SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

OTRIVIN PLUS 0.5 mg/ml + 0.6 mg/ml Metered-dose Nasal Spray, Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 0.5 mg xylometazoline hydrochloride and 0.6 mg ipratropium bromide.

1 puff (approx. 140 microlitres) contains 70 micrograms xylometazoline hydrochloride and 84 micrograms ipratropium bromide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Metered-dose nasal spray, solution.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short term symptomatic treatment of nasal congestion and rhinorrhea associated with common colds in adults.

4.2 Posology and method of administration

Posology

Adults:

1 puff in each nostril up to 3 times daily. At least 6 hours should elapse between two doses. Do not exceed 3 applications daily into each nostril. The treatment duration should not exceed 7 days (see section 4.4).

It is recommended to stop treatment, when the symptoms have diminished, even before the maximum duration of treatment of 7 days, in order to minimize the risk of adverse reactions (see section 4.8).

Paediatric Population

OTRIVIN PLUS is not recommended for use in children and adolescents below 18 years of age due to lack of sufficient documentation.

Elderly (> 70 years)

There is only limited experience of use in patients above 70 years of age.

Method of administration

Before the first application, prime the pump by actuating 4 times. Once primed the pump will normally remain charged throughout regular daily treatment periods. Should the spray not be ejected during the full actuation stroke, or if the product has not been used for longer than 6 days, the pump will need to be reprimed with 4 actuations as initially performed.

4.3 Contraindications

- OTRIVIN PLUS should not be given to children under the age of 18 due to lack of sufficient documentation.
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Known hypersensitivity to atropine or similar substances, e.g. hyoscyamine and scopolamine.
- After surgical operations where dura mater may have been penetrated, e.g. transsphenoidal
- hypophysectomy or other transnasal operations.
- In patients with glaucoma.
- In patients with rhinitis sicca.

4.4 Special warnings and precautions for use

The medicinal product must be administered with caution to patients with:

- hypertension, cardiovascular diseases

- hyperthyroidism, diabetes mellitus

- hypertrophy of the prostate, stenosis of the bladder bar

- phaeochromocytoma

Caution is recommended in patients predisposed to:

- angle closure glaucoma

- epistaxis (e.g. elderly)

- paralytic ileus

- cystic fibrosis

Immediate hypersensitivity including urticaria, angioedema, rash, bronchospasm, pharyngeal oedema and anaphylaxis may occur.

The medicinal product must be used with caution in patients who are sensitive to adrenergic substances, which may give symptoms such as sleeping disturbances, dizziness, tremor, cardiac dysrhythmias or elevated blood pressure.

The treatment duration should not exceed 7 days, as chronic treatment with xylometazoline hydrochloride may cause swelling of the nasal mucosa and hypersecretion because of increased sensibility in the cells, rebound effect" (rhinitis medicamentosa).

Patients should be instructed to avoid spraying OTRIVIN PLUS in or around the eye. If OTRIVIN PLUS gets in contact with the eyes, the following may occur: temporary blurred vision, irritation, pain, red eyes. Aggravation of angle closure glaucoma may also develop. The patient should be instructed to rinse their eyes with cold water if OTRIVIN PLUS gets in direct contact with the eyes and to contact a doctor if they experience pain in the eyes or blurred vision.

4.5 Interaction with other medicinal products and other forms of interaction

Monoaminoxidase inhibitors (MAO inhibitors): Concomitant use or use within the last 2 weeks of sympathomimetic preparations may induce severely elevated blood pressure and is therefore not recommended. Sympathomimetic preparations release catecholamine, which results in a major release of noradrenaline which in turn has a vasoconstrictive effect resulting in elevated blood pressure. In critical cases of elevated blood pressure, treatment with OTRIVIN PLUS should be discontinued and the elevated blood pressure treated.

Tri- and tetra-cyclic antidepressants: Concomitant use or use within the last 2 weeks of tri-cyclic antidepressants and sympathomimetic preparations may result in an increased sympathomimetic effect of xylometazoline and is therefore not recommended.

Concomitant administration of other *anticholinergic drugs* may enhance the anticholinergic effect of ipratropium bromide.

The above interactions have been studied individually for both of the active substances of OTRIVIN PLUS, not in combination.

No formal interaction studies with other substances have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use during pregnancy has not been proven.

There are no adequate data from the use of OTRIVIN PLUS in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development. The potential risk for humans is unknown.

Breast-feeding

It is not known whether ipratropium bromide and xylometazoline hydrochloride are excreted in the mother's milk. Therefore, mothers using OTRIVIN PLUS are advised not to breastfeed their infants.

4.7 Effects on ability to drive and use machines

Visual disturbances (including blurred vision and mydriasis), dizziness and fatigue have been reported with OTRIVIN PLUS. Patients should be advised that if affected they should not drive, operate machinery or take part in activities where these symptoms may put themselves or others at risk.

4.8 Undesirable effects

a) Summary of the safety profile

The most commonly reported adverse reactions are epistaxis occurring in 14.8 % and nasal dryness occurring in 11.3 % of patients.

b) Tabulated list of adverse reactions

The following adverse reactions were reported in two randomised clinical studies and one noninterventional post-marketing study with the product as well as from post-marketing surveillance.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as:

Very common (≥1/10)

Common (≥1/100 t<1/10)

Uncommon(≥1/1000and<1/100)

Rare (≥1/10000 and <1/1000)

Very rare (< 1/10,000)

Not known (cannot be estimated from the available data)

Immune system disorders

Not known: hypersensitivity

Psychiatric disorders

Uncommon: insomnia

Nervous system disorders

Common: dysgeusia, headache
Uncommon: parosmia, dizziness, tremor

Eye disorders

Uncommon: eye irritation, dry eye

Not known: accommodation disorder, aggravation of angle closure glaucoma, eye pain, photopsia, intraocular pressure increased, blurred vision, mydriasis, halo vision

Cardiac disorders

Uncommon: Palpitations, tachycardia

Not known: Atrial fibrillation

Respiratory, thoracic and mediastinal disorders

Very common: epistaxis, nasal dryness

Common: nasal discomfort, nasal congestion, dry throat, throat irritation, rhinalgia

Uncommon: Nasal ulcer, sneezing, oropharyngeal pain, cough, dysphonia

Rare: Rhinorrhoea

Not known: Paranasal sinus discomfort, laryngospasm, pharyngeal oedema

Gastrointestinal disorders
Common: dry mouth

Uncommon: dyspepsia, nausea

Not known: dysphagia

Skin and subcutaneous disorders

Not known: pruritis, rash, urticaria

Renal and urinary disorders

Not known: urine retention

General disorders and administration site conditions

Uncommon: discomfort, fatigue

Not unknown: chest discomfort, thirst

c) Description of selected adverse reaction

Several of the adverse reactions listed under "Not known" have only been reported once for the product in clinical trials or are reported from post marketing surveillance only, thus an estimate of the frequency based on the present number of patient treated with OTRIVIN PLUS cannot be given.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdose of oral or excessive administration of xylometazoline hydrochloride may cause severe dizziness, perspiration, severely lowered body temperature, headache, bradycardia, hypertension, respiratory depression, coma and convulsions. Hypertension may be followed by hypotension.

The treatment is symptomatic and supportive.

Overdose of oral or excessive administration of ipratropium bromide may cause dry mouth, accommodation difficulties and tachycardia. The treatment is symptomatic and supportive.

A considerable overdose may cause anticholinergic CNS symptoms such as hallucinations, which must be treated with cholinesterase inhibitors.

Appropriate supportive measures should be initiated in all individuals suspected of an overdose of OTRIVIN PLUS, and urgent symptomatic treatment under medical supervision is indicated when warranted. This would include observation of the individual for at least 6 hours. In the event of a severe overdose with cardiac arrest, resuscitation should be continued for at least 1 hour.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sympathomimetics, combinations excluding corticosteroids.

ATC code: R 01 AB 06

Xylometazoline hydrochloride is a sympathomimetic which acts on α-adrenergic receptors.

Xylometazoline has a vasoconstrictive effect. An effect is obtained after 5-10 minutes and lasts for 6-8 hours.

Ipratropium bromide is a quaternary ammonium combination with anticholinergic effect. Nasal administration reduces the nasal secretion through competitive inhibition of cholinergic receptors situated around the nasal epithelium. An effect is usually obtained within 15 minutes and lasts for 6 hours on an average.

5.2 Pharmacokinetic properties

After administration of one puff/nostril of 140 µg xylometazoline and 84 µg ipratropium bromide in 24 healthy subjects, mean maximum concentrations of 0.085 ng/ml and 0.13 ng/ml were reached 1 hour and 2 hours post administration for ipratropium bromide and xylometazoline, respectively. The blood levels are very low. However, based on data available, it is expected that ipratropium bromide and especially xylometazoline will accumulate at the proposed 3 times per day dosing.

5.3 Preclinical safety data

Both ipratropium bromide and xylometazoline were tested in preclinical studies, which revealed no relevant clinical safety problems with the actual doses of OTRIVIN PLUS. Intranasal daily

dose of OTRIVIN PLUS in dogs for 28 days in doses up to four times the intended clinical dosing regimen has shown no local or systemic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Glycerol (85 per cent)

Hydrochloric acid (for pH – adjustment)

Sodium hydroxide (for pH – adjustment)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Store at or below 25 °C. Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

10 ml multidose (approx. 70 puffs) HDPE bottle mounted with metered-dose spray pump (materials in contact with the solution: LDPE, HDPE, PE / butyl, stainless steel) and PP nozzle with protective cap.

6.6 Special precautions for disposal

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

PROFESSIONAL INFORMATION

7. HOLDER OF CERTIFICATE OF REGISTRATION

Haleon South Africa (Pty) Ltd

11 Hawkins Avenue

Epping Industria 1

Cape Town, 7450

8. REGISTRATION NUMBER

46/16.1/0819

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

23 February 2021

10. DATE OF REVISION OF THE TEXT

Date of the most recently revised professional information: 23 February 2021