Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Otrivine Extra Dual Relief 0.5mg/ml + 0.6mg/ml nasal spray, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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).

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
Otrivine Extra Dual Relief 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.

3 PHARMACEUTICAL FORM

Nasal spray, solution.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

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

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4.3 Contraindications

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 arrythmias or elevated blood pressure.

The medicinal product must be administered 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 is recommended 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 sensibility in the cells, "rebound effect" (rhinitis medicamentosa).

Patients should be instructed to avoid spraying Otrivine Extra Dual Relief in or around the eye. If Otrivine Extra Dual Relief 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 Otrivine Extra Dual Relief gets in direct contact with the eyes and to contact a doctor if they experience pain in the eyes or blurred vision.

Keep out of the sight and reach of children.

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
- pheochromocytoma

Caution is recommended in patients predisposed to:
- angle closure glaucoma
- epistaxis (e.g. elderly)
- paralytic ileus
- cystic fibrosis

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Patients should be instructed to avoid spraying Otrivine Extra Dual Relief in or around the eye. If Otrivine Extra Dual Relief 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 Otrivine Extra Dual Relief 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 interactions

Monoaminoxidase inhibitors (MAO inhibitors) or tri- and tetra-cyclic 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 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 Otrivine Extra Dual Relief should be discontinued and the elevated blood pressure 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 Otrivine Extra Dual Relief, not in combination.

No formal interaction studies with other substances have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are insufficient data on the use of this product 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 with Otrivine Extra Dual Relief. 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

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 events reported are also symptoms of common cold.

Tabulated list of adverse reactions

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

Very common (≥1/10);Common (≥1/100 to <1/10); Uncommon (≥1/1000 and <1/100); Rare (≥1/10000 and <1/1000); Very rare (< 1/10,000); Not known (can not be estimated from the 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 non-interventional 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
	Rhinorrhoea	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 post-marketing 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
Gastrointestinal disorders	Nausea	Common
General disorders and administration site conditions	Application site burn	Common
Respiratory, thoracic and mediastinal disorders	Nasal dryness, nasal discomfort	Common
	Epistaxis	Uncommon

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, hypersensitivity	Not known
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 from post-marketing surveillance only, thus an estimate of the frequency based on the present number of patient treated with Otrivine Extra Dual Relief cannot be given.

Reporting of suspected adverse reactions
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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

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 a 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 s ympathomimetic which acts on a-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

Non-clinical data 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 or 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

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.
After first opening, the nasal spray can be used until the end of the shelf-life.

6.4 Special precautions for storage

Do not store above 25°C.

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.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Consumer Healthcare (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0678/131/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th December 2012

Date of last renewal: 9th October 2017

10 DATE OF REVISION OF THE TEXT

June 2021