

DATA SHEET

Name of Medicine

Spiriva® Respimat®
Tiotropium 2.5 mcg

Presentation

SPIRIVA Respimat 2.5 micrograms/puff, solution for inhalation. Each puff contains tiotropium 2.5 micrograms, equivalent to tiotropium bromide monohydrate 3.124 micrograms. The cartridge containing the solution for inhalation is used with the Respimat inhaler.

SPIRIVA Respimat cartridges contain a clear, colourless, solution for inhalation filled into a plastic container which is inside an aluminium cylinder (cartridge) for use with the Respimat inhaler. SPIRIVA Respimat is for oral inhalation only.

Uses

Actions

Pharmacotherapeutic group: Anticholinergic

ATC code: R03B B

Tiotropium is a long-acting, specific antimuscarinic (anticholinergic) agent. It has similar affinity to the muscarinic receptor subtypes M₁ to M₅ (K_D 5-41 pM). In the airways, inhibition by tiotropium of M₃-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 preclinical *in vitro* as well as *in vivo* studies, bronchoprotective effects were dose-dependent lasting at least 24 hours. The long duration of effect of tiotropium is likely to be due to its very slow dissociation from M₃-receptors, exhibiting a significantly longer dissociation half-life than that seen with ipratropium.

Tiotropium, a N-quaternary anticholinergic agent, is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before giving rise to systemic anti-cholinergic effects. 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 is associated with a significant and long-acting bronchodilation in patients with chronic obstructive pulmonary disease (COPD).

The bronchodilation following inhalation of tiotropium is primarily a local effect on the airways, not a systemic one.

Pharmacokinetics

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 of tiotropium Respimat 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.

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 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 bromide plasma concentrations were observed 5 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 bromide plasma levels in COPD patients at peak were 10.5-11.7 pg/ml when measured 10 minutes after administration of a 5 µg 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. 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.

Metabolism

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 [30]. Tiotropium bromide, an ester, is nonenzymatically [34] 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 bromide even in supra-therapeutic concentrations does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Excretion

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 bromide is mainly excreted unchanged in urine (74 %). After inhalation of the solution urinary excretion is 20.1-29.4% of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces. The renal clearance of tiotropium bromide exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached on day 7 with no accumulation thereafter.

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

Elderly 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 intra-individual variability (43 % increase in AUC₀₋₄ after dry powder inhalation).

Renally Impaired Patients

In common with all other drugs that undergo predominantly renal excretion, renal impairment was associated with increased plasma drug concentrations and reduced renal drug

clearance after both intravenous infusion and dry powder 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 AUC_{0-4h} 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 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 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).

Indications

SPIRIVA Respimat is indicated for the long term once daily maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA reduces the frequency of exacerbations and improves exercise tolerance and health-related quality of life.

Dosage and Administration

The recommended dosage of SPIRIVA Respimat is two puffs once daily at the same time each day (see Respimat inhaler instructions for use under Further Information).

Contraindications

SPIRIVA Respimat 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.

Warnings and Precautions

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

Immediate hypersensitivity reactions may occur after administration of SPIRIVA Respimat.

As with other anticholinergic drugs, SPIRIVA Respimat 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 Respimat 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 Respimat. Care must be taken not to allow the spray 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 Respimat should not be used more frequently than once daily (see Overdose).

SPIRIVA solution for inhalation is to be used only with Respimat® inhaler (see Respimat inhaler instructions for use).

Hepatic Impairment

There are no data on the use of tiotropium in patients with hepatic impairment. As tiotropium is primarily cleared by renal mechanisms, no dosage adjustment is recommended. However patients should be monitored closely.

Renal Impairment

Renally-impaired patients can use SPIRIVA Respimat at the recommended dose. However, as with all predominantly renally excreted drugs, SPIRIVA Respimat use should be monitored closely in patients with moderate to severe renal impairment.

Use in the elderly

Elderly patients can use SPIRIVA Respimat at the recommended dose. Renal clearance of tiotropium is likely to be slower in elderly patients (see Renal Impairment).

Use in children

The safety and effectiveness of SPIRIVA Respimat in paediatric patients has not been established. Therefore, SPIRIVA Respimat should not be used in paediatric patients.

Use in Pregnancy

Category B1

For tiotropium bromide, no clinical data on its use during pregnancy are available. Preclinical studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal / foetal development, parturition or postnatal development.

SPIRIVA Respimat should be used in pregnancy only if the potential benefit exceeds the potential risk.

Use in Lactation

Clinical data from lactating women exposed to tiotropium are not available. Based on studies in lactating rats, a small amount of tiotropium is excreted in breast milk.

Therefore, SPIRIVA Respimat should not be used in lactating women unless the expected benefit outweighs any possible risk to the infant.

Effects on ability to drive or operate machinery

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.

Adverse Effects

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

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 2,802 tiotropium patients from 5 placebo-controlled clinical trials with treatment periods ranging between twelve weeks and one year, contributing 2,248 person years of exposure to tiotropium.

Metabolism and nutrition disorders:

dehydration

Nervous system disorders:

dizziness

insomnia

Eye disorders:

vision blurred
intraocular pressure increased
glaucoma

Cardiac disorders:

supraventricular tachycardia
atrial fibrillation
palpitations
tachycardia

Respiratory, thoracic and mediastinal disorders:

dysphonia
cough
pharyngitis
epistaxis
laryngitis
sinusitis
bronchospasm

Gastrointestinal disorders:

dry mouth, usually mild
oropharyngeal candidiasis
gastro-oesophageal reflux disease
dysphagia
gingivitis
glossitis
stomatitis
constipation
intestinal obstruction incl. paralytic ileus

Skin and subcutaneous tissue disorders, Immune system disorders:

pruritus
angioneurotic oedema
rash
urticaria
skin infection and skin ulcer
dry skin
hypersensitivity (including immediate reactions)

Musculoskeletal and connective tissue disorders:

joint swelling

Renal and urinary disorders:

dysuria
urinary retention (usually in men with predisposing factors)
urinary tract infection

Interactions

Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs which are commonly used in the treatment of COPD, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids without clinical evidence of drug interactions.

The chronic co-administration of tiotropium bromide with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of other anticholinergic drugs with SPIRIVA Respimat is not recommended.

Overdosage

High doses of tiotropium 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. Additionally, no relevant adverse effects, beyond dry mouth, were observed following 7 day dosing of up to 141 micrograms tiotropium in healthy volunteers. In a multiple dose study in COPD patients, with a maximum daily dose of 36 micrograms tiotropium over four weeks, no significant undesirable effects were observed.

No relevant adverse events, beyond dry mouth/throat and dry nasal mucosa, were observed following 14-day dosing of up to 40 micrograms tiotropium solution for inhalation in healthy subjects with the exception of pronounced reduction in salivary flow from day 7 onwards. No significant undesirable effects have been observed in six long-term studies in COPD patients when a daily dose of 10 micrograms tiotropium solution for inhalation was given over 4-48 weeks.

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

Pharmaceutical Precautions

Store below 25°C in a safe place out of the reach of children. Do not freeze.

The SPIRIVA Respimat cartridge has an in-use shelf-life of 3 months after insertion in the Respimat inhaler.

Medicine Classification

Prescription Medicine

Package Quantities

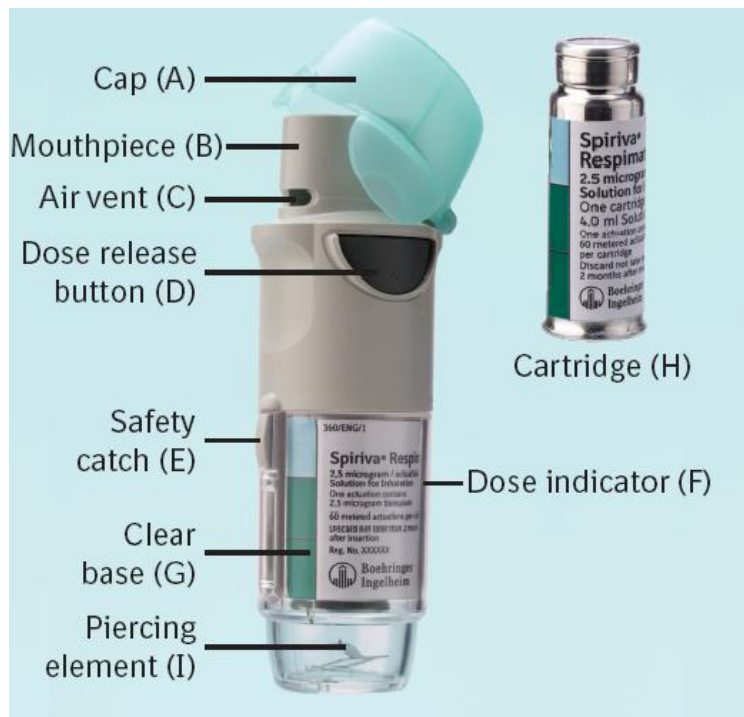
Each pack consists of one Respimat inhaler and one cartridge, delivering 60 metered puffs. Each puff contains tiotropium 2.5 micrograms, equivalent to tiotropium bromide monohydrate 3.1 micrograms.

Further Information

SPIRIVA® and Respimat® are registered trademarks.

Instructions for Use

Please read and carefully follow these instructions.



Inserting the cartridge and preparation for use

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



1

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



2a

2. Take the cartridge (H) out of the box. Push the **narrow** end of the cartridge into the inhaler until it clicks into place. The cartridge should be pushed **gently** against a firm surface to ensure that it has gone all the way in (2b).



2b

Do not remove the cartridge once it has been inserted into the inhaler.



3

3. Replace the clear base (G).

Do not remove the clear base again.

To prepare the SPIRIVA RESPIMAT inhaler for first-time use



4

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



5

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



6

6. Point the SPIRIVA RESPIMAT inhaler towards the ground. Press the dose release button (D). Close the green cap (A).

Repeat steps 4, 5 and 6 until a cloud is visible.

Then repeat steps 4, 5 and 6 three more times to ensure the inhaler is prepared for use.

Your SPIRIVA RESPIMAT inhaler is now ready to use.

These steps will not affect the number of doses available. After preparation your SPIRIVA RESPIMAT inhaler will be able to deliver your 30 doses (60 puffs).

Using SPIRIVA RESPIMAT inhaler



1

1. Hold your SPIRIVA RESPIMAT inhaler upright, with the green cap (A) closed, to avoid accidental release of dose. Turn the clear 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.

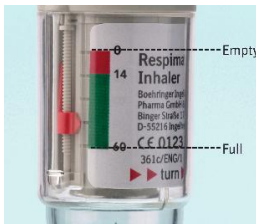
III Repeat Steps I and II so that you get the full dose.

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

Close the green cap until you use your SPIRIVA RESPIMAT inhaler again.

If your SPIRIVA RESPIMAT inhaler has not been used for more than 7 days release one puff towards the ground. If your 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 30 doses (60 puffs). 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 (14 puffs) left. 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), your SPIRIVA RESPIMAT inhaler is empty and locks automatically. At this point, the base cannot be turned any further.

At the latest, three months after first use the SPIRIVA RESPIMAT inhaler should be discarded even if not all medication has been used.

Care of 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 the performance of your SPIRIVA RESPIMAT inhaler. If necessary, wipe the outside of your SPIRIVA RESPIMAT inhaler with a damp cloth.

Clinical Trials

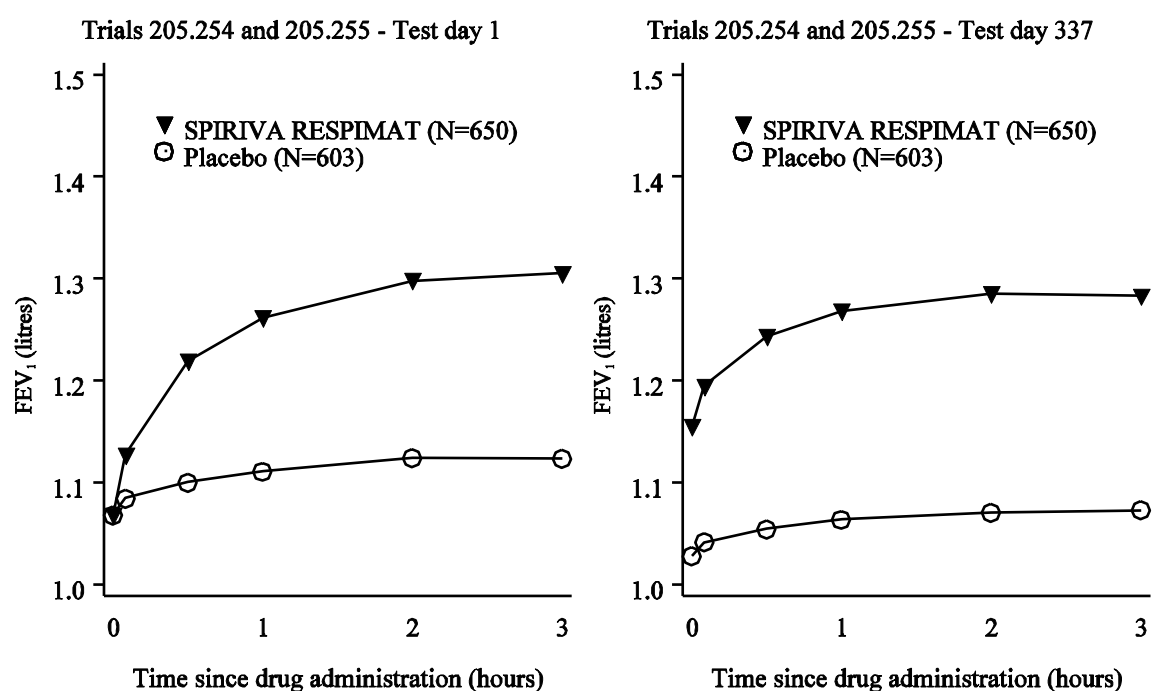
The clinical Phase III programme included two 1-year, two 12-week and two 4-week randomised, double-blind studies in 2901 COPD patients (1038 receiving the 5 micrograms tiotropium dose). The 1-year programme consisted of two placebo-controlled trials. The two 12-week trials were both active (ipratropium) – and placebo-controlled. All six studies included lung function measurements. In addition, the two 1-year studies included health outcome measures of health-related quality of life, dyspnoea, and effect on exacerbations .

In the aforementioned studies, SPIRIVA Respimat 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. Improvement of lung function was maintained for 24 hours at steady state. 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. The use of SPIRIVA Respimat resulted in a reduction of rescue bronchodilator use compared to placebo.

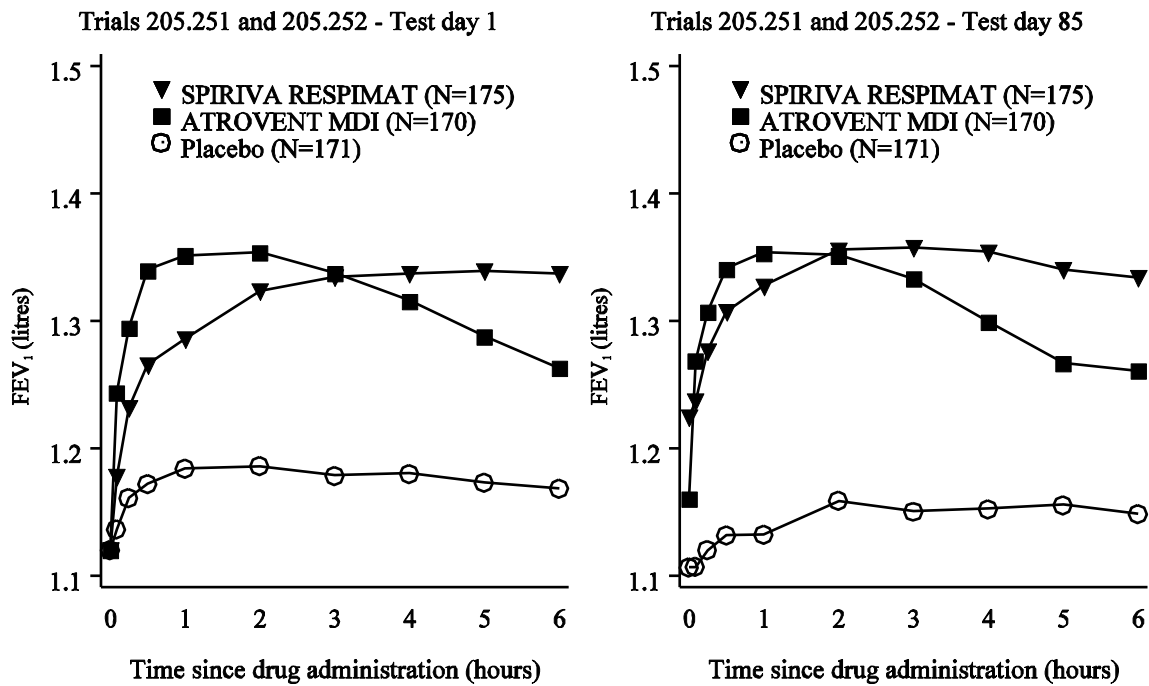
The bronchodilator effects of SPIRIVA Respimat were maintained throughout the 48-week period of administration with no evidence of tolerance.

Figure 1: Mean FEV₁ (litres) at each time point (prior to and after administration of study drug) on Days 1 and 337 respectively (combined data from two 1-year, parallel-group trials)*



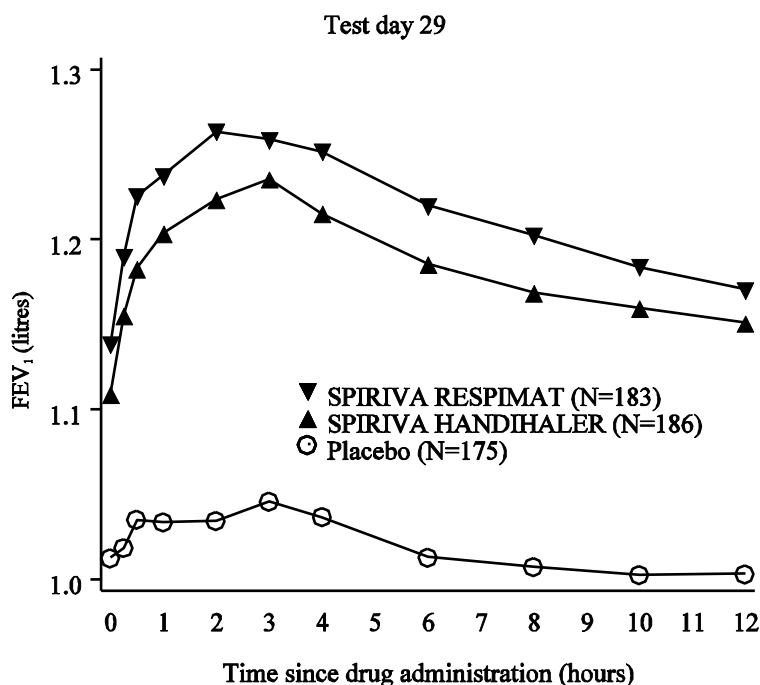
*Means adjusted for center, smoking status and baseline effect. A total of 545 and 434 patients in the SPIRIVA and placebo groups, respectively completed test day 337. The data for the remaining patients were imputed using last observation or least favourable observation carried forward.

Figure 2: Mean FEV₁ (litres) at each time point (prior to and after administration of study drug) on Days 1 and 85 respectively (combined data from two 12-week, parallel-group trials)



Day 85, a total of 155, 142 and 152 patients in the SPIRIVA[®], ATROVENT[®] MDI and placebo groups, respectively completed test day 85. The data for the remaining patients were imputed using last observation or least favourable observation carried forward.

Figure 3: Mean FEV₁ (litres) at each time point (prior to and after administration of study drug) on Day 29 (combined data from two 4-week cross-over studies 205.249 and 205.250)*



*Means adjusted for center, patient (within center), period and baseline effect. The data for patients who discontinued a test day early were imputed using last observation or least favourable observation carried forward. Patients who completed the trials took all 3 treatments.

A combined analysis of two randomised, placebo-controlled, crossover, clinical studies demonstrated that the bronchodilator response for SPIRIVA Respimat (5 µg) was numerically higher compared to SPIRIVA HandiHaler (18 µg) inhalation powder after a 4-week treatment period.

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

(a) SPIRIVA Respimat significantly improved dyspnoea (as evaluated using the Transition Dyspnoea Index). An improvement was maintained throughout the treatment period.

(b) Patients' evaluation of their Quality of Life (as measured using the St. George's Respiratory Questionnaire) showed that SPIRIVA Respimat had positive effects on the psychosocial impacts of COPD, activities affected by COPD and distress due to COPD symptoms.

The improvement in mean total score between SPIRIVA Respimat versus placebo at the end of the two 1-year studies was statistically significant and maintained throughout the treatment period.

(c) SPIRIVA Respimat significantly reduced the number of COPD exacerbations and delayed the time to first COPD exacerbation.

In a one-year, randomised, double-blind, placebo-controlled clinical trial, 1939 COPD patients received SPIRIVA Respimat and 1953 received placebo. During the trial patients were permitted to use all respiratory medications (i.e. long-acting beta-agonists and inhaled corticosteroids) except for inhaled anticholinergics. SPIRIVA Respimat treatment resulted in a 31% reduced risk of a COPD exacerbation (95% CI: 23% to 37%; $p < 0.0001$), a 27% reduced risk of a hospitalisation due to a COPD exacerbation (95% CI: 10% to 41%; $p = 0.003$), 21% fewer COPD exacerbations (95% CI: 13% to 28%; $p < 0.0001$) and 19% fewer hospitalisations due to a COPD exacerbation (95% CI: 7% to 30%; $p = 0.004$) compared with placebo.

In a retrospective pooled analysis of the three 1-year and one 6-month placebo-controlled trials with Spiriva Respimat including 6,096 patients a numerical increase in all-cause mortality was seen in patients treated with Spiriva Respimat (68; incidence rate (IR) 2.64 cases per 100 patient-years) compared with placebo (51, IR 1.98) showing a rate ratio (95% confidence interval) of 1.33 (0.93, 1.92) for the planned treatment period. Subgroup analyses including but not limited to respiratory co-medication, demographic factors and cardiac disorders at baseline describe that the imbalance in mortality was observed in patients with known rhythm disorders. However, these analyses are limited due to the retrospective approach, multiple comparisons and subgroups resulting in small numbers. A pooled analysis of studies > 4 weeks including 17,014 patients assigned to Spiriva HandiHaler or placebo showed a rate ratio (95% CI) for all-cause mortality of 0.85 (0.75–0.97). Reasons for the apparent difference in the risk of all-cause mortality between the HandiHaler and Respimat formulations are unclear, should be interpreted with caution, and may reflect trial related factors or variability of outcomes.

Excipients

Benzalkonium chloride, disodium edetate, purified water and hydrochloric acid for pH adjustment.

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