

Otrivin Complete

1. Name of the medicinal product

Otrivin Complete

2. Qualitative and quantitative composition

IPRATROPIUM BROMIDE 0.6 MG/ML

XYLOMETAZOLINE HYDROCHLORIDE 0.5 MG/ML

1 puff approx. 140 microliters contains 70 micrograms xylometazoline hydrochloride and 84 micrograms ipratropium bromide.

For the full list of excipients see 6.1.

3. Pharmaceutical form

Nasal spray, solution

The product is a clear, colorless to slightly coloured solution solution.

4. Clinical particulars

4.1 Therapeutic indications

Symptomatic treatment of nasal congestion and rhinorrhea in connection with common cold 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.

The treatment duration should not exceed 7 days (see section 4.4)

Do not exceed the stated dose. The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment.

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

Geriatrics

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.

1. Clear the nose.
2. Hold the bottle upright with thumb under base and nozzle between two fingers.
3. Lean forward slightly and insert the nozzle into a nostril.
4. Spray and breathe in gently through the nose at the same time.
5. Repeat this procedure in the other nostril.
6. Clean and dry the nozzle before replacing back the cap right after use.

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. If the full spray is not administered, the dose should not be repeated.

To avoid possible spread of infection, the spray should only be used by one person. Be careful not to spray in the eyes.

4.3 Contraindications

- Otrivin Complete 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 atropine like substances, such as hyoscyamine and scopolamine.
- After surgical procedures where dura mater may have been penetrated, e.g. transphenoidal hypophysectomy or other trans-nasal operations.
- In patients with glaucoma.
- In patients with rhinitis sicca or atrophic rhinitis.

4.4 Special warnings and precautions for use

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

- Hypertension, cardiovascular diseases Patients with long QT syndrome treated with xylometazoline may be at increased risk of serious ventricular arrhythmias.
- Hyperthyroidism, diabetes mellitus.
- Hypertrophy of the prostate, stenosis of the bladder bar.
- Pheochromocytoma
- Cystic fibrosis
- monoamine oxidase inhibitor (MAOI) treatment or who have received them in the last two weeks (see section 4.5 Interactions)
- Tri and tetra-cyclic antidepressants treatment or who have received them in the last two weeks (see section 4.5 Interactions)
- Beta 2-agonists treatment (see section 4.5 Interactions)

Caution should be exercised in patients predisposed to:

- Angle closure glaucoma
- Epistaxis (e.g. elderly)
- Paralytic ileus

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

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 sensitivity of the cells, "rebound effect" (rhinitis medicamentosa).

Patients should be instructed to avoid spraying Otrivin Complete in or around the eyes. If Otrivin Complete 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 Complete gets in direct contact with the eyes and must seek medical attention if they experience eye pain in the eyes or blurred vision.

Keep out of the sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOi) or Tricyclic and tetracyclic antidepressants: 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 catecholamines, which results in a major release of noradrenaline whose vasoconstrictive effects cause an increase in blood pressure. In critical cases of hypertension, treatment with Otrivin Complete should be discontinued and the elevated blood pressure should be treated. (see section 4.4 Warnings and Precautions)

Beta 2-agonists

Concomitant use with ipratropium may cause an increased risk of acute glaucoma in patients with a history of angle closure glaucoma. There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma and eye

pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta 2-agonist, has come into contact with the eyes. (see section 4.4 Warnings and Precautions)

Concomitant administration of other anticholinergic drugs may enhance the anticholinergic effect.

The above interactions have been studied individually for both of the active substances of Otrivin Complete, and not in combination.

No formal interaction studies with other substances have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Otrivin Complete in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see Non-clinical information). It is advisable not to take this product during pregnancy.

Xylometazoline

The available data indicate the potential for xylometazoline to exert a systemic vasoconstrictor effect. In view of its systemic vasoconstrictor effect, it is advisable not to take xylometazoline during pregnancy.

Ipratropium

The clinical safety ipratropium bromide during human pregnancy has not been established. Non-clinic data have demonstrated embryotoxicity following administration of ipratropium bromide to rabbits via inhalation at doses greater than the clinical dose (see Non-clinical information).

Breast-feeding

There are insufficient data to determine if this product is excreted in human breast milk. This product should only be used while breast feeding under medical advice. If the expected benefit to the mother is greater than possible risk to the infant, the lowest effective dose and the duration of treatment should be considered.

Xylometazoline

There is no evidence of any adverse effect on the breast-fed infant. It is unknown if xylometazoline is excreted in breast milk.

Ipratropium

It is not known whether ipratropium bromide is excreted in breast milk.

Fertility

There are insufficient data on the impact of this product on fertility.

Xylometazoline

There are no adequate data for the effects of xylometazoline hydrochloride on fertility and no animal studies are available.

Ipratropium

Non-clinical data have demonstrated no evidence of impaired fertility following oral administration of ipratropium bromide to rats at doses greater than the clinical dose (see Preclinical safety data).

4.7 Effects on ability to drive and use machines

Visual disturbances (including blurred vision and mydriasis), dizziness and fatigue have been reported after using Otrivin Complete. Patients should be advised that if they experience these symptoms 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

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.

Many of the adverse reactions reported are also symptoms of a common cold.

Tabulated list of adverse reactions

The adverse reactions are listed by system organ class and by frequency.

Frequencies are defined as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1000$ and $< 1/100$)

Rare ($\geq 1/10,000$ and $< 1/1000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from available data)

Xylometazoline and Ipratropium

The following adverse reactions for the combination of xylometazoline and ipratropium were reported in two randomised clinical studies and one noninterventioanl post-marketing study with the product as well as from post-marketing surveillance.

| MeDRA SOC | Adverse Reactions | Frequency |
|-------------------------|--|-----------|
| Immune system disorders | Hypersensitivity reaction (angioedema, rash, pruritis) | Very rare |

| | | |
|--|--|-------------|
| Psychiatric disorders | Insomnia | Uncommon |
| Nervous system disorders | Dysgeusia | Common |
| | Parosmia, Tremor | Uncommon |
| Eye disorders | Eye irritation, dry eye | Uncommon |
| | Photopsia | Not known |
| Cardiac disorders | Palpitations, tachycardia | Uncommon |
| Respiratory, thoracic and mediastinal disorders | Epistaxis | Very common |
| | Nasal congestion, rhinalgia | Common |
| | Nasal ulcer, dysphonia, oropharyngeal pain, sneezing | Uncommon |
| | Rhinorrhea | Rare |
| | Paranasal sinus discomfort | Not known |
| Gastrointestinal disorder | Dyspepsia | Uncommon |
| | Dysphagia | Not known |
| General disorders and administration site conditions | Fatigue, discomfort | Uncommon |
| | Chest discomfort, thirst | Not Known |

Xylometazoline

The following adverse reactions have been reported in clinical trials and postmarketing surveillance with xylometazoline.

| MeDRA SOC | Adverse Reactions | Frequency |
|--|---------------------------------|-----------|
| Nervous system disorders | Headache | Common |
| Eye disorders | Visual impairment | Very rare |
| Respiratory, thoracic and mediastinal disorders | Nasal dryness, nasal discomfort | Common |
| | Epistaxis | Uncommon |
| Gastrointestinal disorders | Nausea | Common |
| General disorders and administration site conditions | Application site burn | Common |

Ipratropium bromide

The following adverse reactions were identified from data obtained in clinical trials and pharmacovigilance during post approval use of the drug.

| MeDRA SOC | Adverse Reactions | Frequency |
|-------------------------|------------------------|-----------|
| Immune system disorders | Anaphylactic reaction, | Not known |

| | | |
|---|--|-----------|
| | hypersensitivity | |
| Nervous system disorders | Dizziness, headache | Common |
| Eye disorders | Corneal oedema, conjunctival hyperaemia | Uncommon |
| | Glaucoma, intraocular pressure increased, accommodation disorder, blurred vision, halo vision, mydriasis, eye pain | Not known |
| Cardiac disorders | Supraventricular tachycardia, palpitations | Uncommon |
| | Atrial fibrillation | Not known |
| Respiratory, thoracic and mediastinal disorders | Throat irritation, dry throat | Common |
| | Cough | Uncommon |
| | Laryngospasm, pharyngeal oedema | Not known |
| Gastrointestinal disorders | Dry mouth | Common |
| | Nausea | Uncommon |
| Skin and subcutaneous tissue disorders | Rash, urticaria pruritis | Not known |
| Renal and urinary disorders | Urinary retention | Not Known |

Description of selected adverse reactions

Several of the adverse reactions listed under "Not known" have only been reported once for the product in clinical trials or are reported during postmarketing surveillance only, thus, an estimate of the frequency based on the present number of patients treated with Otrivin Complete cannot be given.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

[/https://sideeffects.health.gov.il](https://sideeffects.health.gov.il)

Additionally, please also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

Overdose of oral or excessive administration of topical 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. Small children are more sensitive to toxicity than adults.

The absorption being very small after nasal or oral administration, an acute overdose after intranasal ipratropium bromide is unlikely, but if an overdose occurs the symptoms are dry mouth, accommodation difficulties and tachycardia. The treatment is symptomatic.

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, 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 severe overdose with cardiac arrest, resuscitation should be continued for at least 1 hour. Further management should be as clinically indicated or as recommended by the national poison centres where available.

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 between 6- 8 hours.

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

5.2 Pharmacokinetic properties

After administration of one puff/nostril of 140 μg of xylometazoline and 84 μg of 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 of Ipratropium bromide and Xylometazoline, respectively. The blood levels are very low. However, based on the available data, it is expected that Ipratropium bromide and especially Xylometazoline will accumulate at the proposed dosage of 3 sprays per day.

5.3 Preclinical safety data

Non-clinical safety data for xylometazoline hydrochloride and ipratropium bromide have not revealed findings which are of relevance to the recommended dosage and use of the product.

Carcinogenesis and Mutagenesis

There are no carcinogenicity data available for xylometazoline hydrochloride. However, the available in-vitro and in-vivo genotoxicity data on this active ingredient do not indicate a genotoxic potential. Non-clinical studies with ipratropium bromide

demonstrated this compound was not mutagenic, genotoxic, or carcinogenic.

Reproductive toxicology

Non-clinical data are not available on the reproductive and developmental toxicology of xylometazoline. Non-clinical data for ipratropium bromide demonstrated embryotoxicity following inhalation administration to rabbits at a dose that was approximately 14-fold greater than the clinical dose based on human equivalent dose.

6. Pharmaceutical particulars

6.1 List of excipients

Purified water, Glycerol (85 per cent), Disodium edetate dihydrate, Hydrochloric acid concentrated, Sodium hydroxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the label and packaging.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

10 ml HDPE bottle with a metered-dose spray pump, with an actuator and a protective cap.

6.6 Special precautions for disposal and other handling

Keep all medicines out of the reach of children

7. Manufacturer

GSK Consumer Healthcare SARL
ROUTE DE L'ETRAZ 1260 NYON, SWITZERLAND

8. License holder and Importer

GSK CONSUMER HEALTHCARE ISRAEL LTD., P.O.B. 3256, Petach-Tikva

9. License number

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OtrCom DR V4

