Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tiotropium Clonmel 18 microgram inhalation powder, hard capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 22.5 microgram tiotropium bromide monohydrate equivalent to 18 microgram tiotropium.

The delivered dose (the dose that leaves the mouthpiece of the Vertical-Haler device) is 10 microgram tiotropium.

Excipient with known effect:
Each capsule contains 5.204 milligram of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule.

Opaque, green capsule with a size of 16 mm x 5.8 mm containing the inhalation powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tiotropium Clonmel 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 recommended dosage of tiotropium bromide is inhalation of the contents of one capsule once daily with the Vertical-Haler at the same time of day. You must breathe in 2 times from the same capsule.
The recommended dose should not be exceeded.
Tiotropium Clonmel should only be inhaled with the Vertical-Haler device.

Special populations

Elderly
Elderly patients can use tiotropium at the recommended dose.

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

Hepatic impairment
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 Clonmel in children and adolescents has not been established. No data are available.

Method of administration

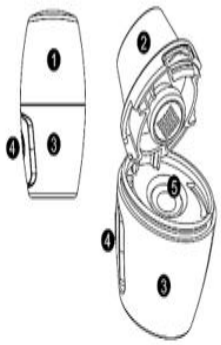
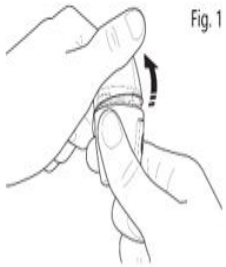
For inhalation use only.
The capsule must not be swallowed.

The capsule should only be removed from the blister immediately before using the inhaler!

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

Instructions for handling and use

The patient must be advised to carefully follow the doctor's instructions for using Tiotropium Clonmel. The Vertical-Haler is especially designed for Tiotropium Clonmel. It must not be use to take any other medication. The Vertical-Haler can be used for up to 90 days to take the medication.

	**Vertical-Haler - explanation of different parts** 1 Cap 2 Mouthpiece 3 Base 4 Push button 5 Capsule chamber
 Fig. 1	**1. Removing the cap** Hold the Vertical-Haler and remove the cap upwards from the base to expose mouthpiece as shown (Fig. 1).

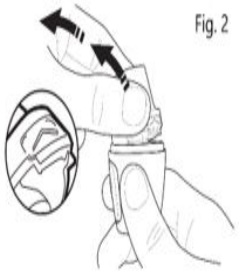
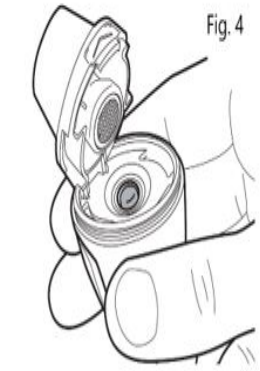
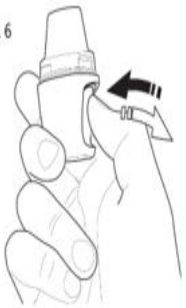
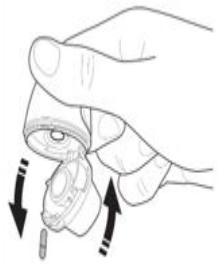
 Fig. 2	**2. Opening** To open the Vertical-Haler, hold it on the base sides. Press the "^" marked area (as shown on enlarged picture) with your fingertip. Open the inhaler by pulling the mouthpiece up away from the base as shown (Fig. 2).
 Fig. 3	**3. Inserting the capsule** Hold the Vertical-Haler opened upward. Insert the capsule shell inside the capsule chamber (Fig. 3). Please note: The capsule should only be removed from the blister immediately before using the inhaler!
 Fig. 4	Make sure that the capsule shell is correctly inserted (Fig. 4).
 Fig. 5	**4. Closing the compartment** Close the mouthpiece firmly against the base until you will hear a "click" (Fig. 5).

Fig. 6 	**5. Piercing the capsule** Hold the Vertical-Haler with the mouthpiece upwards. Press the button firmly once full course until it is totally hidden (Fig. 6). Release the button back up. This will pierce the capsule, so you can inhale the medication when you breathe in. **Attention: In case you need to repeat Step 5, open the capsule chamber (Fig. 2) to make sure the capsule shell is correctly inserted (Fig. 4).**
Fig. 7 	**6. Prepare to use** Hold the Vertical-Haler away from your mouth and breathe out emptying your lungs of air. (Fig. 7) **Do not blow into the Vertical-Haler.**
Fig. 8 	**7. Inhalation** Hold your next breath with the head in upright position, seal your lips around the mouthpiece. Inhale slowly and deeply as possible (Fig. 8). You will hear a vibrating sound of the capsule rotating inside the capsule chamber for dispersion of the drug. Breathe in until your lungs are full; then hold your breath as long as comfortable and at the same time take the Vertical-Haler out of your mouth. Resume normal breathing. **Repeat steps 6 and 7 one more time. You must breathe in 2 times from the same capsule.**
	Attention: **When holding the inhaler during inhalation, make sure not to block the airways located on the sides of the mouthpiece. This can impede the air to flow inside the inhaler, reducing the capsule movement, and drug dispersion. Do not push the mouthpiece down during inhalation. This can block the capsule movement.**

	**Cleaning your Vertical-Haler** After use, open the mouthpiece. Hold the inhaler facing down to remove the capsule from the capsule chamber. Clean the mouthpiece and the capsule chamber with a clean, dry cloth. Alternatively, a soft, clean brush can be used to remove residual powder inside the capsule chamber. Close the mouthpiece and place the cap on. This will keep the dry powder inhaler clean and dry. If needed, the outside of the mouthpiece should be cleaned with a damp cloth.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients 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, 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 medicinal product 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 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 inhalation 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).

Excipients
Tiotropium Clonmel contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

The excipient lactose 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 section 5.3). As a precautionary measure, it is preferable to avoid the use of Tiotropium Clonmel 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 tiotropium 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 tiotropium should be made taking into account the benefit of breast-feeding to the child and the benefit of tiotropium 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 Clonmel.

Tabulated list 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.

Adverse reactions are listed by System Organ Class and frequency. Frequencies are defined according to 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**
Immune system disorders	
Hypersensitivity (including immediate reactions)	**Rare**
Anaphylactic reaction	**Not known**
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**
Dysphonia	**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	
Rash	**Uncommon**
Urticaria	**Rare**
Pruritus	**Rare**
Angioedema	**Rare**
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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

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 340 microgram tiotropium bromide in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following 7 day dosing of up to 170 microgram tiotropium bromide in healthy volunteers. In a multiple dose study in COPD patients with a maximum daily dose of 43 microgram tiotropium bromide over four weeks no significant undesirable effects have been observed.

Acute intoxication by inadvertent oral ingestion of tiotropium bromide capsules is unlikely due to low oral bioavailability.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, anticholinergics; ATC code: R03BB04

Mechanism of action
Tiotropium 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 inhibits the cholinergic

(bronchoconstrictive) effects of acetylcholine, released from parasympathetic nerve endings. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, tiotropium competitively and reversibly antagonises the M_3 receptors, resulting in relaxation. The effect was dose dependent and lasted longer than 24 h. The long duration is probably due to the very slow dissociation from the M_3 receptor, exhibiting a significantly longer dissociation half-life than ipratropium. As an N-quaternary anticholinergic, tiotropium 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 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.

Cardiac electrophysiology
Electrophysiology: In a dedicated QT study involving 53 healthy volunteers, tiotropium 18 microgram and 54 microgram (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 2 663 patients (1 308 receiving tiotropium). 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, 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 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 significantly improved morning and evening PEFR (peak expiratory flow rate) as measured by patient's daily recordings. The bronchodilator effects of tiotropium 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 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 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, randomised, double-blind, placebo-controlled clinical trial of 492 patients, tiotropium 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 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 randomised, double-blind, placebo controlled trial of 1 829 patients with moderate to very severe COPD, tiotropium 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 group and 9.5% of patients in the placebo group were hospitalised due to a COPD exacerbation (p=0.056). The number of hospitalisations due to COPD was reduced by 30 % (0.25 to 0.18 events per patient year of exposure).

A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 microgram 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 (inhalation powder) N=3 707	Salmeterol 50 microgram HFA pMDI N=3 669	Ratio (95 % CI)	p-value
Time [days] to first exacerbation [1]	**187**	**145**	**0.83 (0.77-0.90)**	**< 0.001**
Time to first severe (hospitalised) exacerbation [2]	**-**	**-**	**0.72 (0.61-0.85)**	**< 0.001**
Patients with ≥ 1 exacerbation, n (%) [3]	**1277 (34.4)**	**1414 (38.5)**	**0.90 (0.85-0.95)**	**< 0.001**
Patients with ≥ 1 severe (hospitalised) exacerbation, n (%) [3]	**262 (7.1)**	**336 (9.2)**	**0.77 (0.66-0.89)**	**< 0.001**

[1] 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.
[2] 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.
[3] 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 inhalation powder and tiotropium inhalation solution (5 694 patients receiving tiotropium inhalation powder; 5 711 patients receiving tiotropium 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 inhalation powder and tiotropium soft mist inhaler (hazard ratio (tiotropium inhalation powder/ tiotropium soft mist inhaler) 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 inhalation powder and 756 days for tiotropium soft mist inhaler.

The bronchodilator effect of tiotropium inhalation powder was sustained over 120 weeks and was similar to tiotropium soft mist inhaler. The mean difference in trough FEV_1 for tiotropium inhalation powder versus tiotropium soft mist inhaler was 0.010 l (95 % CI -0.018 to 0.038 l).

In the post-marketing TIOSPIR study comparing tiotropium soft mist inhaler and tiotropium inhalation powder, all-cause mortality including vital status follow up was similar during the study with tiotropium inhalation powder and tiotropium soft mist inhaler (hazard ratio (tiotropium inhalation powder/tiotropium soft mist inhaler) 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 the reference medicinal product containing tiotropium 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

General introduction
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 than recommended for therapy.

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 multicompartmental manner. Steady state trough plasma concentrations were 1.71 pg/ml. Systemic exposure following the inhalation of tiotropium inhalation powder was similar to tiotropium inhaled via the soft mist inhaler.

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 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 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 glutathionconjugation 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 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 in steady-state, urinary excretion is 7 % (1.3 micrograms) 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/non-linearity
Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

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 $AUC_{0-6, ss}$ or $C_{max, ss}$ values.

Renal impairment: Following once daily inhaled administrations of tiotropium to steady-state in COPD patients, mild renal impairment (CL_{CR} 50-80 ml/min) resulted in slightly higher $AUC_{0-6, ss}$ (between 1.8-30 % higher) and similar $C_{max, ss}$ values compared to patients with normal renal function(CL_{CR} > 80 ml/min).
In COPD patients with moderate to severe renal impairment (CL_{CR} < 50 ml/min), the intravenous administration of tiotropium resulted in doubling of the total exposure (82 % higher AUC_{0-4h}) and 52 % higher C_{max}) 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 population: See section 4.2

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. 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 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

Capsule content:
Lactose monohydrate (which may contain small amount of milk protein)

Capsule shell:
Gelatin (E441)
Water, purified
Macrogol 4000 (E1521)
Titanium Dioxide (E171)
Yellow Iron Oxide (E172)
Brilliant Blue (E133)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Discard the inhaler 90 days after first use.

The capsule should be used directly after opening the blister.

6.4 Special precautions for storage

Do not store above 30 °C.

For storage conditions after first opening of the medical product, see section 6.3.

6.5 Nature and contents of container

Heat-sealed Aluminium / Aluminium push-through blister containing 5 or 10 capsules.

The Vertical-Haler device is a single dose inhaler made from acrylonitrile
butadiene styrene (ABS) plastic materials and stainless steel. Materials that come in direct contact with the product at the time of inhalation are: stainless steel 304 (needles that pierce the capsule), acrylonitrile butadiene styrene-ABS-(forming the mouthpiece through which the drug flows and the capsule chamber).

Package size:

- Carton box containing Vertical-Haler device and 10 capsules
- Carton box containing Vertical-Haler device and 15 capsules
- Carton box containing Vertical-Haler device and 30 capsules
- Carton box containing Vertical-Haler device and 60 capsules
- Carton box containing Vertical-Haler device and 90 capsules
- Hospital pack: Carton box containing Vertical-Haler device and 5x30 capsules (bundle pack)

- Carton box containing two Vertical-Haler devices and 60 capsules
- Carton box containing three Vertical-Haler devices and 90 capsules

- Hospital pack: Carton box containing 5x60 capsules (bundle pack)
- Carton box containing 30 capsules
- Carton box containing 60 capsules
- Carton box containing 90 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd

Waterford Road
Clonmel, Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/360/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd August 2024

10 DATE OF REVISION OF THE TEXT