European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
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COMMITTEE OF EXPERTS ON THE CLASSIFICATION OF MEDICINES AS REGARDS THEIR SUPPLY (CD-P-PH/PHO)

Report classification of

- Medicines belonging to ATC group S01GA (Sympathomimetics used as decongestants)

- Medicines belonging to ATC group S01GX (Other antiallergics)

(2022)

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INTRODUCTION

The availability of medicines with or without a medical prescription has implications on patient safety, accessibility of medicines to patients and responsible management of healthcare expenditure.

The decision on prescription status and related supply conditions is a core competency of national health authorities. The conditions of the supply of medicines vary considerably in Council of Europe member states, due to the fact that the provisions are differently interpreted and implemented by the member states, and that important additional classification criteria are not harmonised.

The Committee of Experts on the Classification of Medicines as regards their Supply (CD-P-PH/PHO)[1] is co-ordinated by the European Directorate for the Quality of Medicines and HealthCare (EDQM, Council of Europe) and its working programme is based on Committee of Ministers Resolution CM/Res(2018)1 on the classification of medicines as regards their supply[2].

In its work, the CD-P-PH/PHO focuses on public health promotion and uses scientific approaches, taking account of the national assessments of direct and indirect risks which may occur under normal treatment conditions and under medical surveillance, as well as from foreseeable misuse or abuse of medicines.

The CD-P-PH/PHO issues twice a year recommendations to health authorities of Council of Europe member states (EU and non-EU member states) on the classification of medicines and establishes good classification practices.

The recommendations are also useful for pharmaceutical manufacturers and commercial operators of mail-order trade in medicines where such trade is legal.

A pioneer in this field, Council of Europe bodies have been concerned since 1961 with issues relating to the classification of medicines into prescription and non-prescription medicines and have inspired relevant EU legislation.

The classification criteria set out in the Council of Europe resolutions have been supplanted by Directives 92/26/CEE and 2001/83/EC (Art. 70-75). Directive 2001/83/EC refers to the Council of Europe in its Whereas 32: "*It is therefore appropriate, as an initial step, to harmonise the basic principles applicable to the classification for the supply of medicinal products in the Community or in the Member State concerned, while taking as a starting point the principles already established on this subject by the Council of Europe*"[3].

It is important to note that:

- The CD-P-PH/PHO does not issue recommendations on the classification of particular medicines, but on active substances used in a medicine for a specific therapeutic purpose.

- In its work, the CD-P-PH/PHO uses the Anatomical Therapeutic Chemical (ATC) classification maintained by the WHO Collaborating Centre for Drug Statistics Methodology[4] to identify active substances or combinations of active substances.

- The CD-P-PH/PHO does not give advice relating to pending marketing authorisation procedures.

The CD-P-PH/PHO supervises a database (i.e. *Melclass*[5]), hosted by the EDQM, which stores the recommendations that the Committee of Experts issues twice a year to health authorities of the Council of Europe member states which are parties to the Convention on the Elaboration of a European Pharmacopoeia, as well as national information about the classification status and supply conditions of

[1] http://go.edqm.eu/PHO

[2] https://go.edqm.eu/CMRes20181

[3] https://bit.ly/469vnNN

[4] https://www.whocc.no/atc_ddd_index/

[5] https://melclass.edqm.eu/

medicines in these member states. The information is publicly available. Recommendations about 2100 medicines are published in the *Melclass* database.

Providing a platform for dialogue and consensus building on the supply conditions of medicines in Europe as facilitated by Council of Europe Committee of Ministers Resolution CM/Res(2018)1, the CD-P-PH/PHO promotes patient safety and, where appropriate, access to medicines without a prescription across Europe, which helps to foster public health and to responsibly manage healthcare resources.

GENERAL NOTE

This report focuses on the legal classification of medicines containing active substances belonging to ATC group S01GA (Sympathomimetics used as decongestants) and to ATC group S01GX (Other antiallergics).

The classification reviews included in this document have no legal status and no binding character. They reflect the debates and conclusions of the reviews of scientific classifications of medicines that took place at the autumn 2022 meeting of the CD-P-PH/PHO.

GLOSSARY OF TERMS USED IN THIS DOCUMENT

ATC	Anatomical Therapeutic Chemical classification [1]
CNS	Central nervous system
EDQM	European Directorate for the Quality of Medicines and HealthCare
EMA	European Medicines Agency
MAOI	Monoamine oxidase inhibitor
MDD	Maximal daily dose
MQP	Maximal quantity per pack
MS	Maximal strength
POM	Prescription-only medicine
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PSUSA	Periodic safety update single assessment
SmPC	Summary of product characteristics
WHO	World Health Organization

Classification used throughout this document

Following the stipulations of Resolution CM/Res(2018)1, the lists of active substances classified according to the conditions of supply of the medicines which contain them are drawn up with reference to all the risks, direct or indirect, which they may represent to human health whether they are used in accordance with the product information leaflet or not.

The differentiation into two prescription lists (List I and List II) applies only to the countries which classify prescription medicines into two categories based on whether the prescription can be renewed or not.

1. Active substances in medicines subject to prescription

List I: the supply of a medicine containing one of the substances in this list should not be renewed without the prescriber having so specified. This classification should apply to active substances of medicines indicated for conditions calling for short-term treatment and/or for which continuous medical supervision is necessary, either because of potential undesirable effects or to check the efficacy of treatment; or active substances of medicines administered for diagnostic purposes; or active substances with a new pharmacological mechanism of action.

List II: the supply of a medicine containing one of the substances in this list can be renewed. This classification should apply to active substances in medicines indicated for conditions for which the patient may continue the regular or intermittent treatment without new medical advice, and for which well-known undesirable effects do not call for frequent clinical examination.

Exemptions from Lists I and II under certain circumstances: depending on the conditions of use of the medicine, active substances contained in prescription medicines may also be contained in medicines classified under the same ATC code but which are not subject to prescription.

Under certain circumstances, exemptions from the prescription requirement may be set out in the Melclass database:

- in respect of a low dosage or concentration of the active substances and/or the therapeutic indications of medicines in which they are contained;
- according to the route of administration and the composition of the medicine;
- according to the total amount of the medicine per container.

2. List of active substances in medicines not subject to prescription: active substances in medicines which are not classified as subject to prescription in Lists I or II.

[1] World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology - https://www.whocc.no/atc_ddd_index/

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Naphazoline

1.2 ATC code: S01GA01

1.3 Therapeutic indications: short-term symptomatic treatment of ocular congestion, conjunctival redness (hyperaemia) and irritation due to allergic and inflammatory ocular conditions in the non-infected eye.

1.4 Posology and duration of treatment: conjunctivitis: in adults and children from 12 years: 1-2 drops of 0.012% or 0.1% ophthalmic solution should be administered into each eye every 3-4 hours or four times daily as needed.

As the safety and efficacy of use is not well established in children under the age of 12, most products are authorised from 12 years of age.

Topical use of naphazoline is associated with rebound vasodilation and congestion. It is intended for short-term symptomatic relief only and should not be used for longer than 5 to 7 days without medical supervision. Shorter periods of use are recommended in the event of non-improvement or worsening of symptoms, or when used in children younger than 12 years.

1.5 Pharmaceutical forms: eye drops, solution.

1.6 Contraindications: the product should not be used in the following cases: known hypersensitivity to naphazoline, other adrenergic agents or to any of the excipients in the formulation; anatomical narrow angle; closed-angle glaucoma; corneal damage; acute iritis; other serious eye disease.

1.7 Relevant warnings: if there is any eye pain, vision changes, continued redness or irritation of the eye, or if the condition worsens or persists for more than 24 hours, discontinuation of the medicinal product should be considered with re-evaluation of diagnosis and treatment. The product should not been used when taking MAOIs or within 14 days of stopping this medication. As with other sympathomimetics, the product should be used with caution in the presence of hypertension, diabetes, asthma, hyperthyroidism, cardiovascular abnormalities and arteriosclerosis. Products containing naphazoline should be used with caution in elderly patients with severe cardiovascular disease, including cardiac arrhythmias and hypertension, since systemic absorption may theoretically exacerbate these conditions. Use should be discontinued prior to anaesthesia with agents that sensitise the myocardium to sympathomimetics (e.g. trichloroethylene, cyclopropane, halothane). Contact lens wear during ophthalmic use is not recommended. Rebound vasodilation and congestion can occur, so the products should be limited to short-term use only.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): there are no serious direct risks associated with use of ophthalmological naphazoline due to the topical nature of authorised products and low systemic exposure when used in accordance with the authorised indication. Available evidence is inconclusive or inadequate for determining foetal risk when used in pregnancy, or infant risk when used during breastfeeding. Although toxicity during pregnancy or breastfeeding is not anticipated, caution should be exercised with use in these populations. Adverse drug reactions tend to be limited to site-of-application reactions, including eye irritation, eye pain, burning pain in the eye. Changes in vision, pupillary dilation, increased intraocular pressure, conjunctival hyperaemia (including rebound hyperaemia) and topical-decongestant-induced conjunctivitis (in particular, follicular conjunctivitis) have been reported. Other adverse reactions include nausea, headache and dizziness. Naphazoline may interact with MAOIs and should not be used by patients receiving such treatment or within 14 days of ceasing therapy. Naphazoline may reverse the blood pressure lowering effects of antihypertensive drugs and may increase the risk of arrhythmias in patients receiving cardiac glycosides, quinidine or tricyclic antidepressants. Proposed interactions are theoretical in nature and unlikely due to low systemic absorption of naphazoline. As with all ocular medicinal products, it is recommended that an interval of approximately 15 minutes, unless otherwise specified, be left between concomitant use of multiple ocular medicinal products. Naphazoline use may lead to blurring of vision. Appropriate measures should be considered when driving or operating machinery. All identified direct risks may be mitigated by adequate product information and labelling.

2.2 Indirect risks (incorrect use): indirect risks may arise from incorrect diagnosis or self-assessment of the underlying medical condition, which may lead to masking of symptoms or the delayed diagnosis of a more serious underlying condition of the eye. Overdosage by accidental administration by mouth of large quantities of solution may cause depression of the CNS, reduction of body temperature, drowsiness and coma, particularly in children. All identified indirect risks may be mitigated by adequate product information and labelling.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
Armenia (AM)	Not subject to prescription	0.3 mg/mL	4 times daily		Conjunctival hyperaemia; allergic conjunctivitis	
Austria (AT)	List II + Exemption	Ex: 0.1%			For the treatment of non-infectious conjunctivitis	Not for children under 2 years
Bosnia and Herzegovina (BA)	Not authorised					
Belgium (BE)	Not subject to prescription	1 mg/mL		15 mg	Symptomatic treatment of mild/moderate/severe eye irritation and irritation of the conjunctiva in adults	
Bulgaria (BG)	Not authorised					
Switzerland (CH)	Not authorised					
Cyprus (CY)	Not subject to prescription					
Czech Republic (CZ)	Not authorised					
Estonia (EE)	Not authorised					
Spain (ES)	Not subject to prescription					
Finland (FI)	Not subject to prescription					
France (FR)	Not authorised					
Georgia (GE)	Not subject to prescription					
Greece (GR)	Not authorised					
Croatia (HR)	Not subject to prescription	0.3 mg/mL		10 mL	Temporary relief of eye hyperaemia in adults caused by non-infectious eye irritations	
Hungary (HU)	Not authorised					
Ireland (IE)	Not subject to prescription					
Italy (IT)	Not subject to prescription					
Lithuania (LT)	Not authorised					
Luxembourg (LU)	Not authorised					
Latvia (LV)	Not authorised					
Montenegro (ME)	POM					
North Macedonia (MK)	Not subject to prescription					
Netherlands (NL)	Not authorised					
Poland (PL)	Not authorised					
Portugal (PT)	Not authorised					
Romania (RO)	Not authorised					
Serbia (RS)	Not subject to prescription					

Sweden (SE)	POM + Exemption			Ex.: 5 mL		
Slovenia (SI)	Not authorised					
Slovakia (SK)	Not authorised					
Türkiye (TR)	Not authorised					
United Kingdom (UK)	Not subject to prescription					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **Not subject to prescription**

Criteria: a) good safety profile with low systemic exposure; b) direct and indirect dangers can be safely mitigated through appropriate product labelling in the non-prescription setting; c) well-established use in the non-prescription setting in most countries in which medicinal products are authorised.

3.2.2 Paediatric use: safety and efficacy is not well established in children under the age of 12. The benefit-risk of use in the non-prescription setting in this population warrants more careful evaluation.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale - Available at: https://www.medicinescomplete.com/#/

Melclass database - Available at: https://melclass.edqm.eu/

Micromedex - Available at: https://www.micromedexsolutions.com/micromedex2/librarian/deeplinkaccess

Uppsala Monitoring Centre - Available at: VigiLyze (who-umc.org)

WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD Index - Available at: https://www.whocc.no/atc_ddd_index/

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Tetryzoline

1.2 ATC code: S01GA02

1.3 Therapeutic indications: short-term symptomatic treatment of ocular congestion, conjunctival redness (hyperaemia) and irritation due to allergic and inflammatory ocular conditions in the non-infected eye.

1.4 Posology and duration of treatment: conjunctivitis: in adults and children over 6 years old, 1 to 2 drops 0.05% tetrahydrozoline (tetryzoline) ophthalmic solution should be administered up to four times daily.

Topical use of tetryzoline is associated with rebound vasodilation and congestion. It is intended for short-term symptomatic treatment only and should not be used for longer than 5 to 7 days without medical supervision. Shorter periods of use are recommended in the event of non-improvement or worsening of symptoms, or when used in children under 12 years.

1.5 Pharmaceutical forms: eye drops, solution.

Contraindications: the product should not be used in the following cases: known hypersensitivity to tetryzoline, other adrenergic agents or to any of the excipients in the formulation; closed-angle glaucoma.

Relevant warnings: if there is any eye pain, vision changes, continued redness or irritation of the eye, or if the condition worsens or persists for more than 24 hours, discontinuation of the medicinal product should be considered with re-evaluation of diagnosis and treatment. The product should not been used when taking MAOIs or within 14 days of stopping this medication. As with other sympathomimetics, use with caution in the presence of hypertension, diabetes, asthma, prostatic enlargement, hyperthyroidism, cardiovascular abnormalities and arteriosclerosis. Contact lens wear during ophthalmic use is not recommended. Rebound vasodilation and congestion can occur, so the product should be limited to short-term use only. Due to potential systemic absorption of tetryzoline, caution is advised with concurrent administration of tricyclic antidepressants and phenothiazines.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): there are no serious direct risks associated with the use of ophthalmological tetryzoline due to the topical nature of authorised products and low systemic exposure when used in accordance with the authorised indication. Available evidence is inconclusive or inadequate for determining foetal risk when used in pregnancy, or infant risk when used during breastfeeding. Although toxicity during pregnancy or breastfeeding is not anticipated, caution should be exercised with use in these populations. Adverse drug reactions tend to be limited to site-of-application reactions, including burning sensation in and around the eyes, reactive hyperaemia, irritation, pain and itching. Mydriasis has been reported and is at greater risk of occurrence in patients with light irises or corneal abrasions, and in users of contact lenses. Topical decongestant-induced conjunctivitis, associated with conjunctival hyperaemia, has been reported with tetryzoline use. Other reported adverse reactions include nausea, headache and dizziness. Tetryzoline should not been used when taking MAOIs or within 14 days of stopping this medication. Due to potential systemic absorption of tetryzoline, caution is advised with concurrent use of tricyclic antidepressants and phenothiazines. Proposed interactions are theoretical in nature and unlikely due to low systemic absorption. As with all ocular medicinal products, it is recommended that an interval of approximately 15 minutes, unless otherwise specified, is left between concomitant use of multiple ocular medicinal products. Tetryzoline use may lead to blurring of vision. Appropriate measures should be considered when driving or operating machinery. All identified direct risks may be mitigated by adequate product information and labelling.

2.2 Indirect risks (incorrect use): indirect risks may arise from incorrect diagnosis or self-assessment of the underlying medical condition, which may lead to masking of symptoms or the delayed diagnosis of a more serious underlying condition of the eye. Overdosage by accidental administration by mouth of large quantities of solution may cause depression of the CNS, reduction of body temperature, drowsiness and coma, particularly in children. Oral administration of tetryzoline ophthalmic solution 0.05% has been implicated in drug-facilitated sexual assault to obtain a flaccid victim who is unable to resist or recall events (Spiller HA, Siewert DJ. Drug-facilitated sexual assault using tetrahydrozoline. *J Forensic Sci* 2012;57(3):835-8). All identified indirect risks may be mitigated by adequate product information and labelling, and appropriate supply status.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
AM	Not subject to prescription	0.5 mg/mL	3 times daily	10 mL	Symptomatic treatment of ocular congestion, conjunctival oedema, hyperaemia due to eye allergies and non-specific catarrhal conjunctivitis	Not more than 4 days
AT	Not authorised					
BA	Non-prescription					
BE	Not subject to prescription	0.5 mg/mL		10 mL	Symptomatic treatment of ocular congestion, conjunctival oedema, hyperaemia due to eye allergies and so-called non-specific or catarrhal conjunctivitis	
BG	Not subject to prescription					
CH	Not subject to prescription					
CY	Not subject to prescription					
CZ	Not subject to prescription					
EE	Not subject to prescription					
ES	Not subject to prescription					
FI	Not subject to prescription					
FR	Not authorised					
GE	Not subject to prescription					
HR	Not subject to prescription	0.5 mg/mL		15 mL	Temporary relief of eye hyperaemia caused by non-infectious eye irritations in adults and children over 2 years	Not more than 3 days
HU	Not subject to prescription					
IE	Not authorised					
IT	Not subject to prescription					
LT	Not subject to prescription					
LV	Not subject to prescription					
ME	POM					
MK	Not subject to prescription					
NL	Not authorised					
PL	Not subject to prescription					
PT	Not subject to prescription (pharmacy only supply)	0.5 mg/mL		15 mL	Temporary relief of eye hyperaemia caused by non-infectious eye irritations, for example, due to smoke, dust, wind, chlorinated water, light or allergic conjunctivitis, for adults and children over 2 years	
RO	Not subject to prescription					
RS	Not subject to prescription					
SE	Not authorised					
SI	Not subject to prescription					
SK	Not subject to prescription					
TR	POM					
UK	Not authorised					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **Not subject to prescription**

Criteria: a) good safety profile with low systemic exposure; b) direct and indirect dangers can be safely mitigated through appropriate product labelling in the non-prescription setting; c) well-established use in the non-prescription setting in most countries in which medicinal products are authorised.

3.2.2 Paediatric use: safety and efficacy is not well established in children under the age of 6 years. The risk-benefit of use in the non-prescription setting in this population warrants more careful evaluation.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale - Available at: https://www.medicinescomplete.com/#/

Melclass database - Available at: https://melclass.edqm.eu/

Micromedex - Available at: https://www.micromedexsolutions.com/micromedex2/librarian/deeplinkaccess

Spiller HA, Siewert DJ. Drug-facilitated sexual assault using tetrahydrozoline. *J Forensic Sci* 2012;57(3):835-8

Uppsala Monitoring Centre - Available at: VigiLyze (who-umc.org)

WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD Index - Available at: https://www.whocc.no/atc_ddd_index/

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Xylometazoline

1.2 ATC code: S01GA03

Note: xylometazoline is a direct-acting sympathomimetic with marked alpha-adrenergic activity. It is a vasoconstrictor which reduces swelling and congestion when applied to mucous membranes. Preparations containing 0.05% xylometazoline hydrochloride with 0.5% antazoline sulfate are typical. These, however, are categorised under ATC code S01GA53, xylometazoline, combinations.

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: no data available in Melclass (based on the available data, no medicines containing this active substance are authorised in member states).

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Oxymetazoline

1.2 ATC code: S01GA04

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, medicines containing this active substance are only authorised in Portugal (classification status: not subject to prescription).

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: based on the available data, medicines containing this active substance are not authorised in at least three member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Phenylephrine

1.2 ATC code: S01GA05

1.3 Therapeutic indications: phenylephrine is used as a mydriatic in concentrations of up to 10% (generally, solutions containing 2.5% or 10% are used, but systemic absorption can occur and the 10% strength should be used with extra caution. Both strengths are indicated for mydriasis in diagnostic and therapeutic procedures). Low strength: ocular solutions containing lower concentrations (usually 0.12% phenylephrine hydrochloride) are used as a conjunctival decongestant.

1.4 Posology and duration of treatment: a) Mydriatic effect: adults, including the elderly: 1 drop should be applied topically to each eye. If necessary, this dose may be repeated 3-4 hourly. Timing of administration prior to diagnostic procedure or therapeutic intervention is dependent on the specific purpose for induction of mydriasis. Paediatric population: 1 drop should be applied topically to the eye. It is not usually necessary to exceed this dose. The use in preterm and newborn infants is not recommended unless clearly necessary and only with caution because of safety concerns associated with the risk of systemic adverse reactions, including transient increases in blood pressure. If treatment is medically justified, the lowest possible concentration and dose should be used and instillation of more than 1 drop per eye must be avoided. Of note, especially in children and the elderly, it is advisable to minimise systemic absorption and the risk of systemic adverse reactions by compressing the lacrimal sac at the medial canthus or gently closing the eye for a few minutes after instillation. To minimise cutaneous absorption, excess fluid should be wiped away from the periocular area.

b) Conjunctival decongestant: adults: 1 drop of a 0.12% phenylephrine hydrochloride solution should be applied to the conjunctiva every 3 to 4 hours as needed. Not to be used for periods exceeding 3 to 5 days. Paediatric population: contraindicated for use in children under 12 years of age. Due to limited data, not recommended for use in children and adolescents from 12 to 18 years of age.

1.5 Pharmaceutical forms: eye drops, solution.

1.6 Contraindications: a) Mydriatic effect: known hypersensitivity to phenylephrine, other adrenergic agents or to any of the excipients in the formulation; anatomical narrow angle; closed-angle glaucoma; corneal damage; concomitant use of MAOIs (or within 21 days prior to initiation of treatment), tricyclic antidepressants or antihypertensive agents; elderly patients with severe arteriosclerotic, cardiovascular or cerebrovascular disease; newborns and infants with cardio- and cerebrovascular disease; patients with cardiac disease, hypertension, aneurysms, thyrotoxicosis, long-standing insulin-dependent diabetes mellitus and tachycardia; 10% strength eye drops in children; 10% strength eye drops in neonates.

b) Conjunctival decongestant: known hypersensitivity to phenylephrine, other adrenergic agents or to any of the excipients in the formulation; anatomical narrow angle; closed-angle glaucoma; children under 12 years of age; treatment with MAOIs (concomitant or within 21 days prior to initiation of treatment); treatment with tricyclic antidepressants; elderly patients with severe arteriosclerotic, cardiovascular or cerebrovascular disease.

1.7 Relevant warnings: a) Mydriatic effect: to be used with caution in the following cases: elderly patients with sympathetic denervation (e.g. patients with insulin-dependent diabetes, orthostatic hypotension, hypertension, hyperthyroidism); patients with cerebral arteriosclerosis or long-standing bronchial asthma; inflamed eyes, as hyperaemia greatly increases the rate of systemic absorption through the conjunctiva. Children: the lowest dose necessary to produce the desired effect should always be used. Both full-term and, in particular, low-birth-weight and preterm infants may be at an increased risk of systemic adverse reactions including transient increases in blood pressure which potentially increases the risk of intraventricular haemorrhage; therefore, the infant should be monitored after application and routines to adequately deal with emergency situations should be in place.

b) Conjunctival decongestant: to be used with caution in the following cases: patients with arterial hypertension, advanced arteriosclerosis, orthostatic hypotension, long-standing insulin-dependent diabetes mellitus or heart disease, including severe ischemic heart disease. In addition, rebound vasodilation and congestion can occur with prolonged use; therefore, the product should be limited to short-term use only. Contact lens wear during ophthalmic use is not recommended. If there is any eye pain, vision changes, continued redness or irritation of the eye, or if the condition worsens or persists for more than 24 hours, discontinuation of the medicinal product should be considered with re-evaluation of diagnosis and treatment.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): since phenylephrine is absorbed through the mucosa, systemic effects may follow application to the eyes. In particular, phenylephrine-containing eye drops can have powerful systemic effects. They should be avoided or only used with extreme caution in infants, the elderly and in patients with cardiac disease, significant hypertension or advanced arteriosclerosis. Fatalities have been reported in patients with pre-existing cardiovascular disease. Available evidence is inconclusive or inadequate for determining foetal risk when used in pregnancy, or infant risk when used during breastfeeding. Phenylephrine should be used only if benefits outweigh risks. Systemic adverse effects have occurred after the use of phenylephrine as eye drops (particularly at a strength of 10%). Hypertension, hypertension with pulmonary oedema and hypertension with arrhythmias have been reported in children after 10% phenylephrine hydrochloride ophthalmological use. Systemic cardiovascular reactions (palpitations, hypertension, arrhythmias), including fatal myocardial infarctions, have been reported after the use of phenylephrine 10% solutions in the eye. Although the incidence of such reactions is low, the use of lower concentrations and caution in susceptible patients, such as those with cardiovascular disorders or the elderly, is advised. A reduction in the eye-drop volume has been found to produce adequate mydriasis and may reduce systemic absorption and the risk of adverse cardiovascular effects. Lower concentrations, e.g. 0.12% phenylephrine hydrochloride, are significantly less likely to result in the described systemic adverse effects. Other reported adverse reactions have included those categorised under eye disorders: allergic conjunctivitis, eye pain, eye irritation, conjunctival hyperaemia, increased lacrimation, blurred vision, photophobia, closed-angle glaucoma, corneal oedema, punctuate keratitis, floaters and periorbital pallor. Periorbital contact dermatitis has also been reported as an adverse reaction. Acute and chronic conjunctivitis have been reported after use of low-dose, non-prescription ophthalmic decongestant preparations of phenylephrine. As phenylephrine is absorbed through the mucosa, interactions may follow topical application. Of note, there is an increased risk of adrenergic reactions when used simultaneously with, or up to 3 weeks after, the administration of MAOIs. Phenylephrine may reverse the blood pressure lowering effects of antihypertensive drugs and may increase the risk of arrhythmias in patients receiving cardiac glycosides, quinidine or tricyclic antidepressants. Because of the increased risk of ventricular fibrillation, phenylephrine should be used with caution during general anaesthesia with anaesthetic agents which sensitise the myocardium to sympathomimetics. Phenylephrine may cause photophobia and blurred vision. Patients are advised not to drive or operate hazardous machinery until vision is clear. The mydriatic effect of phenylephrine hydrochloride can occur at concentrations as low as 0.12%.

2.2 Indirect risks (incorrect use): indirect risks may be associated primarily with incorrect diagnosis or self-assessment of the underlying medical condition, which may lead to masking of symptoms or the delayed diagnosis of a more serious underlying condition of the eye. Misuse, as in excessive or prolonged use, of phenylephrine hydrochloride at doses as low as 0.12% may lead to rebound eye congestion and other adverse effects, particularly those ocular in nature. Overdosage by accidental administration by mouth of large quantities of solution may result in a severe toxic reaction to phenylephrine with rapid onset. Adrenergic manifestations include tachycardia, hypertension, headache, anxiety, nausea and drowsiness. Urgent supportive treatment is required.

2.1 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
AM	Not authorised					
AT	Not authorised					
BE	POM					
BG	Not authorised					
CH	Not authorised					
CY	Not authorised					
CZ	Not authorised					
EE	Not authorised					
ES	Not subject to prescription					

FI	Not authorised					
FR	Not authorised					
GE	Not subject to prescription					
GR	Not authorised					
HR	Not authorised					
HU	Not authorised					
IE	List II					
IT	Not authorised					
LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	Not authorised					
NL	Not authorised					
PL	Not authorised					
PT	POM					
RO	Not authorised					
RS	Not authorised					
SE	Not authorised					
SI	Not authorised					
SK	Not authorised					
TR	POM					
UK	Not authorised					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **List I + Exemption** - Exemptions: short-term use of low-dose formulations (i.e. 0.10% of phenylephrine base) in adults only.

Criteria: a) rationale for List I: phenylephrine is primarily indicated for diagnostic purposes and for short-term treatment where medical supervision is necessary due to the potential for direct harm at therapeutic levels. b) Rationale for Exemption: exemption to prescription control may be considered for short-term use of low-dose formulations (i.e. 0.10% phenylephrine base), in adults only where product labelling and conditions of supply can mitigate risk of harm associated with use.

3.2.2 Paediatric use: in the non-prescription setting, safety and efficacy at the lowest strength (0.12% phenylephrine hydrochloride) is not well established in children and adolescents under the age of 18. The risk-benefit of use in the non-prescription setting in this population has not been established and cannot therefore be recommended.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Health Products Regulatory Authority (HPRA) (Ireland) - Available at: https://www.hpra.ie/

Martindale - Available at: https://www.medicinescomplete.com/#/
Melclass database - Available at: https://melclass.edqm.eu/

Micromedex - Available at: https://www.micromedexsolutions.com/micromedex2/librarian/deeplinkaccess

Spanish Agency of Medicines and Medical Devices (AEMPS) - Available at:

https://cima.aemps.es/cima/publico/home.html

Uppsala Monitoring Centre - Available at: VigiLyze (who-umc.org)

WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD Index - Available at: https://www.whocc.no/atc_ddd_index/

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Oxedrine

1.2 ATC code: S01GA06

Note: Oxedrine is a sympathomimetic agent with alpha-adrenergic activity. Oxedrine tartrate has been used in eye drops as an ocular decongestant. The hydrochloride has also been used. There are no known authorised products in any member states.

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: no data available in Melclass (based on the available data, no medicines containing this active substance are authorised in member states).

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Brimonidine

1.2 ATC code: S01GA07

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: no data available in Melclass (based on the available data, no medicines containing this active substance are authorised in member states).

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Naphazoline, Combinations

1.2 ATC code: S01GA51

1.3 Therapeutic indications: there are many different naphazoline combinations authorised in the member states (with diphenhydramine hydrochloride, zinc sulfate, hamamelis water, pheniramine maleate and antazoline). These products are used for temporary symptomatic relief of redness of the eye due to minor eye irritations, allergic swelling of the mucous membranes and hay fever conjunctivitis.

1.4 Posology and duration of treatment: adults and children over 12 years: 1 or 2 drops into each eye, no more than four times daily. Some combinations are authorised for adults and children over 6 years (e.g. diphenhydramine hydrochloride, zinc sulfate), while others are authorised for adults only (e.g. antazoline).

1.5 Pharmaceutical forms: eye drops.

1.6 Contraindications: these combination products should not be used in the following cases: persons suffering from closed-angle glaucoma; persons with serious eye disease or who have had previous eye surgery; concomitant use of MAOIs or within 14 days of stopping this medication.

1.7 Relevant warnings: patients being treated for high blood pressure, depression, heart disease, arteriosclerosis, diabetes or increased thyroid activity should consult their doctor before using the drops as naphazoline may exacerbate vasoconstriction. For the same reason, these combination products should not be used as a long-term ocular irrigant. In case of eye pain, changes in vision or continued redness of the eye, or if the condition worsens or persists for more than 24 hours, patients should consult a doctor. In addition, it should be noted that these products may interact with other topically applied medications used in the treatment of glaucoma, they may interact with MAOIs and should not be used by patients receiving such treatment or within 14 days of ceasing therapy, and they may reverse the antihypertensive action of medications used in the treatment of hypertension. There may be an increased risk of arrhythmias in patients receiving cardiac glycosides, quinidine or tricyclic antidepressants.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): undesirable effects: hypersensitivity, headache, dizziness, eye irritation, eye pain, ocular hyperaemia, nausea.

2.2 Indirect risks (incorrect use): excessive or long-term use of these combination products may result in allergic conjunctivitis, allergic blepharitis or rebound conjunctival hyperaemia. Prolonged use may also lead to epithelial xerosis, which can exacerbate symptoms of irritation, pain and dryness experienced in allergic conjunctivitis. Indiscriminate use of decongestants, such as naphazoline and naphazoline-containing products, in an irritated eye can induce papillary dilation and precipitate angle-closure glaucoma in eyes that have narrow anterior chamber angles. Overdosage by mouth may cause nausea, headache, depression of the CNS with marked reduction of body temperature and symptoms of bradycardia, sweating, drowsiness and coma, particularly in children. In addition, naphazoline-containing products may cause hypertension followed by rebound hypotension.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not authorised					
AT	List II				For the symptomatic treatment of mainly allergic swelling of the mucous membranes and catarrhs of the eyes.	Not for children under 6 years

					Allergic eyelid diseases and conjunctivitis (hay fever conjunctivitis) and effects of tear ducts. Conjunctival irritation from the sun and other strong light sources, smoke or chemicals.	
BA	Not authorised					
BE	Not subject to prescription				Symptomatic treatment of eye irritations or ocular congestion caused by allergic eye disorders in adults.	
BG	Not authorised					
CH	Not authorised					
CZ	Not authorised					
CY	Not subject to prescription					
EE	Not authorised					
ES	Not subject to prescription					
FI	Not authorised					
FR	List II					
GE	Not authorised					
HR	Not authorised					
HU	Not subject to prescription					
IE	Not subject to prescription					
IT	Not subject to prescription					
LU	Not authorised					
LT	Not authorised					
LV	Not authorised					
ME	Not subject to prescription					
MK	Not authorised					
NL	Not authorised					
PL	POM					
PT	POM					
RO	Not subject to prescription					
RS	Not authorised					
SI	Not subject to prescription					
SK	Not authorised					
TR	Not authorised					
UK	Not subject to prescription					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **Not subject to prescription** - *Additional information:* for adults and children over 12 and for short-term use only.

Criteria: a) good safety profile with low systemic exposure; b) direct and indirect dangers can be safely mitigated through appropriate product labelling in the non-prescription setting; c) well-established use in the non-prescription setting in most countries in which medicinal products are authorised.

3.2.2 Paediatric use: for children over 12 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

AEMPS (Spain) - Available at: https://cima.aemps.es/cima/publico/home.html

HPRA (Ireland) - Available at: https://www.hpra.ie/

Martindale: The Complete Drug Reference (last update: 13.09.2022)

Medicines and Healthcare products Regulatory Agency (MHRA) (United Kingdom) - https://mhraproducts4853.blob.core.windows.net/docs/9fc5f5bdbe05e8a6ad642e375180972feff38c9f

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Tetryzoline, Combinations

1.2 ATC code: S01GA52

1.3 Therapeutic indications: temporary relief of signs and symptoms of allergic conjunctivitis, including conjunctival hyperaemia, irritation and itching in adults and children 2 years of age and older (most common combination is with antazoline).

1.4 Posology and duration of treatment: adults and adolescents from 12 years of age: 1 drop two to three times a day for 14 days. Children from 2 years to 12 years of age: no specific studies are available for this patient group. Due to the possibility of systemic effects, the dose of 1 to 2 drops per day should not be exceeded. The medicine is not intended for the treatment of children under 2 years of age.

1.5 Pharmaceutical forms: eye drops.

1.6 Contraindications: simultaneous use with MAOIs.

1.7 Relevant warnings: caution is required in elderly patients with more serious cardiovascular disease, including cardiac arrhythmia, with poorly controlled hypertension or diabetes mellitus. Due to the sympathomimetic effect of the medicine, caution is required in patients with diabetes mellitus, hypertension, hyperthyroidism and increased values of thyroid hormones, arrhythmia or tachycardia and phaeochromocytoma. Caution should be exercised in patients at risk of glaucoma or with angle-closure glaucoma if iridectomy (or iridotomy) has not been performed. The patient should be advised that long-term use of vasoconstrictors may lead to rebound hyperaemia.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): hypersensitivity, headache, somnolence, drowsiness, dizziness, tremors and central excitation, eye burning, eye stinging, iris exfoliation, mydriasis, blurred vision, acute conjunctivitis, chronic conjunctivitis, acute follicular conjunctivitis, dry eyes, conjunctival hyperaemia, ocular hyperaemia, angle-closure glaucoma, angina pectoris, hypertension, tachycardia.

2.2 Indirect risks (incorrect use): in children under 2 years of age, accidental ingestion of the entire bottle may cause nausea, drowsiness, arrhythmia or tachycardia, or even shock. CNS depression, hypotension and coma have occurred with tetryzoline overdose.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not authorised					
AT	Not authorised					
BA	Not authorised					
BE	Not authorised					
BG	Not subject to prescription (combination with antazoline)					
CH	Not subject to prescription					
CZ	POM					
EE	Not authorised					
ES	Not authorised					

FI	Not authorised					
FR	Not authorised					
GE	Not authorised					
HR	Not authorised					
HU	POM					
IE	Not authorised					
IT	List II + Exemption	Ex.: combination products containing tetryzoline and pheniramine (MQP: 10 mL)				
LU	Not authorised					
LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	Not authorised					
NL	Not authorised					
PL	POM					
PT	Not authorised					
RO	Not subject to prescription (combination with antazoline)					
RS	Not authorised					
SI	Not subject to prescription					
SK	POM					
TR	Not authorised					
UK	Not authorised					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation**: Not subject to prescription** (adults and children above 6 years of age; short-term use).

Criteria: a) good safety profile with low systemic exposure; b) direct and indirect dangers can be safely mitigated through appropriate product labelling in the non-prescription setting; c) well-established use in the non-prescription setting in most countries in which medicinal products are authorised.

3.2.2 Paediatric use: for adults and adolescents from 6 years of age. The medicine is not intended for the treatment of children under 2 years of age.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale - Available at: https://www.medicinescomplete.com/#/

Melclass database - Available at: https://melclass.edqm.eu/

Micromedex - Available at: https://www.micromedexsolutions.com/micromedex2/librarian/deeplinkaccess

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Xylometazoline, Combinations

1.2 ATC code: S01GA53

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, medicines containing xylometazoline in combination with other active substances are only authorised in Ireland and the UK (classification status: not subject to prescription).

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: based on the available data, medicines containing xylometazoline in combination with other active substances are not authorised in at least three member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Phenylephrine, Combinations

1.2 ATC code: S01GA55

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: no data available in Melclass (based on the available data, no medicines containing phenylephrine in combination with other active substances are authorised in member states).

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: based on the available data, no medicines containing phenylephrine in combination with other active substances are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Oxedrine, Combinations

1.2 ATC code: S01GA56

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: no data available in Melclass (based on the available data, no medicines containing oxedrine in combination with other active substances are authorised in member states).

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: based on the available data, no medicines containing oxedrine in combination with other active substances are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Cromoglicic acid

Note: in eye drops available as the salt sodium cromoglicate. Sodium cromoglicate acts by inhibiting the release of histamine and various membrane-derived mediators of inflammation from mast cells. Sodium cromoglicate is very poorly absorbed from the gastrointestinal tract (around 1%), has a high systemic clearance and rapid elimination (after 1 hour), and accumulation does not occur. Sodium cromoglicate is not metabolised.

1.2 ATC code: S01GX01

1.3 Therapeutic indications: for the relief and treatment of seasonal and perennial allergic conjunctivitis and vernal keratoconjunctivitis (vernal or spring catarrh).

1.4 Posology and duration of treatment: 20 mg/mL: 1-2 drops into each eye four times daily or as instructed by the physician; 40 mg/mL: 1-2 drops into each eye twice daily. There is no need for dose adjustment in children and the elderly. The medicinal product should be used regularly to ensure optimal control of symptoms. It is recommended that treatment is continued during the period of exposure to allergen. For ocular use only. It should be administered in the conjunctival sac of the affected eye.

1.5 Pharmaceutical forms: eye drops, solution (strength: 20 mg/mL, 40 mg/mL).

1.6 Contraindications: not to be used in patients sensitive to sodium cromoglicate or any of the ingredients.

1.7 Relevant warnings: the usual warnings for most ophthalmic preparations apply: contact lenses should be removed before each application and may be inserted after 15 minutes. In case of concomitant treatment with other eye drops, instillations should be 15 minutes apart. Use during pregnancy only where there is a clear need (caution should be exercised especially during the first trimester of pregnancy). Given that transient stinging or blurred vision may occur on instillation, patients are advised not to drive or operate machinery until proper vision is restored.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): eye disorders (unknown frequency): transient stinging and burning may occur after instillation; other symptoms of local irritation have been reported. Immune system disorders (unknown frequency): local and systemic hypersensitivity reactions have been reported. Interactions with other medicinal products: no known clinically relevant interactions with other medicinal products.

2.2 Indirect risks (incorrect use): overdose: no case of overdose has been reported recently. No action other than medical observation should be necessary.

2.3 Recent cases at European level: none identified - the outcome of assessment of the last two PSURs for cromoglicic acid was without safety variations (PSUSA/00000883/201702, 31/10/2017; PSUSA/00000883/202202, 30/9/2022).

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not subject to prescription	4%	2x daily	5 mL	Allergic conjunctivitis. Use in children below 4 years on medical prescription.	
AT	List II + Exemption	Ex.: 2%			Ex.: treatment of acute (as part of a basic treatment) and chronic conjunctivitis on an allergic basis, e.g. conjunctivitis in the context	

					of hay fever, conjunctivitis vernalis (spring conjunctivitis), keratoconjunctivitis vernalis (in these cases additional steroid therapy may be necessary).	
BA	Not authorised					
BE	Not subject to prescription	4%				
BG	Not subject to prescription					
CH	Not subject to prescription					
CY	Not subject to prescription					
CZ	POM + Exemption	Ex.: 4%		Ex.: 10 mL		
EE	POM + Exemption	Ex.: 2%				
ES	POM					
FI	Not subject to prescription					
FR	Not subject to prescription					
GE	Not subject to prescription					
GR	Not subject to prescription					
HR	Not authorised					
HU	Not subject to prescription					
IE	List II + Exemption	Ex.: 2%		Ex.: 10 mL		
IT	Not authorised					
LU	Not subject to prescription					
LT	Not subject to prescription	40 mg/mL				
LV	Not subject to prescription					
ME	Not authorised					
MK	POM	2%		10 mL		
NL	Not subject to prescription					
PL	Not subject to prescription					
PT	Not subject to prescription	20 mg/mL		10 mL	Symptomatic and prophylactic treatment of perennial or seasonal allergic conjunctivitis. Not for use in children below 4 years.	
RO	List II					
RS	POM				Acute and chronic allergic conjunctivitis and vernal keratoconjunctivitis	
SI	Not authorised					
SK	POM					
TR	POM					
UK	Not subject to prescription	2%			Not for use in children below 6 years.	

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **List II + Exemption** - Exemptions: ocular use, seasonal and perennial allergic conjunctivitis, MS: 4% w/v, MQP: 10 mL; adults and children above 2 years of age. Use in vernal keratoconjunctivitis and prolonged use upon medical advice.

Criteria: a) rationale for List II: severe cases (as in vernal keratoconjunctivitis) as well as prolonged use and use in children require a physician's assessment. b) Rationale for Exemption: known safety profile (local side effects) and pharmacokinetic profile (poor systemic absorption, short elimination half-life); self-diagnosis possible (well-known indication); short-term use.

3.2.2 Paediatric use: limited data on sodium cromoglicate use in children are available. Different countries may have different licensed lower age limits (in some countries use below 4 years or 6 years is not allowed). In children, caregiver supervision and/or assistance may be required.

3.2.3 Social dimension: allergic conjunctivitis is prevalent in 6-30% of the general population. In view of the high prevalence and need for frequent ophthalmic care, it places a high disease burden on healthcare providers.

4. REFERENCES/COMMENTS

4.1 References:

EMA: Cromoglicic acid: PSUSA/00000883/201702, 31/10/2017; PSUSA/00000883/202202, 30/9/2022.

HPRA (Ireland) - Available at: https://www.hpra.ie/

Leonardi A, Castegnaro A, Valerio AL, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. *Curr Opin Allergy Clin Immunol* 2015;15:482-8.

Martindale - Available at: https://www.medicinescomplete.com/#/

4.2 Comments: -

1.THERAPEUTIC PROFILE

1.1 Active ingredient: Levocabastine

Note: in ophthalmic suspension available as levocabastine hydrochloride salt. Levocabastine is a selective histamine H_1 receptor antagonist for topical ophthalmic use. Levocabastine had systemic availability of 30-60% after ocular use, but low peak plasma concentrations, relatively long-lasting effectiveness due to higher terminal half-life (35-40 hours), and is excreted mainly unchanged via the kidneys.

1.2 ATC code: S01GX02

1.3 Therapeutic indications: symptomatic treatment of allergic conjunctivitis including vernal conjunctivitis.

1.4 Posology and duration of treatment: adults, adolescents and children from 8 years: 1 drop per eye twice daily. In the case of severe symptoms, levocabastine can be applied up to three to four times a day. Treatment should only be continued until symptoms disappear. The medicinal product should not be used for more than 2 weeks without a doctor's prescription. In the event of a need for use for more than 2 weeks, a doctor's advice and monitoring are required. There is no experience of a treatment duration of more than 3 months.

1.5 Pharmaceutical forms: ophthalmic suspension, drops (strength: 0.5 mg/mL).

1.6 Contraindications: use in patients sensitive to levocabastine or any of the ingredients.

1.7 Relevant warnings: the usual warnings for most ophthalmic preparations apply: contact lenses should be removed before each application and may be inserted after 15 minutes. In case of concomitant treatment with other eye drops, instillations should be 15 minutes apart. Due to limited clinical data, use during pregnancy is not recommended, and only where there is a clear need. In nursing mothers, levocabastine can be used with caution. Given that eye irritation and pain as well as blurred vision may occur, patients are advised not to drive or operate machinery until proper vision is restored.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): immune system disorders: angioneurotic oedema, hypersensitivity, anaphylaxis. Nervous system disorders: headache. Eye disorders: eye pain, blurred vision, eyelid oedema, conjunctivitis, eye swelling, blepharitis, ocular hyperaemia, watery eyes. Cardiac disorders: palpitations. Skin and subcutaneous tissue disorders: contact dermatitis, urticaria. General disorders and administration site conditions: administration site discomfort including burning/stinging sensation and irritation of the eyes. Interactions with other medicinal products: no known clinically relevant interactions with other medicinal products.

2.2 Indirect risks (incorrect use): no cases of overdose have been reported. Some sedative effects after ingestion of the contents of an eye dropper bottle cannot be ruled out.

2.3 Recent cases at European level: the outcome of assessment of the last PSUR for levocabastine was without safety variations (PSUSA/00001849/201711, 19/7/2018).

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not authorised					
AT	Not subject to prescription	0.5%			Symptomatic treatment of allergic conjunctivitis including vernal conjunctivitis.	

					Use in children below 8 years with doctor's advice.	
BA	Not authorised					
BE	Not subject to prescription					
BG	Not authorised					
CH	Not subject to prescription				Seasonal allergic conjunctivitis. Use in children above 6 years.	
CZ	Not subject to prescription				Seasonal and chronic allergic conjunctivitis. Use in children above 6 years.	
DE	Not subject to prescription					
EE	Not authorised					
ES	POM + Exemption	Ex.: 0.05%		Ex.: 5 mL	Use in children below 12 years on medical prescription.	
FI	Not subject to prescription					
FR	List II + Exemption	Ex.: 0.05%		Ex.: 0.0025 g		
GE	Not subject to prescription					
HR	Not authorised					
HU	Not authorised					
IE	Not authorised					
IT	Not subject to prescription	0.05%				
LU	Not subject to prescription					
LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	Not authorised					
NL	POM					
PL	Not authorised					
PT	Not authorised					
RO	Not authorised					
RS	POM					
SI	Not authorised					
SK	Not subject to prescription					
TR	Not authorised					
UK	Not authorised					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **List II + Exemption** - Exemption: ocular use; short-term symptomatic treatment of allergic conjunctivitis; MS: 0.5 mg/mL and MQP: 5 mL; adults and children above 6 years of age. Prolonged use upon medical advice.

Criteria: a) rationale for List II: severe cases (as in vernal keratoconjunctivitis) as well as prolonged use and use in children (limited clinical data) requiring prior doctor's recommendation. b) Rationale for exemption: known safety profile (local side effects) and pharmacokinetic profile (low plasma concentrations); self-diagnosis possible (well-known indication); short-term use.

3.2.2 Paediatric use: limited data on levocabastine use in children are available. Different countries may have different licensed lower age limits (in some countries use below 6/8/12 years is not allowed). In children, caregiver supervision and/or assistance may be required.

3.2.3 Social dimension: allergic conjunctivitis is prevalent in 6-30% of the general population. In view of the high prevalence and need for frequent ophthalmic care, it places a high disease burden on healthcare providers.

4. REFERENCES/COMMENTS

4.1 References:

Austrian Agency for Health and Food Safety (AGES): Summary of product characteristics (SmPC) for LIVOSTIN Augentropfen (date of text revision September 2020)

EMA: Levocabastine: PSUSA/00001849/201711, 19/7/2018.

Martindale - Available at: https://www.medicinescomplete.com/#/

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Spaglumic acid

Note: in eye drops, spaglumic acid is available as a salt of *N*-acetyl-l-aspartyl-glutamate. Spaglumic acid is a mast cell stabiliser. Maximum spaglumic acid levels were reached in the conjunctiva and cornea within 30 minutes and decreased only slowly over the following 8 hours. No systemic absorption was demonstrated.

1.2 ATC code: S01GX03

1.3 Therapeutic indications: symptomatic treatment of acute and chronic allergic conjunctivitis and keratoconjunctivitis, as well as blepharoconjunctivitis of allergic origin.

1.4 Posology and duration of treatment: adults and children above 4 years of age: 1 drop per eye four times a day. Treatment duration: it is important that treatment is continued for the duration of the allergy risk.

1.5 Pharmaceutical forms: eye drops, solution (strength: 49 mg/mL).

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients.

1.7 Relevant warnings: the usual warnings for most ophthalmic preparations apply: in case of concomitant treatment with other eye drops, instillations should be 10 minutes apart. There have been no clinical studies in children under 4 years of age. Administration during the first 3 months of pregnancy as well as during lactation should be avoided. Given that transient stinging or blurred vision may occur on instillation, patients are advised not to drive or operate machinery until proper vision is restored.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): transient stinging and burning may occur after instillation. Interactions with other medicinal products: no known clinically relevant interactions with other medicinal products.

2.2 Indirect risks (incorrect use): overdose: there is practically no risk of undesirable effects if the medication is accidentally swallowed.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not authorised					
AT	Not authorised					
BA	Not authorised					
BE	Not authorised					
BG	Not authorised					
CH	List II	4.9%			Allergic acute or chronic (kerato) conjunctivitis	
CY	Not authorised					
CZ	Not authorised					
DE	Not authorised					
EE	Not authorised					
ES	POM	38 mg/mL			Conjunctivitis and blepharoconjunctivitis of allergic origin	
FI	Not authorised					
FR	Not authorised					
GE	Not authorised					

HR	Not authorised					
HU	Not authorised					
IE	Not authorised					
IT	Not subject to prescription	4.9%			Acute and chronic allergic conjunctivitis and keratoconjunctivitis	
LU	Not authorised					
LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	Not authorised					
NL	Not authorised					
PL	Not authorised					
PT	POM	4.9%			Symptomatic treatment of moderate conjunctivitis and blepharoconjunctivitis of allergic origin	
RO	Not subject to prescription	4.9%			Symptomatic treatment of moderate conjunctivitis and blepharoconjunctivitis of allergic origin	
RS	Not authorised					
SI	Not authorised					
SK	Not authorised					
TR	Not authorised					
UK	Not authorised					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **List II + Exemption** - Exemptions: short-term symptomatic treatment of allergic conjunctivitis; MS: 49 mg/mL and MQP: 10 mL; adults and children above 4 years of age; prolonged use upon medical advice.

3.2.2 Paediatric use: no clinical data on spaglumic acid use in children below 4 years are available.

3.2.3 Social dimension: allergic conjunctivitis is prevalent in 6-30% of the general population. In view of the high prevalence and need for frequent ophthalmic care, it places a high disease burden on healthcare providers.

4. REFERENCES/COMMENTS

4.1 References:

AEMPS (Spain) - SmPC of Naaxia 38 mg/mL colirio en solución (Laboratorios Théa S.A.) (date of revision March 2016)

Martindale - Available at: https://www.medicinescomplete.com/#/

Melclass database - Available at: https://melclass.edqm.eu/

Swiss Agency for Therapeutic Products: SmPC of Naabak® 4.9% Augentropfen (Théa PHARMA S.A) (date of revision June 2021)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Nedocromil

Note: in eye drops available as the salt nedocromil sodium. Nedocromil sodium prevents the release of inflammatory mediators from a wide range of inflammatory cell types. Necrodomil sodium is very poorly absorbed after ophthalmic use (< 4%), is not metabolised, is rapidly eliminated from plasma and does not accumulate.

1.2ATC code: S01GX04

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: no data available in Melclass (based on the available data, no medicines containing this active substance are authorised in member states).

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Lodoxamide

Note: in eye drops, available as lodoxamide trometamol. Lodoxamide is a mast cell stabiliser and inhibitor of histamine release. The oral bioavailability of lodoxamide in man is 71%; approximately 87% of the absorbed drug undergoes biotransformation and is excreted in the form of glucuronide and sulfate.

1.2 ATC code: S01GX05

1.3 Therapeutic indications: treatment of non-infectious allergic conjunctivitis (vernal conjunctivitis, giant papillary conjunctivitis and allergic-atopic conjunctivitis).

1.4 Posology and duration of treatment: adults and children above 4 years of age: 1-2 drops in each eye four times a day at regular intervals. Treatment duration: improvements in symptoms are usually evident within a few days, but longer treatment for up to 4 weeks is sometimes required; once symptomatic improvement has been established, therapy should be continued for as long as needed to sustain improvement.

1.5 Pharmaceutical forms: eye drops solution (strength: 0.1% w/v).

1.6 Contraindications: hypersensitivity to lodoxamide or any of the excipients.

1.7 Relevant warnings: the usual warnings for most ophthalmic preparations apply: in case of concomitant treatment with other eye drops, instillations should be 5 minutes apart. Patients should be monitored in case of prolonged use. Due to limited clinical data, it is preferable to avoid lodoxamide use during pregnancy and lactation. Given that transient blurred vision may occur on instillation, patients are advised not to drive or operate machinery until proper vision is restored.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): nervous system disorders: dizziness, headache. Eye disorders: blurred vision, dry eye, eye pruritus, increased lacrimation, ocular hyperaemia, eye pain, eye oedema, asthenopia, corneal deposits, conjunctival oedema, abnormal sensation in eye, foreign body sensation in eye, eye discharge, eye irritation, corneal erosion, corneal scar, corneal abrasion, anterior chamber cell, corneal epithelium defect, keratitis, blepharitis, eye allergy, visual impairment, eyelid oedema, conjunctival disorder. Cardiac disorders: palpitations. Respiratory, thoracic and mediastinal disorders: nasal dryness, sneezing disorders. Gastrointestinal disorders: nausea, abdominal discomfort. Skin and subcutaneous tissue disorders: eyelid exfoliation, rash. General disorders and administration site conditions: feeling hot. Interactions with other medicinal products: no known clinically relevant interactions with other medicinal products.

2.2 Indirect risks (incorrect use): overdose: in the event of a topical overdose, flush from the eye with lukewarm water. In case of accidental ingestion of doses of 0.1 mg to 10.0 mg of lodoxamide, feeling of warmth, flushing, nausea, vomiting, diaphoresis and abdominal cramping may occur. Transient elevations of systolic and diastolic blood pressure have been noted with doses of 3.0 and 10.0 mg of oral lodoxamide, but they resolve spontaneously after a short time. Other possible adverse effects after an oral overdose are: headache, dizziness, fatigue and loose stools.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not authorised					
AT	Not authorised					
BA	Not authorised					

BE	POM					
BG	Not authorised					
CH	Not authorised					
CY	Not authorised					
CZ	Not authorised					
DE	Not authorised					
EE	Not authorised					
ES	Not authorised					
FI	Not authorised					
FR	Not authorised					
GE	Not subject to prescription					
HR	Not authorised					
HU	POM					
IE	Not authorised					
IT	Not authorised					
LU	POM					
LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	Not authorised					
NL	Not authorised					
PL	Not authorised					
PT	Not authorised					
RO	Not authorised					
RS	Not authorised					
SI	Not authorised					
SK	Not authorised					
TR	POM					
UK	POM					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 *Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):*

Proposed recommendation: **List II**

Criteria: not first-line treatment for allergic conjunctivitis.

3.2.2 Paediatric use: there is limited clinical evidence of use in children under 4 years of age, so it is not intended for use in children below 4 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale - Available at: https://www.medicinescomplete.com/#/

MHRA (UK): SmPC of Alomide 0.1% w/v eye drops, solution (Novartis Pharmaceuticals UK Limited) (date of text revision February 2021)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Emedastine

Note: in eye drops, available as emedastine difumarate. Emedastine is a potent selective and topically effective histamine H_1 antagonist. Emedastine is absorbed in small amounts after ocular use. It is metabolised in the liver and eliminated via urine (elimination half-life after topical administration is 10 hours).

1.2 ATC code: S01GX06

1.3 Therapeutic indications: symptomatic treatment of seasonal allergic conjunctivitis.

1.4 Posology and duration of treatment: adults and children over 3 years: 1 drop to be applied to the affected eye(s) twice daily. Not recommended for use in the elderly or patients with hepatic and renal impairment. Treatment duration: emedastine use has not been studied in clinical trials beyond 6 weeks.

1.5 Pharmaceutical forms: eye drops, solution (strength: 0.5 mg/mL).

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients.

1.7 Relevant warnings: when used with other ophthalmic medicines, an interval of 10 minutes should be allowed between applications of each medicinal product. Eye ointments should be administered last. Ocular corneal infiltrates have been reported in conjunction with the use of emedastine. In case of corneal infiltrates, the product should be discontinued and appropriate management should be implemented. Emedastine can be used in recommended doses during pregnancy. Caution is required when it is used during lactation. Given that transient blurred vision may occur on instillation, patients are advised not to drive or operate machinery until proper vision is restored.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): psychiatric disorders: abnormal dreams. Nervous system disorders: headache, sinus headache, dysgeusia. Eye disorders: eye pain, eye pruritus, conjunctival hyperaemia, corneal infiltrates, corneal staining, blurred vision, eye irritation, dry eye, foreign body sensation in eyes, increased lacrimation, asthenopia, ocular hyperaemia. Cardiac disorders: tachycardia. Skin and subcutaneous tissue disorders: rash. Interactions with other medicinal products: no interaction studies have been performed.

2.2 Indirect risks (incorrect use): overdose: no specific reactions are to be expected with an ocular overdose. No data are available in humans regarding overdose by ingestion. In case of ingestion of the contents of a bottle of emedastine, sedative effects may occur and the potential of emedastine to increase the QT interval should be borne in mind.

2.3 Recent cases at European level: the outcome of assessment of the last two PSURs for emedastine was without safety variations (PSUSA/1207/201705, 11/1/2018; PSUSA/1207/202005, 14/1/2021).

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not authorised					
AT	List II					
BA	Not authorised					
BE	POM					
BG	Not authorised					
CH	Not subject to prescription					
CY	List I					
CZ	POM					

EE	POM					
ES	POM					
FI	POM					
FR	List I					
GE	POM					
HR	List II					
HU	POM					
IE	List II					
IT	List II					
LU	POM					
LT	POM					
LV	POM					
ME	Not authorised					
MK	Not authorised					
NL	POM					
PL	POM					
PT	POM					
RO	Not authorised					
RS	Not authorised					
SI	POM					
SK	POM					
TR	POM					
UK	Not authorised					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **List II**

Criteria: centrally authorised product as prescription-only medicine.

3.2.2 Paediatric use: use in children above 3 years of age.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

EMA: SmPC of Emadine 0.5 mg/mL, eye drops, solution (Immedica Pharma AB) (date of text revision April 2022)

Martindale - Available at: https://www.medicinescomplete.com/#/

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Azelastine

Note: azelastine is classified as a potent long-acting antiallergic compound with selective H_1 antagonist properties. An additional anti-inflammatory effect could be detected after topical ocular administration. Data from *in vivo* (pre-clinical) and *in vitro* studies show that azelastine inhibits the synthesis or release of the chemical mediators known to be involved in early and late stage allergic reactions, e.g. leukotriene, histamine, platelet-activating factor (PAF) and serotonin. Ocular pharmacokinetics: after repeated ocular application of azelastine hydrochloride (up to 1 drop in each eye, four times daily), Cmax steady-state plasma levels of azelastine hydrochloride were very low and were detected at or below the limit of quantification.

1.2 ATC code: S01GX07

1.3 Therapeutic indications: treatment and prevention of the symptoms of seasonal allergic conjunctivitis/ non-seasonal (perennial) allergic conjunctivitis.

1.4 Posology and duration of treatment: a) Seasonal allergic conjunctivitis - the usual dosage in adults and children 4 years and older is 1 drop in each eye twice daily that can be increased, if necessary, to four times daily.

b) Non-seasonal (perennial) allergic conjunctivitis - the usual dosage in adults and children 12 years and older is 1 drop in each eye twice daily that can be increased, if necessary, to four times daily. As safety and efficacy have been demonstrated in clinical trials for a period of up to 6 weeks, the duration of any course should be limited to a maximum of 6 weeks. Patients should be advised to contact their doctor if symptoms worsen or do not improve after 48 hours.

1.5 Pharmaceutical forms: eye drops, solution (strength 0.5 mg/mL).

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients.

1.7 Relevant warnings: not intended for treatment of eye infections. Contact with soft contact lenses should be avoided; contact lenses should be removed prior to application and the patient should wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses. Pregnancy and lactation: due to insufficient information, caution should be exercised when using azelastine during pregnancy. Azelastine is excreted into the milk in low quantities. For this reason azelastine is not recommended during lactation. Effects on ability to drive and use machinery: the mild, transient irritation which can be experienced after application is unlikely to affect vision to any great extent. However, if there are any transient effects on vision, the patient should be advised to wait until this clears before driving or operating machinery.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): favourable safety profile. Immune system disorders (very rare): allergic reactions (such as rash and pruritus). Nervous system disorders (uncommon): bitter taste. Eye disorders (common): mild, transient irritation in the eye. Interactions: interaction studies at high oral doses of azelastine have been performed but they are not relevant as systemic levels, after administration of the eye drops, are in the picogram range.

2.2 Indirect risks (incorrect use): commonly (1-10%), a substance-specific bitter taste may be experienced after administration (often due to incorrect method of application, namely tilting the head too far backwards during administration) which, in rare cases, may lead to nausea. Overdose reactions are not anticipated after ocular use.

2.3 Recent cases at European level: no initiated signals/referrals at EU level recently. Regulatory outcomes (PSUSA) conducted at the EU level (EMA) since 2016 resulted in marketing authorisation maintenance/without safety variations.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not subject to prescription	0.5 mg/mL	4 times	6 mL	Treatment and prevention of the symptoms of seasonal allergic conjunctivitis in adults and children from 4 years of age. Treatment of symptoms of non-seasonal (perennial) allergic conjunctivitis in adults and children aged 12 years and over.	
AT	List II + Exemption				Ex.: treatment and prevention of the symptoms of seasonal allergic conjunctivitis in adults and children from 4 years of age. Treatment of symptoms of non-seasonal (perennial) allergic conjunctivitis in adults and children aged 12 years and over.	
BA	POM					
BE	Not subject to prescription					
BG	POM					
CH	List II + Exemption	Ex.: seasonal allergic conjunctivitis List II: perennial allergic conjunctivitis		Ex.: 4 mL		
CY	List II					
CZ	Not subject to prescription					
EE	Not subject to prescription					
ES	POM					
FI	POM					
FR	List I					
GE	Not subject to prescription					
HU	Not subject to prescription					
IE	List II					
IT	Not subject to prescription					
LU	Not subject to prescription					
LT	POM + Exemption	Ex. 0.05 mg/mL and 0.1 mg/mL (2 drops/day for constant allergic conjunctivitis) or 2 mg/mL (seasonal allergic conjunctivitis)				
LV	Not subject to prescription					
ME	List II					

MK	Not authorised					
NL	POM + Exemption	Ex.: 0.05%		Ex.: 10 mL		
PL	Not subject to prescription					
PT	Not subject to prescription	0.5 mg/mL		10 mL	Treatment and prevention of symptoms of seasonal allergic conjunctivitis in adults and children aged 4 years and over. Treatment of symptoms of non-seasonal (perennial) allergic conjunctivitis in adults and children aged 12 years and over.	
RO	List I				Max duration: 6 weeks	
RS	POM					
SI	POM					
SK	POM					
TR	POM					
UK	POM					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **List II + Exemption** - Exemptions: ocular use; seasonal and perennial allergic conjunctivitis; MS: 0.05% and MQP: 10 mL.

Criteria: a) rationale for List II: the duration of any course should be limited to a maximum of 6 weeks as safety and efficacy have been demonstrated in clinical trials for a period of up to 6 weeks. There are restrictions (age group) with regard to type of indication for paediatric use (see below). b) Rationale for Exemption: well-known safety profile; low risk of systemic adverse reactions due to pharmacokinetic profile (plasma levels are very low and were detected at or below the limit of quantification); self-diagnosis possible (well-known indication). Dispensing of the smallest package (6 mL).

3.2.2 Paediatric use: a) seasonal allergic conjunctivitis: approved for children 4 years and older. b) Non-seasonal (perennial) allergic conjunctivitis: approved for children 12 years and older.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Azelastine hydrochloride 0.5 mg/mL eye drops solution, SmPC - Available at: https://www.medicines.org.uk

Periodic Safety Update Report for azelastine (covering period 01 Jan 2018 to 31 Dec 2020)

List of safety concerns per approved Risk Management Plan (RMP) of active substances per product (September 2022) - Available at: https://www.hma.eu

4.2 Comments: review of safety information received cumulatively, since initial marketing authorisation indicates that the current risk-benefit profile of azelastine remains favourable.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Ketotifen

Note: ketotifen is a histamine H_1 receptor antagonist. *In vivo* animal studies and *in vitro* studies suggest the additional activities of mast cell stabilisation and inhibition of infiltration, activation and degranulation of eosinophils. In a pharmacokinetic study, plasma levels of ketotifen after repeated ocular administration for 14 days were in most cases below the limit of quantitation (20 pg/mL).

1.2 ATC code: S01GX08

1.3 Therapeutic indications: symptomatic treatment of seasonal allergic conjunctivitis.

1.4 Posology and duration of treatment: adults, elderly and children (age 3 and older): 1 drop into the conjunctival sac twice a day. The safety and efficacy of ketotifen in children aged from birth to 3 years have not yet been established.

1.5 Pharmaceutical forms: eye drops, solution, 0.25 mg/mL, 5 mL.

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients.

1.7 Relevant warnings: pregnancy and lactation: there are no adequate data on the use of ketotifen eye drops during pregnancy; caution should therefore be exercised when prescribing to pregnant women. Eye drops containing ketotifen can be used during lactation. Ability to drive and use machinery: any patient who experiences blurred vision or somnolence should not drive or operate machinery.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): immune system disorders (uncommon): hypersensitivity. Nervous system disorders (uncommon): headache. Eye disorders (common): eye irritation, eye pain, punctate keratitis, punctate corneal epithelial erosion; (uncommon): blurred vision (during instillation), dry eye, eyelid disorder, conjunctivitis, photophobia, conjunctival haemorrhage. Gastrointestinal disorders (uncommon): dry mouth. Skin and subcutaneous tissue disorders (uncommon): rash, eczema, urticaria. General disorders and administration site conditions (uncommon): somnolence. Adverse drug reactions from post-marketing experience (frequency not known): hypersensitivity reactions including local allergic reaction (mostly contact dermatitis, eye swelling, eyelid pruritis and oedema), systemic allergic reactions including facial swelling/oedema (in some cases associated with contact dermatitis) and exacerbation of pre-existing allergic conditions such as asthma and eczema. Interactions: if ketotifen is used concomitantly with other eye medications, there must be an interval of at least 5 minutes between the two medications.

2.2 Indirect risks (incorrect use): an important potential risk (as per RMP) is the potential for off-label use (for other ophthalmic indications). No cases of overdose have been reported. Clinical results have shown no serious signs or symptoms after oral ingestion of up to 20 mg of ketotifen.

2.3 Recent cases at European level: no initiated signals/referrals at EU level recently. Regulatory outcomes (PSUSA) conducted at the EU level (EMA) since 2016 resulted in marketing authorisation maintenance/without safety variations.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not authorised					
AT	List II				Symptomatic treatment of seasonal allergic conjunctivitis	

BA	Not authorised					
BE	POM					
BG	Not subject to prescription					
CH	List II					
CY	List II					
CZ	POM					
EE	Not authorised					
ES	POM					
FI	POM + Exemption	Ex.: 0.025%		Ex.: 8 mL		
FR	List II					
GE	Not subject to prescription					
HU	POM					
IE	List II					
IT	Not subject to prescription					
LU	POM					
LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	Not authorised					
NL	POM					
PL	Not subject to prescription					
PT	Not subject to prescription	0.25 mg/mL		5 mL	Symptomatic treatment of seasonal allergic conjunctivitis	
RO	List I					
RS	Not authorised					
SI	POM					
SK	POM					
TR	POM					
UK	POM					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **List II + Exemption** - Exemptions: ocular use; seasonal allergic conjunctivitis; MS: 0.25 mg/mL and MQP: 5 mL.

Criteria: a) rationale for List II: well-known safety profile but there is a risk of systemic allergic reactions. An important potential risk (as per RMP) is the potential for off-label use (for other ophthalmic indications). b) Rationale for non-prescription: well-known safety profile; low risk of systemic adverse reactions due to pharmacokinetic profile (plasma levels are very low and were detected at or below the limit of quantification; self-diagnosis possible (well-known indication).

3.2.2 Paediatric use: children aged 3 years and older.

3.2.3 Social dimension:-

4. REFERENCES/COMMENTS

4.1 References:

EMA - Available at: https://www.ema.europa.eu

HPRA (Ireland) - Available at: https://www.hpra.ie/

List of safety concerns per approved RMP of active substances per product (September 2022) - Available at: https://www.hma.eu

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Olopatadine

Note: olopatadine is a potent selective antiallergic/antihistaminic agent that exerts its effects through multiple distinct mechanisms of action. It antagonises histamine (the primary mediator of allergic response in humans) and prevents histamine-induced inflammatory cytokine production by human conjunctival epithelial cells. Data from *in vitro* studies suggest that it may act on human conjunctival mast cells to inhibit the release of pro-inflammatory mediators. In patients with patent nasolacrimal ducts, topical ocular administration of olopatadine was suggested to reduce the nasal signs and symptoms that frequently accompany seasonal allergic conjunctivitis. As for other topically administered medicinal products, olopatadine is absorbed systemically. However, systemic absorption of topically applied olopatadine is minimal with plasma concentrations ranging from below the assay quantitation limit (<0.5 ng/mL) up to 1.3 ng/mL. These concentrations are 50- to 200-fold lower than well tolerated oral doses.

1.2 ATC code: S01GX09

1.3 Therapeutic indications: treatment of ocular signs and symptoms of seasonal allergic conjunctivitis.

1.4 Posology and duration of treatment: the dose is 1 drop of olopatadine eye drops, solution in the conjunctival sac of the affected eye(s) twice daily (8 hourly). Treatment may be maintained for up to four months, if considered necessary. In case of concomitant therapy with other topical ocular medicines, an interval of 5 minutes should be allowed between successive applications. Eye ointments should be administered last.

1.5 Pharmaceutical forms: eye drops, solution, 1 mg/mL.

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients.

1.7 Relevant warnings: olopatadine is an antiallergic/antihistaminic agent and, although administered topically, is absorbed systemically. If signs of serious reactions or hypersensitivity occur, treatment should be discontinued. Close monitoring is required with frequent or prolonged use in dry eye patients or in conditions where the cornea is compromised. Pregnancy and lactation: olopatadine is not recommended during pregnancy and in women of childbearing potential not using contraception. Olopatadine should not be used during breastfeeding. Overdose: in the case of overdose, appropriate monitoring and management of the patient should be implemented.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): adverse reactions from clinical studies: no serious ophthalmic or systemic adverse reactions related to olopatadine were reported in clinical studies. The most frequent treatment-related adverse reaction was eye pain, reported at an overall incidence of 0.7%. Adverse reactions from postmarketing surveillance: common: headache, dysgeusia, eye pain, eye irritation, dry eye, abnormal sensation in eyes, nasal dryness, fatigue; uncommon: rhinitis, dizziness, hypoaesthesia, corneal erosion, dermatitis, corneal epithelium defect, corneal epithelium disorder, punctate keratitis, keratitis, corneal staining, eye discharge, photophobia, blurred vision, reduced visual acuity, blepharospasm, ocular discomfort, eye pruritus, conjunctival follicles, conjunctival disorder, foreign body sensation in eyes, increased lacrimation, erythema of eyelid, eyelid oedema, eyelid disorder, ocular hyperaemia; not known: hypersensitivity, face swelling, somnolence, corneal oedema, eye oedema, eye swelling, conjunctivitis, mydriasis, visual disturbance, eyelid margin crusting, dyspnoea, sinusitis, nausea, vomiting, dermatitis, erythema, asthenia, malaise. Interactions: olopatadine is unlikely to result in metabolic interactions with other concomitantly administered active substances.

2.2 Indirect risks (incorrect use): overdose: no data are available in humans regarding overdose by accidental or deliberate ingestion. A 5 mg oral dose was administered twice daily for 2.5 days to 102 young and elderly male and female healthy volunteers with no significant prolongation of QTc interval compared to placebo. The range of peak steady-state olopatadine plasma concentrations (35 to 127 ng/mL) seen in this study represents at least a 70-fold safety margin for topical olopatadine with respect to effects on cardiac repolarisation.

2.3 Recent cases at European level: none identified. No variations triggered after PSUSA procedures conducted in last three years.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not authorised					
AT	List II				Symptomatic treatment of seasonal allergic conjunctivitis	
BA	POM					
BE	POM					
BG	POM					
CH	List II					
CY	List I					
CZ	POM					
EE	POM					
ES	POM					
FI	POM					
FR	List I					
GE	POM					
HR	List II					
HU	POM					
IE	List II					
IT	Not subject to prescription					
LU	POM					
LT	POM	1 mg/mL		5 mL	Treatment of ocular signs and symptoms of seasonal allergic conjunctivitis	
LV	POM					
ME	List II					
MK	POM					
NL	POM					
PL	POM + Exemption Ex.: adults only	1 mg/mL		5 mL	Symptomatic treatment of seasonal allergic conjunctivitis	
PT	POM					
RO	List II					
RS	POM					
SI	POM					
SK	POM					
TR	POM					
UK	POM					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):
Proposed recommendation: **List II**

Criteria: centrally authorised medicinal product as prescription-only medicine.

3.2.2 Paediatric use: olopatadine may be used in paediatric patients 3 years of age and older at the same dose as in adults. The safety and efficacy of olopatadine in children aged under 3 years has not been established. No data are available.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

European public assessment report for original medicinal product Opatanol (olopatadine)

List of safety concerns per approved RMP of active substances per product (September 2022) - Available at: https://www.hma.eu

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Epinastine

1.2 ATC code: S01GX10

Note: epinastine is a topically active, direct H_1 receptor antagonist. Epinastine has a high binding affinity for the histamine H_1 receptor and a 400 times lower affinity for the histamine H_2 receptor. Epinastine also possesses affinity for the α_1-, α_2-, and 5-HT_2 receptors. It has low affinity for cholinergic, dopaminergic and a variety of other receptor sites. Epinastine does not penetrate the blood/brain barrier and, therefore, does not induce side effects of the CNS, i.e. it is non-sedative.

1.3 Therapeutic indications: treatment of the symptoms of seasonal allergic conjunctivitis.

1.4 Posology and duration of treatment: the recommended dose for adults is 1 drop instilled in each affected eye twice daily, during the symptomatic period. There is no experience in clinical studies with use for more than 8 weeks.

1.5 Pharmaceutical forms: eye drops, solution, 0.5 mg/mL.

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients.

1.7 Relevant warnings: pregnancy and lactation: caution should be exercised when prescribing to pregnant women. Due to the lack of experience, caution should be exercised when prescribing to breastfeeding women. Effects on ability to drive and use machinery: if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): most adverse reactions were ocular and mild. Nervous system disorders (uncommon): headache. Eye disorders (common): burning sensation, eye irritation; (uncommon): conjunctival/ocular hyperaemia, eye discharge, eye dryness, eye pruritus, visual disturbance. Respiratory, thoracic and mediastinal disorders (uncommon): asthma, nasal irritation, rhinitis. Gastrointestinal disorders (uncommon): dysgeusia.

The following adverse reactions were reported during postmarketing use of epinastine in clinical practice: immune system disorders (not known): hypersensitivity reaction including symptoms or signs of eye allergy and extra-ocular allergic reactions, including angioedema, skin rash and redness. Eye disorders (not known): increased lacrimation, eye pain, eye swelling, eyelid oedema.

Adverse reactions reported in phosphate containing eye drops: cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Interactions: no drug-drug interactions are anticipated in humans since systemic concentrations of epinastine are extremely low following ocular dosing. In addition, epinastine is mainly excreted unchanged in humans indicating a low level of metabolism.

2.2 Indirect risks (incorrect use): no cases of overdose have been reported.

2.3 Recent cases at European level: PSUSA procedure PSUSA/00001231/201710: Scientific conclusions and grounds for variation to the terms of the marketing authorisation: based on data from postmarketing experience, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) agreed with the marketing authorisation holder's analysis that a causal relationship between epinastine and hypersensitivity reaction, including symptoms or signs of eye allergy, and extra-ocular allergic reactions, including angioedema, skin rash and redness as well as eye swelling and/or eyelid oedema, cannot be

excluded and therefore agrees with these being added as new adverse drug reactions to section 4.8 of the SmPC with the frequency 'not known'. The package leaflet was updated accordingly. The Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) agreed with the scientific conclusions of the PRAC.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional info
AM	Not authorised					
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BE	POM					
BG	Not authorised					
CH	Not authorised					
CY	Not authorised					
CZ	Not authorised					
EE	Not authorised					
ES	POM					
FI	Not authorised					
FR	List I					
GE	POM					
GR	POM					
HR	Not authorised					
HU	POM					
IE	List I					
IT	Not subject to prescription					
LU	POM					
LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	Not authorised					
NL	POM					
PL	POM					
PT	POM					
RO	Not authorised					
RS	Not authorised					
SI	Not authorised					
SK	POM					
TR	POM					
UK	POM					

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: **List II**

Criteria: see conclusions of PSUSA procedure PSUSA/00001231/201710 - based on these conclusions, the use of epinastine-containing products may require medical supervision.

3.2.2 Paediatric use: the safety and efficacy in children ≥ 12 years has been established in clinical trials. Epinastine may be used in adolescents (12 years of age and older) at the same dosage as in adults. The safety and efficacy of epinastine in children aged less than 3 years have not been established. No data are available. There are limited data on the safety in children aged 3-12 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

PSUSA procedure (PSUSA/00001232/201710) - Available at: https://www.ema.europa.eu/

SmPC of Relestat - Available at: https://www.medicines.org.uk

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Alcaftadine

1.2 ATC code: S01GX11

1.3 Therapeutic indications: antihistamine with antipruritic and local analgesic actions

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: no data available in Melclass (based on the available data, no medicines containing this active substance are authorised in member states).

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Cromoglicic acid, combinations

1.2 ATC code: S01GX51

1.3 Therapeutic indications: antihistamine with antipruritic and local analgesic actions

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: no data available in Melclass (based on the available data, no medicines containing this active substance are authorised in member states).

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

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