Professional information for NEUMOTROPIO

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NEUMOTROPIO 10 µg inhalation powder, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 13 µg tiotropium (as tiotropium bromide methanol solvate), with a delivered dose of 10 µg tiotropium.

Excipient with known effect:

Contains sugar: each capsule contains 18 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsules.

Colourless and transparent, size 3 capsules, partially filled with white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEUMOTROPIO 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

Route of administration:

For inhalation use.

Recommended dosage:

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

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

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

The recommended dose should not be exceeded.

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

Special populations

Elderly population:

Elderly patients can use NEUMOTROPIO at the recommended dose.

Renal impairment:

Renally impaired patients can use NEUMOTROPIO at the recommended dose. However, NEUMOTROPIO use should be closely monitored in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 mL/min), see sections 4.4 and 5.2.

Hepatic impairment:

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

Paediatric population:

The safety and efficacy of NEUMOTROPIO in children have not been demonstrated (see section 4.3).

Method of administration

To ensure proper administration of NEUMOTROPIO the patient should be trained how to use the inhaler by the prescribing doctor or other health care provider.

Instructions for use and handling:

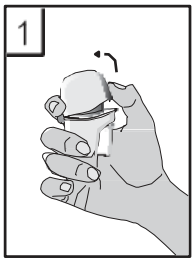
The Zephir inhaler is specifically designed for NEUMOTROPIO capsules. The Zephir inhaler must not be used to take any other medication. Patients should also be advised not to use any other inhalers other that the Zephir inhaler, with NEUMOTROPIO capsules.

To avoid the risk of choking, instruct the patient to never place a capsule directly onto the mouthpiece. Discard the Zephir inhaler after 30 uses (or 15 uses, if used in conjunction with the 15 capsule bottle).

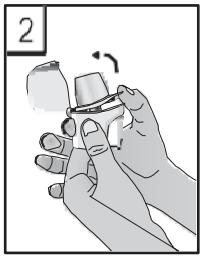


1. Dust cap
2. Mouthpiece
3. Base
4. Piercing button
5. Centre chamber

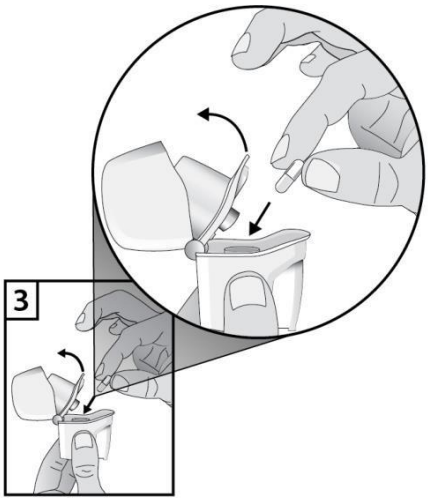
Step 1: Lift the cap upwards.



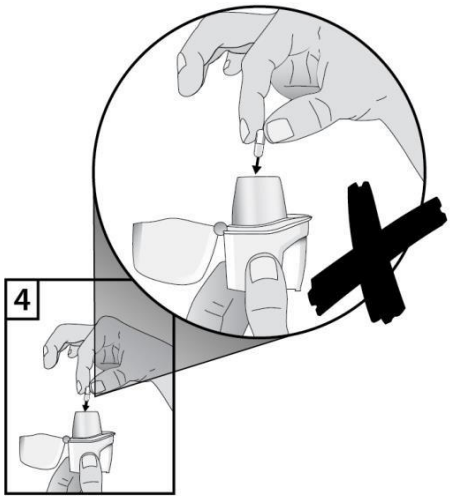
Step 2: Hold the base of the inhaler firmly and open the mouthpiece by lifting it upwards in the direction of the arrow to open it.



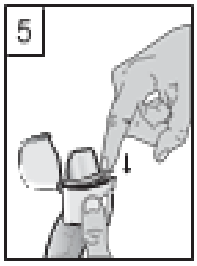
Step 3: Remove a NEUMOTROPIO capsule from the bottle immediately before use and close the bottle tightly. Place one capsule in the centre chamber in the base of the inhaler. Do not store the capsule in the Zephir inhaler.



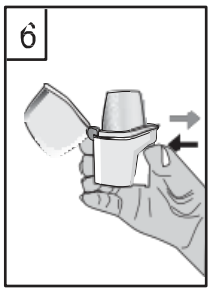
Step 4: To avoid the risk of choking, NEVER place a capsule directly into the mouthpiece.



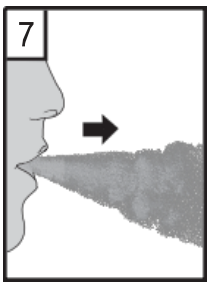
Step 5: Close the mouthpiece until a click is heard, leaving the dust cap open.



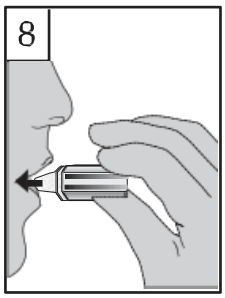
Step 6: Hold the inhaler with the mouthpiece upwards and press the piercing button completely in once. Release the button. This will pierce the capsule and allows the NEUMOTROPIO to be released when the patient breathes in.



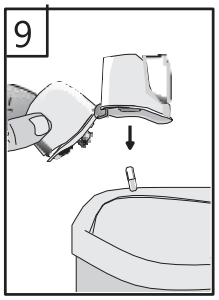
Step 7: Breathe out fully. It is important to do this away from the mouthpiece. Avoid breathing into the mouthpiece at any time.



Step 8: 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 capsule vibrating inside the centre chamber. Hold your breath for as long as you comfortably can whilst taking the inhaler out of your mouth. Then breathe normally. Repeat steps 7 and 8 to empty the capsule completely.



Step 9: After use, open the mouthpiece again, and tip out the empty capsule. Close the mouthpiece and dust cap and store the Zephir inhaler.



4.3 Contraindications

- Hypersensitivity to tiotropium or to any of the excipients listed in section 6.1.
- Hypersensitivity to atropine or its derivatives, e.g. ipratropium or oxitropium.
- Children.

4.4 Special warnings and precautions for use

NEUMOTROPIO, 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 NEUMOTROPIO.

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

Inhaled medicines such as NEUMOTROPIO may cause inhalation-induced bronchospasm.

NEUMOTROPIO 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 medication in the past year; hospitalisation due to 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) NEUMOTROPIO use in these patients should be closely monitored. There is no long term experience in patients with severe renal impairment (see section 5.2).

Patients should be cautioned to avoid getting tiotropium 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 NEUMOTROPIO and consult a doctor immediately.
Miotic eye drops are not considered to be effective treatment for eye symptoms following the use of NEUMOTROPIO.

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

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

4.5 Interaction with other medicines and other forms of interaction

Although no formal medicine interaction studies have been performed, tiotropium bromide inhalation powder such as in NEUMOTROPIO, has been used concomitantly with other medicines without clinical evidence of medicine interactions. These include sympathomimetic bronchodilators, methylxanthines and oral and inhaled steroids, commonly used in the treatment of COPD.

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

The co-administration of tiotropium bromide 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 bromide in pregnant women. As a precautionary measure, it is preferable to avoid the use of NEUMOTROPIO during pregnancy.

Breastfeeding

It is unknown whether tiotropium bromide is excreted in human breast milk. The use of NEUMOTROPIO is not recommended during breastfeeding.

Fertility

Clinical data on fertility are not available for tiotropium bromide.

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 effects can be assigned to the anticholinergic properties of tiotropium bromide such as in NEUMOTROPIO.

Tabulated summary of adverse reactions

The following table is based on data from clinical trials with tiotropium bromide.

System organ class	Frequency
Immune system disorders	
Hypersensitivity (including immediate reactions) Angioedema	Less frequent
Anaphylactic reaction	Not known
Metabolism and nutrition disorders	
Dehydration	Not known
Nervous system disorders	
Dizziness Headache Taste disorders Insomnia	Less fequent
Eye disorders	
Vision blurred Glaucoma Intraocular pressure increased	Less frequent
Cardiac disorders	
Atrial fibrillation Supraventricular tachycardia Tachycardia Palpitations	Less frequent
Respiratory, thoracic and mediastinal disorders	

Pharyngitis Dysphonia Cough Bronchospasm Epistaxis Laryngitis Sinusitis	Less frequent
Gastrointestinal disorders	
Dry mouth	Frequent
Gastro-oesophageal reflux disease Constipation Oropharyngeal candidiasis Intestinal obstruction, including ileus paralytic Gingivitis Glossitis Stomatitis Nausea	Less frequent
Dental caries	Not known
Skin and subcutaneous tissue disorders	
Rash Urticaria Pruritus	Less frequent
Skin infection, skin ulcer Dry skin	Not known
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known
Renal and urinary disorders	

Dysuria Urinary retention Urinary tract infection	Less frequent

Description of selected adverse reactions

Serious undesirable effects consistent with anticholinergic effects include glaucoma, constipation and intestinal obstruction, including ileus paralytic as well as urinary retention.

Other special populations

An increase in anticholinergic effects may occur with increasing age.

Post-marketing experience

The following adverse reactions have been identified through spontaneous reporting: application site irritation (glossitis, mouth ulceration and pharyngolaryngeal pain), dizziness, dysphagia, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation and urticaria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of NEUMOTROPIO is important. It allows continued monitoring of the benefit/risk balance of NEUMOTROPIO. Health care providers are asked to report any suspected adverse reactions 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 NEUMOTROPIO 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.

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 M_3 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 bronchodilatation 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 bronchodilatation in patients with COPD.

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. Generally with the inhaled route of administration, the majority of the delivered dose is deposited in the gastrointestinal 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.

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.

Distribution: 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. 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 CYP2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP2D6 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 CYP1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination: The effective half-life of tiotropium ranges between 27 and 45 hours 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.

Special populations

Elderly patients: As expected for all predominantly renally excreted medicines, 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.

Paediatric patients: See section 4.2.

5.3 Preclinical safety data

No information of relevence available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:

Lactose monohydrate.

Capsule cells:

Hypromellose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

After first opening of the bottle:

Use capsules within 30 days (15 capsule bottle) or 60 days (30 capsule bottle).

6.4 Special precautions for storage

Store at or below 25 °C.

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

Discard the Zephir inhaler after 30 uses (or 15 uses, if used in conjunction with the 15 capsule bottle).

6.5 Nature and contents of container

White and opaque 20 mL or 35 mL HDPE bottle with a white and opaque 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, supplied with a Zephir inhaler. The Zephir inhaler is a single dose inhalation device, with a green body, a perforating system of 2 needles, a green cap and a white mouthpiece and push button, made from ABS plastic materials and stainless steel.

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

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

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap

Mispel Street, Bellville

7530

8. REGISTRATION NUMBER

51/10.2.1/0143

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 July 2021

10. DATE OF REVISION OF THE TEXT

24 February 2022