1. NAME OF THE MEDICINAL PRODUCT

Tiotropium Elpen 10 microgram inhalatiepoeder, voorverdeeld

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each unit dose blister strip contains 16 microgram tiotropium bromide monohydrate equivalent to 13 microgram tiotropium.
The delivered dose (the dose that leaves the mouthpiece of the Elpenhaler) is 10 microgram tiotropium.

Excipient with known effect:
Each unit dose blister strip contains 11.86 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed.
White inhalation powder.

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 blister strip once daily with the Elpenhaler device at the same time of day.

The recommended dose should not be exceeded.

Tiotropium blister strips are only for inhalation and not for oral intake. Tiotropium blister strips must not be swallowed. Tiotropium should only be inhaled with the Elpenhaler device. The Elpenhaler device should be kept inside the sachet to be protected from moisture and should only be removed immediately before first use.

Special populations

Geriatric patients can use tiotropium at the recommended dose.

Renally impaired patients can use tiotropium at the recommended dose. For patients with moderate to severe impairment (creatinine clearance $\leq$ 50 ml/min) see section 4.4 and section 5.2.

Hepatically impaired patients can use tiotropium 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.

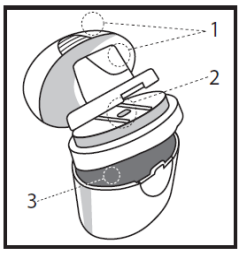
Cystic fibrosis
The safety and efficacy of tiotropium in children and adolescents has not been established. No data are available.

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 USE OF THE ELPENHALER®:

Elpenhaler® is a device for the intake of powder for inhalation in doses.
Each dose is stored in the blister of a specially designed unit dose blister strip.

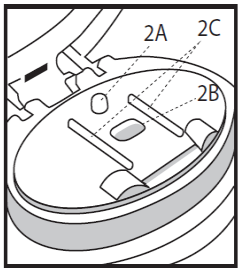
Elpenhaler® device is comprised of 3 parts:



- The mouthpiece and its cap **(1)**.
- The surface **(2)** on which the blister strip is placed (drug supporting surface).
- The storage case **(3)** which houses the blister strips.

The three parts are connected to each other and can be opened separately.

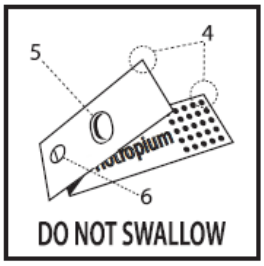
The drug supporting surface contains:



- An attachment point **(2A)** where the blister strip is attached.
- A cavity **(2B)** which accommodates the blister of the strip.
- Two strip guides **(2C)** which firmly secure the blister strip in the correct position on the drug supporting surface.

The blister strip consists of:

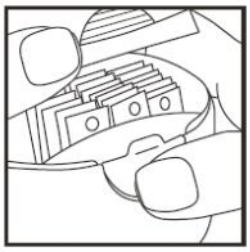
- Two aluminium sheets **(4)**.
- A blister **(5)**, containing the medicine.
- A hole **(6)**.



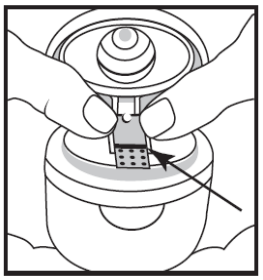
USE OF THE ELPENHALER®

A. Preparing the device

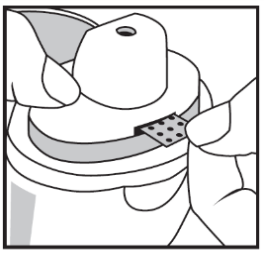
- Open the storage case by pressing as in the figure, take a strip and close the storage case again.



- Uncover the mouthpiece completely by applying light pressure on the striped area.
- Unlock and push the mouthpiece backwards so as to reveal the drug supporting surface.
- Hold the blister strip with its shiny surface upwards, so as to see the blue line, as shown by the arrow in the figure. The labeled surface of the strip should face downwards.
- Place the hole of the strip on the attachment point of the drug supporting surface. By applying light pressure make sure that the strip is securely attached on the attachment point.
- The blister of the strip will fit in the cavity of the drug supporting surface and the guides will secure the strip in the correct position.



- Close the mouthpiece, pull away horizontally the embossed protruding end of the strip so as to be detached, and discard it.



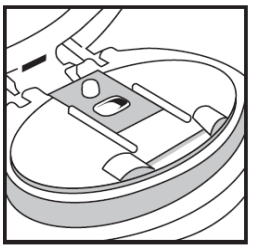
- The dose is now ready to be inhaled.

B. Inhalation of the dose

Hold the device away from your mouth. Exhale completely. Be careful not to exhale on the mouthpiece of the device. Bring Elpenhaler® to your mouth and place your lips tightly around the mouthpiece.

- Breathe in slowly and deeply through your mouth (and not through your nose) until your lungs are full.
- Hold in your breath approximately 5 seconds or as long as you comfortably can and at the same time remove the device from your mouth.
- Exhale and continue to breathe normally.

- Open the mouthpiece.
- You will notice that you have inhaled all the powder and that the blister of the strip is empty.
- Remove the empty strip, discard it, and proceed to step C.



C. Cleaning the device

Following each use, wipe the mouthpiece and the drug supporting surface with a dry cloth or dry paper tissue. Do not use water to clean the device.

Close the mouthpiece and its cap.

4.3 Contraindications

Hypersensitivity to the active substance or to the excipient listed in section 6.1 or to atropine or its derivatives, e.g. ipratropium or oxitropium.

4.4 Special warnings and precautions for use

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

Immediate hypersensitivity reactions may occur after administration of tiotropium bromide 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.

Tiotropium should be used with caution in patients with recent myocardial infarction < 6 months; any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalisation of heart failure (NYHA Class III or IV) within the past year. These patients were excluded from the clinical trials and these conditions may be affected by the anticholinergic mechanism of action.

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).

<Product name> contains 11.86 mg of lactose (as monohydrate). This amount does not normally cause problems in lactose intolerant patients. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. The excipient lactose monohydrate may contain small amounts of milk proteins which may cause allergic reactions.

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.

Use of LABA or ICS was not found to alter the exposure to tiotropium.

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
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 <Product name> 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 <Product name> 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 <Product name> should be made taking into account the benefit of breast-feeding to the child and the benefit of <Product name> 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 tiotropium.

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)

System Organ Class / MedDRA Preferred Term	**Frequency**
Metabolism and nutrition disorders	
Dehydration	Not known
Nervous system disorders	

Dizziness	Uncommon
Headache	Uncommon
Taste disorders	Uncommon
Insomnia	Rare
Eye disorders	
Vision blurred	Uncommon
Glaucoma	Rare
Intraocular pressure increased	Rare
Cardiac disorders	
Atrial fibrillation	Uncommon
Supraventricular tachycardia	Rare
Tachycardia	Rare
Palpitations	Rare
Respiratory, thoracic and mediastinal disorders	
Pharyngitis	Uncommon
Dyshponia	Uncommon
Cough	Uncommon
Bronchospasm	Rare
Epistaxis	Rare
Laryngitis	Rare
Sinusitis	Rare
Gastrointestinal disorders	
Dry mouth	Common
Gastrooesophageal reflux disease	Uncommon
Constipation	Uncommon
Oropharyngeal candidiasis	Uncommon
Intestinal obstruction, including ileus paralytic	Rare
Gingivitis	Rare
Glossitis	Rare
Dysphagia	Rare
Stomatitis	Rare
Nausea	Rare
Dental caries	Not known
Skin and subcutaneous tissue disorders, immune system disorders	
Rash	Uncommon
Urticaria	Rare
Pruritus	Rare
Hypersensitivity (including immediate reactions)	Rare
Angioedema	Rare
Anaphylactic reaction	Not known
Skin infection, skin ulcer	Not known
Dry skin	Not known
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known
Renal and urinary disorders	
Dysuria	Uncommon
Urinary retention	Uncommon
Urinary tract infection	Rare

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.

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 national reporting system listed in Appendix V.

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 powder 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, Tiotropium bromide 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 and safety
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 dyspnoea, exacerbations and health-related quality of life.

Lung function
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.

Clinical trials (up to 12 months)

Dyspnoea, Exercise tolerance
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 tiotropium bromide significantly improved symptom-limited exercise endurance time during cycle ergometry at 75% of maximal work capacity by 19.7% (Trial A) and 28.3% (Trial B) compared with placebo.

Health-related Quality of Life
In a 9-month, randomized, double-blind, placebo-controlled clinical trial of 492 patients, tiotropium bromide improved health-related quality of life as determined by the St. George's Respiratory Questionnaire (SGRQ) total score. The proportion of patients treated with tiotropium 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 tiotropium bromide 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.

COPD Exacerbations
In a randomized, 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

hospitalized due to a COPD exacerbation (p=0.056). The number of hospitalizations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure).

A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 microgram of tiotropium 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

Endpoint	**Tiotropium 18 microgram N = 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

† 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, tiotropium 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). Tiotropium also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001).

Long term clinical trials (more than 1 year, up to 4 years)
In a 4-year, randomised, double-blind, placebo-controlled clinical trial of 5,993 randomised patients (3.006 receiving placebo and 2,987 receiving tiotropium), the improvement in FEV^1 resulting from tiotropium, compared with placebo, remained constant throughout 4 years. A higher proportion of patients completed ≥ 45 months of treatment in the tiotropium group compared with the placebo group (63.8% vs. 55.4%, p<0.001). The annualized rate of decline of FEV^1 compared to placebo was similar between tiotropium 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).

Tiotropium active-controlled study
A long-term, large scale randomised, double-blind, active-controlled study with an observation period up to 3 years has been performed to compare the efficacy and safety of tiotropium bromide

in inhalation powder and tiotropium bromide in inhalation solution (5,694 patients receiving tiotropium bromide in inhalation powder; 5,711 patients receiving tiotropium bromide in inhalation solution). The primary endpoints were time to first COPD exacerbation, time to all-cause mortality and in a sub-study (906 patients) trough FEV1 (pre-dose).

The time to first COPD exacerbation was numerically similar during the study with tiotropium bromide in inhalation powder and tiotropium bromide in inhalation solution (hazard ratio (tiotropium bromide in inhalation powder / tiotropium bromide in inhalation solution) 1.02 with a 95% CI of 0.97 to 1.08). The median number of days to the first COPD exacerbation was 719 days for tiotropium bromide in inhalation powder and 756 days for tiotropium bromide in inhalation solution.

The bronchodilator effect of tiotropium bromide in inhalation powder was sustained over 120 weeks, and was similar to tiotropium bromide in inhalation solution. The mean difference in trough FEV1 for tiotropium bromide in inhalation powder versus tiotropium bromide in inhalation solution was 0.010 L (95% CI -0.018 to 0.038 L).

In the post-marketing TIOSPIR study comparing tiotropium bromide in inhalation solution and tiotropium bromide in inhalation powder, all-cause mortality including vital status follow up was similar during the study with tiotropium bromide in inhalation powder and tiotropium bromide in inhalation solution (hazard ratio (tiotropium bromide in inhalation powder / tiotropium bromide in inhalation solution) 1.04 with a 95% CI of 0.91 to 1.19).

Paediatric population
The European Medicines Agency has waived the obligation to submit results of studies with tiotropium bromide 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. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation.
At steady state, peak tiotropium plasma levels in COPD patients were 12.9 pg/ml and decreased rapidly in a multi- compartmental manner. Steady state trough plasma concentrations were 1.71 pg/ml. Systemic exposure following the inhalation of tiotropium powder was similar to tiotropium solution.

Distribution:
Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium bromide does not penetrate the blood-brain barrier to any relevant extent.

Biotransformation:
The extent of biotransformation is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. The ester tiotropium bromide is nonenzymatically cleaved to the alcohol (N-methylscopine) and acid compound (dithienylglycolic acid) that are inactive on muscarinic receptors. In-vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (< 20% of dose after intravenous administration) is metabolised by cytochrome P450 (CYP) dependent oxidation and subsequent glutathion conjugation to a variety of Phase II-metabolites.

In vitro studies in liver microsomes reveal that the enzymatic pathway can be inhibited by the CYP 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP 2D6 and 3A4 are involved in metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium bromide even in supra-therapeutic concentrations does not inhibit CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination:
The effective half-life of tiotropium ranges between 27-45 h in COPD patients. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation by COPD patients to steady-state, urinary excretion is 7% (1.3 μg) of the unchanged drug over 24 hours, 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 by day 7 with no accumulation thereafter.

Linearity / Nonlinearity:
Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

c) Other special populations
Elderly:
As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (365 mL/min in COPD patients < 65 years to 271 mL/min in COPD patients ≥ 65 years) This did not result in a corresponding increase in AUC0-6,ss or Cmax,ss values.

Renal Impairment:
Following once daily inhaled administrations of tiotropium to steady-state in COPD patients, mild renal impairment (CLCR 50-80 ml/min) resulted in slightly higher AUC0-6,ss (between 1.8-30% higher) and similar Cmax, ss values compared to patients with normal renal function(CLCR >80 ml/min).
In COPD patients with moderate to severe renal impairment (CLCR <50 ml/min), the intravenous administration of tiotropium resulted in doubling of the total exposure (82% higher AUC0-4h) and 52% higher Cmax) compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.

Hepatic Impairment:
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.

Japanese COPD Patients:
In cross trial comparison, mean peak tiotropium plasma concentrations 10 minutes post-dosing at steady-state were 20% to 70% higher in Japanese compared to Caucasian COPD patients following inhalation of tiotropium but there was no signal for higher mortality or cardiac risk in

Japanese patients compared to Caucasian patients. Insufficient pharmacokinetic data is available for other ethnicities or races.

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 may contain small amounts of milk proteins).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After first opening of the aluminum pouch, use within 60 days.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture. After first opening of the aluminum pouch, use within 60 days, stored below 25ºC. Write the date of first opening of the pouch on the sticker provided on the pouch. Place the sticker on the bottom of the device. Discard the aluminum pouch and the desiccant sachet.

6.5 Nature and contents of container

White plastic inhalation device (Elpenhaler). The device compartment and drug supporting surface are made of ABS (Acrylonitrile Butadiene Styrene). The mouthpiece and storage case are made of Polypropylene. The mouthpiece cap is made of MABS (Methylmethacrylate Acrylonitrile Butadiene Styrene).

1 Elpenhaler device which contains 30 unit dose paper/PET/aluminium-PVC/aluminium/OPA blister strips, is packed in a PET/ALU/PE pouch together with a desiccant sachet. The PET/ALU/PE pouch is packed in a carton box together with the patient information leaflet.

Pack of 30 doses.

2 Elpenhaler devices each containing 30 unit dose paper/PET/aluminium-PVC/aluminium/OPA blister strips, are packed in separate PET/ALU/PE pouches, together with a desiccant sachet. The 2 PET/ALU/PE pouches are packed in a carton box together with the patient information leaflet.

Pack of 60 doses.

3 Elpenhaler devices each containing 30 unit dose paper/PET/aluminium-PVC/aluminium/OPA blister strips, are packed in separate PET/ALU/PE pouches, together with a desiccant sachet. The 3 PET/ALU/PE pouches are packed in a carton box together with the patient information leaflet.

Pack of 90 doses.

Not all pack sizes may be marketed.

The desiccant sachet contained in the PET/ALU/PE pouch should be discarded after first opening. It should not be eaten or inhaled.

The unit dose strips placed inside the Elpenhaler should be only used with this specific device, within the respective shelf life.

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

ELPEN Pharmaceutical Co. Inc.
95 Marathonos Ave.
Pikermi Attica, 19009
Griekenland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 126836

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 14 oktober 2021

10. DATE OF REVISION OF THE TEXT