Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Spiriva Respimat 2.5 microgram Solution for Inhalation

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.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Inhalation

Product imported from France:
Clear, colourless, solution for inhalation

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

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.

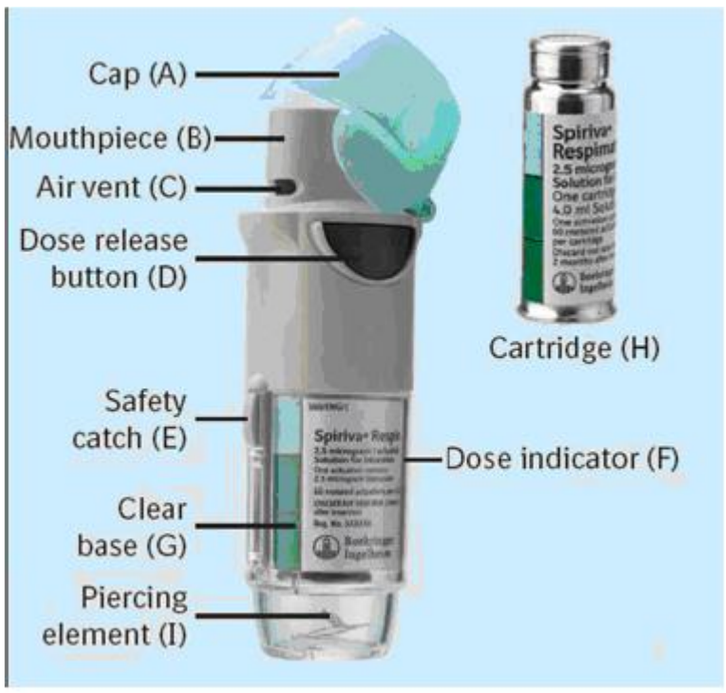
The recommended dose should not be exceeded.

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 patients:
Spiriva Respimat is not recommended for use in children and adolescents below 18 years due to lack of data on safety and efficacy (see 5.1 and 5.2).

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.

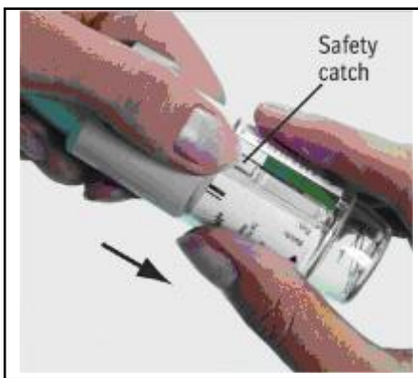
Patient's instructions for use and handling

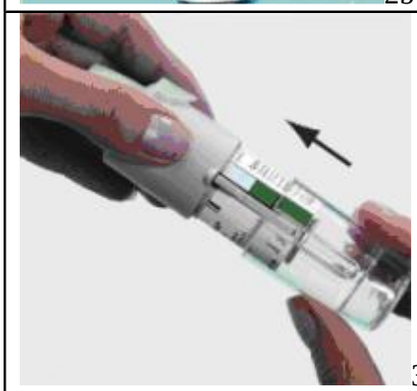


Spiriva Respimat inhaler and Spiriva Respimat cartridge

Inserting the cartridge and preparation for use

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

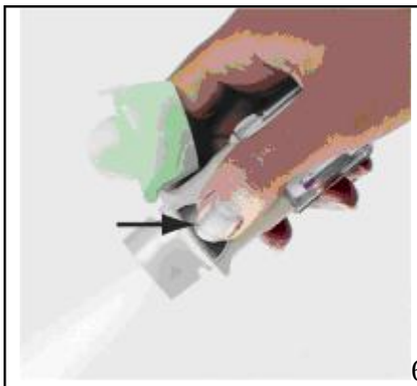
	**1** With the green cap (A) closed, press the safety catch (E) and pull off the clear base (G).

 2a  2b	**2** Take the cartridge (H) out of the box. Push the **narrow** end of the cartridge into the inhaler until it clicks into place. The cartridge should be pushed **gently** against a firm surface to ensure that it has gone all the way in (2b). Do not remove the cartridge once it has been inserted into the inhaler.
 3	**3** Replace the clear base (G). Do not remove the clear base again.

<u>To prepare the Spiriva Respimat inhaler for first-time use</u>

 4	**4** Hold the Spiriva Respimat inhaler upright, with the green cap (A) closed. Turn the base (G) in the direction of the red arrows on the label until it clicks (half a turn).

 5	**5** Open the green cap (A) until it snaps fully open.

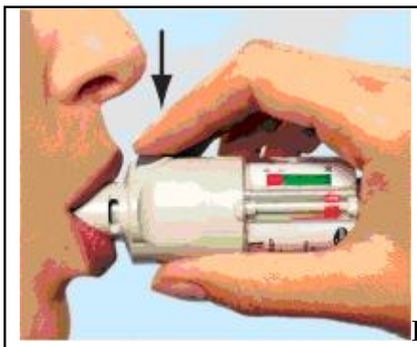
 6	**6** Point the Spiriva Respimat inhaler towards the ground. Press the dose release button (D). Close the green cap (A). **Repeat steps 4, 5 and 6 until a cloud is visible.** **Then repeat steps 4, 5 and 6 three more times to ensure the inhaler is prepared for use.** **Your Spiriva Respimat inhaler is now ready to use.** These steps will not affect the number of doses available. After preparation your Spiriva Respimat inhaler will be able to deliver your 60 puffs (30 medicinal doses).

<u>Using the Spiriva Respimat inhaler</u>

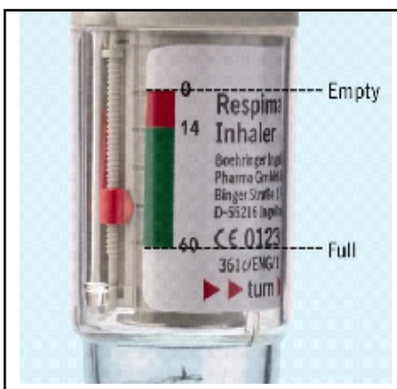
You will need to use this inhaler ONLY ONCE A DAY.

Each time you use it take TWO PUFFS.

 I	**I** Hold the Spiriva Respimat inhaler upright, with the green cap (A) closed, to avoid accidental release of dose. Turn the base (G) in the direction of the red arrows on the label until it clicks (half a turn).

 II	**II** Open the green cap (A) until it snaps fully open. Breathe out slowly and fully, and then close your lips around the end of the mouthpiece without covering the air vents (C). Point your Spiriva Respimat inhaler to the back of your throat. While taking in a slow, deep breath through your mouth, press the dose release button (D) and continue to breathe in slowly for as long as you can. Hold your breath for 10 seconds or for as long as comfortable. **III Repeat steps I and II so that you get the full dose.** **You will need to use this inhaler only ONCE A DAY.** **Close the green cap until you use your Spiriva Respimat inhaler again.** If Spiriva Respimat inhaler has not been used for more than 7 days release one puff towards the ground. If Spiriva Respimat inhaler has not been used for more than 21 days repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

When to get a new Spiriva Respimat inhaler

	The Spiriva Respimat inhaler contains 60 puffs (30 medicinal doses). The dose indicator shows approximately how much medication is left. When the pointer enters the red area of the scale, there is, approximately, medication for 7 days left (14 puffs). This is when you need to get a new Spiriva Respimat inhaler prescription. Once the dose indicator has reached the end of the red scale (i.e. all 30 doses have been used), the Spiriva Respimat inhaler is empty and locks automatically. At this point, the base cannot be turned any further. At the latest, three months after use the Spiriva Respimat inhaler should be discarded even if not all medication has been used.

How to care for your inhaler

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

4.3 Contraindications

Spiriva Respimat is contraindicated in patients with hypersensitivity to tiotropium bromide, atropine or its derivatives, e.g. ipratropium or oxitropium or to any of the excipients (see 6.1).

4.4 Special warnings and precautions for use

Tiotropium bromide, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy.

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

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.

Spiriva Respimat should be used with caution in patients with known cardiac rhythm disorders(see 5.1).

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).

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

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

For tiotropium bromide, no clinical data on exposed pregnancies are available. Animal studies have shown reproductive toxicity associated with maternal toxicity (see 5.3). The potential risk for humans is unknown. Spiriva Respimat should therefore only be used during pregnancy when clearly indicated.

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.

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

a) General description

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

b) Table of Undesirable effects according to the MedDRA terminology

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 (2,802 patients) pooled from 5 placebo-controlled clinical trials with treatment periods ranging from twelve 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).

System Organ Class / MedDRA Preferred Term	**Frequency**
Metabolism and nutrition disorders	
Dehydration	Not known*
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Insomnia	Not known*
Eye disorders	
Glaucoma	Rare
Intraocular pressure increased	Rare
Vision blurred	Rare
Cardiac disorders	
Atrial fibrillation	Uncommon
Palpitations	Uncommon
Supraventricular tachycardia	Uncommon
Tachycardia	Uncommon
Respiratory, thoracic and mediastinal disorders	
Cough	Uncommon
Epistaxis	Uncommon
Pharyngitis	Uncommon
Dysphonia	Uncommon
Bronchospasm	Rare
Laryngitis	Rare
Sinusitis	Not known*

Gastrointestinal disorders	
Dry Mouth	Common
Constipation	Uncommon
Oropharyngeal candidiasis	Uncommon
Dysphagia	Uncommon
Gastrooesophageal reflux disease	Rare
Dental caries	Rare
Gingivitis	Rare
Glossitis	Rare
Stomatitis	Rare
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*
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known*
Renal and urinary disorders	
Urinary retention	Uncommon
Dysuria	Uncommon
Urinary tract infection	Rare

* frequency not known, no adverse drug reaction observed in 2,802 patients

c) Information characterising individual serious and/or frequently occurring undesirable effects

In controlled clinical studies, the commonly observed undesirable effects were anticholinergic undesirable effects such as dry mouth which occurred in approximately 3.2% of patients. In 5 clinical trials, dry mouth led to discontinuation in 3 of 2,802 tiotropium treated patients (0.1 %). Serious undesirable effects consistent with anticholinergic effects include glaucoma, constipation, intestinal obstruction including ileus paralytic and urinary retention.

Additional information on special populations
An increase in anticholinergic effects may occur with increasing age.

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 solution for inhalation in healthy volunteers with the exception of pronounced reduction in salivary flow from day 7 onwards. No significant undesirable effects have been observed in four long term-studies in COPD patients with a daily dose of 10 microgram tiotropium solution for inhalation over 4-48 weeks.

Acute intoxication by inadvertent oral ingestion of tiotropium solution for inhalation from the cartridge is unlikely due to low oral bioavailability.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticholinergics
ATC code: R03B B04

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.

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.

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.

In the aforementioned studies, tiotropium solution for inhalation, 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.

The following health outcome effects were demonstrated in the long term 1-year studies:

(a) 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.

(b) 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.

(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			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.

In a retrospective pooled analysis of the three 1-year and one 6-month placebo-controlled trials with Spiriva Respimat including 6,096 patients a numerical increase in all-cause mortality was seen in patients treated with Spiriva Respimat (68; incidence rate (IR) 2.64 cases per 100 patient-years) compared with placebo (51, IR 1.98) showing a rate ratio (95% confidence interval) of 1.33 (0.93, 1.92) for the planned treatment period; the excess in mortality was observed in patients with known rhythm disorders.

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 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 than recommended for therapy.

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

Absorption: Following inhalation of the solution by young healthy volunteers, urinary excretion data suggest that approximately 33% of the inhaled dose reach the systemic circulation. It is expected from the chemical structure of the compound (quaternary ammonium compound) and from in-vitro experiments that tiotropium bromide is poorly absorbed from the gastrointestinal tract (10-15%). Oral solutions of tiotropium bromide have an absolute bioavailability of 2-3%. At steady state, tiotropium bromide plasma levels in COPD patients at peak were 10.5-11.7 pg/ml when measured 10 minutes after administration of a 5 microgram dose delivered by the Respimat inhaler and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.49-1.68 pg/ml. Food is not expected to influence the absorption of this quaternary ammonium compound.

Distribution: The drug is bound by 72% to plasma proteins 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. 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 terminal elimination half-life of tiotropium bromide is between 5 and 6 days following inhalation. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers with an interindividual variability of 22%. Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). After inhalation of the solution 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. The renal clearance of tiotropium bromide exceeds the creatinine clearance, indicating secretion into the urine.

Linearity / Nonlinearity: Tiotropium bromide demonstrates linear pharmacokinetics in the therapeutic range after intravenous administration, dry powder inhalation and inhalation of the solution.

c) Characteristics in Patients

Geriatric Patients: As expected for all predominantly renally excreted drugs, advanced age was associated with a decrease of tiotropium bromide renal clearance (326 ml/min in COPD patients < 58 years to 163 ml/min in COPD patients > 70years) which may be explained by decreased renal function. Tiotropium bromide excretion in urine after inhalation decreased from 14 % (young healthy volunteers) to about 7 % (COPD patients); however plasma concentrations did not change significantly with advancing age within COPD patients if compared to inter- and intraindividual variability (43 % increase in AUC_{0-4} after dry powder inhalation).

Renally Impaired Patients: In common with all other drugs that undergo predominantly renal excretion, renal impairment was associated with increased plasma drug concentrations and reduced renal drug clearance after both intravenous infusion and dry powder inhalation. Mild renal impairment (CL_{CR} 50-80 ml/min) which is often seen in elderly patients increased tiotropium bromide plasma concentrations slightly (39% increase in AUC_{0-4h} after intravenous infusion). In COPD patients with moderate to severe renal impairment (CL_{CR} < 50 ml/min) the intravenous administration of tiotropium bromide resulted in doubling of the plasma concentrations (82% increase in AUC_{0-4h}), which was confirmed by plasma concentrations after dry powder inhalation and also by inhalation of the solution via the Respimat inhaler.

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.

Paediatric Patients: See 4.2

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.

Harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. Tiotropium bromide was not teratogenic in rats or rabbits. The respiratory (irritation) and urogenital (prostatitis) changes and reproductive toxicity 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 shelf life expiry date of this product is the date shown on the cartridge and outer carton of the product as marketed in the country of origin.

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

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Profind Wholesale Ltd
Unit 625 Kilshane Avenue
Northwest Business Park
Ballycoolin
Dublin 15
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1500/043/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd September 2011.

10 DATE OF REVISION OF THE TEXT