SPIRIVA® 18 microgram, inhalation powder, hard capsule

tiotropium

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
SPIRIVA® 18 microgram, inhalation powder, hard capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 22.5 microgram tiotropium bromide monohydrate equivalent to 18 microgram tiotropium.

The delivered dose (the dose that leaves the mouthpiece of the HandiHaler® device) is 10 microgram tiotropium.

Excipient: Lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Inhalation powder, hard capsule.

Light green hard capsules with the product code TI 01 and company logo printed on the capsule.

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

Posology
The medicinal product is intended for inhalation use only.

The recommended dosage of tiotropium bromide is inhalation of the contents of one capsule once daily with the HandiHaler® device at the same time of day.

The recommended dose should not be exceeded.

Tiotropium bromide capsules are only for inhalation and not for oral intake. Tiotropium bromide capsules must not be swallowed.

Tiotropium bromide should only be inhaled with the HandiHaler® device.

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 section 4.4 and section 5.2.

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

Paediatric population

COPD

There is no relevant use in the paediatric population (below 18 years) in the indication stated under section 4.1.

Cystic fibrosis

The safety and efficacy of SPIRIVA® 18 microgram in children and adolescents has not been established. No data are available.

Method of administration

To ensure proper administration of the medicinal product the patient should be trained how to use the inhaler by the physician or by other healthcare professionals.

Instructions for handling and use

Remember to carefully follow your doctor's instructions for using SPIRIVA®. The HandiHaler® is especially designed for SPIRIVA®. You must not use it to take any other medication. You can use your HandiHaler® for up to one year to take your medication.

The HandiHaler®

1 Dust cap
2 Mouthpiece
3 Base
4 Piercing button
5 Centre chamber

1. To release the dust cap press the piercing button completely in and let go.
2. Open the dust cap completely by pulling it upwards. Then open the mouthpiece by pulling it upwards.

3. Remove a SPIRIVA® capsule from the blister (only immediately before use) and place it in the centre chamber (5), as illustrated. It does not matter which way the capsule is placed in the chamber.

4. Close the mouthpiece firmly until you hear a click, leaving the dust cap open.

5. Hold the HandiHaler® device with the mouthpiece upwards and press the piercing button completely in only once, and release. This makes holes in the capsule and allows the medication to be released when you breathe in.

6. Breathe out completely. Important: Please avoid breathing into the mouthpiece at any time.
7. Raise the HandiHaler® to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position and breathe in slowly and deeply but at a rate sufficient to hear or feel the capsule vibrate. Breathe in until your lungs are full; then hold your breath as long as comfortable and at the same time take the HandiHaler® out of your mouth. Resume normal breathing. Repeat steps 6 and 7 once, in order to empty the capsule completely.

8. Open the mouthpiece again. Tip out the used capsule and dispose. Close the mouthpiece and dust cap for storage of your HandiHaler® device.

Clean the HandiHaler® once a month. Open the dust cap and mouthpiece. Then open the base by lifting the piercing button. Rinse the complete inhaler with warm water to remove any powder. Dry the HandiHaler® thoroughly by tipping excess of water out on a paper towel and air-dry afterwards, leaving the dust cap, mouthpiece and base open. It takes 24 hours to air-dry, so clean it right after you used it and it will be ready for your next dose. If needed, the outside of the mouthpiece may be cleaned with a moist but not wet tissue.

A. Separate the blister strips by tearing along the perforation.
B. Peel back foil (only immediately before use) using the tab until one capsule is fully visible. In case a second capsule is exposed to air inadvertently this capsule has to be discarded.

C. Remove capsule.

SPIRIVA® capsules contain only a small amount of powder so that the capsule is only partially filled.

4.3 Contraindications
Tiotropium bromide inhalation powder is contraindicated in patients with a hypersensitivity to tiotropium bromide, atropine or its derivatives, e.g. ipratropium or oxitropium or to the excipient lactose monohydrate which contains milk protein.

4.4 Special Warnings and Special 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 inhalation powder.

Consistent with its anticholinergic activity, tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction (see section 4.8).

Inhaled medicines may cause inhalation-induced bronchospasm.

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 section 5.2).

Patients should be cautioned to avoid getting the drug powder 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 section 4.9).

SPIRIVA® capsules contain 5.5 mg lactose monohydrate.

4.5 Interaction with other medicinal products and other forms of interaction
Although no formal drug interaction studies have been performed, tiotropium bromide inhalation powder has been used concomitantly with other drugs without clinical evidence of drug interactions. These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, commonly used in the treatment of COPD.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
For tiotropium bromide, no documented clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity associated with maternal toxicity (see section 5.3). The potential risk for humans is unknown. SPIRIVA® should therefore only be used during pregnancy when clearly indicated.

Breast-feeding
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® 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® should be made taking into account the benefit of breast-feeding to the child and the benefit of SPIRIVA® 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 section 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, blurred vision, or headache 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 SPIRIVA®.
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 (9,647 patients) from 28 pooled placebo-controlled clinical trials with treatment periods ranging from four weeks to four years.

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)

<table>
<thead>
<tr>
<th>System Organ Class/MedDRA Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Taste disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Rare</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Rare</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>Rare</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>Rare</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Rare</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Rare</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cough</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Rare</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Rare</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>Rare</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrooesophageal reflux disease</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Constipation</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Oropharyngeal candidiasis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Intestinal obstruction, including ileus paralytic</td>
<td>Rare</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>Rare</td>
</tr>
<tr>
<td>Glossitis</td>
<td>Rare</td>
</tr>
</tbody>
</table>
### Description of selected adverse reactions

In controlled clinical studies, the commonly observed undesirable effects were anticholinergic undesirable effects such as dry mouth which occurred in approximately 4% of patients.

In 28 clinical trials, dry mouth led to discontinuation in 18 of 9,647 tiotropium treated patients (0.2%).

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

**Other special population**

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, were observed following 7-day dosing of up to 170 microgram tiotropium bromide in healthy volunteers.

In a multiple dose study in COPD patients with a maximum daily dose of 43 microgram tiotropium bromide over four weeks no significant undesirable effects have been observed.

Acute intoxication by inadvertent oral ingestion of tiotropium bromide capsules is unlikely due to low oral bioavailability.
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, muscarinic receptor antagonist, in clinical medicine often called an anticholinergic. By binding to the muscarinic receptors in the bronchial smooth musculature, tiotropium bromide inhibits the cholinergic (bronchoconstrictive) effects of acetylcholine, released from parasympathetic nerve endings. It has similar affinity to the subtypes of muscarinic receptors, M₁ to M₅. In the airways, tiotropium bromide competitively and reversibly antagonises the M₃ receptors, resulting in relaxation. The effect was dose dependent and lasted longer than 24h. The long duration is probably due to the very slow dissociation from the M₃ receptor, exhibiting a significantly longer dissociation half-life than ipratropium. 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 bronchodilation is primarily a local effect (on the airways), not a systemic one. 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.

Cardiac electrophysiology
Electrophysiology: In a dedicated QT study involving 53 healthy volunteers, SPIRIVA® 18 mcg and 54 mcg (i.e. three times the therapeutic dose) over 12 days did not significantly prolong QT intervals of the ECG.

Clinical efficacy
The clinical development programme included four one-year and two six-month randomised, double-blind studies in 2663 patients (1308 receiving tiotropium bromide). The one-year programme consisted of two placebo-controlled trials and two trials with an active control (ipratropium). The two six-month trials were both salmeterol and placebo controlled. These studies included lung function and health outcome measures of dyspnea, exacerbations and health-related quality of life.

In the aforementioned studies, tiotropium bromide, administered once daily, provided significant improvement in lung function (forced expiratory volume in one second, FEV₁, and forced vital capacity, FVC) within 30 minutes following the first dose which was maintained for 24 hours. Pharmacodynamic steady state was reached within one week with the majority of bronchodilation observed by the third day. Tiotropium bromide significantly improved morning and evening PEFR (peak expiratory flow rate) as measured by patient's daily recordings. The bronchodilator effects of tiotropium bromide were maintained throughout the one-year period of administration with no evidence of tolerance.

A randomised, placebo-controlled clinical study in 105 COPD patients demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo regardless of whether the drug was administered in the morning or in the evening.

The following health outcome effect was demonstrated in the long-term (6-month and one-year) trials:

Tiotropium bromide significantly improved dyspnoea (as evaluated using the Transition Dyspnoea Index). This improvement was maintained throughout the treatment period.
The impact of improvements in dyspnoea on exercise tolerance was investigated in two randomised, double-blind, placebo-controlled trials in 433 patients with moderate to severe COPD. In these trials, six weeks of treatment with SPIRIVA® significantly improved symptom-limited exercise endurance time during cycle ergometry at 75% of maximal work capacity by 19.7% (Trial A: 640 seconds with SPIRIVA® vs. 535 seconds with placebo, compared with a pre-treatment baseline of 492 seconds) and 28.3% (Trial B: 741 seconds with SPIRIVA® vs. 577 seconds with placebo, compared with a pre-treatment baseline of 537 seconds).

In a randomised, double-blind, placebo-controlled trial of 1,829 patients with moderate to very severe COPD, tiotropium bromide statistically significantly reduced the proportion of patients who experienced exacerbations of COPD (32.2% to 27.8%) and statistically significantly reduced the number of exacerbations by 19% (1.05 to 0.85 events per patient year of exposure). In addition, 7.0% of patients in the tiotropium bromide group and 9.5% of patients in the placebo group were hospitalised due to a COPD exacerbation (p=0.056). The number of hospitalisations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure).

In a 9-month, randomised, double-blind, placebo-controlled clinical trial of 492 patients, SPIRIVA® improved health-related quality of life as determined by the St. George's Respiratory Questionnaire (SGRQ) total score. The proportion of patients treated with SPIRIVA® which achieved a meaningful improvement in the SGRQ total score (i.e. > 4 units) was 10.9% higher compared with placebo (59.1% in the SPIRIVA® groups vs. 48.2% in the placebo group (p=0.029). The mean difference between the groups was 4.19 units (p=0.001; confidence interval: 1.69 – 6.68). The improvements of the subdomains of the SGRQ score were 8.19 units for “symptoms”, 3.91 units for “activity” and 3.61 units for “impact on daily life”. The improvements of all of these separate subdomains were statistically significant.

In a 4-year, randomised, double-blind, placebo-controlled clinical trial of 5,993 randomised patients (3,006 receiving placebo and 2,987 receiving SPIRIVA®), the improvement in FEV1, resulting from SPIRIVA®, compared with placebo, remained constant throughout 4 years. A higher proportion of patients completed ≥ 45 months of treatment in the SPIRIVA® group compared with the placebo group (63.8% vs. 55.4%, p<0.001). The annualized rate of decline of FEV1, compared to placebo was similar between SPIRIVA® and placebo. During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97). Treatment with tiotropium reduced the risk of respiratory failure (as recorded through adverse event reporting) by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 0.999).

A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 microgram of SPIRIVA® once daily with that of 50 microgram of salmeterol HFA pMDI twice daily on the incidence of moderate and severe exacerbations in 7,376 patients with COPD and a history of exacerbations in the preceding year.
Table 1: Summary of exacerbation endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SPIRIVA® 18 microgram (HandiHaler®) N = 3,707</th>
<th>Salmeterol 50 microgram (HFA pMDI) N = 3,669</th>
<th>Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time [days] to first exacerbation†</td>
<td>187</td>
<td>145</td>
<td>0.83 (0.77 - 0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to first severe (hospitalised) exacerbation‡</td>
<td>–</td>
<td>–</td>
<td>0.72 (0.61 - 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with ≥1 exacerbation, n (%)*</td>
<td>1,277 (34.4)</td>
<td>1,414 (38.5)</td>
<td>0.90 (0.85 - 0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with ≥1 severe (hospitalised) exacerbation, n (%)*</td>
<td>262 (7.1)</td>
<td>336 (9.2)</td>
<td>0.77 (0.66 - 0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

† Time [days] refers to 1st quartile of patients. Time to event analysis was done using Cox’s proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio.
‡ Time to event analysis was done using Cox’s proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio. Time [days] for the 1st quartile of patients cannot be calculated, because proportion of patients with severe exacerbation is too low.
* Number of patients with event were analysed using Cochran-Mantel-Haenszel test stratified by pooled centre; ratio refers to risk ratio.

Compared with salmeterol, SPIRIVA® increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001). SPIRIVA® also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001).

Paediatric population
The European Medicines Agency has waived the obligation to submit results of studies with SPIRIVA® in all subsets of the paediatric population in COPD and cystic fibrosis (see section 4.2 for information on paediatric use).

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 administered by dry powder inhalation. Generally with the inhaled route of administration, the majority of the delivered dose is deposited in the gastro intestinal tract, and to a lesser extent in the intended organ of the lung. Many 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 dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. 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%. Maximum tiotropium bromide plasma concentrations were observed five minutes after inhalation. 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. At steady state, tiotropium bromide plasma levels in COPD patients at peak were 17 – 19 pg/ml when measured 5 minutes after dry powder inhalation of an 18-microgram dose and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 3-4 pg/ml. 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 non-enzymatically 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 (120% of dose after intravenous administration) is metabolised by cytochrome P450 (CYP) dependent oxidation and subsequent glutathione 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 dry powder inhalation urinary excretion is 14% 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. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2-3 weeks with no accumulation thereafter.

Linearity / Non-linearity: Tiotropium bromide demonstrates linear pharmacokinetics in the therapeutic range after both intravenous administration and dry powder inhalation.

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 > 70 years) which may be explained by decreased renal function. Tiotropium bromide excretion in urine after inhalation decreased from 14% 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. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2-3 weeks with no accumulation thereafter.

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 inhalations. Mild renal impairment (CLCR 50-80 ml/min) which is often seen in elderly patients increased tiotropium bromide plasma concentrations slightly (39% increase in AUC0-4h after intravenous infusion). In COPD patients with moderate to severe renal impairment (CLCR < 50 ml/min) the intravenous administration of tiotropium bromide resulted in doubling of the plasma concentrations (82% increase in AUC0-4h), which was confirmed by plasma concentrations after dry powder inhalation.

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

Paediatric Patients: See section 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, repeated 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. 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 were 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
Lactose monohydrate (which contains milk protein)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years
After first opening of the blister: 9 days
Discard the HandiHaler® device 12 months after first use.

6.4 Special precautions for storage
Do not store above 25˚C
Do not freeze.

6.5 Nature and contents of Container
Aluminium / PVC / Aluminium blister strips containing 10 capsules

The HandiHaler® is a single-dose inhalation device made from plastic materials (ABS) and stainless steel.

Package sizes and devices supplied:
- Cardboard box containing 30 capsules (3 blister strips)
- Cardboard box containing 60 capsules (6 blister strips)
- Cardboard box containing 90 capsules (9 blister strips)
- Cardboard box containing HandiHaler® device and 10 capsules (1 blister strip)
- Cardboard box containing HandiHaler® device and 30 capsules (3 blister strips)
- Hospital pack: Bundle pack containing 5 cardboard boxes of 30 capsules plus HandiHaler® device
- Hospital pack: Bundle pack containing 5 cardboard boxes of 60 capsules

The HandiHaler® device is packed/available in a cardboard box.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 14598/0062

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/05/2002; 09/10/2006

10 DATE OF REVISION OF THE TEXT
10/2013

This is the prescribing information approved for use in UK. Please refer to your local prescribing information as this information may vary from country to country.
NAME OF THE MEDICINAL PRODUCT

Spiriva Respimat 2.5 microgram, solution for inhalation

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 the full list of excipients, see section 6.1.

PHARMACEUTICAL FORM

Solution for inhalation
Clear, colourless, solution for inhalation

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 an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥800 µg budesonide/day or equivalent) and long-acting β₂ agonists and who experienced one or more severe exacerbations in the previous year.

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.

**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**

**COPD**
Theard 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).

**Asthma**
The efficacy and safety of Spiriva Respimat in children and adolescents has not yet been established.

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

**Patient’s instructions for use and handling**

**Spiriva Respimat inhaler and Spiriva Respimat cartridge**
1) Inserting the cartridge

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

<table>
<thead>
<tr>
<th>Step</th>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>With the green cap (A) closed, press the safety catch (E) while pulling off the clear base (G).</td>
</tr>
<tr>
<td>2</td>
<td>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 firmly against a firm surface to ensure that it has gone all the way in (2b). The cartridge will not be flush with the inhaler, you will still see the silver ring of the lower end of the cartridge. Do not remove the cartridge once it has been inserted into the inhaler.</td>
</tr>
<tr>
<td>3</td>
<td>Replace the clear base (G). Do not remove the clear base again.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Step</th>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>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).</td>
</tr>
</tbody>
</table>
5  Open the green cap (A) until it snaps fully open.

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).

---

**Daily use of your Spiriva Respimat inhaler**

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

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  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, 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 (first-line) 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 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 $\leq 50$ 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.

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.

Breast-feeding
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 5 placebo-controlled clinical trials in COPD (2,802 patients) and 6 placebo-controlled clinical trials in asthma (1,256 patients) 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)

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

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 3.2% of patients. In asthma the incidence of dry mouth was 1.2%.

In 5 clinical trials in COPD, dry mouth led to discontinuation in 3 of 2,802 tiotropium treated patients (0.1%). No discontinuations due to dry mouth were reported in 6 clinical trials in asthma (1,256 patients).

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard
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.

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: 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, M1 to M5. In the airways, tiotropium bromide competitively and reversibly binds to the M3 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 M3-receptors is very slow, exhibiting a significantly longer dissociation half-life than ipratropium. 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, 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.

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 (FEV1 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 (FEV1 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

<table>
<thead>
<tr>
<th>Study (Nspiriva, Nplacebo)</th>
<th>Endpoint</th>
<th>Spiriva Respimat</th>
<th>Placebo</th>
<th>% Risk Reduction (95% CI)a</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year Ph III studies, pooled analysisd (670, 653)</td>
<td>Days to first COPD exacerbation</td>
<td>160a</td>
<td>86a</td>
<td>29 (16 to 40)b</td>
<td>&lt;0.0001b</td>
</tr>
<tr>
<td></td>
<td>Mean exacerbation incidence rate per patient year</td>
<td>0.78c</td>
<td>1.00c</td>
<td>22 (8 to 33)c</td>
<td>0.002c</td>
</tr>
<tr>
<td></td>
<td>Time to first hospitalised COPD exacerbation</td>
<td></td>
<td></td>
<td>25 (-16 to 51)b</td>
<td>0.20b</td>
</tr>
<tr>
<td></td>
<td>Mean hospitalised exacerbation incidence rate per patient year</td>
<td>0.09c</td>
<td>0.11c</td>
<td>20 (-4 to 38)c</td>
<td>0.096c</td>
</tr>
<tr>
<td>1-year Ph IIIb exacerbation study (1939, 1953)</td>
<td>Days to first COPD exacerbation</td>
<td>169a</td>
<td>119a</td>
<td>31 (23 to 37)b</td>
<td>&lt;0.0001b</td>
</tr>
<tr>
<td></td>
<td>Mean exacerbation incidence rate per patient year</td>
<td>0.69c</td>
<td>0.87c</td>
<td>21 (13 to 28)c</td>
<td>&lt;0.0001c</td>
</tr>
<tr>
<td></td>
<td>Time to first hospitalised COPD exacerbation</td>
<td></td>
<td></td>
<td>27 (10 to 41)b</td>
<td>0.003b</td>
</tr>
<tr>
<td></td>
<td>Mean hospitalised exacerbation incidence rate per patient year</td>
<td>0.12c</td>
<td>0.15c</td>
<td>19 (7 to 30)c</td>
<td>0.004c</td>
</tr>
</tbody>
</table>

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).

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

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

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 COPD 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.

Clinical efficacy and safety in asthma

The clinical Phase III programme for persistent asthma 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 FEV₁ 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)

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

<sup>a</sup> ≥800 µg budesonide/day or equivalent

<sup>b</sup> 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).

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

<sup>d</sup> 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

**COPD**
The European Medicines Agency has waived the obligation to submit the results of studies with Spiriva Respimat in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

Asthma

The European Medicines Agency has deferred the obligation to submit the results of studies with Spiriva Respimat in one or more subsets of the paediatric population in the treatment of asthma (see section 4.2 for information on paediatric use).

Clinical efficacy and safety in cystic fibrosis (CF):

The clinical development programme in CF included 3 multicentre studies in 959 patients aged 5 months and above. Patients below 5 years used a spacer (AeroChamber Plus®) with face mask and were included for safety assessment only. The two pivotal studies (a dose finding Phase II study and a confirmatory Phase III study) compared lung function effects (percent predicted FEV₁ AUC<sub>0-4h</sub> and trough FEV₁) of Spiriva Respimat (tiotropium 5 µg: 469 patients) versus placebo (315 patients) in 12-weeks randomised, double-blind periods; the Phase III study also included a long term open label extension, up to 12 months. In these studies, all respiratory medications, except anticholinergics, were allowed as concomitant treatment, e.g. long acting beta agonists, mucolytics and antibiotics.

Effects on lung function are displayed in Table 3. No significant improvement in symptoms and health status (exacerbations by Respiratory and Systemic Symptoms Questionnaire and quality of life by Cystic Fibrosis Questionnaire) have been observed.
Table 3: Adjusted mean difference from placebo for absolute changes from baseline after 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>≤11 years</td>
</tr>
<tr>
<td></td>
<td>(N_{Spiriva} = 176, N_{placebo} = 168)</td>
<td>(N_{Spiriva} = 95, N_{placebo} = 47)</td>
</tr>
<tr>
<td>FEV₁ AUC_{0-4h}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% predicted)</td>
<td>3.39 (1.67, 5.12)</td>
<td>1.64 (-0.27, 3.55)</td>
</tr>
<tr>
<td></td>
<td>p-value &lt;0.001</td>
<td>0.092</td>
</tr>
<tr>
<td>Absolute changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ AUC_{0-4h}</td>
<td>0.09 (0.05, 0.14)</td>
<td>0.07 (0.02, 0.12)</td>
</tr>
<tr>
<td>(litres) Absolute changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trough FEV₁ (% predicted)</td>
<td>2.22 (0.38, 4.06)</td>
<td>1.40 (-0.50, 3.30)</td>
</tr>
<tr>
<td>Absolute changes</td>
<td>0.06 (0.01, 0.11)</td>
<td>0.07 (0.02, 0.12)</td>
</tr>
<tr>
<td>Trough FEV₁ (litres)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Co-primary endpoints

All Adverse Drug Reactions (ADRs) observed in the CF studies are known undesirable effects of tiotropium (see 4.8). The most commonly observed adverse events considered related during the 12 week double blind period were cough (4.1%) and dry mouth (2.8%).

The number and percentage of patients reporting adverse events (AEs) of special interest in cystic fibrosis irrespective of relatedness are shown in Table 4. Signs and symptoms considered to be manifestations of cystic fibrosis increased numerically, although not statistically significantly, with tiotropium, especially in patients ≤11 years old.

Table 4: Percentage of patients with AEs of special interest in cystic fibrosis by age group over 12 weeks of treatment irrespective of relatedness (pooled Phase II and Phase III)

<table>
<thead>
<tr>
<th></th>
<th>≤11 years</th>
<th>≥12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N_{placebo} = 96</td>
<td>N_{Spiriva} = 158</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7.3</td>
<td>7.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Distal intestinal obstruction syndrome</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Respiratory tract infections</td>
<td>34.4</td>
<td>36.7</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>1.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>10.4</td>
<td>14.6</td>
</tr>
</tbody>
</table>

*Distal intestinal obstruction syndrome" and "Sputum increased" are MedDRA preferred terms. "Respiratory tract infections" is the MedDRA higher level group term. "Abdominal pain", "Constipation" and "Exacerbations" are collections of MedDRA preferred terms.

Thirty-four (10.9 %) patients randomised to placebo and 56 (12.0 %) patients randomised to Spiriva Respimat experienced a serious adverse event.

The European Medicines Agency has waived the obligation to submit the results of studies with Spiriva Respimat in the subset of paediatric patients below 1 year of age.
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%. Food is not expected to influence the absorption of this quaternary ammonium compound.

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. 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 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 (dithietylglycolic 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 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 with an interindividual variability of 22%. Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). 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 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 > 70 years) 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 AUC0-4h after dry powder inhalation). Exposure to tiotropium was not found to differ with age in patients with asthma.

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 (CLCR 50-80 ml/min) which is often seen in elderly patients increased tiotropium bromide plasma concentrations slightly (39% increase in AUC0-4h after intravenous infusion). In COPD patients with moderate to severe renal impairment (CLCR < 50 ml/min) the intravenous administration of tiotropium bromide resulted in doubling of the plasma concentrations (82% increase in AUC0-4h), which was confirmed by plasma concentrations after dry powder inhalation and also by inhalation of the solution via the Respimat inhaler. 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.

Paediatric Patients:

There were no paediatric patients in the COPD programme (see 4.2). Paediatric patients were studied as part of the CF clinical programme also covering adults.

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

3 years
In-use shelf life: 3 months

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

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

Pack sizes and devices supplied:

Single pack: 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)
Double pack: 2 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)
Triple pack: 3 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)
Eight pack: 8 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Not all pack sizes may be marketed.
6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

PL 14598/0084

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/07/2012

10. DATE OF REVISION OF THE TEXT

09/2014

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