PROFESSIONAL INFORMATION FOR TIORES

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TIORES capsules for inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule for inhalation contains 15,6 µg tiotropium bromide equivalent to 13 µg tiotropium, with a delivered dose of 10 µg tiotropium.

Contain sugar (lactose monohydrate, 18 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules for inhalation

Colourless and transparent, size 3 capsule, containing white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TIORES 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:

TIORES capsules are intended for inhalation use only and must not be swallowed.

The recommended dosage of TIORES:

PROFESSIONAL INFORMATION FOR TIORES

Inhale the contents of one capsule once daily, at the same time each day, using the Zephir inhaler (see Instructions for handling and use).

The recommended dose should not be exceeded.

The contents of TIORES capsules should only be inhaled using the Zephir inhaler.

Special populations

Elderly:

Elderly patients can use TIORES at the recommended dose

Renal impairment:

Renally impaired patients can use TIORES at the recommended dose.

For patients with moderate to severe impairment (creatinine clearance ≤ 50 mL/min)

See section 4.5.

Hepatic impairment:

Hepatically impaired patients can use TIORES at the recommended dose.

Method of administration:

For oral inhalation.

Instructions for handling and use:

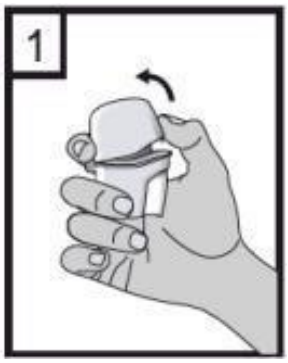
To ensure proper use of TIORES, the patient should be trained how to use the Zephir inhaler by the medical practitioner or other healthcare professionals. The Zephir inhaler is specifically designed for TIORES capsules. The Zephir inhaler must not be used to take any other medication. Patients should also be advised not to use any other inhalers other that the Zephir inhaler, with TIORES capsules.

Discard the Zephir inhaler after 30 uses.

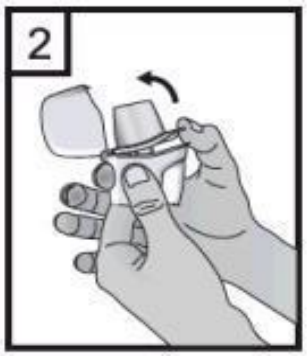


1. Dust cap
2. Mouthpiece
3. Base
4. Piercing button
5. Centre chamber

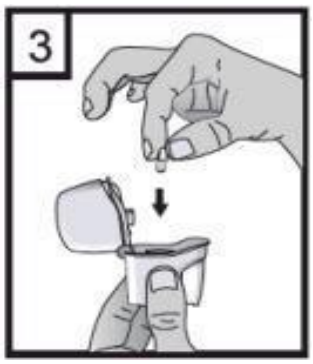
Step 1: Pull the cap upwards.



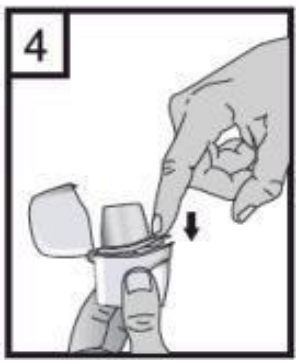
Step 2: Hold the base of the inhaler firmly and open the mouthpiece by pulling it upwards in the direction of the arrow to open it.



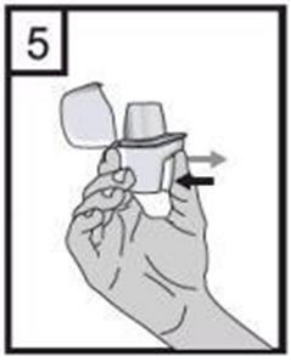
Step 3: Remove a TIORES capsule from the bottle immediately before use. Place one capsule in the capsule-shaped compartment in the base of the inhaler. It doesn't matter which way the capsule is placed in the chamber.



Step 4: Close the mouthpiece until a click is heard, leaving the cap open

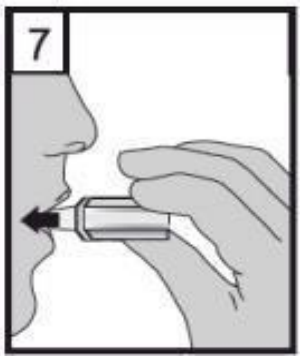


Step 5: Hold the inhaler with the mouthpiece upwards, and press the piercing button completely in only once. Release the button. This will pierce the capsule and allows TIORES to be released when the patient breathes in.



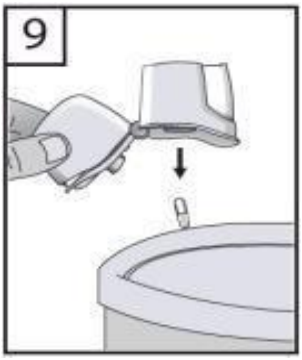
Step 6: Breathe out fully. It is important to do this away from the mouthpiece. Avoid breathing into the mouthpiece at any time.

Step 7: Place the mouthpiece in your mouth and keep your head in an upright position. Close your lips around the mouthpiece and breathe in slowly and deeply enough, to hear or feel the TIORES capsule vibrating inside the compartment. Hold your breath for as long as you comfortably can whilst taking the Zephir inhaler out of your mouth.
Resume normal breathing.



Step 8: Repeat steps 6 and 7 to empty the capsule completely

Step 9: After use, open the mouthpiece again. Tip out and dispose of the empty TIORES capsule. Close the mouthpiece and cap, and store the Zephir inhaler.



4.3 Contraindications

- Hypersensitivity to tiotropium or atropine and any of its derivatives (e.g. ipratropium, oxitropium), or to any of the inactive ingredients of TIORES (listed in section 6.1).
- Children, as safety and efficacy have not been demonstrated.

4.4 Special warnings and precautions for use

TIORES 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 TIORES. Should this happen, TIORES should be stopped and other treatment should be considered.

Inhaled TIORES may cause inhalation-induced bronchospasm. Should this happen, TIORES should be stopped, and other treatment should be considered.

Consistent with its anticholinergic activity, TIORES should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Patients should be cautioned to avoid getting TIORES powder into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle

glaucoma. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these eye symptoms develop, patients should stop using TIORES and a medical practitioner should be sought immediately. Miotic eye drops are not considered to be effective treatment for eye symptoms following the use of TIORES.

Dry mouth, which has been observed with TIORES use, may in the long term be associated with dental caries.

An increase in anticholinergic activity may occur with increasing age.

The use of TIORES should be monitored closely in patients with moderate to severe renal impairment ($CL_{CR} \leq 50$ mL/min).

TIORES should not be used more frequently than once daily (see section 4.2).

Excipient warning

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

4.5 Interaction with other medicines and other forms of interaction

TIORES has been used concomitantly with other medications without clinical evidence of medicine interactions. These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, commonly used in the treatment of COPD.

The co-administration of TIORES with other anticholinergic-containing medicines

has not been studied and is therefore not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Studies in animals have shown reproductive toxicity associated with maternal toxicity. The potential risk for humans is unknown. TIORES should only be used during pregnancy when clearly indicated.

Breastfeeding

Safety in lactation has not been established.

It is unknown whether TIORES is excreted in breast milk. Therefore the use of TIORES is not recommended during breastfeeding.

4.7 Effects on ability to drive and use machines:

The occurrence of dizziness, blurred vision, or headache may influence the ability to drive and use machinery. Patients should be advised to take special care before performing tasks requiring their attention, until they know how TIORES will affect them.

4.8 Undesirable effects

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Less frequent	Infections (fever or chills, lower back or side pain), herpes zoster.
Immune system disorders	Less frequent	Hypersensitivity (including immediate reactions),

	Frequency unknown	angioedema. Anaphylactic reaction.
Metabolism and nutrition disorders	Less frequent Frequency unknown	Oedema, hyperglycaemia, hypercholesterolemia. Dehydration.
Psychiatric disorders	Less frequent	Depression.
Nervous system disorders	Less frequent	Dizziness, headache, taste disorders, insomnia, paraesthesia.
Eye disorders	Less frequent	Blurred vision, glaucoma, increased intraocular pressure.
Cardiac disorders	Frequent Less frequent	Angina pectoris, chest pain. Atrial fibrillation, supraventricular tachycardia, tachycardia, palpitations.
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Pharyngitis, rhinitis, sinusitis, upper respiratory tract infection Dysphonia, cough, bronchospasm, epistaxis, laryngitis.
Gastrointestinal disorders	Frequent Less frequent	Dry mouth, dyspepsia Gastroesophageal reflux disease, constipation, oropharyngeal candidiasis, intestinal obstruction (including

	Frequency unknown:	ileus paralytic), gingivitis, glossitis, dysphagia, stomatitis, nausea, vomiting, abdominal pain, monsiliasis. Dental caries.
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Rash, urticaria, pruritus. Skin infection, skin ulcer, dry skin.
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Leg pain, myalgia, skeletal pain Swelling of the joint.
Renal and urinary disorders	Frequent Less frequent	Urinary tract infection Dysuria, urinary retention.

Post-marketing experience:

General disorders and administrative site conditions:

Application site irritation (glossitis, mouth ulceration, pharyngolaryngeal pain), oral candidiasis, throat irritation.

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. Health care professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms:

High doses of TIORES may lead to anticholinergic signs and symptoms. Acute intoxication by inadvertent oral ingestion of TIORES capsules is unlikely due to low oral bioavailability.

Treatment:

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 is a long-acting, specific, muscarinic receptor antagonist. In vitro, it has similar affinity to subtypes of muscarinic receptors, M1 to M5. In the airways, tiotropium 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 M3 receptor, exhibiting a significantly longer dissociation half-life than ipratropium.

5.2. Pharmacokinetic properties

Tiotropium is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium is administered by dry powder inhalation. $_{04-}$Generally, with the inhaled route of administration, part of the delivered dose is also deposited in the gastrointestinal tract. 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 is 19,5 %. Oral solutions of tiotropium have an absolute bioavailability of 2 – 3 %. Maximum tiotropium plasma concentrations were observed 5 minutes after inhalation. Food is not expected to influence the absorption of tiotropium.

Distribution:

Tiotropium has a plasma protein binding of 72 % and shows a volume of distribution of 32 Ll/kg after intravenous administration. At steady state, tiotropium plasma levels in COPD patients at peak, were 17 – 19 pg/mL when measured 5 minutes after dry powder inhalation of an 18 µg/mL dose and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 3 – 4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier to any relevant extent.

Biotransformation:

The extent of biotransformation is small. This is evident from a urinary excretion of 74 % of unchanged substance after an intravenous dose to young healthy volunteers. The ester tiotropium is non-enzymatically cleaved to the alcohol (N-methylscopine) and acid compound (dithienylglycolic acid) that are inactive on muscarinic receptors. Some faecal excretion is seen in rats and dogs. In vitro experiments with human liver microsomes and human hepatocytes suggest that some tiotropium (< 20 % of dose after intravenous administration) is metabolised by cytochrome P450 (CYP) dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-metabolites. 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 terminal elimination half-life of tiotropium is between 5 and 6 days following inhalation. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers with an inter-individual variability of 22 %. Intravenously administered tiotropium is mainly excreted unchanged in urine (74 %). Following dry powder inhalation, urinary excretion is 14 % of the dose, the remainder being mainly non-absorbed medicine in the gut and eliminated via the faeces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2 – 3 weeks with no accumulation thereafter. Tiotropium demonstrates linear pharmacokinetics in the therapeutic range after both intravenous administration and dry powder inhalation.

Special populations:

Elderly patients:

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

Renally impaired patients:

Renal impairment was associated with increased plasma concentrations and reduced renal clearance, after both intravenous infusion and dry powder inhalations. Mild renal impairment (CL_{CR} 50 – 80 mL/min) which is often seen in elderly patients, increased tiotropium plasma concentrations slightly (39 % increase in AUC_{0-4h} after intravenous infusion). In COPD patients with moderate to severe renal impairment (CL_{CR} <50 mL/min) the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82 % increase in AUC_{0-4h}), which was confirmed by plasma concentrations after dry powder inhalation.

Hepatically impaired patients:

Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74 % in young healthy volunteers) and by simple non-enzymatic ester cleavage to pharmacologically inactive products.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC

Once opened, keep the bottle tightly closed. Store in the original bottle to protect

from moisture.

Discard the Zephir inhaler after 30 uses.

6.5 Nature and contents of container

A white HDPE bottle and white polypropylene screw-cap closure, with a polyethylene seal. The screw-cap includes a desiccant compartment containing silica gel. Each HDPE bottle is packed in an outer carton, together with a green and white Zephir inhaler.

Pack sizes: 15 capsules and 1 inhaler, 30 capsules and 1 inhaler, or 3 x 30 capsules and 3 inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd.

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8. REGISTRATION NUMBERS

50/10.2.1/0671

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 28 November 2019

10. DATE OF REVISION OF THE TEXT

23 July 2025