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Technical information	
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Additional Requirements of \ackaging site	
Template name: TDPI_540x325	Index: b

MASS D 0,35 mm
MASS E 1,0 mm
MASS F 6,0 mm
MASS G 0,65 mm

Example
Technical information
Control Code Type: Laetus Mini

Spiriva®

18μg, inhalation powder, hard capsule

Boehringer Ingelheim

Spiriva®

18μg, inhalation powder, hard capsule

Boehringer Ingelheim

Spiriva®

18μg, inhalation powder, hard capsule

Boehringer Ingelheim

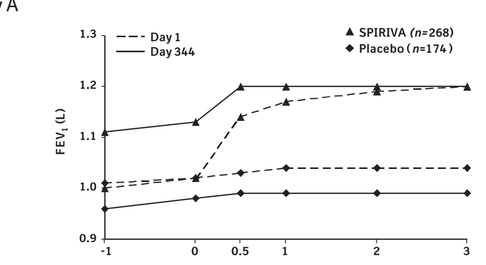
Composition
1 capsule for inhalation contains
tiotropium 18 mcg
equivalent to 22.5 mcg tiotropium bromide monohydrate (INN = tiotropium bromide)

Excipient
Lactose monohydrate (Lactose H_2O, 200M); Lactose monohydrate (Lactose H_2O); Capsule (Titanium dioxide; Yellow iron oxide; Indigo carmine)

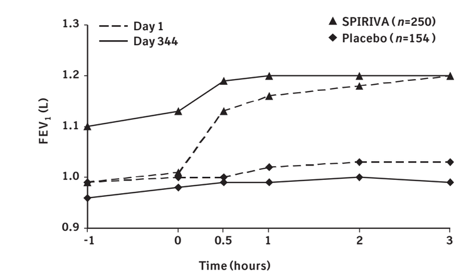
Pharmacological properties
Tiotropium is a long-acting, specific antimuscarinic agent, in clinical medicine often called an anticholinergic. It has a similar affinity to the subtypes of muscarinic receptors M_1 to M_5. In the airways, inhibition of M_3-receptors at the smooth muscle results in relaxation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In non-clinical *in vitro* as well as *in vivo* studies bronchoprotective effects were dose-dependent and lasted longer than 24 hours. The long duration of effect is likely to be due to its very slow dissociation from 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.
The improvement in lung function with SPIRIVA was demonstrated throughout the period of administration in the six long-term trials (Figures 1-3). These improvements were maintained with no evidence of tolerance.

Figure 1: Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 344 in Two 1-Year Placebo-Controlled Trials*

Study A



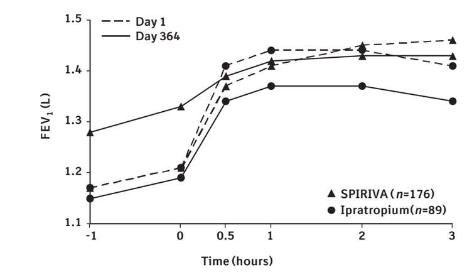
Study B



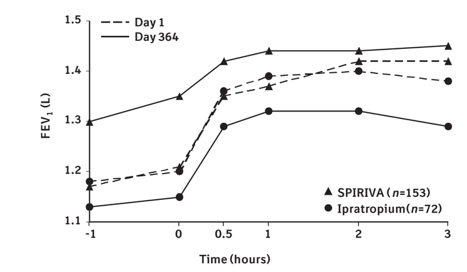
*Means are adjusted for centre and baseline effects.

Figure 2: Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 364 in Two 1-Year Ipratropium-Controlled Trials*

Study A



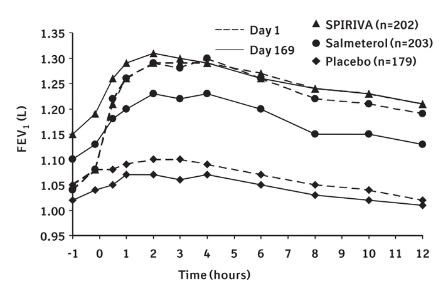
Study B



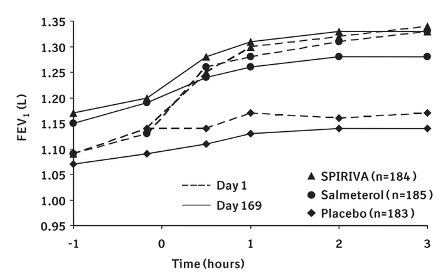
*Means are adjusted for centre and baseline effects.

Figure 3: Mean FEV1 Over Time (prior to and after administration of study drug) on Days 1 and 169 in Two 6-Month Salmeterol- and Placebo -Controlled Trials*

Study A



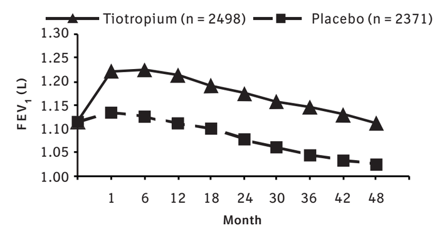
Study B



*Means are adjusted for centre and baseline effects.

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 COPD trials with a duration of up to one year.
SPIRIVA significantly improved dyspnoea (as evaluated using the Transition 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.
The impact of improvement in dyspnea on functional activities was investigated in two randomised double blind placebo controlled trials in COPD patients. In these trials SPIRIVA significantly improved symptom limited exercise tolerance by 19.7% and 28.3% compared with placebo.
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 prolong QT intervals of the ECG.
In a 4-year trial of 5,993 patients SPIRIVA maintained improvements in FEV_1 throughout 4 years but did not alter the annualized rate of decline of FEV_1.

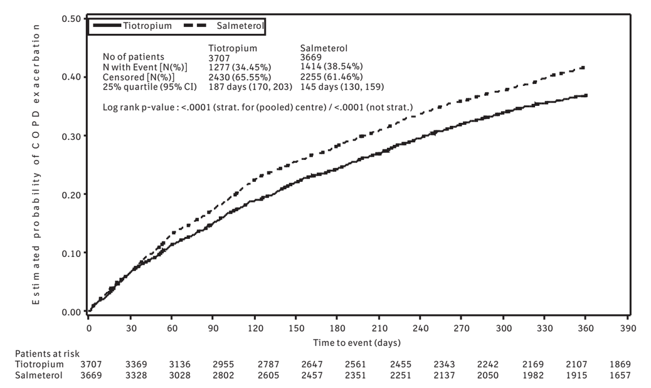
Figure 4. Morning pre-dose FEV1 (i.e. trough) in the tiotropium and placebo groups over 4 years.
P<0.001 for all post-randomization time points.



During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.78 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 by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00).

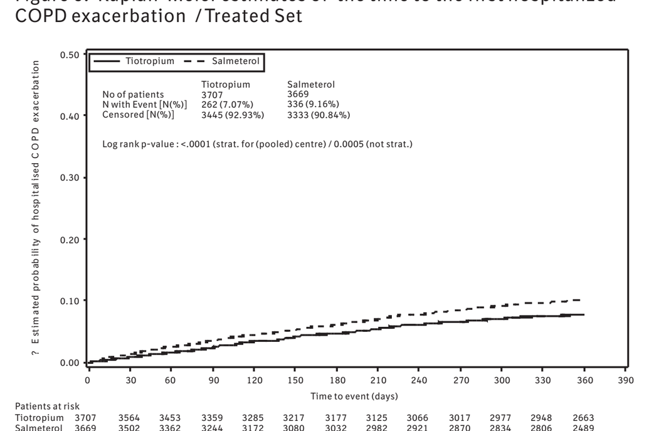
A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 mcg of SPIRIVA once daily with that of 50 mcg of salmeterol HFA pMDI twice daily on the incidence of moderate and severe exacerbations in 7,376 patients with COPD and a history of exacerbations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

Figure 5: Kaplan-Meier estimates of the time to the first COPD exacerbation / Treated Set



Tiotropium
Salmeterol
No of patients 3707 3669
N with Event [N(%)] 1277 (34.45%) 1414 (38.54%)
Censored [N(%)] 2430 (65.55%) 2255 (61.46%)
25% quartile (95% CI) 187 days (170, 203) 145 days (130, 159)
Log rank p-value : <.0001 (strat. for (pooled) centre) / <.0001 (not strat.)
Estimated probability of COPD exacerbation
Time to event (days)
Patients at risk
Tiotropium 3707 3369 3136 2955 2787 2647 2561 2455 2343 2242 2169 2107 1869
Salmeterol 3669 3328 3028 2802 2605 2457 2351 2251 2137 2050 1982 1915 1657

Figure 6: Kaplan-Meier estimates of the time to the first hospitalized COPD exacerbation / Treated Set



Tiotropium
Salmeterol
No of patients 3707 3669
N with Event [N(%)] 262 (7.07%) 336 (9.16%)
Censored [N(%)] 3445 (92.93%) 3333 (90.84%)
Log rank p-value : <.0001 (strat. for (pooled) centre) / 0.0005 (not strat.)
Estimated probability of hospitalised COPD exacerbation
Time to event (days)
Patients at risk
Tiotropium 3707 3564 3453 3359 3285 3217 3177 3125 3066 3017 2977 2948 2663
Salmeterol 3669 3502 3362 3244 3172 3080 3032 2982 2921 2870 2834 2806 2489

Table 1: Summary of exacerbation endpoints

Endpoint	SPIRIVA 18 microgram (HandiHaler) 3,707	Salmeterol 50 microgram (HFA pMDI) N = 3,669	Ratio (95% CI)	p-value
Time[days] to first exacerbation†	187	145	0.83 (0.77-0.90)	<0.001
Time to first severe (hospitalised) exacerbation§	-	-	0.72 (0.61-0.85)	<0.001
Patients with ≥ 1 exacerbation, n (%)*	1,277 (34.4)	1,414 (38.5)	0.90 (0.85-0.95)	<0.001
Patients with ≥ 1 severe (hospitalised) exacerbation, n (%)*	262 (7.1)	336 (9.2)	0.77 (0.66-0.89)	<0.001
Mean exacerbation incidence rate per patient year#	0.64	0.72	0.89 (0.83-0.96)	=0.002
Mean severe (hospitalised) exacerbation incidence rate per patient year#	0.09	0.13	0.73 (0.66-0.82)	<0.001

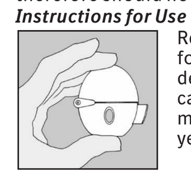
† Time [days] refers to 1st quartile of patients. Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio.
§ Time to event analysis was done using Cox's proportional hazards regression model with (pooled) 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.
\# Number of event analysis was done using Poisson regression correcting for overdispersion and adjusting for treatment exposure; ratio refers to rate 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), reduced the annual number of moderate or severe (hospitalised) exacerbations (0.64 vs. 0.72; rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.002), and reduced the annual number of severe (hospitalised) exacerbations (0.09 vs. 0.13; rate ratio, 0.73; 95% CI, 0.66 to 0.82; P<0.001).

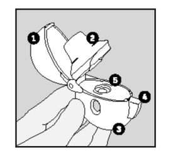
Pharmacokinetics
Tiotropium is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium is administered by dry powder inhalation. Generally with the inhaled route of administration, the majority of the delivered dose is deposited in the gastro-intestinal tract, and to a lesser extent in the intended organ of the lung. Many of the pharmacokinetic data described below were obtained with higher doses as recommended for therapy.
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 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. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier to any relevant extent.
Biotransformation: The extent of biotransformation is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, both not binding to muscarinic receptors. In-vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (<20% of dose after intravenous administration) is metabolised by cytochrome P450 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-metabolites. This enzymatic pathway can be inhibited by the CYP450 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium even in supra-therapeutic concentrations does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.
Elimination: The 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.
Linearity/nonlinearity: Tiotropium demonstrates linear pharmacokinetics in the therapeutic range after both intravenous administration and dry powder inhalation.
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 by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

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

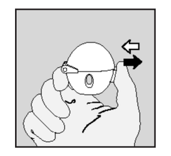
Dosage and administration
The product should be used by physician prescription.
The recommended dosage of SPIRIVA is inhalation of the contents of one capsule once daily with the HandiHaler inhalation device at the same time of day (see Instructions for use).
SPIRIVA capsules must not be swallowed.
Elderly 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



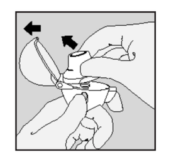
Remember to carefully follow your doctor's instructions for using SPIRIVA The HandiHaler is an inhalation device especially designed for inhalation from SPIRIVA capsules. You must not use it to take any other medication. You can use your HandiHaler for up to one year to take your medication.



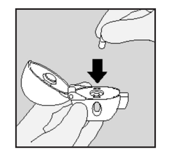
1. dust cap
2. mouthpiece
3. base
4. piercing button
5. Centre chamber



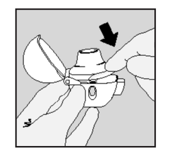
1. To release the dust cap press the piercing button completely in and let go.



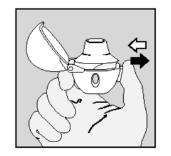
2. Open the dust cap completely by pulling it upwards. Then open the mouthpiece by pulling it upwards.



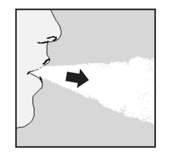
3. Remove a SPIRIVA capsule from the blister (only immediately before use, see blister handling) and place it in the centre chamber (5), as illustrated. It does not matter which way the capsule is placed in the chamber.



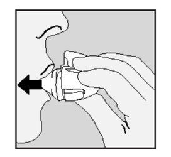
4. Close the mouthpiece firmly until you hear a click, leaving the dust cap open.



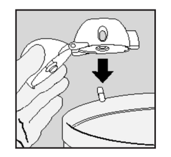
5. Hold the HandiHaler device with the mouthpiece upwards and press the piercing button completely in only once, and release.
This makes holes in the capsule and allows the medication to be released when you breathe in.



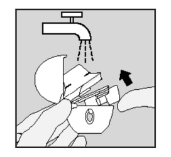
6. Breathe out completely.
Important: Please avoid breathing into the mouthpiece at any time.



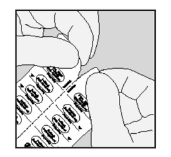
7. Raise the HandiHaler to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position and breathe in slowly and deeply but at a rate sufficient to hear or feel the capsule vibrate.
Breathe in until your lungs are full; then hold your breath as long as comfortable 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.

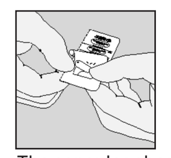


Cleaning the HandiHaler
Clean the HandiHaler once a month.
Open the dust cap and mouthpiece. Then open the base by lifting the piercing button. Rinse the complete inhaler with warm water to remove any powder. Dry the HandiHaler thoroughly by tipping excess water out onto a paper towel and air-dry afterwards,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



Blister handling
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.

The capsules should not be exposed to extreme temperatures.
SPIRIVA capsules contain only a small amount of powder so that the capsule is only partially filled.

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 the excipient lactose monohydrate which contains milk protein 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-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.
This product contains 5.5 mg of lactose monohydrate per capsule.

Interactions
Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs, commonly used in the treatment of COPD, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids without clinical evidence of drug interactions.
Limited information about co-administration of other anticholinergic drugs with SPIRIVA is available from two clinical trials: Acute single dose administration of ipratropium bromide with chronically administered SPIRIVA in COPD patients (n=64) and healthy volunteers (n= 35) was not associated with an increase in adverse events, changes in vital signs or electrocardiographic findings. However, chronic co-administration of other anticholinergic drugs with SPIRIVA has not been studied and is, therefore, not recommended.

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.

Fertility, 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.
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 (please refer to section Toxicology).

Side effects
Many of the listed undesirable effects can be assigned to the anticholinergic properties of SPIRIVA.
Adverse drug reactions were identified from data obtained in clinical trials and spontaneous reporting during post approval use of the drug. The clinical trial database includes 9,647 tiotropium patients from 28 placebo-controlled clinical trials with treatment periods ranging between four weeks and four years, contributing 12,469 person years of exposure to tiotropium .
Metabolism and nutrition disorders:
- dehydration
Nervous system disorders:
- dizziness
- insomnia
Eye disorders:
- vision blurred
- glaucoma
- intraocular pressure increased
Cardiac disorders:
- atrial fibrillation
- supraventricular tachycardia
- tachycardia
- palpitations
Respiratory, thoracic and mediastinal disorders:
- cough
- dysphonia
- pharyngitis
- bronchospasm
- epistaxis
- laryngitis
- sinusitis
Gastrointestinal disorders:
- dry mouth, usually mild
- constipation
- gastrooesophageal reflux disease
- oropharyngeal candidiasis
- intestinal obstruction incl. ileus paralytic
- dysphagia
- gingivitis
- glossitis
- stomatitis
Skin and subcutaneous tissue disorders, Immune system disorders:
- rash
- angioedema
- hypersensitivity (including immediate reactions)
- pruritus
- urticaria
- dry skin
- skin infection and skin ulcer
Musculoskeletal and connective tissue disorders:
- joint swelling
Renal and urinary disorders:
- urinary retention (usually in men with predisposing factors)
- dysuria
- urinary tract infection

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.

Toxicology
The **acute inhalation and oral toxicity** in mice, rats, and dogs was low; therefore, toxic effects from acute human drug over-dosage are unlikely. The single dose safety pharmacology studies showed the expected effects of an anticholinergic drug including mydriasis, increased heart rate and prolonged gastro-intestinal transit time.
The side effects of the **repeated dose studies** in rats, mice and dogs were related to anticholinergic properties of tiotropium including mydriasis, increased heart rate, constipation, decreased body weight gain, reduced salivary and lacrimal gland secretion. Other relevant changes noted were: mild irritancy of the upper respiratory tract in rats evinced by rhinitis and epithelial changes of the nasal cavity and larynx, and prostatitis along with proteinaceous deposits and lithiasis in the bladder of male rats, increased lung weights in rats and decreased heart weights in dogs.
In the **reproduction studies** in rabbits and rats harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. In a general reproduction and fertility study in rats, there was no indication of any adverse effect on fertility or mating performance of either treated parents or their offspring at any dosage.
In a series of *in vivo* and *in vitro* **mutagenicity assays**, tiotropium bromide monohydrate did not cause gene mutations in prokaryotes and in eucaryotes, chromosomal damage *in vitro* and *in vivo* conditions or primary DNA damage.

Availability
2 – 1000 capsules for inhalation in aluminium blister with paper box.

Storage conditions
After first opening of the blister, use within 9 days

Store in a safe place out of the reach of children!
Do not store above 25°C!
Do not freeze!

Mfg by
Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein, Germany
For
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

20110629