Spiriva® 18 mcg

Boehringer Ingelheim

Composition
1 capsule for inhalation contains tiotropium 18 mcg equivalent to 22.5 mcg tiotropium bromide monohydrate (INN = tiotropium bromide)
Excipients: lactose monohydrate

Pharmacological properties
Tiotropium is a long-acting, specific antimuscarinic agent, in clinical medicine often called an anticholinergic. It has a similar affinity to the subtypes of muscarinic receptors M_1 to M_5. In the airways, inhibition of M_3-receptors at the smooth muscle results in relaxation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In pre-clinical in vitro as well as in vivo studies bronchoprotective effects were dose-dependent and lasted longer than 24 hours. The long duration of effect is likely to be due to its very slow dissociation from M_3-receptors, exhibiting a significantly longer dissociation half-life than that seen with ipratropium. As an N-quaternary anticholinergic tiotropium is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before giving rise to systemic anticholinergic effects. Dissociation from M_2-receptors is faster than from M_3, which in functional in vitro studies, elicited (kinetically controlled) receptor subtype selectivity of M_3 over M_2. The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD.
The bronchodilation following inhalation of tiotropium is primarily a local effect (on the airways) not a systemic one.
The clinical development program included four one-year and two six-month randomised, double-blind studies in 2663 patients with COPD (1308 receiving SPIRIVA). The one-year program consisted of two placebo-controlled and two ipratropium-controlled trials. The six-month trials were both salmeterol- and placebo-controlled. These studies included evaluation of lung function, dyspnoea, exacerbations of COPD and patients assessments of their health-related quality of life. In the aforementioned studies, SPIRIVA administered once daily, provided significant improvement in lung function (forced expiratory volume in one second, FEV_1 and forced vital capacity, FVC) within 30 minutes following the first dose and was maintained for 24 hours. Pharmacodynamic steady state was reached within one week with the majority of bronchodilation observed by the third day. SPIRIVA significantly improved morning and evening peak expiratory flow rate (PEFR) as measured by patient's daily recordings. A randomised, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24 hour dosing interval in comparison to placebo regardless of whether SPIRIVA was administered in the morning or in the evening. The following health outcome effects were demonstrated in the long-term (6 month and 1 year) trials:

- SPIRIVA significantly improved dyspnoea (as evaluated using the Mahler Transitional Dyspnoea Index). This improvement was maintained throughout the treatment period.
- SPIRIVA significantly reduced the number of COPD exacerbations and delayed the time to first exacerbation in comparison to placebo.
- SPIRIVA significantly improved health-related quality of life as demonstrated by the disease-specific St. George's Respiratory Questionnaire. This improvement was maintained throughout the treatment period.
- Additionally, in the one-year placebo controlled trials SPIRIVA significantly reduced the number of hospitalisations associated with COPD exacerbations and delayed the time to first hospitalisation.

inhalation of a 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.
Biotransformation: The extent of biotransformation is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, both not binding to muscarinic receptors.
Elimination: The terminal elimination half-life of tiotropium 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 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 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.
Elderly Patients: As expected for all predominantly renally excreted drugs, advanced age was associated with a decrease of tiotropium 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 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 intra-individual variability (43% increase in AUC_{0-4h} 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 inhalations. Mild renal impairment (CL_{CR} 50–80 ml/min) which is often seen in elderly patients increased tiotropium 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 resulted in doubling of the plasma concentrations (82% increase in AUC_{0-4h}), 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 pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and simple non-enzymatic ester cleavage to pharmacologically inactive products.

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

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

Special warnings and precautions
SPIRIVA, 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 SPIRIVA inhalation powder. As with other anticholinergic drugs, SPIRIVA should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. Inhaled medicines may cause inhalation-

Pharmacokinetics

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) that tiotropium is poorly absorbed from the gastro-intestinal tract. Food is not expected to influence the absorption of tiotropium for the same reason. Oral solutions of tiotropium have an absolute bioavailability of 2–3%. Maximum tiotropium plasma concentrations were observed five minutes after inhalation.

Distribution: The drug is bound by 72% to plasma proteins and shows a volume of distribution of 32 L/kg. At steady state, tiotropium plasma levels in COPD patients at peak were 17–19 pg/ml when measured 5 minutes after dry powder

induced bronchospasm. As with all predominantly renally excreted drugs, SPIRIVA use should be monitored closely in patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 ml/min). Patients must be instructed in the correct administration of SPIRIVA capsules. Care must be taken not to allow the powder to enter into the eyes. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma.

Should any combination of these symptoms develop specialist advice should be sought immediately. Miotic eye drops are not considered to be effective treatment.

SPIRIVA should not be used more frequently than once daily. SPIRIVA capsules are to be used only with the HandiHaler® device.

Interactions
The co-administration of SPIRIVA with other anticholinergic-containing drugs has not been studied and is therefore not recommended.
Although no formal drug interaction studies have been performed, tiotropium inhalation powder has been used concomitantly with other drugs without adverse drug reactions. These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, commonly used in the treatment of COPD.

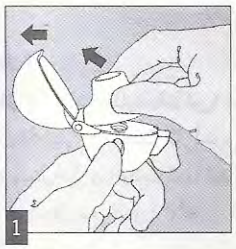
Pregnancy and lactation
For SPIRIVA, no clinical data on exposed pregnancies are available. Preclinical studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal / foetal development, parturition or postnatal development.
Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, a small amount of tiotropium is excreted into breast milk.
Therefore, SPIRIVA should not be used in pregnant or nursing women unless the expected benefit outweighs any possible risk to the unborn child or the infant.

Side effects
The undesirable effects listed below were attributed to the administration of SPIRIVA based on reasonable grounds to suggest a causal relationship. The frequencies given below are reporting incidences regardless of the assessment of causality in any individual case. The information is based on four clinical trials involving 906 patients who have been treated with SPIRIVA over a period of up to one year.
Gastro-intestinal tract:
14%: dry mouth usually mild, which often resolved with continued treatment
> 1% and < 10%: constipation
Respiratory system:
> 1% and < 10%: cough and local irritation including throat irritation (as with other inhaled treatment)
Cardiovascular system:
> 0.1% and < 1%: tachycardia
In addition isolated cases of supraventricular tachycardia and atrial fibrillation were reported in association with the use of tiotropium, usually in susceptible patients.
Urinary system:
> 0.1% and < 1%: difficulty urinating and urinary retention (in men with predisposing factors)
Allergic reactions:
> 0.1% and < 1%: hypersensitivity reactions including isolated cases of angio-oedema
Most of the above mentioned adverse reactions can be attributed to the anticholinergic properties of SPIRIVA. Other anticholinergic effects such as blurred vision and acute glaucoma may occur.
As with other inhaled therapy, inhalation-induced bronchospasm may occur.

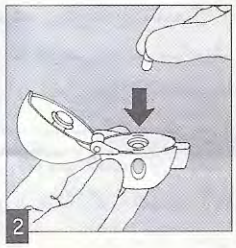
Dosage and administration
The recommended dosage of SPIRIVA is inhalation of the contents of one capsule once daily with the HandiHaler® inhalation device at the same time of day (see Instructions for use). ***SPIRIVA capsules must not be swallowed.***
Elderly patients can use SPIRIVA at the recommended dose.
Renally impaired patients can use SPIRIVA at the recommended dose. However, as with all predominantly renally excreted drugs, SPIRIVA use should be monitored closely in patients with moderate to severe renal impairment .
Hepatically impaired patients can use SPIRIVA at the recommended dose. There is no experience with SPIRIVA in infants and children and therefore should not be used in this age group.

Instructions for Use

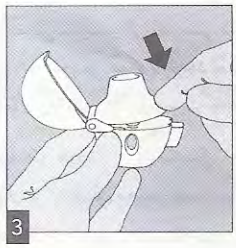
The HandiHaler® device is especially designed for SPIRIVA. It must not be used to take any other medication.
You can use your HandiHaler® device for up to one year to take your medication.



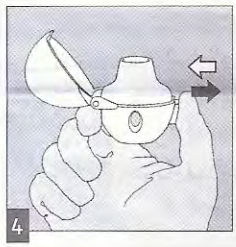
Open the dust cap by pulling it upwards.
Then open the mouthpiece.



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

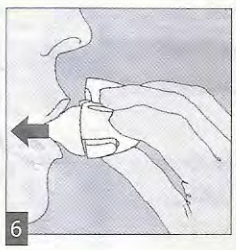


Close the mouthpiece firmly until you hear a click, leaving the dust cap open.

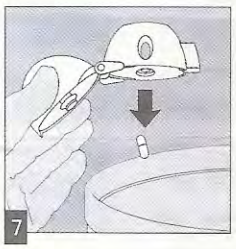


Hold the HandiHaler® device with the mouthpiece upwards and press the piercing button completely in once, and release.
This makes holes in the capsule and allows the medication to be released when you breathe in.

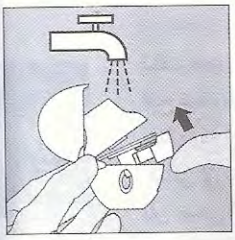
Breathe out completely.
Important: Please avoid breathing into the mouthpiece at any time.



Raise the HandiHaler® device 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 the capsule vibrate.
Breathe until your lungs are full; then hold your breath as long as comfortable and at the same time take the HandiHaler® device out of your mouth. Resume normal breathing. **Repeat step 5 and 6 once,** this will empty the capsule completely.

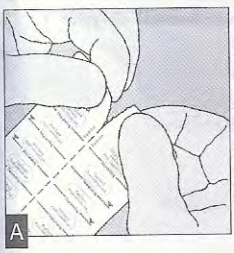


Open the mouthpiece again. Tip out the used capsule and dispose.
Close the mouthpiece and dust cap for storage of your HandiHaler® device.

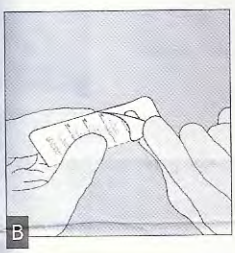


Clean the HandiHaler® device once a month.
Open the dust cap and mouthpiece. Then open the base by lifting the piercing button. Rinse the complete inhaler with warm water to remove any powder. Dry the HandiHaler® device thoroughly by tipping excess of water out on a paper towel and air-dry afterwards, 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. Outside of the mouthpiece may be cleaned with a moist but not wet tissue if needed.

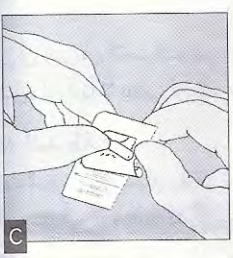
Blisterhandling



Separate the blister strips by tearing along the perforation.



Peel back (only immediately before use) using the tab until one capsule is fully visible.



Remove capsule.

The capsules should not be exposed, neither packed nor in the inhaler, to extreme temperatures i.e. they should not be exposed to sunlight or to heating.

Overdose
High doses of SPIRIVA may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 micrograms tiotropium in healthy volunteers.
Bilateral conjunctivitis in addition to dry mouth was seen in healthy volunteers following repeated once daily inhalation of 141 micrograms in healthy volunteers, which resolved while still under treatment. In a multiple dose study in COPD patients with a maximum daily dose of 36 micrograms tiotropium over four weeks dry mouth was the only observed adverse event attributable to tiotropium.
Acute intoxication by oral ingestion of tiotropium capsules is unlikely due to low oral bioavailability.

Availability
Capsules for inhalation

Date of package insert: November 2001