT® should not be used in pregnant or nursing women unless the expected benefit outweighs any possible risk to the unborn child or the infant.

Fertility

Clinical data on fertility are not available for tiotropium. A pre-clinical study performed with tiotropium showed no indication of any adverse effect on fertility (please refer to section Toxicology).

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. The occurrence of dizziness or blurred vision may influence the ability to drive and use machinery.

Side Effects

Many of the listed undesirable effects can be assigned to the anticholinergic properties of SPIRIVA® RESPIMAT®.

Adverse drug reactions were identified from data obtained in clinical trials and spontaneous reporting during post approval use of the drug.

The clinical trial database for COPD includes 3,282 SPIRIVA® RESPIMAT® patients from 7 placebo-controlled clinical trials with treatment periods ranging between four weeks and one year, contributing 2,440 person years of exposure.

The clinical trial database for asthma includes 1,930 tiotropium treated patients from 12 placebo controlled trials with treatment period ranging between twelve weeks and one year, contributing 1,128 person years of exposure to tiotropium.

Metabolism and nutrition disorders:

- dehydration

Nervous system disorders:

- dizziness
- insomnia

Eye disorders:

- glaucoma
- intraocular pressure increased
- vision blurred

Cardiac disorders:

- atrial fibrillation
- palpitations
- supraventricular tachycardia
- tachycardia

Respiratory, thoracic and mediastinal disorders:

- cough
- epistaxis
- pharyngitis
- dysphonia
- bronchospasm
- laryngitis
- sinusitis

Gastrointestinal disorders:
- dry mouth, usually mild
- constipation
- oropharyngaeal candidiasis
- dysphagia
- gastrooesophageal reflux disease
- gingivitis
- glossitis
- stomatitis
- intestinal obstruction incl. ileus paralytic

Skin and subcutaneous tissue disorders, Immune system disorders:
- rash
- pruritus
- angioneurotic oedema
- urticaria
- skin infection and skin ulcer
- dry skin
- hypersensitivity (including immediate reactions)

Musculoskeletal and connective tissue disorders:
- joint swelling

Renal and urinary disorders:
- urinary retention (usually in men with predisposing factors)
- dysuria
- urinary tract infection

Paedriatic population:

The frequency, type, and severity of adverse reactions in the paediatric population are similar as in adults.

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

High doses of SPIRIVA® RESPIMAT® 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.

Pharmacological properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, anticholinergics; ATC code: R03B B04.

Tiotropium bromide is a long-acting, specific antimuscarinic agent, in clinical medicine often called an anticholinergic. It has a similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, inhibition of M3-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 non-clinical *in vitro* as well as *in vivo* studies bronchoprotective effects were dose-dependent and lasted longer than 24 hours. The long duration of effect is likely to be due to its very slow dissociation from M3-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 M2-receptors is faster than from M3, which in functional *in vitro* studies, elicited (kinetically controlled) receptor subtype selectivity of M3 over M2.

The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD and asthma. The bronchodilation following inhalation of tiotropium is primarily a local effect (on the airways) not a systemic one.

COPD

The clinical Phase III programme for COPD included two 1-year, two 12-weeks and two 4-weeks randomised, double-blind studies in 2901 COPD patients (1038 receiving the 5 µg tiotropium dose). The 1-year programme consisted of two placebo-controlled trials. The two 12-week trials were both active (ipratropium) - and placebo-controlled. All six studies included lung function measurements. In addition, the two 1-year studies included health outcome measures of dyspnoea, health-related quality of life and effect on exacerbations.

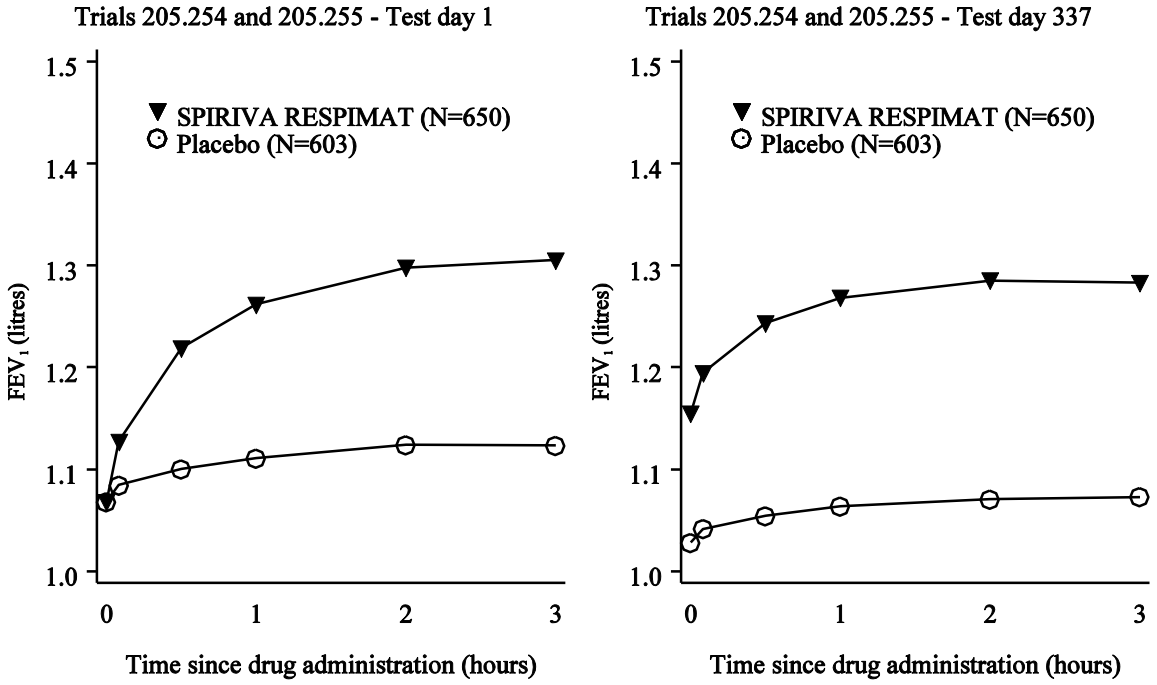
Placebo-controlled studies

Lung function

SPIRIVA® RESPIMAT®, administered once daily, provided significant improvement in lung function (forced expiratory volume in one second and forced vital capacity) within 30 minutes following the first dose, compared to placebo. Improvement of lung function was maintained for 24 hours at steady state.
Pharmacodynamic steady state was reached within one week. SPIRIVA® RESPIMAT® significantly improved morning and evening PEFR (peak expiratory flow rate) as measured by patient's daily recordings. The use of SPIRIVA® RESPIMAT® resulted in a reduction of rescue bronchodilator use compared to placebo.

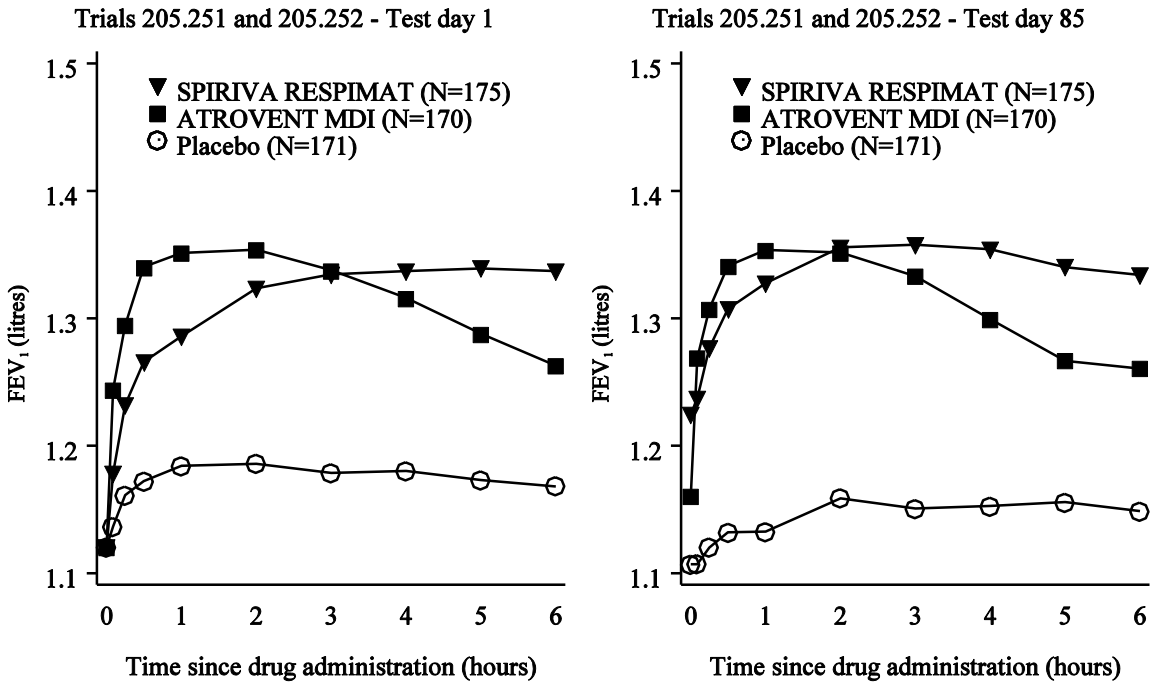
The bronchodilator effects of SPIRIVA® RESPIMAT® were maintained throughout the 48-week period of administration with no evidence of tolerance.

Figure 1: Mean FEV_1 (litres) at each time point (prior to and after administration of study drug) on Days 1 and 337 respectively (combined data from two 1-year, parallel-group trials)*



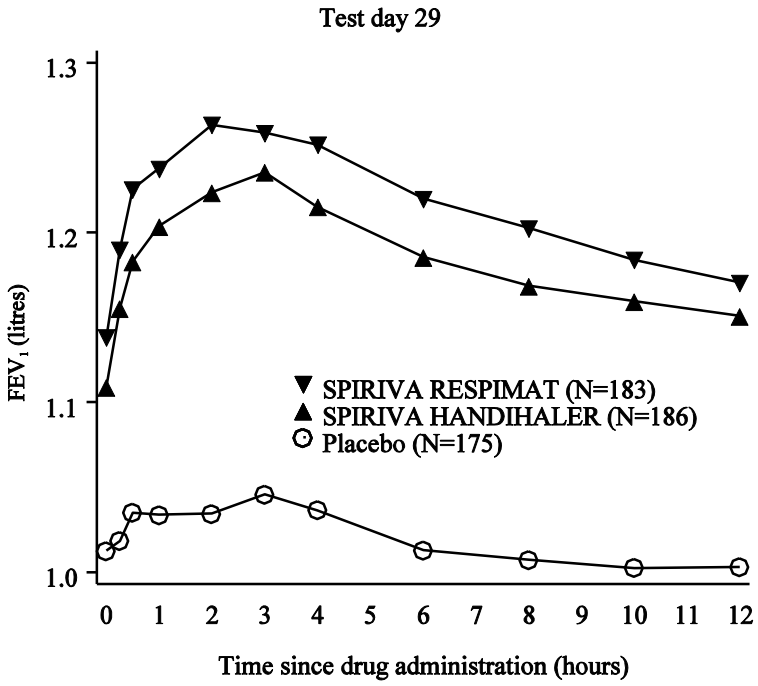
*Means adjusted for center, smoking status and baseline effect. A total of 545 and 434 patients in the SPIRIVA® RESPIMAT® and placebo groups, respectively completed test day 337. The data for the remaining patients were imputed using last observation or least favourable observation carried forward.

Figure 2: Mean FEV_1 (litres) at each time point (prior to and after administration of study drug) on Days 1 and 85 respectively (combined data from two 12-week, parallel-group trials)



*Day 85, a total of 155, 142 and 152 patients in the SPIRIVA® RESPIMAT®, ATROVENT® MDI and placebo groups, respectively completed test day 85. The data for the remaining patients were imputed using last observation or least favourable observation carried forward.

Figure 3: Mean FEV_1 (litres) at each time point (prior to and after administration of study drug) on Day 29 (combined data from two 4-week cross-over studies 205.249 and 205.250)*



*Means adjusted for center, patient (within center), period and baseline effect. The data for patients who discontinued a test day early were imputed using last observation or least favourable observation carried forward. Patients who completed the trials took all 3 treatments.

A combined analysis of two randomised, placebo-controlled, crossover, clinical studies demonstrated that the bronchodilator response for SPIRIVA® RESPIMAT® (5 µg) was numerically higher compared to SPIRIVA® HandiHaler® (18 µg) inhalation powder after a 4-week treatment period.

Dyspnoea, Health-related Quality of Life, COPD Exacerbations in long-term 1 year studies

a) SPIRIVA® RESPIMAT® significantly improved dyspnoea (as evaluated using the Transition Dyspnoea Index). An improvement was maintained throughout the treatment period.

(b) Patients' evaluation of their Quality of Life (as measured using the St. George's Respiratory Questionnaire) showed that SPIRIVA® RESPIMAT® had positive effects on the psychosocial impacts of COPD, activities affected by COPD and distress due to COPD symptoms.
The improvement in mean total score between SPIRIVA® RESPIMAT® versus placebo at the end of the two 1-year studies was statistically significant and maintained throughout the treatment period.

(c) COPD Exacerbations
In three one-year, randomised, double-blind, placebo-controlled clinical trials SPIRIVA® RESPIMAT® treatment resulted in a significantly reduced risk of a COPD exacerbation in comparison to placebo. Exacerbations of COPD were defined as "a complex of at least two respiratory events/symptoms with a duration of three days or more requiring a change in treatment (prescription of antibiotics and/or systemic corticosteroids and/or a significant change of the prescribed respiratory medication)". SPIRIVA® RESPIMAT® treatment resulted in a reduced risk of a hospitalisation due to a COPD exacerbation (significant in the appropriately powered large exacerbation trial).
The pooled analysis of two Phase III trials and separate analysis of an additional exacerbation trial is displayed in Table 1. All respiratory medications except anticholinergics and long-acting beta-agonists were allowed as concomitant treatment, i.e. rapidly acting beta-agonists, inhaled corticosteroids and xanthines. Long-acting beta-agonists were allowed in addition in the exacerbation trial.

Table 1: Statistical Analysis of Exacerbations of COPD and Hospitalized COPD Exacerbations in Patients with Moderate to Very Severe COPD

Study ($N_{Spiriva}$, $N_{placebo}$)	Endpoint	Spiriva Respimat	Placebo	% Risk Reduction (95% CI)[a]	p-value
1-year Ph III studies, pooled analysis[d] (670, 653)	Days to first COPD exacerbation	160[a]	86[a]	29 (16 to 40)[b]	<0.0001 [b]
	Mean exacerbation incidence rate per patient year	0.78[c]	1.00[c]	22 (8 to 33)[c]	0.002[c]
	Time to first hospitalised COPD exacerbation	NA[e]	NA[e]	25 (-16 to 51)[b]	0.20[b]
	Mean hospitalised exacerbation incidence rate per patient year	0.09 [c]	0.11 [c]	20 (-4 to 38) [c]	0.096 [c]

Study ($N_{Spiriva}$, $N_{placebo}$)	Endpoint	Spiriva Respimat	Placebo	% Risk Reduction (95% CI)[a]	p-value
1-year Ph IIIb exacerbation study (1939, 1953)	Days to first COPD exacerbation	169[a]	119[a]	31 (23 to 37)[b]	<0.0001[b]
	Mean exacerbation incidence rate per patient year	0.69[c]	0.87[c]	21 (13 to 28)[c]	<0.0001[c]
	Time to first hospitalised COPD exacerbation	NA[e]	NA[e]	27 (10 to 41)[b]	0.003[b]
	Mean hospitalised exacerbation incidence rate per patient year	0.12[c]	0.15[c]	19 (7 to 30)[c]	0.004[c]

[a] Time to first event: days on treatment by when 25% of patients had at least one exacerbation of COPD / hospitalized COPD exacerbation. *In study A 25% of placebo patients had an exacerbation by day 112, whereas for Spiriva Respimat 25% had an exacerbation by day 173 (p=0.09);in study B 25% of placebo patients had an exacerbation by day 74, whereas for Spiriva Respimat 25% had an exacerbation by day 149 (p<0.0001).*

[b] Hazard ratios were estimated from a Cox proportional hazard model. The percentage risk reduction is 100(1 - hazard ratio).

[c] Poisson regression. Risk reduction is 100(1 - rate ratio).

[d] Pooling was specified when the studies were designed. The exacerbation endpoints were significantly improved in individual analyses of the two one year studies.

[e]Less than 25% of patients had a COPD exacerbation leading to hospitalisation

Long-term tiotropium active - controlled study

A long term, large scale, randomised, double-blind, active-controlled study with a treatment period up to 3 years has been performed to compare the efficacy and safety of SPIRIVA® RESPIMAT® and SPIRIVA® HANDIHALER® (5,711 patients receiving SPIRIVA® RESPIMAT® 2.5 microgram (5 microgram medicinal dose); 5,694 patients receiving SPIRIVA® HANDIHALER®). The primary endpoints were time to first COPD exacerbation, time to all-cause mortality and in a sub-study (906 patients) trough FEV_1 (pre-dose).

The time to first COPD exacerbation was similar during the study with SPIRIVA® RESPIMAT® and SPIRIVA® HANDIHALER® (hazard ratio (SPIRIVA® RESPIMAT® / SPIRIVA® HANDIHALER®) 0.98 with a 95% CI of 0.93 to 1.03).

The median number of days to the first COPD exacerbation was 756 days for SPIRIVA® RESPIMAT® and 719 days for SPIRIVA® HANDIHALER®

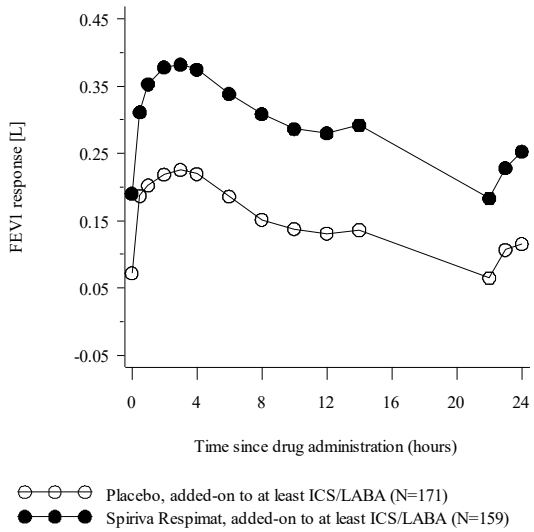
The bronchodilator effect of SPIRIVA® RESPIMAT® was sustained over 120 weeks, and was similar to SPIRIVA® HANDIHALER®. The mean difference in trough FEV_1 for SPIRIVA® RESPIMAT® versus SPIRIVA® HANDIHALER® was -0.010 L (95% CI -0.038 to 0.018 mL).
All-cause mortality was similar during the study with SPIRIVA® RESPIMAT® and SPIRIVA® HANDIHALER® (hazard ratio (SPIRIVA® RESPIMAT® / SPIRIVA® HANDIHALER®) 0.96 with a 95% CI of 0.84 to 1.09).

Asthma
Adult patients

The clinical Phase III programme for persistent asthma included two 1-year, 19andomized, double-blind, placebo-controlled studies in a total of 907 asthma patients (453 receiving SPIRIVA® RESPIMAT®) on a combination of ICS with a LABA.
In the two 1-year PrimoTinA-asthma studies in patients who were symptomatic on maintenance treatment of at least high-dose ICS plus LABA, SPIRIVA® RESPIMAT® showed significant improvements in lung function (FEV1) over placebo when used as add-on to background treatment.

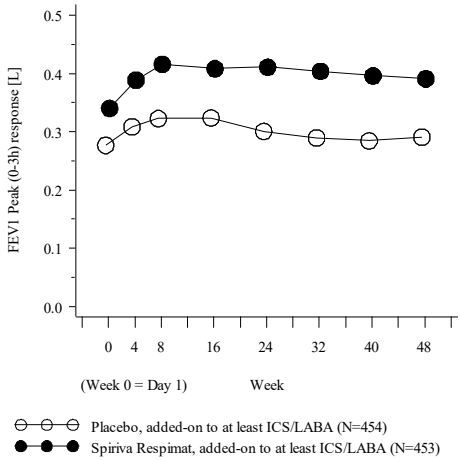
- At week 24, mean improvements in peak and trough FEV_1 were 0.110 litres (95% CI: 0.063 to 0.158 litres, $p<0.0001$) and 0.093 litres (95% CI: 0.050 to 0.137 litres, $p<0.0001$), respectively.
- The improvement of lung function compared to placebo was maintained for 24 hours (Figure 4).

Figure 4: FEV_1 profiles over 24 hours in a subset of patients in the PrimoTinA-asthma studies at week 24



- At week 24, SPIRIVA® RESPIMAT® significantly improved morning and evening peak expiratory flow (PEF; mean improvement in the morning 23 L/min; 95% CI: 16 to 29 L/min, p< 0.0001; evening 26 L/min; 95% CI: 20 to 33 L/min, p<0.0001
- The bronchodilator effects of SPIRIVA® RESPIMAT® were maintained throughout the 1 year period of administration with no evidence of tachyphylaxis or tolerance. (Figure 5)

Figure 5: Peak FEV_1 response over 48 weeks in the PrimoTinA-asthma studies



Paediatric Patients:

The clinical Phase III program for persistent asthma in paediatric patients (1-17 years) included:

• Adolescents (12-17 years): one 1-year and one 12-week randomised, double-blind, placebo-controlled studies in a total of 789 asthma patients (264 receiving SPIRIVA® RESPIMAT®)

• Children (6-11 years): one 1-year and one 12-week randomised, double-blind, placebo-controlled studies in a total of 801 asthma patients (265 receiving SPIRIVA® RESPIMAT®)
• Children (1-5 years): one 12-week randomised, double-blind placebo-controlled study in a total of 101 asthma patients (31 receiving SPIRIVA® RESPIMAT®)

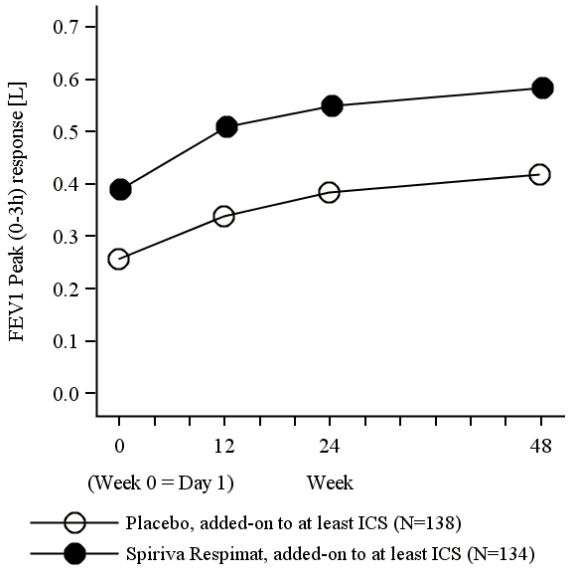
In all these studies, patients were on background treatment of at least ICS.

Adolescents (12-17 years)

In the 1-year RubaTinA-asthma study in patients who were symptomatic on maintenance treatment of at least medium-dose ICS, SPIRIVA® RESPIMAT® showed significant improvements in lung function over placebo when used as add-on to background treatment.

• At week 24, mean improvements in peak and trough FEV1 were 0.174 litres (95% CI: 0.076 to 0.272 litres, p=0.0005) and 0.117 litres (95% CI: 0.010 to 0.223 litres, p=0.0320), respectively. [9]
• At week 24, SPIRIVA® RESPIMAT® significantly improved morning and evening PEF (morning 15.8 L/min; 95% CI: 2.3, 29.3 L/min, p=0.0214; evening 16.7 L/min; 95% CI: 3.4, 30.0 L/min, p=0.0137). [25]
• The bronchodilator effects of SPIRIVA® RESPIMAT® were maintained throughout the 1 year period of administration with no evidence of tachyphylaxis (Figure 6).

Figure 6 : Peak FEV1 response over 48 weeks in the RubaTinA-asthma study



In the 12-week PensieTinA-asthma study in patients who were symptomatic on maintenance treatment of at least medium dose ICS in combination with 1 or more controller medication,

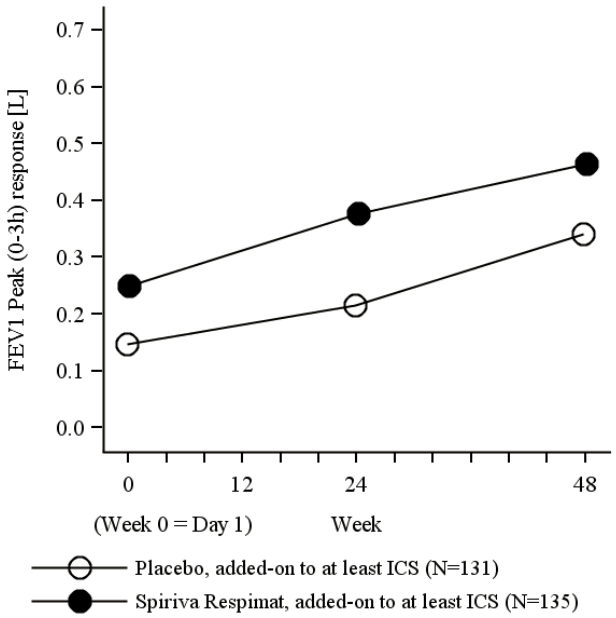
SPIRIVA® RESPIMAT® showed improvements in lung function over placebo when used as add-on to background treatment, however, the differences in peak and trough FEV_1 were not statistically significant.

• At week 12, mean improvements in peak and trough FEV_1 were 0.090 litres (95% CI: -0.019 to 0.198 litres, p=0.1039) and 0.054 litres (95% CI: -0.061 to 0.168 litres, p=0.3605), respectively. [9]
• At week 12, SPIRIVA® RESPIMAT® significantly improved morning and evening PEF (morning 17.4 L/min; 95% CI: 5.1 to 29.6 L/min; evening 17.6 L/min; 95% CI: 5.9 to 29.6 L/min).

Children (6-11 years)

In the 1-year CanoTinA-asthma study in patients who were symptomatic on maintenance treatment of at least medium-dose ICS, SPIRIVA® RESPIMAT® showed significant improvements in lung function and asthma control over placebo when used as add-on to background treatment.
• At week 24, mean improvements in peak and trough FEV1 were 0.164 litres (95% CI: 0.103 to 0.225 litres, p<0.0001) and 0.118 litres (95% CI: 0.048 to 0.188 litres, p=0.0010), respectively. [9]
• The bronchodilator effects of SPIRIVA® RESPIMAT® were maintained throughout the 1 year period of administration with no evidence of tachyphylaxis (Figure 7).

Figure 7: Peak FEV1 response over 48 weeks in the CanoTinA-asthma study



In the 12-week VivaTinA-asthma study in patients who were symptomatic on maintenance treatment of at least medium dose ICS in combination with 1 or more controller medication,

SPIRIVA® RESPIMAT® showed significant improvements in lung function over placebo when used as add-on to background treatment.

- At week 12, mean improvements in peak and trough FEV1 were 0.139 litres (95% CI: 0.075 to 0.203 litres, p<0.0001) and 0.087 litres (95% CI: 0.019 to 0.154 litres, p=0.0117), respectively.

Pharmacokinetics

Tiotropium bromide is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium bromide is available as inhalation solution for inhalation administered by the Respimat inhaler. Approximately 40% of the inhaled dose is deposited in the lungs, the target organ, the remaining amount being deposited in the gastrointestinal tract. Some of the pharmacokinetic data described below were obtained with higher doses as recommended for therapy.

Absorption: Following inhalation by young healthy volunteers, urinary excretion data suggest that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of tiotropium for the same reason. Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation. At steady state, peak tiotropium plasma concentrations of 10.5 pg/mL were achieved in COPD patients and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.60 pg/mL.
A steady-state tiotropium peak plasma concentration of 5.15 pg/mL was attained 5 minutes after the administration of the same dose to patients with asthma.

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

Biotransformation: The extent of biotransformation is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium bromide, an ester, is nonenzymatically cleaved to the alcohol N methylscopine and dithienylglycolic acid, both not binding to muscarinic receptors.

In-vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (<20% of dose after intravenous administration) is metabolised by cytochrome P450 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-metabolites. This enzymatic pathway can be inhibited by the CYP450 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium bromide even in supra-therapeutic concentrations does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination: The effective half-life of tiotropium ranges between 27 to 45 h following inhalation by COPD patients. The effective half-life was 34 hours in patients with asthma.

Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74 %). After inhalation of the inhalation solution by COPD patients urinary excretion is 18.6% (0.93 µg) of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces.

In patients with asthma, 11.9% (0.595 µg) of the dose is excreted unchanged in the urine over 24 hours post dose at steady state.

The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Linearity/nonlinearity: Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

Elderly Patients:
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.

Exposure to tiotropium was not found to differ with age in patients with asthma.

Paediatric Patients:
The peak and total exposure to tiotropium was not found to differ between paediatric patients (aged 6 to 17 years) and adults with asthma.

Renally Impaired Patients:

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 COPD patients with moderate to severe renal impairment (CLCR <50 ml/min) the intravenous administration of tiotropium bromide resulted in doubling of the total exposure (82% higher AUC_{0-4h} and 52% higher C_{max}) compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.

In asthma patients with mild renal impairment (CLCR 50-80 mL/min) inhaled tiotropium did not result in relevant increases in exposure compared to patients with normal renal function.

Hepatically Impaired Patients:

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

Toxicology

The **acute inhalation and oral toxicity** in mice, rats, and dogs was low; therefore, toxic effects from acute human drug over-dosage are unlikely. The single dose safety pharmacology studies showed the expected effects of an anticholinergic drug including mydriasis, increased heart rate and prolonged gastro-intestinal transit time.

The side effects of the **repeat-dose studies** in rats, mice and dogs were related to anticholinergic properties of tiotropium bromide including mydriasis, increased heart rate, constipation, decreased body weight gain, reduced salivary and lacrimal gland secretion. Other relevant changes noted were: mild irritancy of the upper respiratory tract in rats evinced by rhinitis and epithelial changes of the nasal cavity and larynx, and prostatitis along with proteinaceous deposits and lithiasis in the bladder of male rats, increased lung weights in rats and decreased heart weights in dogs.

In the **reproduction studies** in rabbits and rats harmful effects with respect to pregnancy, embryo/foetal 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.

In juvenile rats exposed from postnatal day 7 to sexual maturity, the same direct and indirect pharmacological changes were observed as in the repeat-dose toxicity studies as well as rhinitis. No systemic toxicity was noted and no toxicologically relevant effects on key developmental parameters, tracheal or key organ development were seen.

In a series of in vivo and in vitro **mutagenicity assays**, tiotropium bromide did not cause gene mutations in prokaryotes and in eucaryotes, chromosomal damage in vitro and in vivo conditions or primary DNA damage.

Availability

Inhalation Solution

1 Respimat Reusable inhaler and 1 cartridge Reg. No: DKIXXXXXXXXXXX

1 Cartridge (singe refill pack) Reg. No: DKIXXXXXXXXXXX

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.

Shelf life: please see packaging for expiry date.
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: 13-1025

Produk Informasi untuk Pasien

SPIRIVA® RESPIMAT®

Tiotropium bromide
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 kemungkinan efek samping obat yang tidak terdaftar dalam leaflet ini.

Apa saja yang terdapat dalam leaflet ini

1. Apakah SPIRIVA® RESPIMAT® dan digunakan untuk apa

SPIRIVA® RESPIMAT® membantu pasien yang mengalami penyakit paru obstruktif kronik (PPOK) atau asma agar dapat bernapas lebih mudah. Penyakit paru obstruktif kronik adalah penyakit paru jangka panjang yang menyebabkan sesak napas dan batuk. Istilah PPOK dikaitkan dengan kondisi bronkitis kronik dan emfisema. Gejala PPOK meliputi nafas menjadi pendek, batuk, rasa tidak nyaman di dada dan batuk berdahak. Asma adalah penyakit paru jangka panjang yang ditandai dengan peradangan saluran napas dan penyempitan saluran udara. Karena PPOK dan asma merupakan penyakit jangka panjang oleh sebab itu anda sebaiknya menggunakan SPIRIVA® RESPIMAT® setiap hari dan tidak hanya ketika anda sedang mengalami masalah sesak napas atau gejala lainnya. Ketika digunakan untuk mengobati asma, anda harus menggunakan SPIRIVA® RESPIMAT® sebagai tambahan dari inhalasi kortikosteroid.

SPIRIVA® RESPIMAT® merupakan bronkodilator kerja panjang yang membantu membuka saluran napas anda sehingga memudahkan udara masuk dan keluar dari paru. Penggunaan SPIRIVA® RESPIMAT® secara teratur dapat juga membantu anda yang mengalami sesak napas berkepanjangan akibat penyakit ini dan akan membantu meminimalkan efek penyakit ini dalam keseharian anda. Penggunaan sehari-hari SPIRIVA® RESPIMAT® juga akan membantu mencegah perburukan gejala COPD yang mendadak dan dapat berlangsung selama beberapa hari.

Dosis yang tepat untuk SPIRIVA® RESPIMAT® dapat anda lihat pada bab 3. Bagaimana cara menggunakan SPIRIVA® RESPIMAT® dan instruksi penggunaannya tersedia pada bagian yang terpisah dari leaflet ini.

2. Apakah yang perlu anda ketahui sebelum anda menggunakan SPIRIVA® RESPIMAT®

Bacalah pertanyaan di bawah ini dengan seksama
Jika ada dapat menjawab salah satu dari pertanyaan berikut dengan **"YA",** bicarakan kepada dokter anda **sebelum** menggunakan SPIRIVA® RESPIMAT®

- Apakah anda alergi (hipersensitif) terhadap tiotropium, atropine atau obat-obat lain yang sejenis, seperti ipratropium atau oxitropium?
- Apakah anda sedang menggunakan obat-obatan lain yang mengandung ipratropium atau oxitropium?
- Apakah anda hamil, apakah anda berpikir bahwa anda sedang hamil, atau apakah anda tengah menyusui?
- Apakah anda menderita penglihatan kabur, sakit mata dan / atau mata merah, masalah prostat atau mengalami kesulitan buang air kecil?
- Apakah Anda memiliki masalah ginjal?
- Apakah Anda pernah menderita infark miokard selama 6 bulan terakhir atau jantung berdetak tidak teratur yang tidak stabil atau mengancam jiwa atau gagal jantung parah dalam satu tahun terakhir?

Jangan gunakan SPIRIVA® RESPIMAT®
- Bila anda alergi (hipersensitif) terhadap zat aktifnya tiotropium atau bahan lainnya yang terkandung dalam obat ini (terdaftar dalam bab 6).
- Bila anda alergi (hipersensitif) terhadap atropine atau zat-zat lain yang sejenis, seperti ipratropium atau oxitropium?

Peringatan dan tindakan pencegahan
Bicarakan kepada dokter anda sebelum menggunakan SPIRIVA® RESPIMAT®

Ketika menggunakan SPIRIVA® RESPIMAT®, hati-hati untuk tidak membiarkan semprotannya masuk ke mata Anda. Hal ini dapat mengakibatkan sakit mata atau ketidaknyamanan, penglihatan kabur, melihat lingkaran cahaya di sekitar lampu atau gambar berwarna yang berhubungan dengan mata merah (yaitu glaukoma sudut sempit). Gejala mata bisa disertai dengan sakit kepala, mual atau muntah. Cuci mata Anda dengan air hangat, berhenti menggunakan tiotropium bromida dan segera berkonsultasi dengan dokter Anda untuk saran lebih lanjut.

Jika pernapasan Anda telah memburuk atau jika Anda mengalami ruam, bengkak atau gatal secara langsung setelah menggunakan inhaler Anda, berhenti menggunakannya dan memberitahu dokter Anda segera.

Mulut kering yang telah diamati dengan pengobatan anti-cholinergic mungkin dalam jangka panjang dapat berkaitan dengan karies gigi. Oleh karena itu, harap ingat untuk memperhatikan kebersihan mulut.

SPIRIVA® RESPIMAT® diindikasikan untuk pengobatan pemeliharaan penyakit kronik obstruktif paru atau asma Anda. Jangan menggunakan obat ini untuk mengobati serangan tiba-tiba sesak napas atau mengi. Dokter Anda harus memberikan Anda inhaler lain ("pengobatan penyelamatan") untuk ini. Ikuti petunjuk yang diberikan oleh dokter Anda.

Jika Anda telah diresepkan SPIRIVA® RESPIMAT® untuk asma Anda, harus ditambahkan pada kortikosteroid inhalasi dan *long-acting* β_2*-agonists* . Terus gunakan kortikosteroid inhalasi seperti yang ditentukan oleh dokter Anda, bahkan jika Anda merasa lebih baik.
Dalam kasus Anda telah menderita infark miokard selama 6 bulan terakhir atau jantung berdetak tidak teratur yang tidak stabil atau mengancam jiwa atau gagal jantung berat dalam satu tahun terakhir, harap menginformasikan kepada dokter Anda. Hal ini penting untuk memutuskan apakah SPIRIVA adalah obat yang tepat untuk Anda.
Jangan menggunakan SPIRIVA® RESPIMAT® lebih sering dari sekali sehari.

Anda juga harus menghubungi dokter Anda jika Anda merasa bahwa pernapasan Anda memburuk.

Jika Anda memiliki fibrosis kistik, beritahu dokter Anda karena SPIRIVA® RESPIMAT® bisa membuat gejala fibrosis kistik Anda memburuk.

Anak dan remaja
SPIRIVA® RESPIMAT® tidak dianjurkan untuk diberikan kepada anak usia dibawah 6 tahun.

Obat lain dan SPIRIVA® RESPIMAT®
Beritahukan kepada dokter atau apoteker anda bila anda menggunakan atau akhir-akhir ini menggunakan obat-obatan lainnya, termasuk obat-obatan yang diperoleh tanpa resep dari dokter.
Khususnya, beritahukan kepada dokter atau apoteker anda bila anda tengah atau telah menggunakan obat antikolinergik, seperti ipratropium atau oxitropium.

Tidak ada interaksi efek samping yang telah dilaporkan ketika SPIRIVA® RESPIMAT® telah digunakan bersamaan dengan produk lain untuk mengobati PPOK seperti inhaler pereda (misalnya salbutamol), *methylxanthines* (misalnya teofilin), antihistamin, mukolitik (misalnya ambroxol), pengubah leukotrien (misalnya montelukast), *chromones*, pengobatan anti-IgE (misalnya omalizumab) dan / atau inhalasi atau oral steroid (misalnya budesonide, prednisolon).

Hamil dan menyusui
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. Anda tidak boleh menggunakan obat ini kecuali jika secara spesifik dianjurkan oleh dokter anda.

Mengendarai dan mengoperasikan mesin
Tidak ada studi yang dilakukan mengenai efek terhadap kemampuan untuk mengendarai dan mengoperasikan mesin. Bila anda merasa pusing atau penglihatan kabur maka kemampuan mengendarai atau mengoperasikan mesin telah terganggu.

3. Bagaimana cara menggunakan SPIRIVA® RESPIMAT®

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

SPIRIVA® RESPIMAT® hanya digunakan dengan cara inhalasi saja.

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

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

SPIRIVA® RESPIMAT® tidak dianjurkan untuk digunakan oleh anak usia di bawah 6 tahun karena kurangnya data keamanan dan efikasi.

Pastikan anda mengetahui bagaimana menggunakan SPIRIVA® RESPIMAT® inhaler anda dengan tepat. Instruksi untuk cara menggunakan SPIRIVA® RESPIMAT® inhaler disediakan pada bagian lain dari leaflet ini.

Bila anda menggunakan SPIRIVA® RESPIMAT® melebihi dari seharusnya

Jika anda menggunakan SPIRIVA® RESPIMAT® lebih dari 2 semprot dalam 1 hari, segera bicarakan dengan dokter anda. Anda mungkin memiliki risiko lebih tinggi untuk mengalami efek samping seperti mulut kering, konstipasi, susah buang air kecil, denyut jantung lebih cepat atau penglihatan kabur.

Bila anda lupa menggunakan SPIRIVA® RESPIMAT®
Bila anda terlupa menghisap satu dosis per hari (dua semprot setiap hari), jangan khawatir. Gunakanlah segera setelah anda ingat, tetapi jangan menggandakan dosis pada saat yang sama atau pada hari yang sama. Gunakan dosis berikutnya seperti biasa.

Bila anda menghentikan penggunaan SPIRIVA® RESPIMAT®
Sebelum anda menghentikan penggunaan SPIRIVA® RESPIMAT®, anda sebaiknya berbicara dengan dokter atau apoteker anda. Bila anda menghentikan penggunaan SPIRIVA® RESPIMAT® maka tanda dan gejala PPOK dapat memberat.

Bila anda memiliki pertanyaan lebih lanjut mengenai cara menggunakan obat ini, tanyakan kepada dokter atau apoteker anda.

4. Kemungkinan efek samping

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

Evaluasi efek samping berdasarkan frekuensi terjadinya:

Sering:	mempengaruhi 1 dalam 10 pasien
Tidak sering:	mempengaruhi 1 dalam 100 pasien
Jarang:	mempengaruhi 1 dalam 1000 pasien
Tidak diketahui:	frekuensi tidak dapat dihitung dari data yang tersedia

Berbagai efek samping yang diuraikan dibawah ini telah dialami oleh orang yang menggunakan obat ini dan mereka menyusunnya berdasarkan frekuensi yaitu sering, tidak sering, jarang atau tidak diketahui.

Efek Samping	**Frekuensi pada PPOK**	**Frekuensi pada Asma**
Mulut kering : biasanya ringan	Sering	Sering
Pusing	Tidak sering	Tidak sering
Sakit kepala	Tidak sering	Tidak sering
Susah tidur (insomnia)	Jarang	Tidak sering
Denyut jantung tidak beraturan *(atrial fibrillation, supraventricular tachycardia)*	Jarang	Tidak diketahui
Denyut jantung terasa (palpitasi)	Jarang	Tidak sering
Denyut jantung lebih cepat *(tachycardia)*	Jarang	Tidak diketahui
Batuk	Tidak sering	Tidak sering
Hidung berdarah *(epistaxis)*	Jarang	Tidak diketahui
Radang tenggorokan *(pharyngitis)*	Tidak sering	Tidak sering
Suara serak *(dysphonia)*	Tidak sering	Tidak sering
Sesak dada, terkait dengan batuk, mengi atau sesak napas setelah menghirup (bronkospasma)	Jarang	Tidak sering
Konstipasi	Tidak sering	Jarang
Infeksi jamur pada rongga mulut dan tenggorokan *(oropharyngeal candidiasis)*	Tidak sering	Tidak sering
Susah menelan *(dysphagia)*	Jarang	Tidak diketahui
Ruam	Tidak sering	Jarang

Efek Samping	**Frekuensi pada PPOK**	**Frekuensi pada Asma**
Gatal-gatal *(pruritus)*	Tidak sering	Jarang
Susah buang air kecil *(*retensi urin*)*	Tidak sering	Tidak diketahui
Nyeri saat kencing *(dysuria)*	Tidak sering	Tidak diketahui
Melihat lingkaran cahaya di sekitar lampu atau gambar berwarna yang berhubungan dengan mata merah (glaukoma)	Jarang	Tidak diketahui
Peningkatan tekanan pada mata	Jarang	Tidak diketahui
Penglihatan kabur	Jarang	Tidak diketahui
Radang pangkal tenggorokan (laryngitis)	Jarang	Tidak diketahui
Mulas *(gastrooesophageal reflux disease)*	Jarang	Tidak diketahui
Karies gigi	Jarang	Tidak diketahui
Radang pada gusi *(gingivitis)*	Jarang	Jarang
Radang pada lidah *(glossitis)*	Jarang	Tidak diketahui
Radang pada mulut *(stomatitis)*	Tidak diketahui	Jarang
Reaksi alergi serius yang menyebabkan pembengkakan pada mulut, muka dan tenggorokan *(angioneurotic oedema)*	Jarang	Jarang
Urtikaria	Jarang	Jarang
Infeksi atau luka pada kulit	Jarang	Tidak diketahui
Kulit kering	Jarang	Tidak diketahui
Hipersensitivitas, termasuk reaksi langsung	Tidak diketahui	Jarang
Infeksi saluran kencing	Jarang	Tidak diketahui
Penipisan cairan tubuh (dehidrasi)	Tidak diketahui	Tidak diketahui
Radang sinus (sinusitis)	Tidak diketahui	Tidak diketahui
Penyumbatan usus atau tidak adanya gerakan usus *(intestinal obstruction, including ileus paralytic)*	Tidak diketahui	Tidak diketahui
Perasaan sakit (mual)	Tidak diketahui	Tidak diketahui
Reaksi alergi parah (reaksi anafilaksis)	Tidak diketahui	Tidak diketahui
Pembengkakan sendi	Tidak diketahui	Tidak diketahui

Reaksi alergi segera seperti ruam, urtikaria, bengkak pada mulut dan wajah atau tiba-tiba sulit bernapas (edema angioneurotik) atau reaksi hipersensitivitas lainnya (seperti pengurangan tekanan darah secara tiba-tiba atau pusing) dapat terjadi sendiri atau sebagai bagian dari reaksi alergi parah (reaksi anafilaksis) setelah penggunaan SPIRIVA® RESPIMAT®. Bila hal ini terjadi, 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 SPIRIVA® RESPIMAT®

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

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 disimpan pada suhu beku.

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 SPIRIVA® RESPIMAT®
Substansi aktifnya adalah tiotropium. Dosis pemberiannya adalah 2,5 mikrogram tiotropium per semprot (2 semprot adalah satu dosis obat) dan ekuivalen dengan 3,124 mikrogram tiotropium bromida monohidrat.
Dosis pemberian adalah dosis yang diterima oleh pasien setelah melewati corong.

Bahan lainnya adalah:
Benzalkonium klorida, disodium edetat, air purifikasi dan asam hidroklorida untuk penyesuai pH.

Seperti apakah SPIRIVA® RESPIMAT® dan apakah isi paket

SPIRIVA® RESPIMAT® 2,5 mikrogram terdiri dari satu *cartridge* dengan cairan inhalasi dan satu Respimat inhaler. *Cartridge* harus dimasukkan kedalam inhaler sebelum pertama kali digunakan.

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

Reg. No. DKIXXXXXXXXXXX

Harus dengan resep dokter

Kondisi penyimpanan:
Simpan di bawah suhu 30°C. Jangan dibekukan.
Simpan di tempat yang aman, jauh dari jangkaan 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

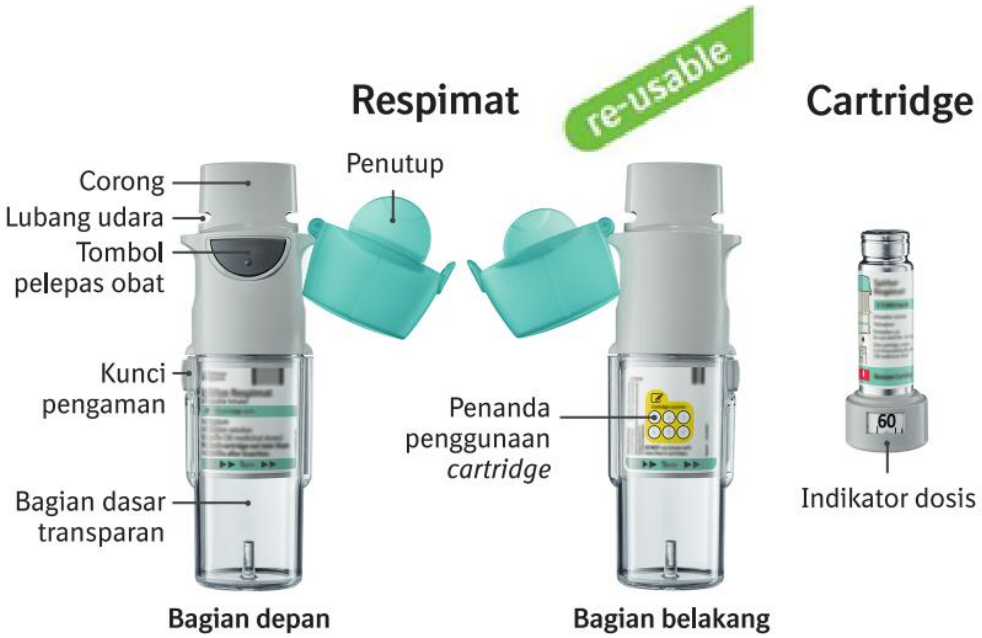
Version: 13-1025

Instruksi Cara Penggunaan

SPIRIVA® RESPIMAT®

Pendahuluan
SPIRIVA® RESPIMAT® (Tiotropium). Bacalah Instruksi Cara Penggunaan ini sebelum Anda menggunakan SPIRIVA® RESPIMAT® *re-usable*.

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



Keterangan Gambar:

Inhaler	Alat Inhalasi
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*
Piercing element	Bagian yang menonjol
Mouthpiece	Corong
Dose indicator	Indikator dosis
Front	Bagian depan
Back	Bagian belakang

- Jika SPIRIVA® RESPIMAT® tidak digunakan selama lebih dari 7 hari, maka Anda sebaiknya melepaskan satu semprotan ke arah bawah.
- Jika SPIRIVA® RESPIMAT® tidak digunakan selama lebih dari 21 hari, maka Anda harus mengulangi langkah 4 hingga 6 dalam bagian *'Prepare for first Use'* hingga kabut terlihat kembali. Kemudian ulangi langkah 4 hingga 6 sebanyak tiga kali.

Bagaimana cara 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 SPIRIVA® RESPIMAT® *re-usable* baru

Jika alat sudah digunakan sebanyak 6 kali, maka harus menggunakan SPIRIVA® 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 untuk memastikan *cartridge* telah masuk seluruhnya.	
3. Tandai penanda penggunaan *cartridge* dan masukkan kembali bagian dasar transparan	

<table>
<tr>
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- Tandai lingkaran yang tersedia pada label *cartridge*
- Pasang kembali dasar transparan hingga terdengar bunyi klik.

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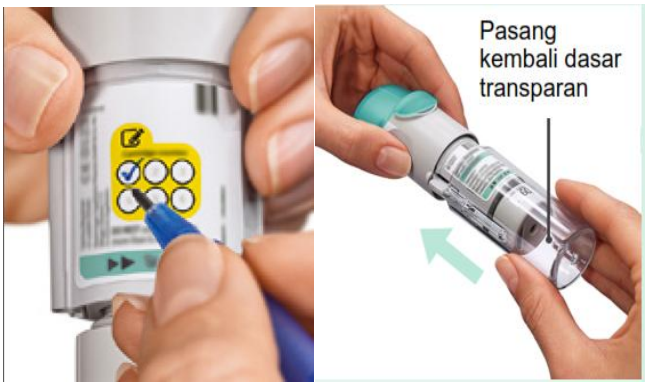
<td> 
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4. Putar

- Pastikan penutup dalam posisi tertutup.
- Putar bagian dasar sesuai arah panah yang terdapat pada label hingga terdengar bunyi klik (setengah putaran).

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5. Buka

- Buka penutup hingga terbuka seluruhnya.

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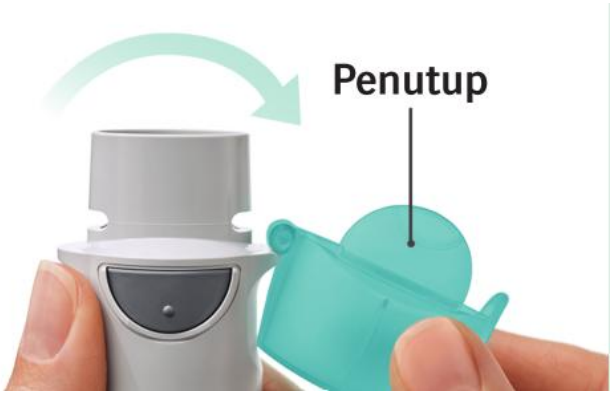
<td> 
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6. Tekan

- 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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</table>

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* SPIRIVA® RESPIMAT®

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

	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, kemudianl masukkan *cartridge*.

Apakah Anda akan mengganti *cartridge*? *Cartridge* baru akan lebih melekat dibandingkan dengan cartridge yang pertama. Masukkan sampai terdengar bunyi *click*, 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

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.