SPIRIVA RESPIMAT
Tiotropium bromide
Solution for inhalation
Full prescribing information

1. NAME OF THE MEDICINAL PRODUCT

Spiriva Respimat

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The delivered dose is 2.5 microgram tiotropium per puff (2 puffs comprise one medicinal dose) and is equivalent to 3.124 microgram tiotropium bromide monohydrate.
The delivered dose is the dose which is available for the patient after passing the mouthpiece.

Excipient with known effect: This medicine contains 0.0011 mg benzalkonium chloride in each actuation.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation solution
Clear, colourless, inhalation solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COPD
Tiotropium is indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

Asthma
Spiriva Respimat is indicated as add-on maintenance bronchodilator treatment in patients aged 6 years and older with severe asthma who experienced one or more severe asthma exacerbations in the preceding year (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Posology
The medicinal product is intended for inhalation use only. The cartridge can only be inserted and used in the Respimat inhaler (see 4.2).
Two puffs from the Respimat inhaler comprise one medicinal dose.

The recommended dose for adults is 5 microgram tiotropium given as two puffs from the Respimat inhaler once daily, at the same time of the day.

The recommended dose should not be exceeded.

In the treatment of asthma the full benefit will be apparent after several doses of the medicinal product. In adult patients with severe asthma, tiotropium should be used in addition to inhaled corticosteroids (≥ 800 µg budesonide/day or equivalent) and at least one controller.

Special populations
Geriatric patients can use tiotropium bromide at the recommended dose.
Renally impaired patients can use tiotropium bromide at the recommended dose. For patients with moderate to severe impairment (creatinine clearance ≤ 50 ml/min, see 4.4 and 5.2).

Hepatically impaired patients can use tiotropium bromide at the recommended dose (see 5.2).

Paediatric population
Asthma
The recommended dose for patients 6 to 17 years of age is 5 microgram tiotropium given as two puffs from the Respimat inhaler once daily, at the same time of the day.

In adolescents (12 - 17 years) with severe asthma, tiotropium should be used in addition to inhaled corticosteroids (> 800 - 1600 µg budesonide/day or equivalent) and one controller or in addition to inhaled corticosteroids (400 - 800 µg budesonide/day or equivalent) with two controllers.

For children (6 - 11 years) with severe asthma, tiotropium should be used in addition to inhaled corticosteroids (> 400 µg budesonide/day or equivalent) and one controller or in addition to inhaled corticosteroids (200 - 400 µg budesonide/day or equivalent) with two controllers.

The safety and efficacy of Spiriva Respimat in children aged 6 - 17 years with moderate asthma has not been established.The safety and efficacy of Spiriva Respimat in children below 6 years of age has not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

COPD
There is no relevant use of Spiriva Respimat in children and adolescents below 18 years

Cystic fibrosis
The efficacy and safety of Spiriva Respimat has not been established (see sections 4.4 and 5.1).

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 professionals.

Instructions for Use

Introduction

Read these Instructions for Use before you start using Spiriva Respimat. Children should use Spiriva Respimat with an adult's assistance.

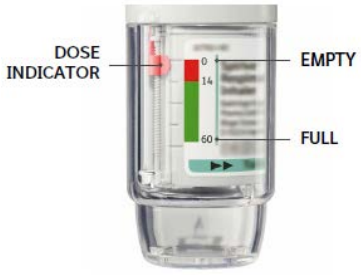
The patient will need to use this inhaler only ONCE A DAY. Each time used take TWO PUFFS.

- 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 under 'Prepare for use' until a cloud is visible. Then repeat steps 4 to 6 three more times.

How to care for Spiriva Respimat

Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.
Any minor discoloration in the mouthpiece does not affect Spiriva Respimat inhaler performance.
If necessary, wipe the outside of Spiriva Respimat inhaler with a damp cloth.

When to get a new Spiriva Respimat



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

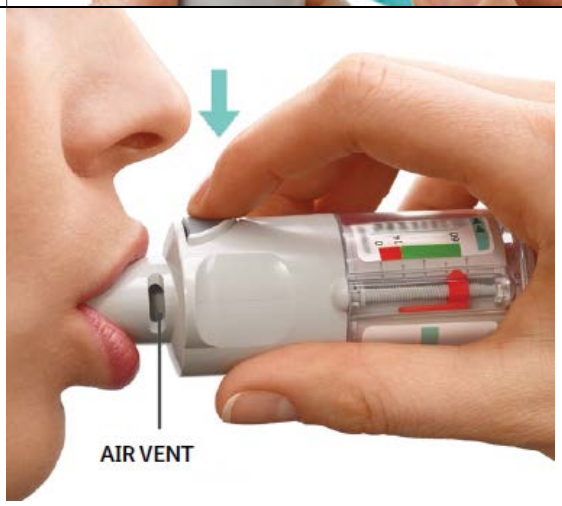
Prepare for first use

1. Remove clear base • Keep the cap closed. • Press the safety catch while pulling off the clear base with the other hand.	
2. Insert cartridge • Insert thenarrow end of the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it clicks into place. • Do not remove the cartridge once it has been inserted into the inhaler.	

3. Replace clear base • Put the clear base back into place until it clicks. • Do not remove the clear base again.	

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. • **After a cloud is visible**, repeat steps 4-6 three more times. The 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 the lips around the mouthpiece without covering the air vents. Point the inhaler to the back of the throat. • While taking a slow, deep breath through the mouth, **PRESS** the dose-release button and continue to breathe in slowly for as long as comfortable. • Hold the breath for 10 seconds or for as long as comfortable. • Repeat **TURN, OPEN, PRESS** for a total of 2 puffs. • Close the cap until the inhaler is used again.	

4.3 Contraindications

Hypersensitivity to tiotropium bromide or to any of the excipients listed in section 6.1 or to atropine or its derivatives, e.g. ipratropium or oxitropium.

4.4 Special warnings and precautions for use

Excipients

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

Tiotropium bromide, 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 monotherapy for asthma. Asthma patients must be advised to continue taking anti-inflammatory therapy, i.e. inhaled corticosteroids, unchanged after the introduction of Spiriva Respimat, even when their symptoms improve.

Immediate hypersensitivity reactions may occur after administration of tiotropium bromide inhalation solution.

Consistent with its anticholinergic activity, tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Inhaled medicines may cause inhalation-induced bronchospasm.

Tiotropium should be used with caution in patients with recent myocardial infarction < 6 months; any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalisation of heart failure (NYHA Class III or IV) within the past year. These patients were excluded from the clinical trials and these conditions may be affected by the anticholinergic mechanism of action.

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

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

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

Tiotropium bromide should not be used more frequently than once daily (see 4.9).

Spiriva Respimat is not recommended in cystic fibrosis (CF). If used in patients with CF, Spiriva Respimat may increase the signs and symptoms of CF (e.g. serious adverse events, pulmonary exacerbations, respiratory tract infections).

4.5 Interaction with other medicinal products and other forms of interaction

Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs commonly used in the treatment of COPD and asthma, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leukotriene modifiers, cromones, anti-IgE treatment without clinical evidence of drug interactions.

Use of LABA or ICS was not found to alter the exposure to tiotropium.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a very limited amount of data from the use of tiotropium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (see 5.3). As a precautionary measure, it is preferable to avoid the use of Spiriva Respimat during pregnancy.

Breastfeeding
It is unknown whether tiotropium bromide is excreted in human breast milk. Despite studies in rodents which have demonstrated that excretion of tiotropium bromide in breast milk occurs only in small amounts, use of Spiriva Respimat is not recommended during breast-feeding. Tiotropium bromide is a long-acting compound. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Spiriva Respimat should be made taking into account the benefit of breast-feeding to the child and the benefit of Spiriva Respimat therapy to the woman.

Fertility
Clinical data on fertility are not available for tiotropium. A non-clinical study performed with tiotropium showed no indication of any adverse effect on fertility (see 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Many of the listed undesirable effects can be assigned to the anticholinergic properties of tiotropium bromide.

Tabulated summary of adverse reactions
The frequencies assigned to the undesirable effects listed below are based on crude incidence rates of adverse drug reactions (i.e. events attributed to tiotropium) observed in the tiotropium group pooled from 7 placebo-controlled clinical trials in COPD (3,282 patients) and 12 placebo-controlled clinical trials in adult and paediatric patients with asthma (1,930 patients) with treatment periods ranging from four weeks to one year.

Frequency is defined using the following convention:
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)

COPD:

System Organ Class / MedDRA Preferred Term	**Frequency COPD**
Metabolism and nutrition disorders	
Dehydration	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Insomnia	Rare

System Organ Class / MedDRA Preferred Term	**Frequency COPD**
Eye disorders	
Glaucoma	Rare
Intraocular pressure increased	Rare
Vision blurred	Rare
Cardiac disorders	
Atrial fibrillation	Rare
Palpitations	Rare
Supraventricular tachycardia	Rare
Tachycardia	Rare
Respiratory, thoracic and mediastinal disorders	
Cough	Uncommon
Pharyngitis	Uncommon
Dysphonia	Uncommon
Epistaxis	Rare
Bronchospasm	Rare
Laryngitis	Rare
Sinusitis	Not known
Gastrointestinal disorders	
Dry Mouth	Common
Constipation	Uncommon
Oropharyngeal candidiasis	Uncommon
Dysphagia	Rare
Gastrooesophageal reflux disease	Rare
Dental caries	Rare
Gingivitis	Rare
Glossitis	Rare
Stomatitis	Not known
Intestinal obstruction, including ileus paralytic	Not known
Nausea	Not known
Skin and subcutaneous tissue disorders, immune system disorders	
Rash	Uncommon
Pruritus	Uncommon
Angioneurotic oedema	Rare
Urticaria	Rare
Skin infection/skin ulcer	Rare
Dry skin	Rare
Hypersensitivity (including immediate reactions)	Not known
Anaphylactic reaction	Not known
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known
Renal and urinary disorders	
Urinary retention	Uncommon
Dysuria	Uncommon
Urinary tract infection	Rare

Asthma:

System Organ Class / MedDRA Preferred Term	**Frequency Asthma**
Metabolism and nutrition disorders	
Dehydration	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Insomnia	Uncommon
Eye disorders	
Glaucoma	Not known
Intraocular pressure increased	Not known
Vision blurred	Not known
Cardiac disorders	
Atrial fibrillation	Not known
Palpitations	Uncommon
Supraventricular tachycardia	Not known
Tachycardia	Not known
Respiratory, thoracic and mediastinal disorders	
Cough	Uncommon
Pharyngitis	Uncommon
Dysphonia	Uncommon
Epistaxis	Rare
Bronchospasm	Uncommon
Laryngitis	Not known
Sinusitis	Not known
Gastrointestinal disorders	
Dry Mouth	Uncommon
Constipation	Rare
Oropharyngeal candidiasis	Uncommon
Dysphagia	Not known
Gastrooesophageal reflux disease	Not known
Dental caries	Not known
Gingivitis	Rare
Glossitis	Not known
Stomatitis	Rare
Intestinal obstruction, including ileus paralytic	Not known
Nausea	Not known
Skin and subcutaneous tissue disorders, immune system disorders	
Rash	Uncommon
Pruritus	Rare
Angioneurotic oedema	Rare
Urticaria	Rare
Skin infection/skin ulcer	Not known

System Organ Class / MedDRA Preferred Term	**Frequency Asthma**
Dry skin	Not known
Hypersensitivity (including immediate reactions)	Rare
Anaphylactic reaction	Not known
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known
Renal and urinary disorders	
Urinary retention	Not known
Dysuria	Not known
Urinary tract infection	Rare

Description of selected adverse reactions
In controlled clinical studies in COPD, the commonly observed undesirable effects were anticholinergic undesirable effects such as dry mouth which occurred in approximately 2.9 % of patients. In asthma the incidence of dry mouth was 0.83%.

In 7 clinical trials in COPD, dry mouth led to discontinuation in 3 of 3,282 tiotropium treated patients (0.1 %). No discontinuations due to dry mouth were reported in 12 clinical trials in asthma (1,930 patients).

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

Paediatric population
The safety database includes 560 paediatric patients (296 patients aged 1 to 11 and 264 patients aged 12 to 17) from 5 placebo-controlled clinical trials with treatment periods ranging between 12 weeks to one year. The frequency, type and severity of adverse reactions in the paediatric popuation are similar as in adults.

Other special population
An increase in anticholinergic effects may occur with increasing age.

Reporting of suspected adverse reactions
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il)

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Tiotropium bromide is a long-acting, specific antagonist at muscarinic receptors. It has similar affinity to the subtypes, M_1 to M_5. In the airways, tiotropium bromide competitively and reversibly binds to the M_3 receptors in the bronchial smooth musculature, antagonising the cholinergic (bronchoconstrictive) effects of acetylcholine, resulting in bronchial smooth muscle relaxation. The effect was dose dependent and lasted longer than 24h. As an N-quaternary anticholinergic, tiotropium bromide is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before systemic anticholinergic effects may occur.

Pharmacodynamic effects
The dissociation of tiotropium from especially M_3-receptors is very slow, exhibiting a significantly longer dissociation half-life than ipratropium. 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, very slow receptor dissociation and topical inhaled selectivity found its clinical correlate in significant and long-acting bronchodilation in patients with COPD and asthma.

Clinical efficacy and safety in COPD
The clinical Phase III development programme 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
Tiotropium inhalation solution, 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 (FEV_1 mean improvement at 30 minutes: 0.113 litres; 95% confidence interval (CI): 0.102 to 0.125 litres, $p< 0.0001$). Improvement of lung function was maintained for 24 hours at steady state compared to placebo (FEV_1 mean improvement: 0.122 litres; 95% CI: 0.106 to 0.138 litres, $p< 0.0001$).
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 compared to placebo (PEFR mean improvement: mean improvement in the morning 22 L/min; 95% CI: 18 to 55 L/min, $p< 0.0001$; evening 26 L/min; 95% CI: 23 to 30 L/min, $p<0.0001$). The use of Spiriva Respimat resulted in a reduction of rescue bronchodilator use compared to placebo (mean reduction in rescue use 0.66 occasions per day, 95% CI: 0.51 to 0.81 occasions per day, $p<0.0001$).

The bronchodilator effects of Spiriva Respimat were maintained throughout the 1-year period of administration with no evidence of tolerance.

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

Dyspnoea
Spiriva Respimat significantly improved dyspnoea (as evaluated using the Transition Dyspnoea Index) compared to placebo (mean improvement 1.05 units; 95% CI: 0.73 to 1.38 units, p<0.0001). An improvement was maintained throughout the treatment period.

Health-related Quality of Life
The improvement in mean total score of patient's evaluation of their Quality of Life (as measured using the St. George's Respiratory Questionnaire) between Spiriva Respimat versus placebo at the end of the two 1-year studies was 3.5 units (95% CI: 2.1 to 4.9, p<0.0001). A 4-unit decrease is considered clinically relevant.

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			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]
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			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.

Long-term tiotropium active- controlled study

A long-term large scale randomised, double-blind, active-controlled study with an observation 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; 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 numerically 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 FEV1 for Spiriva Respimat versus Spiriva HandiHaler was -0.010 L (95% CI -0.038 to 0.018 L).
In the post-marketing TIOSPIR study comparing Spiriva Respimat and Spiriva HandiHaler, all-cause mortality (including vital status follow up) was similar with hazard ratio (Spiriva Respimat/Spiriva HandiHaler) = 0.96 , 95% CI 0.84 -1.09). Respective treatment exposure was 13,135 and 13,050 patient-years.
In the placebo-controlled studies with vital status follow-up to the end of the intended treatment period, Spiriva Respimat showed a numerical increase in all-cause mortality compared to placebo (rate ratio (95% confidence interval) of 1.33 (0.93, 1.92) with treatment exposure to Spiriva Respimat of 2,574 patient years; the excess in mortality was observed in patients with known rhythm disorders. Spiriva HandiHaler showed a 13 % reduction in the risk of death ((hazard ratio including vital status follow-up (tiotropium/placebo) = 0.87; 95% CI, 0.76 to 0.99)). Treatment exposure to Spiriva HandiHaler was 10,927 patient-years. No excess mortality risk was observed in the subgroup of patients with known rhythm disorders in the placebo controlled Spiriva HandiHaler study as well as in the TIOSPIR Spiriva Respimat to HandiHaler comparison.

Clinical efficacy and safety in asthma

The clinical Phase III programme for persistent asthma in adults included two 1-year randomised, double-blind, placebo-controlled studies in a total of 907 asthma patients (453 receiving Spiriva Respimat) on a combination of ICS (≥800 µg budesonide/day or equivalent) with a LABA. The studies included lung function measurements and severe exacerbations as primary endpoints.

PrimoTinA-asthma studies
In the two 1-year studies in patients who were symptomatic on maintenance treatment of at least ICS (≥800 µg budesonide/day or equivalent) plus LABA, Spiriva Respimat showed clinically relevant improvements in lung function 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.

In the PrimoTinA-asthma studies, treatment of symptomatic patients (N=453) with ICS plus LABA plus tiotropium reduced the risk of severe asthma exacerbations by 21% as compared to treatment of symptomatic patients (N=454) with ICS plus LABA plus placebo. The risk reduction in the mean number of severe asthma exacerbations/patient year was 20%.

This was supported by a reduction of 31% in risk for asthma worsening and 24% risk reduction in the mean number of asthma worsenings/patient year (see Table 2).

Table 2: Exacerbations in Patients Symptomatic on ICS (≥800 µg budesonide/day or equivalent) plus LABA (PrimoTinA-asthma studies)

Study	Endpoint	Spiriva Respimat, added-on to at least ICS[a]/LABA (N=453)	Placebo, added-on to at least ICS[a]/LABA (N=454)	% Risk Reduction (95% CI)	p-value
two 1-year Phase III studies, pooled analysis	Days to 1st severe asthma exacerbation	282[c]	226[c]	21[b] (0, 38)	0.0343
	Mean number of severe asthma exacerbations/ patient year	0.530	0.663	20[d] (0, 36)	0.0458
	Days to 1st worsening of asthma	315[c]	181[c]	31[b] (18, 42)	<0.0001
	Mean number of asthma worsenings/ patient year	2.145	2.835	24[d] (9, 37)	0.0031

[a] ≥800 µg budesonide/day or equivalent

[b] Hazard ratio, confidence interval and p-value obtained from a Cox proportional hazards model with only treatment as effect. The percentage risk reduction is 100(1 - hazard ratio).

[c] Time to first event: days on treatment by when 25%/50% of patients had at least one severe asthma exacerbation/worsening of asthma

[d] The rate ratio was obtained from a Poisson regression with log exposure (in years) as offset. The percentage risk reduction is 100 (1-rate ratio).

Paediatric population

Asthma

All studies in the clinical Phase III program for persistent asthma in paediatric patients (1 - 17 years) were randomised, double-blind and placebo-controlled. All patients were on background treatments that include an ICS.

Severe Asthma

Adolescents (12 - 17 years)

In the 12-week PensieTinA-asthma study a total of 392 patients (130 receiving Spiriva Respimat) who were symptomatic on a high dose of ICS with one controller or a medium dose of ICS with 2 controllers were included.

For patients aged 12 - 17 years, a high dose ICS was defined as a dose of > 800 - 1600 µg budesonide/day or equivalent; a medium dose ICS as 400 - 800 µg budesonide/day or equivalent. In addition, patients aged 12 - 14 years could receive an ICS dose > 400 µg budesonide/day or equivalent and at least one controller or ≥ 200 µg budesonide/day or equivalent and at least two controllers.

In this study, 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.
- 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 12-week VivaTinA-asthma study a total 400 patients (130 receiving Spiriva Respimat) who were symptomatic on a high dose ICS with one controller or a medium dose ICS with 2 controllers were included. A high dose ICS was defined by a dose of > 400 µg budesonide/day or equivalent, a medium dose as 200 - 400 µg budesonide/day or equivalent.
In this study, 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 FEV_1 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.

Moderate Asthma
Adolescents (12 - 17 years)
In the 1-year RubaTinA-asthma study in a total of 397 patients (134 receiving Spiriva Respimat) who were symptomatic on a medium dose ICS (200 - 800 µg budesonide/day or equivalent for patients aged 12 - 14 years or 400 - 800 µg budesonide/day or equivalent for patients aged 15 - 17 years), Spiriva Respimat showed significant improvements in lung function over placebo when used as add-on to background treatment.

Children (6 - 11 years)
In the 1-year CanoTinA-asthma study in a total of 401 patients (135 receiving Spiriva Respimat) who were symptomatic on a medium dose ICS (200 - 400 µg budesonide/day or equivalent), Spiriva Respimat showed significant improvements in lung function over placebo when used as add-on to background treatment.

5.2 Pharmacokinetic properties

a) General Introduction

Tiotropium bromide is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium bromide is available as inhalation solution 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 than recommended for therapy.

b) General Characteristics of the Active Substance after Administration of the Medicinal Product

Absorption: Following inhalation by young healthy volunteers, urinary excretion data suggests that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium bromide have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of this quaternary ammonium compound.
Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation.

At steady state, peak tiotropium plasma levels in COPD patients of 10.5 pg/ml were achieved 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.
Systemic exposure to tiotropium following the inhalation of tiotropium via the Respimat inhaler was similar to tiotropium inhaled via the HandiHaler device.

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 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. The ester tiotropium bromide is nonenzymatically cleaved to the alcohol (N-methylscopine) and acid compound (dithienylglycolic acid) that are inactive on 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 (CYP) dependent oxidation and subsequent glutathion conjugation to a variety of Phase II-metabolites.
In vitro studies in liver microsomes reveal that the enzymatic pathway can be inhibited by the CYP 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP 2D6 and 3A4 are involved in 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 CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination: The effective half-life of tiotropium ranges between 27 - 45 h following inhalation by healthy volunteers and 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 is mainly excreted unchanged in urine (74%).
After inhalation of the solution by COPD patients to steady-state, 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. After inhalation of the solution by healthy volunteers urinary excretion is 20.1-29.4 % 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 by COPD patients, 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.

c) Characteristics in Patients

Geriatric Patients: As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (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.

Renally Impaired Patients: Following once daily inhaled administrations of tiotropium to steady-state in COPD patients, mild renal impairment (CL_{CR} 50 - 80 ml/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 1.8 - 30% higher) and similar $C_{max,ss}$ values compared to patients with normal renal function(CL_{CR} >80 ml/min).

In COPD patients with moderate to severe renal impairment (CL_{CR} < 50 ml/min), the intravenous administration of a single dose of tiotropium 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 (CL_{CR} 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 pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and simple non-enzymatic ester cleavage to pharmacologically inactive products.

Japanese COPD Patients: In cross trial comparison, mean peak tiotropium plasma concentrations 10 minutes post-dosing at steady-state were 20% to 70% higher in Japanese compared to Caucasian COPD patients following inhalation of tiotropium but there was no signal for higher mortality or cardiac risk in Japanese patients compared to Caucasian patients. Insufficient pharmacokinetic data is available for other ethnicities or races.

Paediatric Patients:
Asthma
The peak and total (AUC and urinary excretion) exposure to tiotropium is comparable between patients with asthma who were 6 - 11 years old, 12 - 17 years old and ≥18 years old. Based on urinary excretion, the total exposure to tiotropium in patients 1 to 5 years of age was 52 to 60% lower than in other older age groups. The total exposure data when adjusted for body surface area were found to be comparable in all age groups. Spiriva Respimat was administered with a valved holding chamber with face mask in patients 1 to 5 years of age.

COPD
There were no paediatric patients in the COPD programme (see 4.2).

Cystic Fibrosis
Following inhalation of 5 µg tiotropium, the tiotropium plasma level in CF patients ≥5 years was 10.1 pg/ml 5 minutes post-dosing at steady-state and decreased rapidly thereafter. The fraction of the dose available in CF patients <5 years old who used the spacer and mask was approximately 3- to 4-fold lower than that observed in CF patients 5 years and older. Tiotropium exposure was related to body-weight in CF patients <5 years.

d) Pharmacokinetic / Pharmacodynamic Relationship(s)

There is no direct relationship between pharmacokinetics and pharmacodynamics.

5.3 Preclinical safety data

Many effects observed in conventional studies of safety pharmacology, repeat-dose toxicity, and reproductive toxicity could be explained by the anticholinergic properties of tiotropium bromide. Typically in animals reduced food consumption, inhibited body weight gain, dry mouth and nose, reduced lacrimation and salivation, mydriasis and increased heart rate were observed. Other relevant effects noted in repeated dose toxicity studies were: mild irritancy of the respiratory tract in rats and mice evinced by rhinitis and epithelial changes of the nasal cavity and larynx, and prostatitis along with proteinaceous deposits and lithiasis in the bladder in rats.

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.

Harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. Tiotropium bromide was not teratogenic in rats or rabbits. 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.
The respiratory (irritation) and urogenital (prostatitis) changes and reproductive toxicity was observed at local or systemic exposures more than five-fold the therapeutic exposure. Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Water, purified
Hydrochloric acid 3.6 % (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.In-use shelf life: 3 months

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Type and material of the container in contact with the medicinal product:
Solution filled into a polyethylene/polypropylene cartridge with a polypropylene cap with integrated silicone sealing ring. The cartridge is enclosed within an aluminium cylinder.

Pack sizes and devices supplied:

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

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION NUMBER(S)

154-11-34255-00

8. MANUFACTURER

Boehringer Ingelheim Pharma GmbH & Co. KG
Ingelheim/Rhein, Germany

9. MARKETING AUTHORISATION HOLDER

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This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved in July 2019.