1.5.5.2 Clean Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TIOTOR 10 hard capsules for inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule for inhalation contains 16 micrograms of tiotropium bromide equivalent to 13 micrograms of tiotropium.

The delivered dose (the dose that leaves the mouthpiece of the Zephir Inhaler) is 10 micrograms of tiotropium per capsule.

Excipient with known effect: TIOTOR 10 contains sugar (lactose monohydrate) 17,98 mg per capsule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule for inhalation.

TIOTOR 10 is colourless and transparent, size 3 capsules, containing white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TIOTOR 10 is indicated for the long-term maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and chronic bronchitis associated with emphysema.

4.2 Posology and method of administration

Posology

Recommended dosage: Inhale the contents of one capsule once daily, at the same time each day, using the Zephir Inhaler device.

TIOTOR 10 capsules must not be swallowed.

Optimum efficacy can only be expected within a few days of usage.

Special Populations:

Elderly patients can use the recommended dose of TIOTOR 10 capsules for inhalation.

Renally impaired patients can use tiotropium at the recommended dose. However, TIOTOR 10 use should be monitored closely in patients with moderate to severe renal impairment (see sections 4.4 and 5.2).

Hepatically impaired patients can use TIOTOR 10 at the recommended dose (see section 5.2).

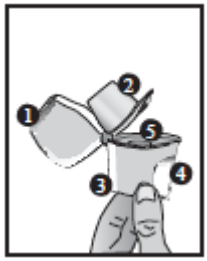
Paediatric population

The safety and efficacy in children have not been established. No data are available.

Method of administration

To ensure proper administration of the TIOTOR 10 the patient should be trained how to use the inhaler by the medical practitioner or by other healthcare professionals.

The Zephir Inhaler is especially designed for TIOTOR 10. The Zephir Inhaler must not be used ~~it~~ to take any other medication. Zephir Inhaler can be used for up to one year to take TIOTOR 10.



1. Dust cap

2. Mouthpiece

3. Base

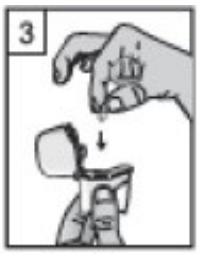
4. Piercing button

5. Centre chamber

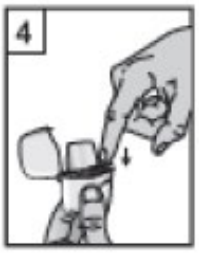
1. Pull the dust cap upwards.

2. Hold the base of the inhaler firmly and open the mouthpiece by pulling it upwards, in the direction of the arrow.

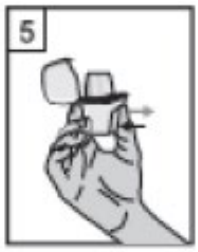
3. Place one capsule in the capsule-shaped compartment in the base of the inhaler.



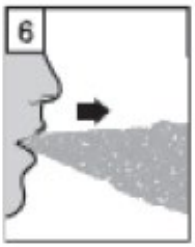
4. Close the mouthpiece until you hear a click, leaving the dust cap open.



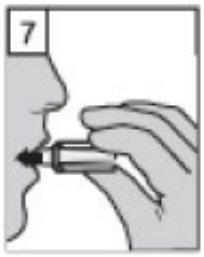
5. Hold the inhaler with the mouthpiece upwards, and firmly press the piercing button completely in once. Release the button. This will pierce the capsule.



6. Breathe out fully. It is important to do this away from the mouthpiece.

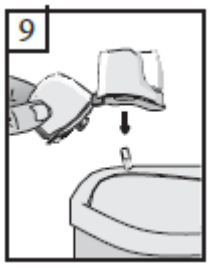


7. Place the mouthpiece in your mouth and tilt your head in an upright position. Close your lips around the mouthpiece and breathe in slowly and deeply enough to hear or feel the capsule vibrating inside the compartment.



8. Hold you breath for as long as you comfortably can while taking the inhaler out of your mouth. Then breathe normally. Repeat steps 6 to 8 to empty the capsule completely.

9. After use, tip out the empty capsule. Close the mouthpiece and dust cap, and store your Zephir inhaler.



TIOTOR 10 capsules contain only a small amount of powder, so that the capsule is only partially filled.

If necessary, the patient may wipe the mouthpiece of the Zephir inhaler after use with a dry cloth or tissue.

4.3 Contraindications

Hypersensitivity to tiotropium bromide or to atropine or its derivatives, e.g. ipratropium or oxitropium or to any excipient of TIOTOR 10 listed in section 6.1.

Contraindicated in children below 18 years as safety and efficacy have not been demonstrated

4.4 Special warnings and precautions for use

Tiotropium bromide as contained in TIOTOR 10, 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 TIOTOR 10 inhalation powder.

Consistent with its anticholinergic activity, TIOTOR 10 should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. (see section 4.8).

Inhaled TIOTOR 10 may cause inhalation-induced bronchospasm.

TIOTOR 10 should be used with caution in patients with recent myocardial infarction < 6 months; any unstable or life-threatening cardiac dysrhythmia or cardiac dysrhythmia requiring intervention or a

change in medicine 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), the use of TIOTOR 10 should be monitored closely in these patients. There is no long-term experience in patients with severe renal impairment (see section 5.2).

Patients should be cautioned to avoid getting the medicine 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 TIOTOR 10 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.

TIOTOR 10 should not be used more frequently than once daily (see section 4.9).

TIOTOR 10 contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TIOTOR 10.

4.5 Interaction with other medicines and other forms of interaction

Although no formal medicine interaction studies have been performed, TIOTOR 10 inhalation powder has been used concomitantly with other medicines without clinical evidence of medicine interactions.

These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, commonly used in the treatment of COPD.

Use of long-acting β2 agonists (LABA) or inhaled corticosteroids (ICS) was not found to alter the exposure to tiotropium.

The co-administration of TIOTOR 10 with other anticholinergic-containing medicines 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 TIOTOR 10 during pregnancy.

Breastfeeding

It is unknown whether TIOTOR 10 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 TIOTOR 10 is not recommended during breast-feeding. Tiotropium bromide as contained in TIOTOR 10 is a long-acting compound. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with TIOTOR 10 should be made taking into account the benefit of breast-feeding to the child and the benefit of TIOTOR 10 therapy to the woman.

Fertility

Clinical data on fertility are not available for TIOTOR 10. An animal 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

a. Summary of the safety profile

Many of the listed undesirable effects can be assigned to the anticholinergic properties of TIOTOR 10.

b. 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 placebo controlled clinical trials with treatment periods ranging from four weeks to four years.

System Organ Class (MedDRA)	**Frequency**	**Adverse reaction**
Metabolism and nutrition disorders	*Frequency unknown*	Dehydration
Nervous system disorders	*Less frequent*	Dizziness, headache, taste disorders, insomnia
Eye disorders	*Less frequent*	Blurred vision, glaucoma, increased intraocular pressure
Cardiac disorders	*Less frequent*	Atrial fibrillation, supraventricular tachycardia, tachycardia, palpitations
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Pharyngitis, dysphonia, cough, bronchospasm, epistaxis, laryngitis, sinusitis

Gastrointestinal disorders	*Frequent*	Dry mouth
	Less frequent	Gastro-oesophageal reflux disease, constipation, oropharyngeal candidiasis, intestinal obstruction, including ileus paralytic, gingivitis, glossitis, dysphagia, stomatitis, nausea
	Frequency unknown	Dental caries, mouth ulceration, pharyngolaryngeal pain, hoarseness, throat irritation
Skin and subcutaneous tissue disorders	*Less frequent*	Rash, urticaria, pruritus, hypersensitivity (including immediate reactions), angioedema
	Frequency unknown	Anaphylactic reaction, skin infection, skin ulcer, dry skin, pruritis
Musculoskeletal and connective tissue disorders	*Frequency unknown*	Joint swelling
Renal and urinary disorders	*Less frequent*	Dysuria, urinary retention, urinary tract infection

Description of selected adverse reactions

The most commonly observed undesirable effects were anticholinergic undesirable side effects such as dry mouth.

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

High doses of tiotropium bromide may lead to anticholinergic signs and symptoms.

Acute intoxication by inadvertent oral ingestion of TIOTOR 10 capsules is unlikely due to low oral bioavailability. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, anticholinergics.

ATC code: R03B B04

Pharmacological classification: A10.2.1 Bronchodilators - inhalants

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, M_1 to M_5. In the airways, tiotropium bromide competitively and reversibly antagonises the M3 receptors, resulting in relaxation. The effect was dose dependent and lasted longer than 24 hours. 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 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 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

Reports from a QT study shows that tiotropium bromide did not significantly prolong QT intervals of the ECG.

5.2 Pharmacokinetic properties

Tiotropium bromide is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium bromide is administered by dry powder inhalation. After oral administration of aqueous solutions, tiotropium is not readily absorbed into the systemic circulation of rats and dogs. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability ~~of~~ is 19,5 %. Oral solutions of tiotropium have an absolute observed bioavailability of 2 - 3 %. Maximum tiotropium plasma concentrations were observed five minutes after inhalation.

Distribution

Tiotropium has a plasma protein binding of 72 % and shows a volume of distribution (V_{SS}) of 32 L/kg after intravenous administration in young healthy volunteers. At steady state, peak tiotropium plasma levels in COPD patients were 17 - 19 pg/ml when measured five minutes following dry powder inhalation of an 18 µg dose and decreased rapidly in a multicompartmental manner. Steady state trough plasma concentrations were 3 - 4 pg/ml. 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 major metabolic pathway is ~~T~~the ester tiotropium bromide which is nonenzymatically cleaved to the alcohol (N-methylscopine) and acid compound (dithienylglycolic acid) that are inactive on muscarinic receptors. Some faecal excretion is seen in the rat and dog.

In-vitro experiments with human liver microsomes and human hepatocytes suggest that some further medicine (< 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.

This enzymatic pathway can be inhibited by the CYP 450 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Therefore, CYP 450 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 cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination

The terminal elimination half-life of tiotropium ranges 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 %. Urinary excretion of unchanged substance in young healthy volunteers is 74 % of an intravenous dose. After dry powder inhalation of tiotropium, urinary excretion is 14 % of the dose, the remainder being mainly non-absorbed medicine in the gut that is eliminated via the faeces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2 - 3 weeks.

Linearity / Nonlinearity

Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

Special populations

Elderly patients:

Advanced age was associated with a significant decrease of tiotropium renal clearance (326 mL/min in COPD patients < 58 years to 163 mL/min in COPD patients > 70 years), which is probably explained by decreased renal function. Tiotropium excretion in urine after inhalation decreased from 14 % (young healthy volunteers) to about 7 % (COPD Patients), however plasma concentrations did not change significantly with advanced age within COPD patients if compared to inter-and intra-individual variability (43 % increase in AUC_{0-4h} after dry powder inhalation).

Renally impaired patients:

Renal impairment was associated with increased plasma drug concentrations and reduced renal drug clearance after both intravenous infusion and dry powder inhalations. Mild renal impairment (CL_{CR} 50 - 80 mL/min), which is often seen in elderly patients increased tiotropium plasma concentrations by 39 % for AUC_{0-4h} after intravenous infusion. In COPD patients with moderate to severe renal impairment (CL_{CR} < 50 mL/min) the intravenous administration of tiotropium resulted in doubling of the plasma

concentrations (82 % increase in AUC_{0-4h}) which was confirmed by plasma concentrations after dry powder inhalation.

Hepatically impaired patients:

Although formal studies in patients with impaired liver function have not been done, ~~L~~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 that do not bind to muscarinic receptors.

Paediatric patients:

See section 4.2

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 (capsule powder)

Hydroxypropylmethylcellulose (HPMC), commonly known as hypromellose (capsule shell).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

An in-use stability of 60 days for the 30 capsules packed in HDPE bottle and 30 days for the 15 capsules packed in HDPE bottle.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the bottle tightly closed. Store in the original package to protect from moisture.

Do not refrigerate or freeze.

6.5 Nature and contents of container

Cartons containing a Zephir Inhaler device and 15 or 30 hard capsules for inhalation.

The capsules are packaged in plastic (HDPE) bottles closed with a polypropylene screw cap with PE safety ring and a LDPE desiccant capsule containing silica gel.

Zephir Inhaler Device: The inhaler consists of a green cap and lower, white mouthpiece and body and perforating system with 2 needles. The internal grid includes a pin. The push-bottom is white. The Zephir inhaler is a single dose inhalation device made from plastic materials (ABS) and stainless steel.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

51/10.2.1/1120

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 August 2021

10. DATE OF REVISION OF THE TEXT

04 May 2022