

Department of Biological Standardisation,
European Network of Official Medicines Control Laboratories & HealthCare (DBO)

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

Report classification/justification of

- Anti-histamines for systemic use (medicines belonging to the ATC Group R06A)
 - Acetylsalicylic acid (ATC D01AC06)
 - Azelaic acid (ATC D10AX03)
 - Codeine (ATC R05DA04)
- Loperamide (ATC A07DA03)
 - Omeprazol (ATC A02BC01)

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INTRODUCTION

The legal classification of medicines as regards their supply with or without a medical prescription has implications on patient safety, the accessibility of medicines to patients and the responsible management of health care expenditure.

Since long, the **Council of Europe (which is distinct from the European Union)**¹ has been concerned with the supply conditions of medicines for human use and the harmonisation of national legal provisions from the perspective of patient safety and public health protection. The initial Recommendation AP(61)2 was drawn up in 1961 to control a growing tendency of miss- and overuse of sedative and narcotic medicines by empowering the competent authorities to classify new medicines into prescription and non-prescription medicines by considering risks associated to the active substance as well as conditions of use.

Council of Europe Committee of Ministers Resolution ResAP(2007)1 on the classification of medicines as regards their supply²

“...1. Recommends to the governments of the member states of the Partial Agreement in the Social and Public Health Field that they supply information on the national legal classification of medicines as regards their supply on a regular basis;

*2. Recommends to the same governments that they apply the general provisions and the classification of active substances depending on the supply conditions of the medicines which contain them, **as set out in the appendices**;...”*

A Council of Europe Committee of Ministers resolution text comprises a recommendation of the Committee of Ministers (Foreign Affairs Ministers, representing the governments of states participating in an activity) to member states to implement the stipulations of the resolution into national legislation or to adapt national legislation.

Although recommendations are not legally binding, they are legal instruments; they may create soft law, and contain a political statement. The Committee of Ministers may also invite the member states to report on their efforts to implement a recommendation.

As regards national licenses, industry will be impacted if the national authorities implement the revisions, as applicable. It needs to be borne in mind that the decisions take account national assessments and scientific rationale. The revisions will be available only and completed in the November meeting, 2nd bi-annual meeting (Appendices 2011, ResAP (2007) 1).

As regards the international context, the annually revised appendices of Council of Europe Resolution ResAP(2007)1 on the classification of medicines as regards their supply are a relevant reference for the European pharmaceutical industry.

The classification criteria set out in the Council of Europe resolutions have been included in **European Union** legislation, such as directive 92/26/EC and directive 2001/83/EC (art 70-75). In the preamble of the latter directive (whereas 32) reference is made to the Council of Europe: *«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.....»*.

Today, the classification of medicines remains a competency of states in Europe. This holds also true for member states of the European Union.

¹ www.coe.int

² [CM](#) Council of Europe Resolution ResAP(2007)1.

The Committee of Experts on the classification of medicines as regards their supply, coordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, does not issue recommendations on the classification of particular medicines but on **active substances used in a medicine for a specific therapeutic purpose**. For this purpose, the Committee reviews the classification of medicines (INN³/ATC) authorised in Europe via the national and European marketing authorisation procedures (the latter only applicable to those of the 47 Council of Europe member states, European Union member states) in order to establish recommendations for the classification of medicines (INN/ATC) and their supply conditions (see also Glossary of Terms, pg 7).

- which have not yet been included in Council of Europe recommendations,
- which qualify for being released from prescription status (switch to "over the counter" –OTC status)/and vice-versa,
- revisions of current classifications.

The Committee of Experts finalises the annual review of the recommendations, appendices of the above resolution, in two bi-annual meetings. The review will be completed at the 2nd bi-annual meeting and published on the website of the EDQM. These recommendations are an integral part of the Council of Europe's Committee of Ministers Resolution ResAP (2007)¹ on the classification of medicines as regards their supply. The resolution is aimed to promote patient safety, the accessibility of medicines to the patient and puts public health in the centre.

The Committee does not give advice relating to pending marketing authorisation procedures. It uses scientific approaches and methods taking account of medicines' pharmacological properties, issues relating to direct and indirect risks (pharmacovigilance) as well as miss/abuse, matters of public health concern.

In its work, the Committee uses the ATC classification maintained by the WHO Collaborating Centre for Drug Statistics Methodology. The Commission of the European Union is entitled to participate in the meetings of the Committee.

DISCLAIMER

This document is published for information only. The reports included in this document have no legal status and no binding character.

They reflect the conclusions of the reports presenting scientific classification reviews and rationale and the debates on which the recommendations about the classification of medicines as regards their supply taken by the Committee of Experts on the Classification of Medicines as regards their supply (CD-P-PH/PHO) at its 46th meeting on 24-25 February 2009, and its 47th meeting on 15-16 September 2009 were based. The document was reviewed and endorsed by the Committee of Experts CD-P-PH/PHO at its 48th meeting on 15-17 March 2010.

The reviews carried out do not commit the parent authorities of the experts nor the Council of Europe/the EDQM.

³ INN: International non-proprietary name; ATC: Anatomical Therapeutic Chemical (ATC) classification

GLOSSARY OF TERMS USED IN THIS DOCUMENT

MS	Maximal strength
MQP	Maximal quantity per pack
MDD	Maximal daily dose
ATC	Anatomical-chemical-therapeutical classification ⁴
SC	Subcutaneous
IM	Intramuscular
IV	Intravenous
N	

Classification used throughout this document:

Following the stipulations of Council of Europe Committee of Ministers Resolution ResAP(2007)1 the medicine contains one or more active substances classified in **List I or II** to which the following criteria apply:

List I

The supply of a medicine containing one of the substances in this list may only be repeated if the prescriber specifies so on the prescription.

List II

The supply of a medicine containing one of the substances in this list may be repeated without the prescriber having specified so, provided that he did not explicitly forbid such repetition and that the amount supplied at renewals (and their frequency) be consistent with medical and pharmaceutical data (such as the prescribed daily dose, the duration of treatment, the degree of medical supervision required by the condition, etc.).

Exemptions from Lists I and II

- For certain substances, exemptions from the “prescription only” requirement may appear in Lists I and II.
- in respect of a low dosage or concentration of the active substances and/or 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 content of the medicine per container.
- List of active substances classified according to the conditions of supply of the medicines which contain them, when supplied without prescription (over-the-counter (OTC) medicines) and their conditions of supply.

Medicines not subject to prescription (OTC medicines)

Active substances of medicines which are classified as not subject to prescription according to the criteria listed in item 4 of the General Provisions above will be classified in the list “Medicines not subject to prescription (OTC medicines)”.

For the purpose of this resolution, OTC medicines are understood as having a valid marketing authorisation issued by a competent authority.

It is possible that active substances which are contained in OTC medicines can exist in medicines of the same ATC (Anatomical Therapeutic Chemical Classification), but subject to prescription, because of particular conditions of use of the medicines in question.

⁴ WHO Collaborating Centre Oslo: web link

General criteria for classification in the lists

1. List I

- a.* 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;
- b.* Active substances of medicines administered for diagnostic purposes;
- c.* Active substances with a new pharmacological mechanism of action.

2. List II

Active substances of 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.

3. List of OTC medicines

(see page before)

Active ingredient: ACRIVASTINE

ATC Code: R06AX18
anti-histamines for systemic use – other anti-histamines for systemic use

Therapeutic indications:

- symptomatic relief of allergic rhinitis, including hay fever.
- chronic idiopathic urticaria.

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- 8 mg orally, three times per day

Paediatric:

- Safety and efficacy in children under the age of 12 years has not been established.

Pharmaceutical forms: Capsules

Contraindications - relevant warnings:

a) Contraindications:

- Hypersensitivity to acrivastine, other alkylamine anti-histamines.
- Severe hypertension.
- Severe coronary artery disease.
Concomitant therapy with MAO inhibitors or within 14 days of cessation of use of an MAO inhibitor.

b) Precautions:

- **Concomitant CNS depressants Diabetes mellitus Hypertension Hyperthyroidism Increased intra-ocular pressure**
- Ischaemic heart disease
- Prostatic hypertrophy
- Renal insufficiency
- Stenosing peptic ulcer or pyloroduodenal obstruction

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Nausea, diarrhea, dry mouth, and dyspepsia have been reported occasionally with acrivastine. The incidence of dry mouth is greater with the combination of acrivastine plus pseudoephedrine (8%), as compared to acrivastine alone (6%).

Acrivastine and acrivastine/pseudoephedrine have been associated with rare hypersensitivity reactions. Associated symptoms include anaphylaxis, angioedema, bronchospasm, and erythema multiform.

Headache, vertigo, dizziness, insomnia, somnolence, and jitteriness have been reported occasionally during acrivastine therapy. Insomnia and central nervous system stimulation have been reported with the combination of acrivastine plus pseudoephedrine. The incidence of insomnia with the combination is higher than that observed with acrivastine alone.

Although it occurs less than with conventional anti-histamines, drowsiness is the most common adverse effect of acrivastine. Drowsiness has been observed in up to 30% to 35% of patients treated three times daily with doses of 4 or 8 mg.

1.2. Interactions

Patients should not undertake tasks requiring mental alertness whilst under the influence of alcohol and other CNS depressants. Concomitant administration of acrivastine may, in some individuals, produce additional impairment.

There are no data to demonstrate an interaction between acrivastine and ketoconazole, erythromycin or grapefruit juice. However, due to known interactions between these compounds and other non-sedating anti-histamines, caution is advised.

1.3. Adverse reactions (ADRs)

Reports of drowsiness directly attributable to acrivastine are extremely rare. Indeed for the great majority of patients, the treatment is not associated with clinically significant anticholinergic or sedative side effects.

2. Discussion

Acrivastine has been effective in the treatment of allergic rhinitis and several histamine-mediated dermatologic disorders, and is relatively non-sedating as compared to traditional anti-histamines. Its short onset of action lends itself to "on demand" administration in certain patients (*i.e.* chronic idiopathic urticaria). However, another non-sedating agent, terfenadine, also has a relatively rapid onset of action (1 to 2 hours), and comparative studies have not revealed any difference in efficacy between acrivastine and terfenadine in patients with allergic rhinitis, chronic idiopathic urticaria, or atopic eczema. Both agents appear to have similar toxicity profiles. Although further comparative studies are required, acrivastine does not appear to offer any clinical advantage over terfenadine.

There is some evidence of decreased efficacy over prolonged therapy with acrivastine. Further studies are needed to evaluate the long-term efficacy of the drug, particularly in comparative trials with terfenadine.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices	II	Oral Use				
Publication	II	Oral Use				
A	II	Oral Use				
CH	II	Oral Use				
CZ			Not marketed			
D	II	Oral Use				
DK	OTC	Oral Use				
E	Currently not available	Oral Use	Information from the UMC Drug Dictionary			
F	II exemption +	Oral Use	Indications: Insomnia, cough, rhinitis, conjunctivitis, hives Comments : for adults and children over 12 months short treatment	0.05 %		0.075 g
FIN	II exemption +	Oral Use		8 mg		96 mg
GB	II exemption +	Oral Use	8 mg capsules may be supplied via the General Sales List (GSL) for the symptomatic relief of allergic rhinitis, including hay fever, and chronic idiopathic urticaria, in adults and children aged 12 to 65 years		24 mg	240 mg
GB	Currently not available	Oral Use	Information from the UMC Drug Dictionary			
H			Not marketed			
HR			Not marketed			
I	II	Oral Use				
IRL	II	Oral use				
LV	OTC	Oral use				
MK			Not marketed			
NL	II	Oral Use				
P	II	Oral Use				
RO			Not marketed			
S	II	Oral Use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

ACRIVASTINE, anti-histamines for systemic use – Other anti-histamines for systemic use, Oral administration

List II + exemption

Criteria:

- Safe profile.
- Relatively non-sedating as compared to traditional anti-histamines.
- OTC for short treatment of allergic rhinitis.
- **MS: 8 mg.**
- **MDD: 24 mg.**
- **MQP: 240 mg.**

3.2. Paediatric use

Not for children under 12 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/3D02C8/DUPLICATIONSHIELDSYNC/369026/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/4E1exkk2QBii8k/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/1236/ContentSetId/31/SearchTerm/acrivastine%20/SearchOption/BeginWith#secN1078A
- <http://emc.medicines.org.uk/medicine/7053/SPC/Benadryl+Allergy+Relief/>
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: ALIMEMAZINE
Synonyms: Methylpromazine, Trimeprazine, Trimeprazine Tartrate
ATC Code: R06AD01
Anti-histamines for systemic use – phenothiazine derivatives

Therapeutic indications:

- treatment of pruritic symptoms due to a variety of dermatological conditions.
- pre-operative sedative in young children.
- sedation in severe night-waking in children (short term).
- common cold.
- allergic rhinitis.
- anaesthesia – adjunct.
- conjunctivitis.
- hives.

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- 2.5 mg 4 times daily or, if sustained-release capsules are used, the usual dosage is 5 mg every 12 hours (pruritus).
- 10 mg 3 times daily; in severe cases, adults have been given up to 100 mg daily (pruritic dermatoses).

Geriatric Patients:

- Initiation of the drug at low doses is advisable in geriatric patients.

Paediatric:

- over 12 month of age: 1.25 - 2.5 mg daily (symptoms of common cold).
- over 3 years of age, the usual dose is 2.5 mg at bed-time or 3 times daily if needed (in pruritus).
- 6 months to 3 years of age, the usual dosage is 1.25 mg at bed-time or 3 times daily if needed (in pruritus).
- sustained-release capsules: the usual dosage is 1 capsule (5 mg) daily for children over the age of 6. The sustained-release product is not recommended for younger children.

Pharmaceutical forms: Tablets, sustained-release capsules and syrup

Contraindications - relevant warnings:

a) Contraindications:

- Acutely ill or dehydrated children.
- Nursing mothers.
- Patients with bone marrow depression.

b) Precautions:

- Concomitant administration of narcotics or barbiturates.
- Children with a history of sleep apnea.
- Family histories of sudden infant death syndrome.
- Liver dysfunction.
- Patients with possible intestinal obstruction.
- Brain tumor or drug toxicity.
- Patients with cardiovascular disease.
- Patients with asthma.

- Patients with narrow-angle glaucoma.
- Patients with prostatic hypertrophy or bladder neck obstruction.
- Patients with stenosing peptic ulcer or pyloroduodenal obstruction.
- Use of central nervous system depressants, including alcohol.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Paediatric Use

The risk of apnea or sudden infant death syndrome limits its usefulness. The medicinal product should not be recommended for young children under 12 months of age (France).

The FDA has recently reviewed information about the safety of over-the counter (OTC) cough and cold medicines in infants and children under 2 years of age. The FDA is now recommending that these drugs should not be used to treat infants and children under 2 years of age because serious and potentially life-threatening side effects can occur (FDA, 2007).

1.2. Interactions with:

Belladonna, Belladonna Alkaloids, Cisapride, Duloxetine, Gatifloxacin, Grepafloxacin, Isradipine, Levomethadyl, Lithium, Meperidine, Moxifloxacin, Octreotide, Pentamidine, Phenytoin, Procarbazine, Tramadol (MICROMEDEX).

1.3. Adverse reactions (ADRs)

- prolongation of the Q-T interval.
- severe hypotension and cardiac arrest have been reported.
- leukopenia, agranulocytosis, pancytopenia, hemolytic anemia, and thrombocytopenic purpura.
- severe central nervous system and respiratory depression.
- extrapyramidal reactions.
- neuroleptic malignant syndrome.

1.3.1. Recent case reports (UMC database)

In the period from the 1st of January 2005 to the 7th of February 2009 the Uppsala Monitoring Centre received 231 reports of alimemazine with 401 ADRs. The reports came from Chile, **Spain, France, United Kingdom, Ireland**, Japan, Morocco, **Norway, Sweden**, the USA and South Africa. The most common ADR is somnolence (reported in 22 cases), followed by coma (14 cases), confusional state and urinary retention (10 cases), with 6 cases each of death, neutropenia and neuroleptic malignant syndrome. Over 90% of these serious reports came from France. Elderly patients (over 75 years of age) represented 31 (42.5%) cases, and 5 (6.8%) cases came from children (from 2 to 5 years old). For adults and the elderly, the ADRs are the results of an interaction of alimemazine with other drugs such as anti-psychotics, anti-depressants or benzodiazepines that were prescribed simultaneously with alimemazine. There was only one case of somnolence in an adult, which was caused only by alimemazine alone. In children, all reported ADRs were of somnolence with a daily dose of 30 mg (4 children aged of 2 years and one aged 5 years).

The combination database of the UMC ADR database for somnolence shows that there is an increased risk of usage in children of less than 4 years of age.

2. Discussion

The main therapeutic area of this drug is sedation and the treatment of pruritic symptoms due to a variety of dermatological conditions, but also the treatment of the common cold, allergic rhinitis and conjunctivitis. In Europe, alimenazine is on the market in France, Spain and the United Kingdom. France switched the prescription status from prescription only to OTC for adults and children over 12 month of age in the indications of insomnia, cough, rhinitis, conjunctivitis and hives. The maximum strength per dose in OTC form is 0.05% and the maximal quantity of the active ingredient is 0.075 g.

Most ADRs for alimemazine in the past 3 years were reported in France, with concerns raised in terms of its interaction with anti-depressants, anti-psychotics and benzodiazepines in adult and elderly patients. The ADR of somnolence in children aged approximately 2 years, treated with alimemazine arose due to overdosing.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices	I	Oral Use				
Publication	I	Oral Use				
CZ			Not marketed			
E	Currently not available	Oral Use	Information from the UMC Drug Dictionary			
F	II exemption +	Oral Use	Indications: Insomnia, cough, rhinitis, conjunctivitis, hives Comments : for adults and children over 12 months short treatment	0.05 %		0.075 g
GB	Currently not available	Oral Use	Information from the UMC Drug Dictionary			
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LT			Not marketed			
MK			Not marketed			
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

ALIMEMAZINE, anti-histamines for systemic use – phenothiazine derivatives, Oral administration

List I

Criteria:

- Risk of serious adverse reactions due to interactions with anti-depressants, anti-psyhotics, benzodiazepines (coma, somnolence, neuroleptic malignant syndrome, confusional state and urinary retention) especially in the elderly.
- Somnolence is a common reported ADR in children under the age of 4 years.
- Its efficacy is doubtful because it probably works primarily due to its sedative effects rather than its potency in blocking histamine.
- Misuse.

No exemption from prescription-only status is proposed.

3.2. Paediatric use

Due to the risk of apnea or sudden infant death syndrome List I classification is justified. Although it is indicated for children aged over 12 months in France, it should only be prescribed for children over 4 years.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/35D173/DUPLICATIO NSHIELDSYNC/FE21A1/ND_PG/PRIH/ND_B/HCS/SBK/1/ND_P/Main/PFPUI/7RTTtI2PNzL Jb/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2469/ContentSetId/31/Search Term/ALIMEMAZINE/SearchOption/BeginWith#secN10136
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: ASTEMIZOLE

ATC Code: R06AX11
Anti-histamines for systemic use – Other anti-histamines for systemic use

Janssen Pharmaceutica voluntarily removed astemizole from the market in 1999. Its removal was based on reports of serious **cardiovascular toxicities** associated with the drug, as well as the availability of alternative agents that do not appear to have the same potential for serious drug reactions such as reported with astemizole.

1. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	II	Oral Use				
Publication	II	Oral Use				
A	II	Oral use				
CZ			Not marketed			
F			Not marketed			
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LV			Not marketed			
MK			Not marketed			
RO			Not marketed			

No data available from other Member States.

1.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

ASTEMIZOLE, anti-histamines for systemic use – Other anti-histamines for systemic use, Oral administration.

No recommendation for prescription status because the drug is not on the market.

2. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/22D19E/DUPLICATIONSHIELDSYNC/DF892B/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/4E1exkk2QBrNYJ/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/0782/ContentSetId/31/SearchTerm/astemizole%20/SearchOption/BeginWith
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: AZATADINE

ATC Code: R06AX09
Anti-histamines for systemic use – Other anti-histamines for systemic use

Therapeutic indications:

- common cold
- allergic rhinitis

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- 1 or 2 mg twice daily.

Pharmaceutical forms: Tablets

Contraindications - relevant warnings:

a) Contraindications:

- Hypersensitivity to azatadine or to other related anti-histamines, including cyproheptadine.
- Use of monoamine oxidase inhibitors.
- Narrow-angle glaucoma.
- Urinary retention.

b) Precautions:

- Use of alcohol or other central nervous system depressants.
- Asthma.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

- Palpitations, tachycardia, and extrasystoles have occurred infrequently with azatadine administration.
- The most common gastrointestinal adverse effect is epigastric distress. Anorexia, nausea, and vomiting have also occurred. Paradoxically, either diarrhea or constipation may be experienced.
- Infrequently, hemolytic anemia, hypoplastic anemia, thrombocytopenia, and agranulocytosis have occurred following azatadine administration.
- Sedation and somnolence are the most commonly reported adverse effects associated with azatadine therapy. Two studies demonstrated that azatadine has no significant effect on driving performance when compared with a placebo.
- Very high doses of azatadine induce a dystonic reaction. A 22-year-old patient who ingested 20 to 30 mg over a 24-hour period experienced involuntary, painless neck spasms that progressed to severe opisthotonos. The symptoms resolved following intravenous administration of 2 mg of benzotropine.
- Paradoxically, increased urinary frequency or urinary retention and difficulty to urinate can occur following azatadine use. Early menses has also been reported.
- Thickening of bronchial secretions has been reported as an adverse effect; although the clinical significance of this fluid effect is questionable. Most asthmatic patients can be treated safely with anti-histamines.

1.2. Interactions with:

Theoretically, with procarbazine (CNS depression). (MICROMEDEX)

1.3. Adverse reactions (ADRs)

- see under 1.1. Direct risks (Pharmacovigilance).

2. Discussion

Azatadine is a potent H1-histamine receptor antagonist with similar efficacy to other conventional anti-histamines in the treatment of allergic rhinitis. The incidence of sedation associated with azatadine appears to be similar to other conventional anti-histamines. Based on clinical trials, it does not appear that azatadine possesses any significant advantages over other conventional anti-histamines.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II	Oral Use				
Publication	II	Oral Use				
BG	II	Oral use				
CZ			Not marketed			
D	II	Oral Use				
E	II	Oral Use				
F			Not marketed			
H			Not marketed			
HR			Not marketed			
I			Not marketed			
IRL	II	Oral Use				
LT			Not marketed			
MK			Not marketed			
P	II	Oral Use				
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

AZATADINE, anti-histamines for systemic use – Other anti-histamines for systemic use, Oral administration

List II

Criteria:

- the prescription status in Member States where the drug is available is List II.
- More post-marketing experience is needed.

No exemption from prescription-only status is proposed.

3.2. Paediatric use

Not recommended in children less than 12 year of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/3373F0/DUPLICATIONSHIELDSYNC/4041F2/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/4E1exkk2QBuCMm/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/0528/ContentSetId/31/SearchTerm/azatadine%20/SearchOption/BeginWith#secN10708
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: AZELAIC ACID

ATC Code: D10AX03

Therapeutic indications:

1. Cutaneous treatment of acne.
2. Cutaneous treatment of rosacea.

Posology/duration of treatment:

Acne: 15-20% cream/gel applied twice a day on affected skin for up to 6 months.
Rosacea: 15% cream/gel applied twice a day on affected skin for up to 12 weeks.

Dosage forms: cream, gel

Contraindications - relevant warnings:

- hypersensitivity against the active substance or any of the excipients.

Precautions:

- avoid contact with the eyes.
- pregnancy/breastfeeding.
- may cause hypopigmentation (particularly in patients with dark complexions).

1. Direct/indirect risks (safety profile)

Azelaic acid is a naturally-occurring, saturated, straight-chain dicarboxylic acid (1,7-heptanedicarboxylic acid). It is an endogenous compound produced by microorganisms through fat acid oxidation, solar radiation or during degradation of long chain dicarboxylic acids and omega-oxidation of monocarboxylic acids. Besides endogenous production, azelaic acid found in the body can also be taken up from foodstuffs (animal products, whole meal).

The mechanism of the different effects of azelaic acid remains unclear. Efficacy in acne seems to be due to a combination of anti-microbial activity against acne-causing micro-organisms and anti-keratinising effects on the follicular epidermis. Both actions are attributable to the inhibition of cellular protein synthesis; the direct inhibition of the activity of sebaceous glands is not a significant factor. Additionally, azelaic acid is used in cosmetics and it is listed in the EU Commission Decision 2006/257/EC establishing an inventory and a common nomenclature of ingredients used in cosmetic products.

1.1. Direct risks (Pharmacovigilance)

No cancerogenic or mutagenic properties have been observed in pre-clinical studies. The compound has a very low toxicity: no serious adverse effects of azelaic acid were reported after oral doses of 20 grams for 6 months or the intravenous administration of a 15% solution for 7 days.

Adverse effects associated with the cutaneous use of azelaic acid include pruritus, burning, stinging, and tingling. Infrequent adverse effects include rash, dryness, peeling, irritation, dermatitis, erythema, and contact dermatitis.

1.1.1 Recent cases in Europe
Unknown

1.2. Indirect risks (incorrect use)

Possibility of self-diagnosis:

Acne is a skin disease affecting more than 90% of adolescents, and frequently continues into adulthood. It is usually easy to diagnose. Rosacea and dermatitis perioralis can be, in some cases, misdiagnosed as acne. Due to increased androgen production, acne can also be one of the symptoms accompanying ovarian tumours, polycystic ovary syndrome and Cushing's syndrome.

Rosacea is a skin disease which, in contrast to acne, affects middle aged people, does not cause scars, and does not affect the chest, back and shoulders. There are no comedones. There are four subtypes of rosacea. Laypersons have difficulties in correctly diagnosing rosacea. Therefore, azelaic acid should only be used for this disease with medical advice.

Masking an underlying disease:

It is important to consider the implications of azelaic acid treatment in indications similar to acne (rosacea, dermatitis perioralis) or for treatment of acne as a symptom accompanying ovarian tumours, polycystic ovary syndrome and Cushing's syndrome.

Rosacea – see the above description

Dermatitis perioralis mostly affects young women. The cause is not known; although possible causes include cutaneous corticosteroid creams, cosmetic products, oral contraceptives, and fluoride and anti-tartar ingredients in dental products. It is characterised by itching erythema and red blisters in the perioral area. Initial treatment is "zero therapy", *i.e.* the patient is advised to avoid all cosmetics and fluoride toothpaste.

Polycystic ovary syndrome is clinically characterised by a history of chronic anovulatory bleeding in combination with evidence of androgen excess, such as hirsutism, acne, elevated serum androgen concentrations, or a combination of these symptoms. Its prevalence is about 5%. The fundamental pathophysiologic defect of polycystic ovary syndrome remains unknown, although there is a growing consensus that the key features include insulin resistance, androgen excess and abnormal gonadotropin dynamics. Treatment includes ovulation induction for infertility, oral contraceptives or progestin for menstrual irregularities, and oral contraceptives or spironolactone against hirsutism.

Epithelial ovarian cancer mostly affects peri-menopausal and post-menopausal women. Eighty (80) to 90% of ovarian cancers occur after the age of 40. Less than 1% of epithelial ovarian cancers occur before the age of 20, and two-thirds of ovarian malignancies in these young patients are germ-cell tumours. Ovarian tumours have non-specific symptoms including decreased appetite, weight loss, abdominal discomfort, more frequent urination. Menstrual irregularities appear only in hormone-producing tumours.

Cushing's syndrome is an endocrine disorder caused by long-term, high levels of cortisol. The most frequent symptoms are central obesity affecting the trunk and the face sparing the limbs (94%), "moon face" (84%), hirsutism (82%), gonadal disorders (amenorrhoea, reduced libido, impotence) (76%), hypertension (72%), muscle weakness (58%), backpain and osteoporosis (58%), striae (52%) and acne (40%). The causes of cortisol overproduction are:

- a) central type – caused by pituitary adenoms (women aged 25 – 45 years being mostly affected, 5-25 cases per 1 million).
- b) peripheral type - caused by benign (mainly affects women in their early fifties) or malignant (very low incidence of 0.5-2 cases per 1 million) adrenal cortex tumors.
- c) paraneoplastic type - ectopic cortisol over-production by malignant tumors, most often by bronchogenic cancer (about 1% of bronchogenic cancers produce Adrenocorticotropine (ACTH)).

Using azelaic acid in patients with rosacea or dermatitis perioralis, after confusing these conditions with acne, would not be harmful because the disease is not so serious and delaying their correct diagnosis does not have serious consequences. Moreover, the use of azelaic acid is indicated in rosacea and is expected to improve the condition.

Masking acne, as a symptom of polycystic ovary syndrome, cannot be excluded. Nevertheless, polycystic ovary syndrome is not an acute disease where immediate treatment is necessary, and it

often takes years for correct diagnosis due to its vague symptomology. Thus, a short delay in correct diagnosis would be unlikely to have an important impact on the health of a patient.

Masking and delaying the diagnosis of malignant diseases, symptoms of which can include acne, are considered most important. In order to reduce this risk, the package leaflet should include the following information:

- 1) A warning that azelaic acid should only be used by patients over 20 years of age following consultation with a medical doctor because acne can be a symptom of serious diseases.
In patients younger than 20 years of age, azelaic acid can be used without medical advice, because the incidence of malignant diseases, such as ovarian cancer and bronchogenic cancer, is generally low in this population group and, moreover, this age group suffers most from acne.
- 2) A warning that symptoms of Cushing's syndrome and other symptoms of virilisation could indicate the presence of a more serious disease, in which case adult patients should consult a medical doctor. The leaflet should comprise a description of central obesity, striae, decreased appetite, weight loss, abdominal discomfort, more frequent urination in men and women, deepening of the voice, increased muscle mass, hirsutism and temporal balding in women.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient by Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommended classification)	I					
A	II					
B	I					
CZ	I					
F	OTC					
H	I					
HR	II					
I	OTC					
LV	OTC					
MK	OTC					
P	II					
RO	I					
S	OTC					

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
SLO	I					

3.1. Recommended conditions of supply (indications, administration route, MS, MDD, MQP, as applicable)

Azelaic acid, D10AX03, cutaneous administration

Classification: **I + exemption**

Conditions of supply for the exemption

- treatment of acne.
- MS ≤ 20%.
- Additional information: patients over 20 years of age should consult a doctor.

Justification:

- low direct risk – low toxicity, no serious adverse reactions reported.
- possibility of safe self-diagnosis of acne.
- low risk of masking of underlying serious disease on condition that the above-mentioned warnings have been included in the package leaflet.
- OTC status in several countries.

3.2. Paediatric use

Acne is a common disease of adolescents, who can use prescription-free azelaic acid safely.

4. References:

- CDinfo-DRUGS, Pharmazie.com, DACON GmbH, 2008
- Guzick D. Polycystic ovary syndrome: Symptomatology, pathophysiology, and epidemiology. Am J - Obstet Gynecol. 1998 Dec;179(6 Pt 2):S89-S93.
- Hána V, Marek J. Hyperkortizolismus. Guideline for general practitioners. ČLS JEP 2001 (<http://www.cls.cz/dokumenty2/postupy/r091.rtf>)
- Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors
- Klener P. Klinická onkologie. [Clinical oncology] Galén. 2002
- Klener P. Vnitřní lékařství. [Internal medicine] Galén. 2001
- Martindale, Thomson Healthcare, 2009
- Micromedex, Thomson Healthcare, 2009
- Vohradníková O. Acne vulgaris. Pediatrie pro praxi. 2005; 3: 128-134.
- Vohradníková O. Dermatitis perioralis. Practicus. 2007; 4: 150-151.

Active ingredient: AZELASTINE

ATC Code: R01AC03

Therapeutic indications:

Symptomatic treatment of seasonal and perennial allergic rhinitis (including hay-fever).

Posology/duration of treatment:

0.14mg/0.14ml 1 dose (puff) twice daily into each nostril (adults and children aged 5 years and older).

Pharmaceutical forms: Nasal spray

Contraindications/relevant warnings:

Contraindication: proven allergy against azelastine hydrochloride.

Relevant warnings: in rare cases, a mild, transient irritation of the inflamed nasal mucosa may occur, with symptoms such as stinging, itching, sneezing and epistaxis.

1. List of direct/indirect risks (safety profile)

Azelastine is a relatively selective H1-receptor antagonist that blocks release of histamine from cells involved in the allergic response. It also demonstrates inhibition of other mediators involved in allergic reactions (e.g. leukotrienes and platelet-aggregating factor (PAF)), and reduction of chemotaxis and eosinophil activation.

1.1 . Direct risks (Pharmacovigilance)

When given intra-nasally, irritation of the nasal mucosa and taste disturbances have been reported. Somnolence, headache, and dry mouth have also been noted in some patients.

1.1.1 Teratogenicity/Effects in Pregnancy/Breast-feeding

Due to the nasal route of administration and the low dose administered, minimal systemic exposure can be expected. However, as with all medicines, caution should be exercised with use during pregnancy and lactation.

1.1.2 Elderly

No dose modification is needed.

1.1.3 Recent cases in Europe

None

1.2. Indirect risks (incorrect use)

A substance-specific, bitter taste may be experienced after administration (often due to incorrect methods of application, namely, tilting the head too far backwards during administration) which, in rare cases, may lead to nausea.

2. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
A	II exemption + Nasal, MS 0.1%					
B	I + exemption					
BG	II					
CH	II exemption +					
CZ	I + exemption MS 0.1%, MDD: 10mg MQP : 10mg					
FIN	II					
H	II					
I	II					
NL	II					
P	II					
PL	I					
RO	II					
S	II					
SLO	I					
SLO	II					
Resolution ResAP(2007)1, annually revised appendices (recommendations)	II exemption +					
B	OTC MQP 10 mg					
E	II exemption +					
F	II exemption +					
GB	II exemption +					
IRL	II exemption +					
Publication	II exemption +					
BIH	Not marketed					
D	OTC					
DK	OTC					
LT	OTC					
LV	OTC					
P	OTC Bottles with 10 or 20 ml 6 years old					
UK	List I +					

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
	exemption for seasonal rhinitis, perennial rhinitis, for adults and children more than 5 years old MS 0.14 mg MQP 44.5 mg (36 doses)					

2.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

List II + exemption

Conditions of supply:

- symptomatic treatment of seasonal and perennial allergic rhinitis (including hay-fever), nasal
- MS 0.14 mg/0.14 ml 1 dose (puff).
- MDD 0.56 mg/day.
- for adults and children above the age of 5 years.

Rationale:

- Incorrect use of the spray can occur, causing headache or nausea, especially in children under 5 years of age.
- Apart from the 5 year age limitation, azelastine is widely and safely used as an OTC treatment.
- Azelastine is devoid of sedative effects as a second generation, anti-histamine agent.
- Azelastine lacks the propensity to prolong repolarisation and induce 'torsade de pointes'.

2.2. Paediatric use

Widely used for adults and children aged 5 and older in Europe.

3. References:

- Sweetman, S. (2007) Martindale: The Complete Drug Reference (35th Edition). Pharmaceutical Press.
- Micromedex 2.0, Healthcare Series
- Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition
- Shah S, Berger W, Lumry W, La Force C, Wheeler W, Sacks H. (2009) Efficacy and safety of azelastine 0.15% nasal spray and azelastine 0.10% nasal spray in patients with seasonal allergic rhinitis. *Allergy Asthma Proc.*, Nov-Dec; 30(6):628-33.
- Bernstein JA, Prenner B, Ferguson BJ, Portnoy J, Wheeler WJ, Sacks HJ. (2009) Double-blind, placebo-controlled trial of reformulated azelastine nasal spray in patients with seasonal allergic rhinitis. *Am J Rhinol Allergy*, Sep-Oct; 23(5):512-7.
- Horak F. (2008) Effectiveness of twice daily azelastine nasal spray in patients with seasonal allergic rhinitis. *Ther Clin Risk Manag.*, Oct; 4(5):1009-22.

Active ingredient: AZELASTINE

ATC Code: R06AX19
Anti-histamines for systemic use – Other anti-histamines for systemic use.

S01GX07
Decongestants and anti-allergics - Other anti-allergics.

R01AC03
Decongestants and other nasal preparations for cutaneous use – Anti-allergic agents, excluding corticosteroids.

Therapeutic indications:

- allergic rhinitis
- allergic conjunctivitis
- vasomotor rhinitis

Posology/duration of treatment: nasal and eye solution

MICROMEDEX Dosing Information

Adult:

- Allergic conjunctivitis: 1 drop (0.05%) into affected eye(s) twice daily for up to 8 weeks.
- Seasonal allergic rhinitis: 1 or 2 sprays per nostril twice daily.
- Vasomotor rhinitis: 2 sprays per nostril twice daily.

Paediatric:

- Allergic conjunctivitis:
 - 3 years or older: 1 drop (0.05%) into affected eye(s) twice daily for up to 8 weeks.
- Seasonal allergic rhinitis:
 - 5 to 11 years: 1 spray per nostril twice daily.
 - 12 years and over: 1 or 2 sprays per nostril twice daily.
- Vasomotor rhinitis:
 - over 12 years: 2 sprays per nostril twice daily.

Pharmaceutical forms: nasal and eye drops

Contraindications - relevant warnings:

a) Contraindications:

- concurrent use of alcohol or other central nervous system depressants.
- hypersensitivity to azelastine products.

b) Precautions:

- asthma.
- contact lens use (ophthalmic solution).
- hepatic disease.
- renal impairment.
- use caution when driving or operating potentially dangerous machinery.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Bitter taste has been reported in 9% to 32% of patients using azelastine nasal spray or oral tablets and in approximately 10% patient using ophthalmic azelastine. The bitter taste is usually transient.

Dry mouth and nose, nausea, vomiting, abdominal discomfort, and altered appetite have been observed in less than 5% of patients treated with oral or intra-nasal azelastine.

1.2. Interactions with:

Cimetidine (probable).

1.3. Adverse reactions (ADRs)

- Common
 - **Gastrointestinal:** Abnormal taste in mouth, Bitter
 - **Neurologic:** Headache, Somnolence
 - **Ophthalmic:** Burning sensation in eye, Ophthalmic solution
 - **Respiratory:** Nasal stinging/burning, Nasal spray
 - **Other:** Fatigue

2. Discussion

Ophthalmic azelastine is effective in both adults and Paediatrics (over 3 years of age) for the treatment of itching of the eye associated with allergic conjunctivitis. Azelastine is effective in the symptomatic treatment of seasonal allergic rhinitis and offers no therapeutic benefit over conventional treatment (*i.e.* other anti-histamines and intra-nasal steroids). However, oral azelastine does cause somnolence and has a bitter taste. Observational studies have shown that azelastine nasal spray is well tolerated.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II	Oral Use				
Publication	II	Oral Use				
A	II + exemption	Oral Use				
CZ			Not marketed			
F			Not marketed			
H			Not marketed			
HR			Not marketed			
I			Not marketed			

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
LT			Not marketed			
MK			Not marketed			
RO	II	Oral Use				
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II + exemption	Nasal application				
Publication	II + exemption	Nasal application				
A	II + exemption	Nasal application		0.1%		
B	I + exemption	Nasal application				
BG	II	Nasal application				
CH	II + exemption	Nasal application				
CZ	I + exemption	Nasal application				
D	OTC	Nasal application				
DK	OTC	Nasal application				
E	II + exemption	Nasal application				
FIN	II	Nasal application				
GB	II + exemption	Nasal application				
H	II	Nasal application				
I	II	Nasal application				
IRL	II + exemption	Nasal application				
LT	OTC	Nasal application				
LV	II + exemption	Nasal application				
NL	II	Nasal application				
P	II	Nasal application				
RO	II	Nasal application				
S	II	Nasal application				
SLO	II	Nasal application				
Resolution ResAP(2007) 1, annually	II	Eye application				

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
revised appendices (recommendations)						
Publication	II	Eye application				
D	OTC	Eye application				
E	OTC	Eye application				
GB	II + exemption	Eye application				
I	II	Eye application				
LV	II	Eye application				
RO	II	Eye application				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

AZELASTINE, anti-histamines for systemic use – Other anti-histamines for systemic use, Oral administration.

List II

Criteria:

- risk of somnolence.
- not extensively used.

AZELASTINE, Decongestants and anti-allergics - Other anti-allergics.

List II + exemption

Criteria:

- only for short-term use for allergic conjunctivitis.

Conditions of supply:

- Symptomatic treatment of seasonal and perennial allergic rhinitis (including hay-fever), nasal.
- MS: 0.14 mg/0.14 ml correspond to 1 dose (puff).
- MDD: 0.56 mg/day.

Exemption: above the age of 5 years. AZELASTINE, Decongestants and other nasal preparations for cutaneous use – Anti-allergic agents, excluding corticosteroids.

List II + exemption

Criteria:

- only for short term use for allergic rhinitis.
- 0.1% solution.

Conditions of supply:

- Symptomatic treatment of seasonal and perennial allergic rhinitis (including hay-fever), nasal.
- MS: 0.14 mg/0.14 ml correspond to 1 dose (puff).
- MDD: 0.56 mg/day.
- Exemption: above the age of 5 years.

3.2. Paediatric use

Oral use not recommended for children under 12 years. Nasal and eye drops can be used in children older than 2 years.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/199F27/DUPLICATIONSHIELDSYNC/32F8D6/ND_PG/PRIH/ND_B/HCS/SBK/5/ND_P/Main/PFPUI/4E1exkk2QBCI1A/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/0471/ContentSetId/31#secN10BE4
- <http://emc.medicines.org.uk/medicine/9160/SPC/Rhinolast+Nasal+Spray/>
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: BUCLIZINE

ATC Code: R06AE01
Anti-histamines for systemic use – Piperazine derivatives.

The drug is not marketed in Member States.

No recommendation for prescription status is made.

References:

- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: CARBINOXAMINE (classification proposal adopted at 46th meeting)

ATC Code: R06AA08
Anti-histamines for systemic use – Amino alkyl ethers.

Therapeutic indications:

- allergic rhinitis

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- 4-8 mg orally, three or four times daily.

Paediatric:

- 1-3 years: 2 mg orally, three or four times daily.
- 3-6 years: 2-4 mg orally, three or four times daily.
- over 6 years: 4-6 mg orally, three or four times daily.

Pharmaceutical forms: Tablets, solution

Contraindications - relevant warnings:

a) Contraindications:

- acute asthma attack.
- hypersensitivity to carbinoxamine or other ethanolamine anti-histamines.
- MAOI therapy.
- narrow-angle glaucoma.
- peptic ulcer.
- severe coronary artery disease.
- severe hypertension.
- urinary retention.

b) Precautions:

- asthma
- decreased mental alertness
- diabetes mellitus
- hypertension
- heart disease
- hyperthyroidism
- increased intra-ocular pressure
- not recommended in premature or full-term neonates
- prostatic hypertrophy

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

1.2. Interactions

Theoretically with Belladonna, Belladonna Alkaloids and Procarbazine (CNS depression). (MICROMEDEX)

1.3. Adverse reactions (ADRs)

- Common:
 - Dermatologic: Contact dermatitis
 - Gastrointestinal: Xerostomia
 - Neurologic: Dizziness, Headache, Sedated, Somnolence
 - Respiratory: Dry nasal mucosa

2. Discussion

Carbinoxamine maleate is effective in controlling allergic rhinitis. It is often used in fixed combination products with dextromethorphan and/or pseudoephedrine when anti-tussive and decongestant activity is desired in addition to the anti-histamine effects.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	OTC	Oral Use				
Publication	OTC	Oral Use				
A	II	Oral Use				
CZ			Not marketed			
D	OTC	Oral Use				
E	OTC	Oral Use				
F	OTC	Oral Use				
FIN	II	Oral Use				
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LT			Not marketed			
MK			Not marketed			
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

CARBINOXAMINE, anti-histamines for systemic use – Aminoalkyl ethers, Oral administration

List OTC

Criteria:

- safe profile.
- only for short-term usage in treatment of allergic rhinitis (14 days, recommended only for children over 24 months of age, which is not a condition). Warning.

3.2. Paediatric use

Not indicated in children younger than 12 months of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/35D173/DUPLICATIONSHIELDSYNC/FE21A1/ND_PG/PRIH/ND_B/HCS/SBK/1/ND_P/Main/PFPUI/7RTTtI2PNzLJb/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2469/ContentSetId/31/SearchTerm/ALIMEMAZINE/SearchOption/BeginWith#secN10136
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: CETIRIZINE

ATC Code: R06AE07
Anti-histamines for systemic use – piperazine derivatives

Therapeutic indications:

- symptomatic treatment of perennial rhinitis.
- seasonal allergic rhinitis.
- chronic idiopathic urticaria.
- allergic conjunctivitis.
- urticaria.
- pruritus.
- atopic dermatitis.

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- 5-10 mg orally, once daily (Perennial allergic rhinitis).
- 5-10 mg orally, once daily (Seasonal allergic rhinitis).
- 5-10 mg orally, once daily (Urticaria, chronic).

Paediatric:

- Perennial allergic rhinitis
 - 12 years and older: 5-10 mg orally, once daily.
 - 6-11 years: 5-10 mg orally, once daily.
 - 2-5 years: 2.5-5 mg orally, once daily or 2.5 mg orally, twice daily.
 - 6-23 months: 2.5 mg orally, once daily; the dose in children 12 to 23 months of age can be increased to a maximum dose of 5 mg per day, given as 2.5 mg every 12 hours.
- Seasonal allergic rhinitis
 - 12 years and older: 5-10 mg orally, once daily.
 - 6-11 years: 5-10 mg orally, once daily.
 - 2-5 years: 2.5-5 mg orally, once daily or 2.5 mg orally, twice daily.
- Urticaria, chronic
 - 12 years and older: 5-10 mg orally, once daily.
 - 6-11 years: 5-10 mg orally, once daily.
 - 2-5 years: 2.5-5 mg orally, once daily or 2.5 mg orally, twice daily.
 - 6-23 months: 2.5 mg orally, once daily; the dose in children 12 to 23 months of age can be increased to a maximum dose of 5 mg per day, given as 2.5 mg every 12 hours.

Pharmaceutical forms: tablets, oral drops, oral solution, syrup

Contraindications - relevant warnings:

a) Contraindications:

- hypersensitivity to **cetirizine** or components.
- hypersensitivity to hydroxyzine.

b) Precautions:

- asthma.
- bladder neck obstruction.
- hepatic insufficiency.
- narrow-angle glaucoma.

- pyloroduodenal obstruction.
- sedative effects - patient susceptibility may vary.
- stenosing peptic ulcer.
- symptomatic prostatic hypertrophy.
- dosage should be adjusted according to body weight and renal clearance in case of renal impairment.
- elderly people especially sensitive to the anti-cholinergic effect of anti-histamines (mouth dryness, urinary retention).
- alcohol intake is forbidden during treatment.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

There are no severe direct risks with cetirizine.

1.2. Interactions

Not clinically relevant.

1.3. Adverse reactions (ADRs)

- urticaria.
- diarrhea.
- abdominal pain.
- headache is the most frequently reported side effect in total (40%).
- the most common CNS ADRs are sedation (22%), somnolence (13.7%), fatigue (5.9%), headache (7.5%), and dry mouth (5%).
- toxic hepatitis.

1.3.1. Recent case reports (UMC database)

In the period from the 1st of January 2005 up to the 7th of February 2009, the Uppsala Monitoring Centre received 1,571 reports of CETIRIZINE with 5,015 ADRs. Reports came from **Austria**, Australia, Canada, **Czech Republic**, Chile, Columbia, **Germany**, **Denmark**, **Spain**, **Estonia**, **Finland**, **France**, **United Kingdom**, **Hungary**, **Ireland**, **Italy**, Japan, Mexico, **Norway**, New Zealand, Oman, **Poland**, **Romania**, **Sweden**, Thailand, Tunisia, **Turkey**, the USA, and Venezuela. The most common ADRs reported are somnolence (128 cases), pruritus (94 cases), drug was ineffective (96 cases), medication error (91 cases), headache (60 cases). Eleven cases of death were reported. There were only four cases of neutropenia, and four cases of 'torsades de points' were reported from France, the United Kingdom and Switzerland, but where other medications had also been co-administered.

The combination database of the UMC ADR database indicates a slight signal of aggressive behavior in young children (in children less than 4 years of age).

2. Discussion

The main therapeutic area of this drug is allergic rhinitis and the treatment of chronic urticaria. In Europe, the medicinal product is on the market in the Czech Republic, France, Italy, Latvia, Hungary, Macedonia, Romania and Croatia, which have given it prescription-only status in their countries. From the UMC ADR, DD database and national information from medical classification databases, it is clear that the medicinal product is also marketed in Austria, Belgium, Bulgaria, Croatia, Germany, Denmark, Estonia, Finland, United Kingdom, Ireland, Latvia, Lithuania, the Netherlands, Norway, Poland, Romania, Spain, Slovenia, Switzerland, Sweden and Turkey.

Unlike other second-generation H1 antagonists (e.g. terfenadine and astemizole), cetirizine has not been associated with 'torsade de pointes' (only a few cases in the post-marketing period have been reported as possibly related to the drug). In one study, after cetirizine was administered at up to six times the recommended dosage, it did not significantly alter the corrected QT (QTc) interval. Cetirizine caused no adverse cardiovascular or electrocardiographic effects in Paediatric safety studies.

Cetirizine is well-tolerated, with minimal gastrointestinal side effects.

The most common treatment-related adverse effects of the CNS are somnolence (13.7%), fatigue (5.9%), headache (7.5%), and dry mouth (5%). Other rare (i.e. less than 2%) adverse drug reactions reported with cetirizine included paresthesia, confusion, hyperkinesia, hypertonia, migraine, tremor, vertigo, leg cramps, ataxia, and dysphonia. The following rare adverse reactions have also been reported during post-marketing surveillance: aggressive reactions and convulsions, which are undergoing in-depth investigations.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II + exemption	Oral Use		10 mg	10 mg	
Publication	II + exemption	Oral Use		10 mg	10 mg	
A	II + exemption	Oral Use		10 mg	10 mg	
B	II + exemption	Oral Use	Tablet forms only			
BG	II	Oral use				
CH	II + exemption	Oral Use		10 mg		100mg
CZ	II + exemption	Oral Use	Indications: allergic rhinitis, allergic conjunctivitis, urticaria Caution : only for adults and children >6 years	10 mg or 10mg/ml	10 mg	210mg
D	OTC					
DK	OTC					
E	I + exemption	Oral Use	children 6-12 years		5 mg	
F	II + exemption	Oral Use	Indications: rhinitis, conjunctivitis, hives Caution: for adults and children > 2 years	10 mg	10 mg	75 mg
FIN	II + exemption	Oral Use		10 mg		70 mg
GB	Currently not available	Oral Use				
H	II + exemption	Oral Use	Indications: (film-coated tablets, oral drops) perennial rhinitis, seasonal allergic rhinitis, conjunctivitis, pruritus, chronic idiopathic urticaria, atopic dermatitis.	10 mg or 10 mg/ml oral solution (drops)	10 mg	100 mg or 150 mg for the oral solution
HR	I	Oral use				
I	II	Oral use				

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
IRL	II + exemption	Oral use		10 mg	10 mg	
LT	II	Oral use				
LV	I + exemption	Oral use	Indications: Seasonal allergic rhinitis, allergic rhinitis, urticaria used to relieve itching from hives. Warnings: hypersensitivity to cetirizine in patients with renal insufficiency. MDD adults and children > 12 years, 10mg; Children 6-11 years, 10 mg; Children 1-5 years, 5 mg.	10 mg (5 mg)	10 mg (5 mg)	300 mg
MK	II	Oral use	Indications: Prevention/treatment/relief of symptoms of seasonal and perennial allergic rhinitis, rhino conjunctivitis, atopic dermatitis, (neurodermatitis), chronic urticaria, other allergic diseases. Warnings: to be given with caution and at lower dose to patients with moderate renal function impairment, patients on hemodialysis and patients with hepatic dysfunction. Dose reduction required in some elderly patients. The efficacy and safety of cetirizine for children under 2 years is not established.	10 mg		
N	II + exemption	Oral use	Pack sizes up to 30 tablets to treat pollen allergy.			
NL	OTC	Oral use				
P	II	Oral use				
RO	II + exemption	Oral use	Indications: symptomatic treatment of perennial rhinitis, seasonal allergic rhinitis and chronic idiopathic urticaria in adults and children over 2 years of age. Warnings: MDD 10 mg for children between 6-12 years of age with body mass index > 30 kg; MDD 5mg for children between 6-12 years of age, with body mass index < 30 kg. List II MS 1 mg/ml for syrup. MDD = 5mg for children between 2-6 years of age. MQP 200 mg.	10 mg (5 mg)	10 mg (5 mg)	100 mg
S	II	Oral use				
SLO	OTC	Oral use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

CETIRIZINE, anti-histamines for systemic use – piperazine derivatives, Oral administration

List II + exemption

Criteria:

- Safe profile – no cardiovascular risks, somnolence as an ADR is not common in adults.
- A wide range of prescription statuses: from List I to OTC only (Germany, Denmark, Slovenia, The Netherlands), but most Member States prescribe List II with an exemption prescription status and MS=10 mg and MDD=10 mg.

- Recommendation for OTC prescription status:
 - o MS 10 mg, MDD 10 mg, MQP 100 mg.
 - o short-term use for seasonal allergic rhinitis, conjunctivitis.
 - o only for children > 6 years (somnolence in younger children, convulsions and aggressive reactions were observed).

3.2. Paediatric use

It is indicated for children above 2 years of age for the treatment of chronic urticaria and other allergic diseases (dermatological, rhinitis, conjunctivitis).

3.3. Elderly

Precautions: dose reduction.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/153352/DUPLICATIONSHIELDSYNC/735559/ND_PG/PRIH/ND_B/HCS/SBK/8/ND_P/Main/PFPUI/Ln1apYu2PPSP37/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2536/ContentSetId/31#adverseReactionsSection
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: CHLORPHENAMINE (classification proposal adopted at 46th meeting)

Synonyms: Chlorprophenpyridamine

ATC Code: R06AB04
Anti-histamines for systemic use – Substituted alkylamines

Therapeutic indications:

- for symptomatic control of all allergic conditions responsive to anti-histamines:
 - hay fever
 - vasomotor rhinitis
 - urticaria
 - angioneurotic oedema
 - food allergy
 - drug and serum reactions
 - insect bites
- syrup - treatment in children for cough and bronchitis (France).

Posology/duration of treatment:

- oral and parenteral

MICROMEDEX Dosing Information

Adult:

- 4 mg orally, every 4-6 hrs; maximum dose=24 mg/day.
- sustained-release, 8 or 12 mg orally, every 8-12 hours; maximum dose=24 mg/day.
- 5-40 mg IM, IV, SC as a single dose; maximum dose=40 mg/day.

Paediatric:

- *Not recommended in children less than 6 years of age.*
- 6-11 yrs: 2 mg orally, every 4-6 hrs; maximum dose corresponds to 12 mg/day.
- 12 yrs and over: sustained-release, 8 mg orally every 12 hrs.
- 87.5 mcg/kg or 2.5 mg/m (2) SC, 4 times daily.

Pharmaceutical forms: Tablets, sustained-release capsules, syrup, solution

Contraindications - relevant warnings:

a) Contraindications:

- hypersensitivity to chlorpheniramine.
- newborns.
- patients with hepatic insufficiency.
- narrow angle glaucoma.
- prostatic hypertrophy.
- bladder neck obstruction.

b) Precautions:

- it should be used with caution in epilepsy.
- raised intra-ocular pressure, including glaucoma.
- prostatic hypertrophy.
- severe hypertension or cardiovascular disease.
- bronchitis.

- bronchiectasis and asthma.
- Children and the elderly are more likely to experience the neurological anticholinergic effects.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Serious ADRs can occur including: agranulocytosis, aplastic anemia, thrombocytopenia, dyskinesia, somnolence, and toxic psychosis.

1.2. Interactions with (theoretical):

Belladonna, Belladonna Alkaloids, Phenytoin, Procarbazine (MICROMEDEX).

1.3. Adverse reactions (ADRs)

- cardiac dysrhythmia.
- hypotension.
- gastrointestinal ADR (most common): some of these adversities include anorexia, nausea, vomiting, epigastric distress, and diarrhea or constipation.
- agranulocytosis.
- aplastic anemia.
- thrombocytopenia.
- dyskinesia.
- sedation.
- somnolence.

1.3.1. Recent case reports (UMC database)

In the period from the 1st of January 2005 up to the 7th of February 2009, the Uppsala Monitoring Centre received 295 reports of chlorphenamine with 823 ADRs. Reports came from Canada **Switzerland**, China, Columbia, Cuba, **Germany, France, United Kingdom**, Indonesia, India, **Ireland, Italy**, Japan, Mexico, New Zealand, Peru, Thailand, the USA and South Africa. The most common ADR was cerebrovascular accident, reported in 44 cases (all from the USA). In all cases, an increased number of drugs were given. The ADR is possibly a result of the interactions between the drugs (in all cases more than 5 drugs were given at the same time). The second most common ADR was accidental overdose, drug toxicity and multiple drug overdoses (36 cases, also all from the USA). Of the cardiovascular ADRs, the most common were cardio-respiratory arrest (12 cases) and increased blood pressure (12 cases). The most common gastrointestinal ADR was vomiting (10 cases) and, from the CNS after cerebrovascular accident, the second-most reported ADR was somnolence (12 cases).

2. Discussion

The main therapeutic area of this drug is the symptomatic control of all allergic conditions, most typically for allergic rhinitis. In France, it is additionally indicated for the treatment of bronchitis and cough, for which it is Precautionary in Romania. Chlorphenamine should be used with caution in patients presenting with epilepsy, raised intra-ocular pressure including glaucoma, prostatic hypertrophy, severe hypertension or cardiovascular disease, bronchitis, bronchiectasis and asthma. Children and the elderly are more likely to experience neurological anti-cholinergic effects. There is a potential for misuse and abuse, which has been reported in the post-marketing phase.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	OTC	Oral use				
Publication	OTC	Oral use				
A	OTC	Oral use		5 mg	15 mg	
B	OTC	Oral use				
BG	II					
CH	OTC	Oral use				
CZ			Not marketed			
D	OTC	Oral use				
E	II + exemption	Oral use	Children between 6 - 12 y: combination products for common cold		8 mg	
		Oral use	Adults: combination products for common cold		24 mg	
		Nasal use	Patients over 6 years of age			0.5%
F	OTC	Oral use				
GB	OTC	Oral use				
H			Not marketed			
HR			Not marketed			
I	II	Oral use	Warnings: not indicated for patients with epilepsy and in the treatment of asthma	4 mg	16 mg	
		Intravenous use		1 ml	2 ml	
IRL	OTC	Oral use				
LT			Not marketed			
LV	OTC	Oral use				
MK			Not marketed			
P	OTC	Oral use				
RO	II	Oral use	Indications: symptomatic control of all allergic conditions responsive to anti-histamines, including hay fever, vasomotor rhinitis, urticaria, angioneurotic oedema, food allergies, drug and serum reactions, insect bites. Warnings: to be used with caution in epilepsy, raised into-ocular pressure including glaucoma, prostatic hypertrophy, severe hypertension or cardiovascular disease, bronchitis, bronchiectasis and asthma. Children and elderly are sensitive to neurologic anti-cholinergic effects.	4 mg	MDD=24 mg for adults and children over 12 years of age; MDD= 12 mg for children aged between 6-12 years.	80 mg

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

CHLORPHENAMINE, anti-histamines for systemic use – substituted alkyl amines; Oral administration, Nasal administration

List II + exemption

Criteria:

- Safe profile – no cardiovascular risks, somnolence as an ADR is not common in adults.
- In most Member States it is an OTC drug, except in Bulgaria, Italy and Romania.
- Children and the elderly are sensitive to neurological and anti-cholinergic effects.
- A restriction on the size and the duration of treatment is necessary due to cases of overdosing reported in the post-marketing phase.
- Recommendation for OTC prescription status:
 - o MS corresponds to 4 mg, MDD corresponds to 24 mg, MQP corresponds to 80 mg. Additional short-term use for seasonal allergic rhinitis and conjunctivitis:
 - o only for children > 12 years.

3.2. Paediatric use

Not recommended in children less than 6 years of age.

CHLORPHENAMINE, anti-histamines for systemic use – substituted alkyl amines; parenteral administration.

After discussion it was decided that the drug should be classified as List II + exemption .

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/E1A57B/DUPLICATIONSHIELDSYNC/23357F/ND_PG/PRIH/ND_B/HCS/SBK/1/ND_P/Main/PFPUI/Ln1apYu2PQuajs/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2433/ContentSetId/31/SearchTerm/CHLORPHENAMINE/SearchOption/BeginWith#secN10617
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: CHLORPHENOXAMINE
Anti-histamine, Ethanolamine (class)

ATC Code: D04AA34
[Anti-histamines for cutaneous use.](#)

Therapeutic indications:

For the treatment of allergic and/or pruritic skin disorders including sunburn, insect bites, mild burns, urticaria and eczema.

Posology/duration of treatment:

1.5% cream is applied to the affected area, several times a day, until relief of symptoms occurs.

Pharmaceutical forms: cutaneous cream

Contraindications

- hypersensitivity to chlorphenoxamine.
- hypersensitivity to parabens or cetylstearyl alcohol.

Relevant warnings:

General: Cutaneous preparations containing anti-histamines should not be used on broken or eczematous skin.

It should not be applied to large areas in infants and children because sufficient amounts may be absorbed to cause symptoms of intoxication.

1. List of direct/indirect risks (safety profile)

- **CNS and Ophthalmic:**

Cutaneous application of **chlorphenoxamine** to large body surface areas in infants and children may result in sufficient percutaneous absorption to cause symptoms of toxicity, including excitability, confusion and mydriasis.

1.1. Direct risks (Pharmacovigilance) (see above)

1.1.1 Recent cases in Europe

Between 1 January 2007 and 22 February 2010, the Uppsala Monitoring Center has received one report on chlorphenoxamine, with two serious ADRs, namely dermatitis bullosus and erythema multiforme. Route of administration: topical.

1.2. Indirect risks (incorrect use) (see above)

2. Conclusions – recommendations of legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	II					
B			Not marketed			
BIH			Not marketed			
E	I					
F	II					
H			Not marketed			
HR			Not marketed			
PL			Not marketed			
UK			Not marketed			

No data available from other Member States

2.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

Data is available from eight Member States.

In the two Member States where chlorphenoxamine is marketed, it is classified as POM (list I or II), with no exemptions.

2.2. Paediatric use

Caution required in treating children aged <12 years.

2.3. Conclusion

In the absence of data and the medicine not being marketed in many countries, the Committee have decided to retain the current classification.

List II

3. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/609334/DUP...
- Sweetman, S. (2007) Martindale: The Complete Drug Reference (35th Edition). Pharmaceutical Press.
- <http://emc.medicines.org.uk/>
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)

Active ingredient: CLEMASTINE (classification proposal adopted at 46th meeting)

Synonyms: Meclastine

ATC Code: R06AA04
Anti-histamines for systemic use – Aminoalkyl ethers

Therapeutic indications:

- allergic rhinitis (including hay fever), perennial rhinitis and vasomotor rhinitis.
- allergic dermatoses (including pruritus), atopic eczema and contact dermatitis.
- angioneurotic oedema.
- drug allergy.

Posology/duration of treatment:

- oral

MICROMEDEX Dosing Information

Adult:

- Allergic rhinitis:
 - ½ to 1 tablet (2.68 mg) orally, 1 to 3 times daily; maximum dose is 1 tablet (2.68 mg), 3 times daily.
 - 10 ml (1 mg) of syrup orally, twice daily; maximum dose is 6 mg/day (12 years and older).
- Cutaneous hypersensitivity, urticaria and angioedema:
 - 1 tablet (2.68 mg) orally, one to three times daily; maximum dose is 1 tablet (2.68 mg), three times daily.
 - 20 ml (2 mg) of syrup orally, twice daily; maximum dose is 6 mg/day (12 years and older).

Paediatric:

- Allergic rhinitis:
 - ½ to 1 tablet (2.68 mg) orally, 1 to 3 times daily; maximum dose is 1 tablet (2.68 mg), 3 times daily (12 years and older).
 - 10 ml (1 mg) of syrup orally, twice daily; maximum dose is 6 mg/day (12 years and older).
 - 5 ml (0.5 mg) of syrup orally, twice daily; maximum dose is 3 mg/day (6-12 years).
- Cutaneous hypersensitivity, urticaria and angioedema:
 - 1 tablet (2.68 mg) orally, one to three times daily; maximum dose is 1 tablet (2.68 mg), three times daily (12 years and older).
 - 20 ml (2 mg) of syrup orally, twice daily; maximum dose is 6 mg/day (12 years and older).
 - 10 ml (1 mg) of syrup orally, twice daily; maximum dose is 3 mg/day (6-12 years)

Pharmaceutical forms: Tablets and syrup

Contraindications - relevant warnings:

a) Contraindications:

- hypersensitivity to the active substance or to any of the excipients.
- children under 1 year of age (newborn or premature infants).
- porphyric patients.
- MAOI therapy.
- symptoms of lower respiratory tract infection.
- lactation.

b) Precautions:

- It should be used with caution in patients with:
 - narrow-angle glaucoma
 - stenosing peptic ulcer
 - pyloroduodenal obstruction
 - prostatic hypertrophy with urinary retention
 - bladder neck obstruction

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Precautions because of serious ADR: somnolence. Before using the medicine, symptoms of lower respiratory tract infection should be ruled out.

1.2. Interactions with (theoretical):

Belladonna, Belladonna Alkaloids, Procarbazine (MICROMEDEX)

1.3. Adverse reactions (ADRs)

- dermatological findings such as rash or pruritus.
- very rarely vomiting, nausea and dry mouth.
- rarely headache and dizziness.
- mild drowsiness (dose-dependent).
- shortness of breath.

1.3.1. Recent case reports (UMC database)

In the period from the 1st of January 2005 up to the 7th of February 2009, the Uppsala Monitoring Centre received 66 reports on chlorphenamine with 165 ADRs. Reports came from Chile, Columbia, **Germany**, Iran, **Ireland**, Japan, Mexico, **the Netherlands**, **Poland**, **Sweden** and the USA. The most common ADR is somnolence, but only with 6 reported cases. All other ADRs are represented by only 1 or 2 cases. A single case of death was associated with administration of a number of drugs simultaneously (benzodiazepines and antidepressants). Similarly, a single case of Stevens-Johnson's syndrome was related to simultaneous administration of multiple drugs (antibiotics and benzodiazepines).

2. Discussion

The main therapeutic area of this drug is the symptomatic control of allergic conditions, particularly allergic rhinitis and cutaneous allergic conditions. The profile of the drug is safe; there have been no reported serious cases of ADRs in the past 3 years in Europe. Because the pre-marketing clinical trials showed some breath shortness associated with the use of clemastine, respiratory illness should be ruled out before use. The medicinal product is not authorised for children younger than 12 months, but it is also not recommended for use in children under 6 years of age because of the ADR of somnolence that mostly occurs in children (typically in cases where the daily dose exceeded 2 mg).

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	II exemption +	Oral use		2 mg		
Publication	II exemption +	Oral use		2 mg		
A	II exemption +	Oral use	OTC: only cutaneous use	0.1%		
B			Not marketed			
BG	II					
CH	II exemption +	Oral use		1 mg	4 mg	
CZ	I	Oral use	Indications: hay fever, urticaria, itching	1 mg	6 mg	20 mg
D	OTC	Oral use				
E	II	Oral use				
F			Not marketed			
GB	OTC	Oral use				
H			Not marketed			
HR			Not marketed			
I	OTC	Oral use				
IRL	OTC	Oral use				
LT	II	Oral use				
LV	II exemption +	Oral use	Indications: allergy symptoms; itching, seasonal allergic rhinitis, sneezing, erythema, urticaria. Warnings: Not to be used in patients with allergic reactions to clemastine, should be used with caution in patients with glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, bladder neck obstruction.	1 mg	6 mg	20 mg
MK			Not marketed			
N	II	Oral use				
NL	II	Oral use				
P	OTC	Oral use				
RO	OTC	Oral use				
S	II	Oral use				
SLO	II	Oral use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

CLEMASTINE, anti-histamines for systemic use – aminoalkyl ethers; Oral administration

List II + exemption

Criteria:

- Safe profile – no cardiovascular risks, somnolence or anti-cholinergic effects as ADRs are not common in adults.
- In most Member States it is an OTC drug or the prescription status is List II + exemption .
- Recommendation for OTC prescription status:
 - o Indication: allergic rhinitis.
 - o MS corresponds to 1 mg, MDD corresponds to 6 mg, MQP corresponds to 20 mg.
 - o short-term use for seasonal allergic rhinitis, conjunctivitis.
 - o only for children > 12 years.

3.2. Paediatric use

Not authorised for children below 12 month of age but, in most Member States, also not recommended for children less than 6 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/E1A57B/DUPLICATIONSHIELDSYNC/23357F/ND_PG/PRIH/ND_B/HCS/SBK/1/ND_P/Main/PFPUI/Ln1apYu2PQuajs/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2433/ContentSetId/31/SearchTerm/CLEMASTINE/SearchOption/BeginWith#secN10617
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: CODEINE

ATC Code: R05DA04
Cough suppressants, excluding combinations with expectorants –
opium alkaloids and derivatives

Therapeutic indications: cough suppressants

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult : 10 to 20 mg orally, every 4 to 6 hours, as needed.

Paediatric:

1) aged 2 to 6 years: 1 mg/kg/day orally in 4 divided doses. Maximum dose is 30 mg/day

2) aged 6 to 12 years: 5 to 10 mg orally, every 4 to 6 hours. Maximum dose is 60 mg/day.

Utilisation of anti-tussive drugs must be limited and of short duration.

Pharmaceutical forms: Syrup, oral solution, capsule, tablet

Contraindications - relevant warnings:

- Hypersensitivity to codeine.
- Codeine preparations should not be recommended for the treatment of cough in young children (WHO, 2001) and should be avoided in those under 1 year of age (Sweetman, 2005).
- Utilisation of anti-tussive drugs must be limited, of short duration and without contraindications.
- Codeine is subject to abuse.
- Risk of addiction.
- Pregnancy and breastfeeding
- Might mask/hide underlying disease.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

For ultra-rapid metabolisers

Codeine is an opioid, chemically-related to morphine. It acts on the cough centre of the medulla to depress the cough reflex, perhaps by increasing the cough threshold. Like other opioids, codeine has analgesic and sedative properties, but its action as an anti-tussive is achieved at lower doses than its analgesic and sedative effects (Burton, 1995).

Codeine, which has a half-life in the plasma of 2-4 hours, is metabolised by the liver and excreted in the urine. However, about 10 % is demethylated to form morphine, which may be the active form of the drug for its analgesic activity.

Codeine has an exceptionally low affinity for opioid receptors, and the analgesic effect of codeine is due to its conversion to morphine. But, its anti-tussive actions probably involve distinct receptors that bind codeine itself.

Limited evidence suggests that individuals who are ultra-rapid metabolisers (multiple CYP 2D6 gene copies or those with a specific CYP2D6 genotype) may convert codeine to its active metabolite, morphine, more rapidly and completely than other people, whereas patients that lack functional CYP2D6 genes do not metabolise codeine to morphine and do not experience analgesic effects.

Multiple CYP2D6 gene copies occur in 4 to 5% of the United States population and in up to 29% of the population of Ethiopia and Saudi Arabia (Ingelman-Sundberg *et al.*, 1999). CYP2D6 is absent in 5 to 10% of the Caucasian population (Heiskanen *et al.*, 2000).

A very recent study demonstrated that plasma morphine concentrations are about 50 % higher in ultra-rapid 2D6 metabolisers than in extensive metabolisers (Kirchheiner, 2006). After intake of a single 30 mg codeine dose, 91 % of the ultra-rapid metabolisers felt sedation, compared to 50 % of the extensive metabolisers. Therefore, a serious, opioid-type intoxication can occur in CYP 2D6 ultra-rapid metabolisers (Samer, 2005).

Two cases have been published recently (Gasche *et al.*, 2004, Koren, 2006). Gasche *et al.* (2004) reported a case of CNS depression after the administration of small doses of codeine in patients with a CYP2D6 ultra-rapid metabolism phenotype. In nursing mothers, this metabolic type can result in higher than expected serum and breast milk morphine levels. The published case report of a 13-day old breast-fed infant who died from morphine overdose, raises concerns that nursing babies may be at increased risk of morphine overdose if their mothers are taking codeine and are ultra-rapid metabolisers of the drug (Koren, 2006). The morphine levels in the mother's milk were abnormally high after taking small doses of codeine to treat episiotomy pain.

The estimated number of ultra-rapid metabolisers of **codeine** ranges from less than 1 per 100 people up to 28 per 100 people (US Food and Drug Administration, 2007).

A genetic test is required to identify ultra-rapid metabolisers.

In Paediatric Use

Infants are at special risk from codeine. There have been reports of fatality or near fatality following inappropriate treatment in infants given mixtures containing codeine (Sweetman, 2005). Young infants are more susceptible to codeine intoxication due to their immature hepatic glucuronidation system. Cough medications should not be recommended for young children given that there is a lack of evidence proving effectiveness and that the use of OTC cough medications creates a potential risk for adverse reactions (Chang, 2005).

Acute codeine intoxication in children (n 430) due to accidental ingestion of anti-tussive preparations was analysed by von Mühlendal *et al.* (1976). The children were nearly all aged between 1 and 6 years old. Symptoms in decreasing order of frequency included somnolence, rash, miosis, vomiting and itching. Respiratory failure occurred in eight children and two died (all eight had been administered 5 mg/kg body weight or more).

Adverse effects of codeine

Adverse reactions to codeine in non-intoxicated children include nausea and vomiting, constipation, palpitations and dizziness. After large doses, children may experience somnolence, rash, miosis, vomiting, itching, ataxia and swelling of the skin. Respiratory failure leading to death has also been described.

The FDA has recently reviewed information about the safety of over-the-counter (OTC) cough and cold medicines in infants and children under 2 years of age. The FDA is now recommending that these drugs should not be used to treat infants and children below 2 years of age because serious and potentially life-threatening side-effects can occur (FDA, 2007).

Respiratory depression is a potentially serious or fatal adverse drug reaction associated with the use of codeine. The occurrence of respiratory depression is dose-related and is the mechanism for the potentially fatal consequences of overdose, *i.e.* respiratory or cardiac arrest.

1.2. Indirect risks

Underlying condition requiring medical attention and supervision

Coughing is a protective reflex which can serve to expel secretions or extraneous materials from the respiratory tract. Coughing should not be suppressed when it serves as a productive function, except under special circumstances (e.g. when it exhausts the patient or prevents rest and sleep).

Any symptomatic treatment of cough should be accompanied by measures aimed at diagnosis and treatment of the underlying cause, such as asthma, chronic bronchitis, bronchi dilatation, carcinoma, gastroesophageal reflux, bronchi-pulmonary infections, pneumonia, left ventricular heart failure, pulmonary embolism, pleural disorder, and the adverse effects of angiotensin-converting enzyme (ACE) inhibitors.

Dependence, Abuse and addiction

Both physical and psychological dependence can develop with the chronic use of codeine. Prolonged ingestion of codeine can produce a state of narcotic dependency. However, the potential for dependence is much less than that with morphine.

Although the risk of dependence on codeine is low with normal use, there have been several reports of its deliberate abuse, even though it produces less euphoria and sedation than morphine.

Upon discontinuation of codeine treatment, patients may experience withdrawal symptoms including anxiety, tremors, muscle spasms, sweating, rhinorrhea, and paranoid delusions.

Misuse

The Drug Enforcement Administration (EDA) cites the rising popularity of a concoction that includes codeine-laced syrup mixed with a soft drink (e.g. Sprite), sports drink or alcohol. Such cocktails are known as "Lean," "Syrup," "Sizzurp" and "Purple Drank" (Leinwand, 2006; Peters and Yacoubian, 2007; Peters and Williams, 2007; Matoo, 1997).

2. Discussion

Codeine is an ingredient found in prescription and non-prescription medicines used to relieve pain or treat cough.

There is little evidence as to whether codeine treatments for cough are effective (Schroeder, 2004; Schroeder, 2002; DTB, 1999; Herbert, 2000, Smith, 1993). The efficacy of codeine as cough suppressants in children is also questionable (Chang, 2005).

Codeine is converted (metabolised) into morphine in the liver by an enzyme. Some people, due to their genetic background, have a variation of this enzyme that changes codeine to morphine faster and more completely than in other people. These people, called ultra-rapid metabolisers, are more likely to have higher-than-normal levels of morphine in their blood after taking codeine. Mothers who are ultra-rapid metabolisers may have higher-than-usual levels of morphine in breast milk.

The majority of patients attempt to self-treat coughs and use over-the-counter (OTC) medications to do this. Cough may be a warning sign. It is usually a symptom of another medical condition, but many patients will complain of cough as the primary symptom on presentation to the pharmacy.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions (May 2008):

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	I + exemption	Oral Use Rectal Use		30 mg		120 mg
A	I					
B	II + exemption	Oral Use		30 mg	120 mg	360 mg
BG	II + exemption	Oral Use		12.5 mg		
CH	II + exemption	Oral Use	Indications : anti-tussive.	15 mg		300 mg
CZ	I (1)					
D	I (1)					
E	II					
F	II + exemption	Oral Use	Syrup: exemption is other oral forms (List I).			
GB	II + exemption	Oral Use	In undivided preparations or single dose preparations. Advertising to public possible through all media.	20 mg		
H	II + exemption	Oral Use	Only in combination in cough syrups, tablets, suppositories and effervescent tablets.			
IRL	II + exemption	Oral Use	Advertising to the public is prohibited.	20 mg		
LT	II					
N	II					
NL	II + exemption	Oral Use	Public advertising allowed in all media.	1.5 %		
P	II					
RO	I + exemption		In combination with potassium guajacol sulfonate. Cough treatment is 1 tablet 3-4 times per day (adults and children above 3 years of age). Warnings: doses of codeine more than 0.3 g/kg may cause seizures. List I :mono-product. Cough treatment, moderate pain, some cases of diarrhoea. Recommended dose for children aged 5 years and older is 2-3 mg/kg/day, but no more than 6 mg/kg/day and 1 mg/kg per dose. Warnings: doses of more than 0.3mg/kg can cause seizures.			
S	II					
SLO	II					

No data available from other Member States at the time of initial report.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

Codeine, cough suppressants, oral administration.

List I

Criteria:

- codeine may cause serious adverse reactions in a part of the population (patients with a CYP2D6 ultra-rapid metabolism phenotype) due to direct danger, even when used correctly (*i.e.* according to the patient information).
- the group of persons at risk is not clearly identifiable (no preventive action or genetic test available).
- use of codeine might delay diagnosis of an underlying disease.
- potential for misuse/abuse.
- risk of adverse reactions (such as constipation) in a target population (the elderly).

No exemption from prescription-only status is proposed.

3.2 Paediatric use

Codeine-containing cough medications should not be recommended for young children, given that there is a lack of evidence proving effectiveness and that the use of OTC cough medications creates a potential risk for adverse reactions.

Codeine preparations should not be recommended for the treatment of cough in young children (WHO, 2001) and should be avoided in children under 1 year of age (Sweetman, 2005).

4. Legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions in Member States (October 2010):

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	I (1)					
A	I					
B	II + exemption	Oral Use		30 mg	120 mg	360 mg
BG	II + exemption	Oral Use		12.5 mg		
CH	II + exemption	Oral Use	Indications : anti-tussive.	15 mg		300 mg
CZ	I (1)					
D	I (1)					
E	II					
F	II + exemption	Oral Use	Syrup: exemption is other oral forms (List I). All other forms except syrup: delivery of only 1 pack at a time for presentations without prescription.	20 mg		300 mg
GB	II + exemption	Oral Use	In undivided preparations or single dose preparations. Advertising to public possible	20 mg		

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
			through all media.			
H	II + exemption	Oral Use	Only in combination in cough syrups, tablets, suppositories and effervescent tablets.			
IRL	II + exemption	Oral Use	Advertising to the public is prohibited.	20 mg		
LT	II					
MK	POM	Oral Use	Dry irritant and non-productive cough occurring as an accompanying symptom in respiratory pathway diseases (pharyngitis, pleuritis, influenza, cough of central origin).	30 mg	300 mg	
N	II					
NL	II + exemption	Oral Use	Public advertising allowed in all media.	1.5 %		
P	I					
PL	I (1) + exemption	Oral Use	In combination products only.	8 mg	64 mg	96 mg
RO	I (1)					
S	II					
SLO	II					

A public assessment report on 'Oral liquid cough medicines containing codeine' has recently been published on the MHRA website (October 2010).

5. References:

- Anon. (1991) The Harriet Lane Handbook, 12th edition. Mosby Year Book, St Louis, MO.
- Behrman, R.E., Kliegman, R.M., Jenson, H.B. (2004) Nelson's Textbook of Paediatrics. Saunders 17th Edition.
- Chang, A. (2005) Cough: are children really different to adults? *Cough*; 20(1): 7.
- Coenen, S., Van Royen, P., Van Poeck, K. (2004) Recommandations de Bonne Pratique, La Toux Aigue, Société Scientifique de Médecine Générale.
- DTB (1999) Cough medications in children. *Drugs and Therapeutics Bulletin*; 37:19-21.
- Gasche, Y., et al. (2004) Codeine intoxication associated with ultra-rapid CYP2D6 metabolism. *The New England Journal of Medicine*; 351, (27): 2827.
- Brunton, L. (1995) Goodman and Gilman's The Pharmacological Basis of Therapeutics. Ninth edition, Pergamon Press.
- Heiskanen, T.E., et al. (2000) Morphine or oxycodone in cancer pain?. *Acta Oncol.*, 39(8):941-947.
- Herbert, M.E. (2000) Medical Myth. Myth: Codeine is an effective cough suppressant for upper respiratory tract infections. *West J Med.*, 173, 283.
- Ingelman-Sundberg, M., Oscarson, M., McLellan, R.A: (1999) Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. *Trends Pharmacol Sci.*, 20(8):342-349.

- Koren, G., Cairns, J., Chitayat, D., Gaedigk, A., Leeder, S. (2006) Pharmacogenetics of morphine poisoning in a breastfed neonate of codeine-prescribed mother. *Lancet* 368: 704.
- Leinwand, D. (2006) DEA warns of soft drink-cough syrup mix. *USA Today*, Published 18th October, 2006.
- Sweetman, S. (2007) Martindale: The Complete Drug Reference (35th Edition). Pharmaceutical Press.
- Micromedex, Thomson Healthcare, 2007.
- Peters, R.J., Williams, M., Ross, M.W., Atkinson, J., Yacoubian, G. (2007) Codeine cough syrup use among African-American crack cocaine users. *Journal of Psychoactive Drugs* 39,(1), 97.
- Peters, R.J., Yacoubian, G., Rhodes, W., Forsythe, K., Bowers, K., Eulian, V., Mangum, C., O'Neal, J., Martin, Q., Essien, E. (2007) Beliefs and social norms about codeine and promethazine hydrochloride cough syrup (CPHCS) use and addiction among multi-ethnic college students. *Journal of Psychoactive Drugs* 39,(3), 277.
- Schroeder, K., Fahey, T. (2004) Over-the-counter medications for acute cough in children and adults in ambulatory settings. *The Cochrane Database of Systematic Reviews* 2004 (4), DOI:10.1002/14651858.CD001831.pub2.
- Schroeder, K., Fahey, T. (2002) Over the counter medications for acute cough in children and adults in ambulatory settings. The Cochrane Library. Issue 1. Oxford: Update Software; 2002.
- Smith, M.B.H., Feldman, W. (1993) Over-the-counter cold medications. A critical review of clinical trials between 1950 and 1991. *JAMA* 269:2258-63.
- U.S. FDA (2007) FDA warning on codeine use by nursing mothers. Published 17 August 2007.
- Von Mühlendahl, K.E. *et al.* (1976) Codeine intoxication in childhood. *Lancet* ii: 303-305.
- World Health Organization (2001) Cough and cold remedies for the treatment of acute respiratory infections in young children. Available online at: http://whqlibdoc.who.int/hq/2001/WHO_FCH_CAH_01.02.pdf.

Active ingredient: CROMOGLICIC ACID

ATC Code: R01AC01

Therapeutic indications:

Preventive treatment of seasonal and perennial allergic rhinitis.

Posology:

Adult: 1 actuation/nostril 3-6 times/day (1 puff 2.7 mg or 5.2 mg cromoglycate sodium).

Paediatric: 1 actuation/nostril 3-6 times/day (1 puff 2.7 mg cromoglycate sodium).

Duration of treatment:

Intra-nasal cromoglycate should be used before exposure to allergens and on a regular basis throughout the season or period of exposure normally associated with allergic symptoms. Treatment should not be ceased when symptoms disappear.

Pharmaceutical forms:

Nasal spray (2% or 4%)

Contraindications - relevant warnings:

Hypersensitivity to cromoglicic acid.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Sodium cromoglycate inhibits the release of mediators of the allergic reaction from sensitised mast cells. In the nose, the inhibition of mediator release prevents the symptoms of rhinitis. In general, cromoglycate sodium is well-tolerated by patients.

Adverse event are infrequent and minor. Occasional irritation of the nasal mucosa may occur during the first days of use. In rare cases, wheezing or tightness of the chest has been reported by patients.

1.1.1 Teratogenicity/Effects in Pregnancy/Breast-feeding

Animal reproduction studies have not demonstrated a foetal risk. There are no controlled studies in pregnant women or animal-reproduction studies that have shown adverse effects (other than a decrease in fertility) in women in the first or later trimesters.

When used as a nasal spray, cromoglycate presents a low risk to the developing foetus, and it is considered an alternative to oral anti-histamines.

It is not known whether sodium cromoglycate is excreted in human breast milk but, on the basis of its physico-chemical properties, this is considered unlikely. There is no information to suggest that the use of sodium cromoglycate has any undesirable effects on babies.

1.1.2 Elderly

Cutaneous therapies including sodium cromoglycate are all well-tolerated with minimal adverse effects.

Normal doses can be used in the elderly.

1.1.3 Recent cases in Europe

None

1.2. Indirect risks (incorrect use)

It is best to start using the spray about 1 week before contact with allergens. In order to maintain efficacy, the therapy should not be ceased before the allergy season ends.

2. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
B	OTC; N					
CZ	I					
RO	II					
Resolution ResAP(2007)1, annually revised appendices (recommendations)	II exemption +					
E	II exemption +					
LV	II exemption +					
N	II exemption +					
Publication	II exemption +					
A	List II exemption +					
CH	OTC					
D	OTC					
FIN	OTC					
GB	OTC					
H	OTC					
HR	OTC					
I	OTC					
IRL	OTC					
P	OTC					
PL	OTC; N					

2.1. The proposed classification:

List of classification: **OTC**

- Preventive treatment of seasonal and perennial allergic rhinitis (nasal application).

Rationale:

- Low direct or indirect risk, well-tolerated.
- In several countries, the prescription status is OTC without exemption.
- Safe for Paediatric use and in the elderly.
- No systemic adverse effects are expected, as the systemic absorption from cutaneous use is low.

2.2. Paediatric use

1 puff/nostril 3-6 times/day (1 puff 2.7 mg cromoglycate sodium).

3. References:

- Meltzer EO, NasalCrom Study Group (2002) Efficacy and patient satisfaction with cromolyn sodium nasal solution in the treatment of seasonal allergic rhinitis: a placebo-controlled study. *Clin Ther.*, Jun; 24(6):942-52.
- Mazzotta P, Loebstein R, Koren G. (1999) Treating allergic rhinitis in pregnancy. Safety considerations. *Drug Saf.*, Apr; 20(4):361-75.
- Tan R, Corren J. (1995) Optimum treatment of rhinitis in the elderly. *Drugs Aging*, Sep; 7(3):168-75.
- Sweetman, S. (2007) Martindale: The Complete Drug Reference (35th Edition). Pharmaceutical Press.
- Micromedex 2.0, Healthcare Series
- Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition

Active ingredient: **CYCLIZINE**

ATC Code: R06AE03
Anti-histamines for systemic use – Piperazine derivatives

Therapeutic indications:

- nausea and vomiting, including motion sickness.
- vertigo associated with Meniere's disease and other forms of vestibular disturbance.

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- 50 mg every 4 to 6 hours, as needed (im, iv, per os)

Paediatric:

- 6 to 10 years old: 3 mg/kilogram/day, divided in 3 doses (im)
- Children older than 12 years of age: 50 mg every 4 to 6 hours, not to exceed 200 mg/24 hours. To prevent motion sickness, cyclizine should be taken 30 minutes prior to departure (per os).
- Children 6 to 12 years old: 25 mg every 6 to 8 hours, not to exceed 75 mg/day. To prevent motion sickness, cyclizine should be taken 30 minutes prior to departure (per os).
- Children 6 to 10 years old: 3 mg/kilogram/day, divided in 3 doses may be given orally (per os).

Pharmaceutical forms: Tablets, solution for injections

Contraindications - relevant warnings:

a) Contraindications:

- Hypersensitivity to cyclizine.

b) Precautions:

- Asthma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing.
- Difficulty in urination due to enlarged prostate.
- Glaucoma.
- Obstructive disease of the gastrointestinal or genitourinary tract.
- Severe heart failure - cyclizine may decrease cardiac output and increase heart rate, pulmonary wedge pressure and mean arterial pressure.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Urticaria, drug rash, drowsiness, headache, dryness of the mouth, nose and throat, blurred vision, tachycardia, urinary retention, constipation, restlessness, nervousness, insomnia and auditory and visual hallucinations have been reported, particularly when dosage recommendations have been exceeded. Other CNS effects that have been recorded rarely include: dystonia, dyskinesia, extrapyramidal motor disturbances, tremor, twitching, muscle spasms, convulsions, disorientation, dizziness, decreased consciousness, transient speech disorders, hypertension and paraesthesia. Cholestatic jaundice has occurred in association with cyclizine. Rare reports of cholestatic hepatitis and hypersensitivity reactions, including anaphylaxis, angioedema, allergic skin reactions and bronchospasm, have been reported in association with cyclizine. There have also been a few reports of fixed drug eruption, apnoea, generalised chorea, hypersensitivity hepatitis, hepatic dysfunction and agranulocytosis.

1.2. Interactions

The drug may have additive effects with alcohol and other CNSdepressants, e.g. hypnotics and tranquillisers. Cyclizine enhances the soporific effect of pethidine and, because of its anti-cholinergic activity, cyclizine may compound the side-effects of other anti-cholinergic drugs.

1.2. Adverse reactions (ADRs)

- see under 1.1 Direct risks (Pharmacovigilance).

1.3. Indirect risks

There have been reports of abuse of cyclizine, either oral or intravenous, for its euphoric or hallucinatory effects. The concomitant misuse of cyclizine with large amounts of alcohol is particularly dangerous, since the antiemetic effect of cyclizine may increase the toxicity of alcohol.

Overdose: Peripheral anti-cholinergic symptoms include, dry mouth, nose and throat, blurred vision, tachycardia and urinary retention. CNS effects include drowsiness, dizziness, lack of coordination, ataxia, weakness, hyper-excitability, disorientation, impaired judgement, hallucinations, hyperkinesia, extrapyramidal motor disturbances, convulsions, hyperpyrexia and respiratory depression.

2. Discussion

Cyclizine is a piperazine derivative with properties of anti-histamines. Cyclizine is useful in treating motion sickness in cases where the exposure to motion is mild, e.g. automobile or airplane travel. The precise mechanism of action in inhibiting the symptoms of motion sickness is not known. It may directly affect the labyrinthine apparatus and have central actions on the chemo-receptor trigger zone. Cyclizine exerts a central anti-cholinergic action.

It is not suitable for situations in which more severe types of motion are expected. Cyclizine has also been used to treat nausea and vomiting caused by medications or surgery - being much more beneficial when administered intra-muscularly.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II + exemption	Oral Use, Parenteral use				
Publication	II + exemption	Oral Use, Parenteral use				
CZ			Not marketed			
F			Not marketed			
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LV			Not marketed			
MK			Not marketed			
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

CYCLIZYNE, anti-histamines for systemic use – piperazine derivatives, Oral administration

No recommendation has been made because the drug is not marketed in the Member States from which data was available.

3.2. Paediatric use

Not for children under 6 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/37A968/DUPLICATIONSHIELDSYNC/80B0B0/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/ISLDpZ2QDN8MI/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/1143/ContentSetId/31/SearchTerm/cyclizine%20/SearchOption/BeginWith#secN10B23
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: CYPROHEPTADINE

ATC Code: R06AX02
Anti-histamines for systemic use – Other anti-histamines for systemic use.

Therapeutic indications:

- perennial rhinitis
- seasonal allergic rhinitis
- urticaria, food allergies
- drug and serum reactions
- insect bites, migraine
- vascular headache in adults and children over 2 years of age
- anorexia nervosa (MICROMEDEX)

Posology/duration of treatment:

- oral

MICROMEDEX Dosing Information

Adult:

- Initially, 4 mg orally three times daily, then adjust dose according to the size and response of patient (range: 4 to 20 mg daily); maximum dose is 0.5 mg/kg/day.

Paediatric:

- 2 mg orally, two to three times daily; maximum dose is 12 mg/day (2-6 years).
- 4 mg orally, two to three times daily; maximum dose is 16 mg/day (7-14 years).

Pharmaceutical forms: Tablets and syrup

Contraindications - relevant warnings:

a) Contraindications:

- hypersensitivity to the active substance or to any of the excipients.
- patients undergoing therapy for an acute asthmatic attack.
- newborn or premature infants.
- breast-feeding mothers.
- patients with known sensitivity to ciproheptadine hydrochloride or drugs with similar chemical structure.
- concurrent use with monoamine oxidase inhibitors.
- glaucoma.
- patients with pyloroduodenal obstruction, stenosing peptic ulcer, symptomatic prostatic hypertrophy, predisposition to urinary retention or bladder neck obstruction.
- elderly, debilitated patients.

b) Precautions:

- It should be used cautiously in patients with a history of:
 - bronchial asthma.
 - increased intra-ocular pressure.
 - hyperthyroidism,
 - cardiovascular disease.
 - hypertension.
- Rarely, prolonged therapy with anti-histamines may cause blood dyscrasias.
- Avoid use with alcohol and other CNS depressants.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Increased appetite and weight gain are common side-effects of cyproheptadine in adults, children, and in the elderly. The mechanism involved remains obscure.

1.2. Interactions with (MICROMEDEX):

- Belladonna, Belladonna Alkaloids, Procarbazine (theoretical)
- Clorgyline, Fluoxetine, Iproniazid, Isocarboxazid, Moclobemide, Nialamide, Pargyline, Paroxetine, Phenelzine, Procarbazine, Protirelin, Selegiline, Toloxatone, Tranylcypromine (probably clinical relevant)

1.3. Adverse reactions (ADRs)

- hypotension.
- palpitations.
- tachycardia.
- arrhythmias.
- hepatitis, followed by prolonged cholestasis.
- acute central anti-cholinergic syndrome.
- thickening of bronchial secretions.
- tightness of the chest.
- wheezing.

1.3.1. Recent case reports (UMC database)

In the period from the 1st of January 2005 up to the 7th of February 2009, the Uppsala Monitoring Centre received 103 reports on cyproheptadine with 371 ADRs. Reports came from Australia, Canada, Chile, Cuba, **Germany, France, United Kingdom**, Indonesia, Iran, **Italy**, Japan, Nepal, **Portugal**, Thailand, Uganda and the USA. The majority (more than 90%) of all cases came from the USA. The most common ADR was somnolence (19 cases), followed by insomnia and nausea (11 cases). Six cases of medication errors and two cases of drug toxicity were also received. All other ADRs are represented by 1 or 2 cases.

2. Discussion

The main therapeutic area of this drug is the symptomatic control of allergic conditions, in particular allergic rhinitis and cutaneous allergic conditions. The profile of the drug is safe; but there is a small potential for misuse of the drug as a way to increase appetite. This anti-histamine has the specific ADR of weight gain, and thus may be used in some off-label indications to improve the appetite of children or as an additional therapy in anorexia nervosa. The most common ADR is somnolence, especially in children and, in combination with anti-depressives, benzodiazepines and anti-psychotics, in adults and the elderly. Caution is required in cases where the patients take additional medicinal products like anti-depressives, benzodiazepines and anti-psychotics, and also in cases where patients drink alcohol.

There is a wide range of prescription statuses for the drug among Member States: from List I (1) in the Czech Republic to OTC in Belgium, Denmark, Germany and Great Britain. Most Member States classify the drug prescription status as List II.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II + exemption	Oral use		8 mg		
Publication	II + exemption	Oral use		8 mg		
A	II	Oral use		4 mg	32 mg	
B	OTC	Oral use				
BG	II	Oral use				
CH	II	Oral use				
CZ	I (1)	Oral use	Indications: allergy, carcinoid, migraine, anorexia, cachexy.	4 mg	12 mg	80 mg
D	II	Oral use				
DK	OTC	Oral use				
E	II	Oral use				
F	OTC	Oral use	Indications: rhinitis, conjunctivitis, hives For adults and children > 6 years, because in tablet-only form.			
GB	OTC	Oral use				
H	POM	Oral use	Indications: acute and chronic urticaria, angioneurotic oedema, drug-caused exanthema, pruritus, eczema, contact dermatitis, neurodermatitis, allergic rhinitis, vascular type headaches. Warnings: hepatic or renal impairment requires dosage-modification. Caution with bronchial asthma, increased intra-ocular pressure, hyperthyreosis, cardiovascular diseases, and hypertension. Alcohol intake forbidden. MDD (2-6 years)=12mg; (7-14 years)=16 mg; (>14 years)= 32mg.	4 mg / 0.4 ml	32 mg	
HR			Not marketed			
I	II	Oral use		4 mg / 0.4 ml	12 mg / 30 ml	
IRL	II	Oral use				
LV	II + exemption	Oral use	Indications: allergy symptoms; itching, seasonal allergic rhinitis, sneezing, erythema, urticaria. Warnings: Not to be used in patients with allergic reaction to clemastine, should be used with caution in patients with glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, bladder neck obstruction.	1 mg	6 mg	20 mg
NL	II	Oral use				
MK			Not marketed			
P	II	Oral use				
RO	II	Oral use	Indications: symptomatic treatment of perennial rhinitis, seasonal allergic rhinitis and urticaria,	4 mg /	20 mg	120 mg/ 40

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
			food allergies, drug and serum reactions, insect bites, migraine and vascular headaches in adults and children > 2 years of age. Warnings: to be used cautiously in patients with a history of bronchial asthma, increased intra-ocular pressure, hyperthyroidism, cardiovascular disease, or hypertension. Rarely, prolonged therapy with anti-histamines may cause blood dyscrasias. MS tablet, syrup.	2mg		mg
S	II	Oral use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

CYPROHEPTADINE, anti-histamines for systemic use – Other anti-histamines for systemic use;
Oral administration.

List II + exemption

Criteria:

- Cyproheptadine is an OTC drug or the prescription status is List II or List II + exemption in most Member States.
- Recommendation for OTC prescription status:
 - o Indication: allergic rhinitis or conjunctivitis.
 - o MS corresponds to 4 mg, MDD corresponds to 12 mg, MQP corresponds to 80 mg.
 - o only short-term use for seasonal allergic rhinitis, conjunctivitis.
 - o only for children > 14 years because of the dosage.

3.2. Paediatric use

Not recommended in children less than 2 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/E1A57B/DUPLICATIONSHIELDSYNC/23357F/ND_PG/PRIH/ND_B/HCS/SBK/1/ND_P/Main/PFPUI/Ln1apYu2PQuajs/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2433/ContentSetId/31/SearchTerm/CYPROHEPTADIN/SearchOption/BeginWith#secN10617
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: DESLORATADINE
Synonyms: Descarboethoxyloratadine

ATC Code: R06AX27
Anti-histamines for systemic use – Other anti-histamines for systemic use.

Therapeutic indications:

Chronic idiopathic urticaria, perennial allergic rhinitis, seasonal allergic rhinitis.

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- 5 mg orally, once daily.

Paediatric:

- 12 years and over: 5 mg orally, once daily.
- 6 to 11 years: 5 ml (2.5 mg) of syrup orally, once daily.
- 12 month to 5 years: 2.5 ml (1.25 mg) of syrup orally, once daily.
- 6 to 11 months: 2 ml (1 mg) of syrup orally, once daily.

Pharmaceutical forms: Tablets, syrup

Contraindications - relevant warnings:

a) Contraindications:

- Hypersensitivity to desloratadine or loratadine.

b) Precautions:

- Liver dysfunction. Desloratadine is metabolised in the liver; thus, there is a potential for enhanced toxicity and the need for dose adjustment, Pharmacokinetic data are unavailable.
- Phenylketonuric patients. Orally-disintegrating tablets contain 1.75 mg phenylalanine per tablet.
- Dose adjustment is recommended for patients presenting with renal impairment.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

FDA (USA) Pregnancy Category C.

- **Cardiovascular Effects**

During the marketing of desloratadine, there have been reports of tachycardia. Loratadine, from which desloratadine is derived, has occasionally been associated with supra-ventricular and ventricular arrhythmias, although these reports have been heavily criticised, as no clear causal relationship has yet been established. No similar cases have been reported with desloratadine from available studies.

- **Gastrointestinal Effects**

In clinical trials, patients who received desloratadine (5 mg/day; n 659) reported pharyngitis (5%), dry mouth (4%), and dry throat (2%) compared with incidences of 2%, 2%, and 1%, respectively, for patients who received placebos. Gastrointestinal symptoms (e.g. nausea, dyspepsia) have occurred infrequently.

- **Hepatic Effects**

During the marketing of desloratadine, there were rare reports of elevated liver enzymes, including elevated bilirubin.

- **Immunologic Effects**

During the marketing of desloratadine, there were rare reports of hypersensitivity reactions such as rash, pruritus, urticaria, oedema, dyspnoea, and anaphylaxis.

- **Musculo-skeletal Effects**

In clinical trials, myalgia was reported in 2% of patients who received desloratadine (5 mg/day) compared to less than 1% of patients who received a placebo.

- **Neurologic Effects**

In clinical trials, dizziness was reported in 2% of patients who received desloratadine (5 mg/day) compared to 1% of patients who received a placebo. Headache has been the most frequently reported adverse effect, although the incidence has often been similar with that of placebos. Headache was described by 16-24% of patients following treatment with desloratadine (5 or 7.5 mg daily) and by 14-22% of placebo-treated patients. However, none of these studies has been published in full form, precluding adequate evaluation of adverse effect data.

- **Impaired cognition**

A double-blind, placebo-controlled, cross-over study demonstrated that desloratadine did not have any adverse effects on psychomotor performance, daytime sleep latencies and subjective sleepiness. Each patient (n 9) was tested during three test sessions. At each session, subjects were given a dose of desloratadine (5 mg (mg)), promethazine (25 mg) or a placebo. Performance was assessed using seven different tasks developed to study memory, tracking, sustained attention, digit substitution and reaction time. Patients also underwent a multiple sleep latency test and their moods were assessed with visual analog scales, the multiple Stanford Sleepiness Scale and the Samn-Perelli fatigue rating. Compared with placebos, desloratadine did not demonstrate any differences in tracking, reaction time, attention, digit symbol substitution or memory. Subjective ratings of sleepiness and fatigue with desloratadine were also similar to placebos.

- **Sedation**

In clinical trials, somnolence and fatigue were reported in 3% of patients who received desloratadine (5 mg/day; n 659) and in 2% of patients who received placebos.

The sedation associated with desloratadine is comparable to that of placebos in tests of wakefulness, such as the Stanford Sleepiness Scale, the Digital Symbol Substitution Test, the Psychomotor Vigilance Test, and the Serial Add Subtract Reaction Time test.

In one study, the frequency of somnolence was similar between desloratadine (5 or 7.5 mg daily) (2-4%) and placebos (2%).

- **Influenza-like symptoms**

In clinical trials, influenza-like symptoms were reported in 2% of patients who received desloratadine (5 mg/day; n 659) and 1% of patients who received placebos (n 651).

1.2. Interactions

No clinical data.

1.3. Adverse reactions (ADRs)

- see under 1.1 Direct risks (Pharmacovigilance).

1.3.1. Recent case reports (UMC database)

In the period from 1 January 2005 to 7 February 2009 the Uppsala Monitoring Centre received 721 reports on desloratadine with 1,528 ADRs. Reports came from Australia, **Austria, Bulgaria, Canada, Chile, Columbia, Germany, Denmark, Spain, Finland, France, United Kingdom, Greece, Croatia, Hungary**, India, **Ireland, Iceland, Italy**, Morocco, Mexico, **the Netherlands, Norway**, New Zealand, Peru, **Portugal, Sweden**, Tunisia, **Turkey**, the USA, Venezuela and South Africa. The most frequently reported ADRs in SOC *Cardiac disorders* are tachycardia (16 cases) and palpitations (25 cases). Dry mouth (22 cases) is the most commonly reported ADR in SOC *Gastrointestinal disorders*, along with nausea and diarrhea. There were 17 reports of misuse and medication error. In the SOC *Nervous system disorders*, headache was the principle ADR (59 cases), followed by dizziness (50 cases) and somnolence (28 cases) and a few cases each of loss of consciousness, syncopae, and lethargy.

The combination database of the UMC ADR database indicates a slight risk for cleft palate in newborns.

2. Discussion

The main therapeutic area is the treatment of chronic idiopathic urticaria and allergic rhinitis. Desloratadine is relatively new on the market, as is loratadine. Like all other anti-histamines, the profile of ADRs is similar in terms of CNS depression and gastrointestinal disturbance. The cardiovascular profile of the drug so far seems safe and no cases of QT interval prolongation have been reported.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	POM	Oral Use				
A	II	Oral Use				
CZ	I (1)	Oral Use				
F	II	Oral Use				
H	II	Oral use				
HR	POM	Oral use				
I	II	Oral use		5 mg	5 mg	
LV	II	Oral use				
MK			Not marketed			
RO	II	Oral Use				
SLO	I	Oral use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

DESLORATADINE, anti-histamines for systemic use – other anti-histamines for systemic use, Oral administration.

List II

Criteria:

- desloratadine is new on the market.
- the prescription status is List II in the majority of Member States.

3.2. Paediatric use

- safety and effectiveness have not been established in children less than 6 month of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/563D81/DUPLICATIO NSHIELDSYNC/BFC630/ND_PG/PRIH/ND_B/HCS/SBK/3/ND_P/Main/PFPUI/fX129jh2Q83ck9/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2145/ContentSetId/31/Search Term/desloratadine%20/SearchOption/BeginWith#secN108B5
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: **DEXBROMPHENIRAMINE (classification proposal adopted at 46th meeting)**

ATC Code: R06AB06
Anti-histamines for systemic use – Substituted alkylamines

Therapeutic indications:

- allergic rhinitis
- common cold

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- 3 to 12 mg (1 tablet) every 12 hours.

Paediatric:

- Not for children under 12 years of age.

Pharmaceutical forms: Tablets

Contraindications - relevant warnings:

a) Contraindications:

- Hypersensitivity to dexbrompheniramine.

b) Precautions:

- Alcohol produces an additive effect that impairs motor skills.
- Cardiovascular disease such as heart disease and high blood pressure.
- Endocrine abnormalities such as diabetes or thyroid disease.
- Enlarged prostate gland.
- Patients with breathing difficulties (emphysema or chronic bronchitis).
- Patients with glaucoma.
- Use caution with concomitant use of dexbrompheniramine and pseudoephedrine, monoamine oxidase inhibitors or anti-hypertensives.

1. List of direct/indirect risks (safety profile)

1.1 . Direct risks (Pharmacovigilance)

Appearance of a bright erythematous, maculopapular rash on the trunk and proximal extremities within 12 hours of ingesting a tablet containing 6 mg dexbrompheniramine and 120 mg pseudoephedrine has been reported.

Anti-histamine/decongestant therapy may cause symptoms of dry mouth during treatment. Drowsiness is the most common adverse effect with dexbrompheniramine. Dizziness has also been reported during treatment. Excitability, especially in children, may occur. Nervousness and insomnia may occur if the recommended dosage is exceeded. Severe fatigue persisting for 10 days has been reported with dexbrompheniramine. Oral and facial dyskinesias, associated with short-term use of dexbrompheniramine/pseudoephedrine, has been reported. This may represent an acute dystonic reaction to the anti-histamine.

1.2. Interactions with:

Theoretically with Procarbazine, (CNS depression). (MICROMEDEX).

1.3. Adverse reactions (ADRs)

- see under 1.1 Direct risks (Pharmacovigilance).

2. Discussion

Dexbrompheniramine, the dextrorotatory isomer of bropheniramine, is a propylamine-derivative anti-histamine. It suppresses symptoms attributable to histamine release due to the antigen-antibody reaction. Dexbrompheniramine relieves rhinorrhoea, sneezing, and itching of the nose, throat, and eyes.

Dexbrompheniramine is mostly administered in fixed-combination with pseudoephedrine or other decongestants for relief of symptoms associated with allergic conditions (e.g. seasonal allergic rhinitis) or the common cold in the upper respiratory tract. The anti-cholinergic effects of the anti-histamine may be counter-productive in respiratory conditions characterised by congestion. No ADR reports have been received by the UMC database from 2005.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
B	OTC	Oral use				
CH	OTC	Oral Use				
CZ	II	Oral Use	Not marketed from 2008.			
D	OTC	Oral Use				
E	OTC	Oral Use				
F			Not marketed			
FIN	II	Oral Use				
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LV			Not marketed			
MK			Not marketed			
P	OTC	Oral Use				
RO			Not marketed			
S	II	Oral Use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

DEXBROMPHENIRAMINE, anti-histamines for systemic use – Substituted alkylamines, Oral administration.

List OTC

Criteria:

- short-term treatment of allergic rhinitis.

3.2. Paediatric use

Not for children under 12 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/8ED8AA/DUPLICATIONSHIELDSYNC/8E99FA/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/UI1aphB2QE51MR/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/1125/ContentSetId/31/SearchTerm/Dexbrompheniramine%20/SearchOption/BeginWith#secN103E7
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: DIMETINDENE Alkylamine derivative

Synonyms: Dimethindene

ATC Code: D04AA13 - [Anti-histamines for cutaneous use.](#)

Therapeutic indications:

Cutaneous

For pruritus due to skin disorders such as eczema, urticaria, insect bites, sunburn or first degree burns.

Posology/ duration of treatment:

The 0.1% gel should be applied thinly to the affected skin and massaged in gently, several times daily.

Pharmaceutical forms:

0.1% cutaneous gel.

Contraindications

- hypersensitivity to dimetindene.
- hypersensitivity to parabens (contained in the cutaneous gel).

Relevant warnings:

General: Cutaneous preparations containing anti-histamines should not be used on broken or eczematous skin.

- If dressings or bandages are used, they should not be occlusive.
- Do not use the gel on large areas or broken or inflamed skin, especially in infants or toddlers.
-

1. List of direct/ indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

- skin irritation
- skin burning
- there is a risk of sensitisation

1.1.1 Recent cases in Europe

In the period from 01 January 2007 to 22 February 2010, the Uppsala Monitoring Center received 16 reports on dimetindene, with a total of 63 ADRs. Route of administration: topical

2. Discussion

The 0.1% cutaneous gel is used for itching due to eczema, urticaria, insect bites, sunburn, and first degree burns.

The safety profile indicates safety.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	OTC see	cutaneous	Cutaneous use			
A	List II + exemption	Cutaneous	Cutaneous use			
BG	OTC see	Cutaneous	Cutaneous use			
CH	OTC see	Cutaneous	Cutaneous use			
CZ	OTC see	Cutaneous	Cutaneous use			
E	OTC see	Cutaneous	Cutaneous use			
H	OTC see	Cutaneous	Cutaneous use			
HR	List I	Cutaneous	Cutaneous use			
I	OTC see	Cutaneous	Cutaneous use			
LT	OTC see	Cutaneous	Cutaneous use			
LV	OTC see	Cutaneous	Cutaneous use			
P	OTC see	Cutaneous	Cutaneous use			
PL	OTC see	Cutaneous	Cutaneous use			
SLO	OTC see	Cutaneous	Cutaneous use			
UK			Not marketed			

No data available from other Member States

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

DIMETINDENE, Anti-histamines for cutaneous use, anti-pruritics, anaesthetics.

List OTC

- Safe profile.
- For pruritus due to skin disorders such as eczema, urticaria, insect bites, sunburn, or first degree burns.

3.2. Paediatric use

Caution in neonates and young children aged < 12 months – do not use the gel on large areas or on broken or inflamed skin.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/609334/DUP...
- Sweetman, S. (2007) Martindale: The Complete Drug Reference (35th Edition). Pharmaceutical Press.
- <http://emc.medicines.org.uk/>
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)

Active ingredient: DIMETHINDENE (classification proposal adopted at 46th meeting)
Synonyms: Dimetindene
ATC Code: R06AB03
Anti-histamines for systemic use – substituted alkylamines
D04AA13
Anti-pruritics, including anti-histamines, anesthetics, etc.-Anti-histamines for cutaneous use

Therapeutic indications:

- treatment of itching due to urticaria, dermatitis, eczema, diabetes, liver disease, leukaemia, lymphogranulomatosis, insect bites, allergies and hay fever.

Indications in Romania: allergic rhinitis, including hay fever and perennial rhinitis, vasomotor rhinitis and allergic dermatoses (including pruritus in atopic eczema and contact dermatitis).

Indications in the Czech Republic: allergic rhinitis and urticaria.

Posology/duration of treatment: oral, local (topical)

MICROMEDEX Dosing Information

Adult:

- **Oral route**
 - DROPS
 - 1 to 2 mg (20 to 40 drops of a 1 mg/ml solution), three times daily.
 - IMMEDIATE RELEASE TABLET
 - 1 to 2 mg, three times daily.
 - SUSTAINED-RELEASE TABLET
 - 2.5 mg, twice daily (in the morning and evening).
 - SYRUP
- 5 ml 0.123 mg/ml syrup, up to 9 times daily. **Parenteral route**
 - 4 mg (4 ml) intravenously, once or twice daily. The maximum recommended length of therapy is 7 days.
 - For pre-medication with H₂-receptor antagonists before general anesthesia, parenteral contrast agents or plasma substitutes, the recommended dose is 1 mg (1 ml) per 10 kilograms of body weight, by slow intravenous injection (2 ml/minute).
- **Cutaneous application route**
 - For pruritus arising from skin disorders such as eczema, urticaria, insect bites, sunburn, or first degree burns, the 0.1% gel should be applied thinly to the affected skin and massaged in gently, several times daily. If dressings or bandages are used, they should not be occlusive. Gel should not be used on large areas or on broken or inflamed skin, especially in infants, toddlers or pregnant women. Nursing mothers should not apply the gel to the nipples.

Paediatric:

- **Oral route**
 - DROPS
 - The usual dose for infants is 0.25 mg (or 5 drops of a 1 mg/ml solution), three times daily. Dimethindene is contraindicated in infants aged under one month old and should be used cautiously in infants aged under one year, due to an increased risk of sleep apnea.
 - The recommended dose for children aged 1 to 8 years old is 0.5 to 0.75 mg (or 10 to 15 drops of a 1 mg/ml solution), three times daily.
 - The recommended dose for children aged 9 years and older is 1 mg (20 drops of a 1 mg/ml solution), three times daily.
 - IMMEDIATE RELEASE TABLETS
 - The recommended dose for children aged 3 years and older is 1 mg (1 tablet), three times daily.
 - SUSTAINED-RELEASE TABLETS
 - The recommended dose for children aged 6 years and older is 2.5 mg (1 sustained-release tablet), twice daily (in the morning and evening).
 - SYRUP
 - The recommended dose for children aged 1 to 8 years is 5 ml of a 0.123 mg/ml syrup, up to three times daily.
 - The recommended dose for children aged 9 years and older is 7.5 ml of a 0.123 mg/ml syrup, up to three times daily.
- **Cutaneous application route**
 - For pruritus arising from skin disorders such as eczema, urticaria, insect bites, sunburn, or first degree burns, the 0.1% gel should be applied thinly to the affected skin and massaged in gently, several times daily. If dressings or bandages are used, they should not be occlusive. Do not use the gel on large areas or on broken or inflamed skin, especially in infants or toddlers.

Pharmaceutical forms: Tablets, drops, syrup, gel

Contraindications - relevant warnings:

a) Contraindications:

- Hypersensitivity
- Premature infants and neonates
- Lactation
- Prostate hypertrophy
- Bladder obstruction
- Hypersensitivity to parabens (contained in the cutaneous gel, oral drops and oral syrup)
- Cardiac arrhythmias
- Alcohol abuse

b) Precautions:

- Peptic ulcer
- Pyloroduodenal obstruction
- Cardiovascular disease
- Severe hypertension
- Hyperthyroidism
- Narrow-angle glaucoma
- Asthma

1. List of direct/indirect risks (safety profile)

1.1 . Direct risks (Pharmacovigilance)

- **Cardiovascular Effects**

Dimethindene may cause palpitations.

- **Dermatologic Effects**

Rare cases of rash, peri-orbital and facial oedema, increased itching, and morbilliform eruption have been reported after oral administration of dimethindene.

- **Gastrointestinal Effects**

Dimethindene may cause nausea, gastralgia, anorexia, diarrhoea or dry mouth. Taste changes have been reported after iv injection.

- **Immunologic Effects**

Individual cases of hypersensitivity reactions, mostly of an anaphylactoid nature, have been reported with dimethindene. Dimethindene is associated with a relatively high risk of skin sensitisation, leading to contact dermatitis or eczematous eruptions.

- **Musculoskeletal Effects**

Intravenous dimethindene has been associated with muscle tremors.

- **Neurologic Effects**

Dimethindene may cause paradoxical excitement in children, drowsiness, impaired reaction time, vertigo, headache, and nervousness. Tolerance develops to the sedative effects of dimethindene within one or two days. Iv. Injections may produce feelings of warmth or chills.

- **Ophthalmic Effects**

Blurred vision.

- **Respiratory Effects**

Rarely, dry nose and shortness of breath have been reported after dimethindene administration.

1.2. Interactions with:

- **Procarbazine and ethanol**

- Interaction Effect: CNS depression

To minimise CNS depression and possible synergistic effects, caution should be exercised when co-administering procarbazine and anti-histamines. The severity of the interaction is assessed as moderate, but the substantiation of the interaction is theoretical, and the probable mechanism is unknown.

1.3. Adverse reactions (ADRs)

- see under 1.1 Direct risks (Pharmacovigilance).

1.3.1. Recent case reports (UMC database)

In the period from 1 January 2005 to 7 February 2009, the Uppsala Monitoring Centre received 50 reports on dimethindene with 180 ADRs. Reports came from **Austria, Switzerland, Germany, Italy, Ukraine** and the USA. There were four reports each of dizziness, pyrexia and dyspnea, two cases of somnolence, one case of coma and one case of 'torsades de points'.

The combination database of the UMC ADR database shows a slight risk for contact dermatitis and fatigue.

2. Discussion

The main therapeutic area of this drug is the treatment of itching due to urticaria, dermatitis, eczema, diabetes, liver disease, leukemia, lymphogranulomatosis, insect bites, allergies and hay fever.

The safety profile is safe, which means that there have been no serious ADRs reported within the last three years in Europe. However, as with other anti-histamines, the co-administration of oral or parenteral dimethindene formulations with other CNS depressants may cause somnolence and other CNS ADR symptoms.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	I + exemption	Oral Use				
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	OTC	Cutaneous use				
Publication	OTC	Oral Use				
Publication	OTC	Cutaneous use				
A	II	Oral Use				
A	OTC	Cutaneous use				
B	OTC	Oral Use				
CH	II + exemption	Oral Use				
CH	OTC	Cutaneous use				
CZ	I + exemption	Oral Use	Indications: allergic rhinitis, urticaria. Warnings: only for adults and children > 12 years.	4 mg	4 mg	40 mg
		Nasal Use	Indications: allergic rhinitis. Warning: only for adults and children > 6 years.	0.1 %	0.78 mg	15 mg
CZ	OTC	Cutaneous use				
D	OTC	Oral Use				
E	II + exemption	Oral use	Allergy relief for children.	1 mg	2.5 mg	
E	OTC	Cutaneous use				
F			Not marketed			
H	POM	Oral Use				
H	OTC	Cutaneous use				
HR	I	Oral Use				

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
HR	OTC	Cutaneous use	Apply to skin 2-4 times a day.			30 g
I	OTC	Oral Use				
I	OTC	Cutaneous use				
LT	OTC	Oral Use				
LT	OTC	Cutaneous use				
LV	OTC	Oral Use	Indication: allergy symptoms, itching, seasonal, allergic rhinitis, erythema. Warnings: hypersensitivity to the substance, post-natally. Use under doctor supervisions in children aged < 1 year. Use with caution in patients with glaucoma, prostatic hypertrophy, balder neck obstruction. 0,1mg/kg in children aged < 12 years.	1 mg	6 mg	20 mg
LV	OTC	Cutaneous use				
N	II	Oral Use				
NL	II	Oral Use				
MK			Not marketed			
P	OTC	Oral Use				
P	OTC	Cutaneous use				
RO	OTC	Oral Use	Indication: allergic rhinitis, including hay fever and perennia rhinitis, vasomotor rhinitis, allergic dermatoses (including pruritus in atopic eczema and contact dermatitis). Angioneurotic oedema, drug allergies. MS=1mg/ml, MDD=3-6 mg (adults and adolescents aged over 12 years); 3 mg (children aged between 3-12 years); 1.5-2.5 mg (children aged 1-3 years); 1.5 mg (children aged < 1 year). Warnings: narrow-angle glaucoma, prostatic hypertrophy with urinary retention & bladder neck obstruction.	1 mg	6 mg	50 mg
SLO	OTC	Oral Use				
SLO	OTC	Cutaneous use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

DIMETHINDENE, anti-histamines for systemic use – substituted alkylamines, Oral administration.

List II + exemption

Criteria:

- safe profile, but caution in patients with narrow-angle glaucoma and prostatic hypertrophy.
- only OTC prescription status for the indications of allergic rhinitis and urticaria.
- only for adults and children aged > 12 years.
- MS is 4 mg
- MDD is 4 mg
- MQP is 40 mg

DIMETHINDENE, Anti-pruritics, including anti-histamines, anesthetics, *etc.* - Anti-histamines for cutaneous use.

3.2. Paediatric use

- Caution required for use in children aged less than 12 month.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/A15EC0/DUPLICATIONSHIELDSYNC/3E3A9F/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/4D1exVj2QcLsaY/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/1560/ContentSetId/31/SearchTerm/Dimethindene%20/SearchOption/BeginWith#secN1062F
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: DIPHENHYDRAMINE, a mono-ethanolamine derivative.

Synonyms: Benzhydramine

ATC Code: D04AA32 [Anti-histamines for cutaneous use.](#)

Therapeutic indications: skin pruritus

Posology/ duration of treatment:

Skin pruritus: apply to affected area not more than 3 to 4 times daily.

Pharmaceutical forms:

Cream: 2%; gel: 2%; solutions: 0.5 and 2%.

Contraindications:

– Hypersensitivity to diphenhydramine.

Relevant warnings:

General: Cutaneous preparations containing anti-histamines should not be used on broken or eczematous skin.

- Avoid contact with the eyes (patients should not use cutaneous form on eyes or eyelid).
- Should not be applied to raw or broken surfaces or mucous membranes as this may result in percutaneous absorption giving rise to systemic effects (the cutaneous form should not be used on patients with chicken pox, measles, blisters, or large areas of skin, unless directed by a physician).
- If a burning sensation or rash develops or if the condition persists, treatment should be discontinued. If necessary, remove by washing with soap and water.
- Patients should be instructed to avoid applying occlusive dressings, cosmetics, or other skin products over areas treated with the cutaneous formulation.

1. List of direct/indirect risks (safety profile)

1.1 . Direct risks (Pharmacovigilance)

Rarely, sensitivity, eczematous reactions and photo-sensitivity have been reported after cutaneous application of anti-histamines. If this occurs, treatment should be discontinued.

1.1.1 Recent cases in Europe

During 1 January 2007 to 22 February 2010, the Uppsala Monitoring Center received 97 reports on diphenhydramine, with 320 ADRs (Route of administration: topical, consisting of single reports directly concerning skin sensations).

1.2. Indirect risks (incorrect use)

Accidental ingestion or excessive absorption may lead to dose-related signs of diphenhydramine toxicity. These include drowsiness and sedation, with anti-cholinergic symptoms prevailing.

2. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised Appendices (recommendations)	OTC see	cutaneous	Cutaneous use			
A	OTC see	cutaneous	Cutaneous use			
B	OTC					
BG	OTC see	cutaneous	Cutaneous use			
CZ	OTC see	cutaneous	Cutaneous use; not for children aged less than 6 months			
E	OTC see	cutaneous	Cutaneous use			
F	OTC see	cutaneous	Cutaneous use			
FIN	OTC see	cutaneous	Cutaneous use			
GB			Currently not marketed			
H	OTC see	cutaneous	Cutaneous use			
HR			Not marketed			
I	OTC see	cutaneous	Cutaneous use			
LV	OTC see	cutaneous	Cutaneous use			
P	OTC					
PL			Not marketed			

No data available from other Member States.

2.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

DIPHENHYDRAMINE - anti-histamines for cutaneous use, local anesthetic (anti-pruritic).

List OTC

Criteria:

- safe profile.
- for pruritic skin disorders such as urticaria, eczema, *etc.*

Not for children aged under 2 years (see also patient information leaflet: Benadryl®).

3. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/609334/DUP...
- Sweetman, S. (2007) Martindale: The Complete Drug Reference (35th Edition). Pharmaceutical Press.
- Drugs@FDA
- <http://emc.medicines.org.uk/>
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)

Active ingredient: DIPHENYLPYRALINE

ATC Code: R06AA07
Anti-histamines for systemic use – Aminoalkyl ethers

Therapeutic indications:

- allergic rhinitis
- pruritic skin disorders

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- 6 mg daily, in 3 or 4 divided doses.
-

Pharmaceutical forms: Tablets, nasal solution

Contraindications - relevant warnings:

a) Contraindications:

- Hypersensitivity to diphenylpyraline.

b) Precautions:

- Concomitant administration of narcotics or barbiturates.
- Children with a history of sleep apnea.
- Family histories of sudden infant death syndrome.
- Liver dysfunction.
- Patients with possible intestinal obstruction.
- Patients with narrow-angle glaucoma.
- Patients with prostatic hypertrophy or bladder neck obstruction.
- Patients with stenosing peptic ulcer or pyloroduodenal obstruction.
- Use of CNS depressants, including alcohol.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

The most common adverse effect of sedating anti-histamines is CNS depression, with effects varying from slight drowsiness to deep sleep, and including lassitude, dizziness, and lack of coordination (although paradoxical stimulation may occasionally occur, especially at high doses and in children or the elderly). These sedative effects, when they occur, may diminish after a few days of treatment. Other adverse effects that are more common with sedating anti-histamines include headache, psychomotor impairment and anti-muscarinic effects, such as dry mouth, thickened respiratory-tract secretions, blurred vision, urinary difficulty or retention, constipation and increased gastric reflux. Occasional gastrointestinal adverse effects of anti-histamines include nausea, vomiting, diarrhoea, or epigastric pain.

1.2. Interactions with:

No data available. (MICROMEDEX)

1.3. Adverse reactions (ADRs)

- see under 1.1 Ds (Pharmacovigilance).

1.3.1. Recent case reports (UMC database)

In the period from 1 January 2005 to 7 February 2009, the Uppsala Monitoring Centre received 2 reports on diphenylpyraline from Germany and the USA, with 3 ADRs: anxiety (1 case), convulsion (1 case) and increased hepatic enzyme (1 case).

The combination database of the UMC ADR database does not suggest any other unexpected risks for diphenylpyraline.

2. Discussion

The main therapeutic area for this drug is sedation and the treatment of pruritic symptoms due to a variety of dermatological conditions, but also the treatment of common cold, allergic rhinitis and conjunctivitis. It has also been used in compound preparations for the symptomatic treatment of coughs and the common cold.

Diphenylpyraline hydrochloride, a piperidine derivative, is a sedating anti-histamine with anti-muscarinic and significant sedative properties.

No new ADRs have been reported for diphenylpyraline in the post-marketing period.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
A	II + exemption	Nasal Use	5% in all uses (R06), other than external.	5 %		
B	OTC	Nasal Use	In combination medications only.			
CH	II + exemption	Oral Use			10 mg	50 mg
CZ			Not marketed			
D	OTC	Oral Use				
E	II + exemption	Oral Use	In combination for common cold medications. For adults only.		10 mg	
F	II + exemption	Oral Use		2 mg		100 mg
GB	OTC	Oral Use				
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LV			Not marketed			
MK			Not marketed			
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

DIPHENYLPYRALINE, anti-histamines for systemic use – Aminoalkyl ethers, Oral administration.

List II + exemption

Criteria:

- sedating anti-histamine with anti-muscarinic and significant sedative properties.
- only for short-term treatments of up to 14 days for allergic rhinitis and dermatological symptoms.
- **MS is 2 mg**
- **MDD is 10 mg**
- **MQP is 100 mg**
- **For adults and children aged over 12 years.**

3.2. Paediatric use

Not for use in children aged less than 12 years.

4. References:

- http://ovidsp.tx.ovid.com/spa/ovidweb.cgi?&S=AGEGFPDOAKDDGGLANCGLIACKDMJPAA00&Link+Set=S.sh.36%7c1%7csl_10
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: DOXYLAMINE

ATC Code: R06AA09
Anti-histamines for systemic use – Aminoalkyl ethers

Therapeutic indications:

- common cold
- allergic rhinitis
- insomnia

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- Allergic rhinitis:
 - 12.5 mg orally, every 4 to 6 hours as needed (in combination products).
- Common cold (symptoms control):
 - 7.5 to 12.5 mg, every 4 to 6 hours. Maximum dose is 75 mg/day.
- Insomnia:
 - 25 to 50 mg orally, taken 30 min before bed.

Paediatric:

- Common cold (symptoms control):
 - aged 2 to 6 years: 1.9 to 3.125 mg every 4 to 6 hours. Maximum dose 18.75 mg/day.
 - aged 6 to 12 years: 3.75 to 6.25 mg every 4 to 6 hours. Maximum dose 37.5 mg/day.
- Insomnia:
 - aged 12 years and older: 25 to 50 mg orally, taken 30 min before bed.

Pharmaceutical forms: Tablets, sustained-release capsules and syrup

Contraindications - relevant warnings:

a) Contraindications:

- hypersensitivity to doxylamine.

b) Precautions:

- asthma.
- bladder neck obstruction.
- breast feeding.
- chronic bronchitis.
- concurrent use of alcohol or other CNS depressants.
- driving or performing other tasks that require alertness.
- narrow-angle glaucoma.
- not to be used for insomnia over 2 weeks duration.
- pregnancy.
- pyloroduodenal obstruction.
- stenosing peptic ulcer.
- symptomatic prostatic hypertrophy.

1.1. Direct risks (Pharmacovigilance)

In Paediatric Use

Although there is a dosage protocol for children aged 2 to 12 years, doxylamine is not recommended for use in children under 12 years of age, since children may be more prone than adults to paradoxical CNS stimulation, rather than sedation.

1.2. Interactions with:

Theoretically with procarbazine (CNS depression).

1.3. Adverse reactions (ADRs)

- Common:
 - Neurologic: somnolence.

1.4. Indirect risk

Overdosing can lead to CNS depression and/or stimulation, mydriasis, flushing, dry skin and mouth, tachycardia, decreased bowel sounds, urinary retention, hyperthermia, excitation, hallucinations and seizures. Severe ADRs include: coma, dysrhythmias, and cardiac or respiratory collapse. The onset of ADRs is typically 0.5 to 2 hours following administration. Drowsiness, tachycardia, dilated pupils, decreased bowel sounds, and urinary retention are the most common adverse effects following therapeutic administration. Other adverse effects may include nausea and vomiting, dystonic reactions and hepatotoxicity. The seriousness of ADRs may vary with the class of anti-histamine.

2. Discussion

Doxylamine antagonises many of the effects of endogenous histamine by blocking H₁ receptors. The depressant effects are probably related to a high affinity for H₁ receptors in the brain. Many H₁ antagonists also tend to inhibit responses to acetylcholine, which are mediated by muscarinic receptors.

Doxylamine is an anti-histamine most commonly used as a short-term night time sleep aid. Doxylamine, in combination with decongestants, anti-tussives, and analgesics, is useful for the symptomatic treatment of coughs and colds.

Doxylamine is not recommended for use in children under 12 years of age, since children may be more prone than adults to paradoxical CNS stimulation, rather than sedation.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
A	II	Oral Use				
CZ			Not marketed			
F			Not marketed			
H			Not marketed			
HR			Not marketed			

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
I	OTC	Oral Use	Not marketed			
LT			Not marketed			
MK			Not marketed			
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

DOXYLAMINE, anti-histamines for systemic use – Aminoalkyl ethers, Oral administration.

List II + exemption

Criteria:

- risk of serious adverse reactions like agitation – paradoxical nervous stimulation in children aged less than 12 years.
- only OTC prescription status for short-term usage in therapy of seasonal allergic symptoms.
- not widely-marketed as a single active ingredient.
- MS is 12.5 mg
- MDD is 50 mg
- MQP is 500 mg

3.2. Paediatric use

Not recommended for children aged less than 12 years.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/0A7B9A/DUPLICATIONSHIELDSYNC/298753/ND_PG/PRIH/ND_B/HCS/SBK/5/ND_P/Main/PFPUI/UI1aphB2QEmYyu/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/0507/ContentSetId/31#secN10674
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: EBASTINE

ATC Code: R06AX22
Anti-histamines for systemic use – Other anti-histamines for systemic use.

Therapeutic indications:

- Perennial allergic rhinitis and seasonal allergic rhinitis.

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- Perennial allergic rhinitis:
 - 5 - 10 mg (mg) once daily, taken in the morning. For long-term use, 20 mg/day doses of ebastine may be more effective than lower doses.
- Seasonal allergic rhinitis :
 - 20 mg (mg) once daily, appears to be more effective than a 10 mg dose, but the lower dose is recommended initially and may be increased, if required, for more severe symptoms.

Paediatric:

- Perennial allergic rhinitis:
 - aged 12 to 17 years: 5 to 20 mg/day, taken in the morning, has been effective in adolescents.
 - aged 6 to 12 years: 5 to 10 mg/day.
- Seasonal allergic rhinitis
 - aged 2 to 15 years: 2.5 to 20 mg/day.

Pharmaceutical forms: Tablets

Contraindications - relevant warnings:

a) Contraindications:

- Prior hypersensitivity to ebastine.

b) Precautions:

- Untoward effects during concomitant use of other H₁ receptor antagonist agents (e.g. loratadine, azelastine, cetirizine, astemizole, terfenadine).
- Cardiovascular disease (particularly arrhythmias or established QTc interval prolongation).
- Asthma/upper respiratory tract infection.
- Liver disease.
- Renal insufficiency.
- Combined use with cytochrome P450 enzyme inhibitors (e.g. ketoconazole)

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

- **Cardiovascular Effects**
 - No significant QT interval findings reported. No increase in QTc interval greater than 500 msec or 15% to 25% from baseline in electrocardiogram/Holter monitoring clinical studies (1 to 30 mg/day). No clinical data in patients with cardiovascular disease, including prior or established QTc interval prolongation.
- **Gastrointestinal Effects**
 - Dry mouth (5 to 12%), increased appetite (up to 8%). Less frequently: nausea, vomiting, diarrhea, constipation, gastro intestinal discomfort.
- **Neurologic Effects**
 - Headache is one of the most frequently reported adverse effects (up to 15 % of patients in clinical studies).
- **Impaired psychomotor performance**
 - Impairment was seen with doses of ≥ 50 mg. Driving performance is unaffected by doses of 10 to 30 mg/day.
- **Somnolence**
 - In an open-label, pharmacokinetic study of patients with normal renal function (n 12) compared to patients with impaired renal function (n 24), somnolence was one of the most frequently reported adverse effects following administration of ebastine 20 mg orally, once daily, for five days (Noveck *et al.*, 2007).
 - Drowsiness was observed in up to 15% of patients (a similar proportion to that of patients receiving placebos) in other larger studies (Wiseman & Faulds, 1996; Storms, 1996; Pelaez, 1996; Gehanno *et al.*, 1996; Anker & Warrington, 1989).
- **Renal Effects**
 - Urinary retention (rare) .
 - No evidence of nephrotoxicity.

1.2. Interactions with:

- Droperidol and Levomethadyl (theoretical): co-administration of these drugs with ebastine can lead to an increased risk of cardio-toxicity (QT interval prolongation, 'torsades de pointes', cardiac arrest).
- Administration of Procarbazine with ebastine can theoretically cause CNS depression. To minimise CNS depression and possible potentiation, procarbazine and anti-histamines should be co-administered with caution.

1.3. Adverse reactions (ADRs)

See under 1.1 Direct risks (Pharmacovigilance).

1.3.1. Recent case reports (UMC database)

In the period from 1 January 2005 to 7 of February 2009, the Uppsala Monitoring Centre received 81 reports on ebastine, with 168 ADRs. Reports came from **Germany, Denmark, Spain, Finland, France, Italy**, Japan, **the Netherlands, Norway, Portugal**, the USA and Venezuela.

The most frequently reported ADRs were headache (7 cases), followed by rash and urticaria and somnolence with (6 cases each) and coma (2 cases). Of the six cases of somnolence, four were caused by ebastine alone and, in the other two cases in addition to the cases of coma, other CNS depressants such as anti-depressants and anti-psychotic drugs were involved. In the SOC *Cardiac disorder*, seven ADRs were reported and an additional four cases of QT interval prolongation. All other ADRs are represented by one or two cases.

The combination database of the UMC ADR database does not suggest any other risks with ebastine use.

2. Discussion

In general, there is a similar incidence of somnolence with 10 to 20 mg/day doses of ebastine. Ebastine is at least as well-tolerated as other second-generation H₁-receptor antagonists (e.g. cetirizine, astemizole, terfenadine, loratadine). No new safety data have been presented since this medicinal product has been placed on the market.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
A	II	Oral Use				
B	II	Oral Use				
CZ	II	Oral Use	The drug was withdrawn from the market in 2008 for unknown reasons.			
F	II	Oral Use				
FIN	II + exemption	Oral Use		10 mg		100 mg
GB			Not marketed			
H	POM	Oral use				
HR			Not marketed			
I	II	Oral use				
LT	II	Oral use				
LV	II + exemption	Oral use	Indications: allergic rhinitis, idiopathic chronic urticaria. MDD=10-20mg (adults and children aged > 12 years).	20 mg	20 mg	200 mg
MK			Not marketed			
N	II + exemption	Oral use	Indication: for treatment of allergies.	10 mg		100 mg
NL	II	Oral use				
RO			Not marketed			
S	II + exemption	Oral use	Indications: for temporary allergic symptoms such as red, running and itching eyes, nasal congestion and sneezing.	10 mg		100 mg

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

EBASTINE, anti-histamines for systemic use – other anti-histamines for systemic use, oral administration.

List II + exemption

Criteria:

- only OTC prescription status for temporary allergic symptoms such as red, running and itching eyes, nasal congestion and sneezing.
- safe cardiovascular profile.
- somnolence is the most frequently reported ADR (dose-dependent).
- no dose adjustment is needed for the elderly or patients with renal or hepatic impairment.
- for use in adults and children aged > 12 years.
- MS 10 mg
- MDD 10 mg
- MQP 100 mg

3.2. Paediatric use

- Safety and effectiveness not established in children aged less than 2 years.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/B0CCEF/DUPLICATIONS/HIELDSYNC/A4D438/ND_PG/PRIH/ND_B/HCS/SBK/6/ND_P/Main/PFPUI/Or1apfs2Qo1vn1/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/9400/ContentSetId/31/SearchTerm/EBASTINE%20/SearchOption/BeginWith#secN1071E
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx
- Noveck, R.J., Preston, R.A., Swan, S.K. (2007) Pharmacokinetics and safety of ebastine in healthy subjects and patients with renal impairment. *Clinical Pharmacokinetics*, 46(6):525-534.

Active ingredient: EMEDASTINE

ATC Code: S01GX006

Therapeutic indications:

Allergic conjunctivitis (FDA-approved indications).

Posology/duration of treatment

Dosing Information:

Adult: 1 drop 0.05% ophthalmic solution in affected eye(s), up to four times daily.

Children aged 3 years and older): 1 drop 0.05% ophthalmic solution in affected eye(s) up to four times daily.

Contraindications:

Hypersensitivity to emedastine products.

Precautions:

- ophthalmic solution contains benzalkonium chloride, which may be absorbed by soft contact lenses.
- prevent contamination of dropper tip and solution.
- wait at least 10 minutes after treatment with emedastine drops to insert contact lenses.

1. List of direct/indirect risks (safety profile)

Adverse Reactions

Dermatological:

Pruritus was reported in less than 5% of patients administered with cutaneousophthalmic solution.

Gastrointestinal tract:

Taste disturbances were reported in less than 5% of patients administered with cutaneousophthalmic solution.

Neurologic (CNS):

Headache was the most common adverse effect (11%) reported following treatment with cutaneous ophthalmic solution. Dream disturbances and asthenia were also reported in less than 5% of patients.

Ophthalmic:

Adverse effects reported following cutaneous ophthalmic solution administration in less than 5% of patients included: blurred vision, burning or stinging, corneal infiltrates, corneal staining, keratitis, dry eyes, ocular discomfort, and foreign body sensation.

Respiratory:

With cutaneousophthalmic administration, rhinitis and sinusitis were reported in less than 5% of patients.

Other:

Hyperemia was reported in less than 5% of patients administered with cutaneous ophthalmic solution.

Hepatotoxicity:

Increases in total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactic dehydrogenase, and gamma-glutamyl transpeptidase have been observed with emedastine treatment (Tasaka & Mealy, 1993).

Drug interactions: No information provided (regarding ophthalmic use)

2. Conclusions-recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	POM	Ophthalmic use				
A	NA					
BIH	Not marketed	Ophthalmic use				
CZ	1 (1)	Ophthalmic use				
D	I (3)	Ophthalmic use				
F	I	Ophthalmic use				
H	I	Ophthalmic use				
HR	Not marketed	Ophthalmic use				
MK	Not marketed	Ophthalmic use				
PO	NA					
RO	II					
SLO	I	Ophthalmic use				

2.1. Conditions of supply (indications, Administration Route, MS, MDD, MQP as applicable)

Emedastine, S01GX06, Ophthalmic administration.
MS 0.05%, MQP 5 ml.

The proposed classification: List I

No exemption from prescription status only is recommended

Criteria:

Emedastine for ophthalmic use is not widely distributed in EU countries. Cutaneous ophthalmic emedastine is available in the United States for the treatment of allergic conjunctivitis, although published data are limited. It appears to be well-tolerated and somewhat effective for the treatment of the symptoms associated with asthma, but clinical data are limited. Comparisons with other anti-histamines are needed. More data are needed to determine the relative efficacy of emedastine compared to other H₁-receptor antagonists.

Paediatric use: safety and efficacy have not been established in children less than 3 years of age.

3. References:

- <http://www.micromedex.com/products/hcs/>
- <http://www.rxlist.com/emadin-drug.htm>
- <http://www.micromedex.com/products/pdrlibrary>
- Martindale, Thompson Healthcare 2009

Active ingredient: EPINASTINE

ATC Code: S01GX010

Therapeutic indications:

Allergic conjunctivitis, (FDA-approved indications).

Posology/ duration of treatment:

Dosing Information:

Adults:

The usual dose of epinastine cutaneousophthalmic solution in adults is one drop of 0.05% in each eye, twice a day. Treatment should be continued throughout the period of exposure (*i.e.* until the pollen season is over or until exposure to the offending allergen has come to an end), even when symptoms are absent (Prod Info Elestat(TM), 2003).

Children:

The usual dose of epinastine cutaneousophthalmic solution in Paediatric patients (children aged 3 years and older) is one drop of 0.05% in each eye, twice a day. Treatment should be continued throughout the period of exposure (*i.e.* until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent.

Pharmaceutical forms: ophthalmic solution

Contraindications:

Hypersensitivity to epinastine or any component of the formulation.

Precautions:

Do not wear contact lenses if eye is red.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Adverse Reactions:

Epinastine hydrochloride

Cardiovascular:

Epinastine has not been shown to have arrhythmogenic properties. Cardiotoxicity has not been observed, even in high doses (animal studies) (Kishimoto *et al.*, 1997).

Neurologic (CNS):

Epinastine has shown little to no blood-brain barrier effects, and CNS adverse effects have not been observed, even with oral doses of up to 20 mg (Prod Info Elestat(TM), 2003; Kishimoto *et al.*, 1997; Schilling *et al.*, 1990; Yanai *et al.*, 1995; Adamus *et al.*, 1987).

Ophthalmic:

The most frequently reported ocular adverse effects with epinastine ophthalmic solution, occurring in 1- 10% of patients, include burning sensations in the eye, folliculosis, hyperemia, and pruritus.

Respiratory:

The most frequently reported non-ocular adverse effects with epinastine ophthalmic solution include infection (common cold and upper respiratory infection observed in approximately 10% of patients), and headache, rhinitis, sinusitis, increased cough, and pharyngitis (approximately 1-3% of patients). Some of these events were similar to the disease being treated (Prod Info Elestat(TM), 2003)

Interactions:

Epinastine is poorly metabolised by human liver microsomes *in vitro*, and does not inhibit CYP3A4, which suggests a low potential for drug interactions (Kishimoto *et al.*, 1997).

1.2. Indirect risks (incorrect use)

Overdose: no information provided

2. Conclusions - recommendations for legal classification

- The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	I(3)	Ophthalmic use				
A	II	Ophthalmic use				
BIH	Not marketed	Ophthalmic use				
CH	II	Ophthalmic use				
CZ	I	Ophthalmic use				
D	I(3)	Ophthalmic use				
I	II	Ophthalmic use				
E	1(1)					
H	OTC	Ophthalmic use				
HR	Not marketed	Ophthalmic use				
MK	Not marketed	Ophthalmic use				
RO	II	Ophthalmic use				
SLO	Not marketed	Ophthalmic use				

2.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

EPINASTINE S01GX010 ophthalmic solution

MS 0.05%, MQP 5 ml.

The proposed classification: List II

Criteria:

Epinastine was developed as a non-sedating anti-histamine with no significant arrhythmogenic effects, even at high doses. It has been used in countries outside the United States for the treatment of allergic rhinitis and other inflammatory conditions, but is only approved in the United States in a cutaneousophthalmic formulation for the treatment of itching associated with allergic conjunctivitis. There is little published data regarding its use for any condition, most of which is in the prescribing information of the manufacturers. Although the drug appears to have significant H₁ antagonistic activity and mast-cell stabilising properties, additional comparative clinical trials are needed to determine the utility of epinastine in therapy.

2.2 . Paediatric use

Safety and efficacy have not been established for children under 3 years of age.

3. References:

- <http://www.rxlist.com/elestat-drug.htm>
- <http://www.micromedex.com/products/hcs/>
- <http://www.micromedex.com/products/pdrlibrary>
- Martindale, Thompson Healthcare 2009
- Farmakoterapiski priracnik 2006
- Registar na lekovi 2009

Active ingredient: FEXOFENADINE

ATC Code: R06AX26
Anti-histamines for systemic use – Other anti-histamines for systemic use.

Therapeutic indications:

Chronic idiopathic urticaria and seasonal allergic rhinitis.

Posology/duration of treatment: per os

MICROMEDEX Dosing Information

Adult:

- Chronic idiopathic urticaria: 60 mg orally, twice daily or 180 mg orally, once daily.
- Seasonal allergic rhinitis: 60 mg orally, twice daily or 180 mg orally, once daily.

Paediatric:

- Safety and efficacy not established in children aged less than 6 months.
- Chronic idiopathic urticaria:
 - aged 6 months to 2 years: 15 mg orally, twice daily.
 - aged 2 to 11 years: 30 mg orally, twice daily.
 - aged 12 years and older: 60 mg orally, twice daily or 180 mg orally, once daily.
- Seasonal allergic rhinitis:
 - aged 2 to 11 years: 30 mg orally, twice daily with water.
 - aged 12 years and older: 60 mg orally, twice daily or 180 mg orally, once daily.

Pharmaceutical forms: Tablets

Contraindications - relevant warnings:

a) Contraindications:

Hypersensitivity to the active substance or to any of the excipients.

b) Precautions:

As with most new drugs there is only limited data on use in the elderly and renally- or hepatically impaired patients. Fexofenadine hydrochloride should be administered with caution in these special groups.

Patients with a history of, or on-going, cardiovascular disease should be warned that anti-histamines, as a drug class, have been associated with tachycardia and palpitations.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

In controlled clinical trials, the most commonly reported adverse effects were headache (7.3%), drowsiness (2.3%), nausea (1.5%) and dizziness (1.5%). The incidences of these events observed with use of fexofenadine was similar to those observed with the use of placebos.

Other ADRs that have been rarely reported with incidences of less than 1%, similar to incidences with placebos, in controlled trials and during post-marketing surveillance include: fatigue, insomnia, nervousness and sleep disorders or paroniria (nightmares), tachycardia, palpitations and diarrhea. In rare cases, rash, urticaria, pruritus, and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have also been reported.

1.2. Interactions

Fexofenadine does not undergo hepatic bio-transformation and, therefore, will not interact with other drugs through hepatic mechanisms. Co-administration of fexofenadine hydrochloride with erythromycin or ketoconazole has been found to result in a 2-3 fold increase in the level of fexofenadine in plasma. These changes were not accompanied by any effects on the QT interval and were not associated with any increase in ADRs compared to each drug, administered singly.

1.3. Adverse reactions (ADRs)

See under 1.1 Direct risks (Pharmacovigilance).

1.3.1. Recent case reports (UMC database)

In the period from the 1st of January 2005 to the 7th of February 2009, the Uppsala Monitoring Centre received 629 reports on fexofenadine, with 1,879 ADRs. Reports came from Australia, **Austria**, Brazil, Canada, Chile, Columbia, **Germany, Denmark, Finland, France, United Kingdom, Ireland, Iceland, Italy**, Japan, **Malta, the Netherlands, Norway**, New Zealand, **Sweden**, Thailand, Tunisia, the USA, Venezuela and South Africa. In the SOC *Cardiac disorders*, 27 cases of palpitations were reported and 11 cases of tachycardia. There were also four reports of cardiac arrest from the USA. The most common ADRs from the SOC *Gastrointestinal disorders*, were nausea and vomiting (37 and 27 cases, respectively). About 100 reports of ineffective therapeutic response and 20 reports of medication error were made in this period. The most commonly reported ADRs in the SOC *Nervous system disorders*, were similar to those of other anti-histamines, namely dizziness (48 reports), somnolence (not more than 20 cases), and headache (approximately 35 reports). Twelve cases of confirmed suicide were reported, with an additional 12 cases of depression and suicidal behaviour.

The combination database of the UMC ADR database suggests slight risks for dysmenorrhoea, rhinitis, abnormal lacrimation and epiphora when using fexofenadine.

1.4. Indirect risk

Dizziness, drowsiness, fatigue and dry mouth have been reported in cases of overdose with fexofenadine hydrochloride. Single doses of up to 800 mg, and doses of up to 690 mg, administered twice daily for 1 month, or 240 mg once daily for a year, have been administered to healthy subjects without developing clinical signs of ADRs. The maximum tolerated dose of fexofenadine hydrochloride has not been established.

2. Discussion

The main therapeutic area is treatment of allergic rhinitis. There are reports of cardiac arrhythmia and cardiac arrest and CNS depression, especially in cases where fexofenadine was administered with other CNS depressants. There are few reported incidences of somnolence, but there are a number of cases where no therapeutic effect have been reported, suggesting that a larger daily dose may be needed.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II	Oral Use				
A	II	Oral Use				
B	II	Oral Use				
BG	II	Oral Use				
CZ	I	Oral Use				
D	II	Oral Use				
DK	II	Oral Use				
E	II	Oral Use				
F	II	Oral Use				
FIN	II	Oral Use				
GB	II	Oral Use				
H	POM	Oral use	Indications: seasonal allergic rhinitis (120 mg), chronic idiopathic urticaria (180 mg). Warnings: no data on children aged <12 years. Co-administration with erythromycin or ketoconazole can increase the level of fexofenadine 2-3 fold. No dose adjustment needed in the elderly and patients with renal or hepatic impairment.	120 mg / 180 mg	120 mg / 180 mg	
HR	I	Oral use	Indications: relief of symptoms caused by allergic rhinitis (30-120 mg), relief of symptoms caused by chronic idiopathic urticaria (180 mg).			
I	II	Oral use		180 mg	180 mg	0 mg
IRL	II	Oral Use				
LT	II	Oral use				
LV	I	Oral use	Indications: allergic rhinitis, chronic idiopathic urticaria. Warnings: hypersensitivity to the substance, MDD=180 mg (adults and children aged > 12 years).	180 mg	180 mg	1800 mg
MK	POM	Oral Use	Indications: symptoms associated with seasonal rhinitis, chronic idiopathic urticaria. Warnings: administer with care in the elderly and renally- or hepatically-impaired patients. Associated with tachycardia and palpitations in patients with on-going cardiovascular disease. Only for adults and children aged > 12 years.	180 mg		
N	II	Oral use				
NL	II	Oral use				
P	II	Oral Use				
RO	II	Oral Use	Indications: symptoms associated with allergic rhinitis in adults and children aged > 12 years. Warnings: hypersensitivity to the active	180 mg		10.8 g

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
			substance or to any of the excipients. MS= 60 mg for children aged between 6-12 years.			
S	II	Oral Use				
SLO	II	Oral Use				

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

FEXOFENADINE, anti-histamines for systemic use – other anti-histamines for systemic use, Oral administration.

List II

Criteria:

- the prescription status is classified as List II in over 90% of all Member States, and elsewhere it is POM or classified as List I.
- Precautions are needed in patients with a history of cardiovascular diseases.
- Precautions are needed when fexofenadine is prescribed with other anti-histamines or drugs which cause QT interval prolongation.

3.2. Paediatric use

- Safety and effectiveness has not been established for children less than 6 years of age.

4. References:

http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/916751/DUPLICATIONSHIELD_SYNC/BC25D4/ND_PG/PRIH/ND_B/HCS/SBK/3/ND_P/Main/PFPUI/Or1apfs2QongJ8/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/923709/ContentSetId/100/SearchTerm/FEXOFENADINE%20/SearchOption/BeginWith

https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)

<https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)

http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: KETOTIFEN

ATC Code: S01GX08

Therapeutic indications:

Allergic conjunctivitis, itching (prophylaxis).

Posology/ duration of treatment:

Dosing Information :

Adult: one drop in affected eyes, twice daily, every 8 to 12 hours.

Children aged 3 years and older: one drop in affected eye(s) twice daily, every 8 to 12 hours (Prod Info: ketotifen fumarate ophthalmic solution, 2005).

Pharmaceutical form: ophthalmic solution

Contraindications:

Hypersensitivity to ketotifen products or benzoate compounds.

Precautions:

Not for contact lens-related irritation.

1. List of direct/indirect risks (safety profile)

Adverse Reactions:

Cardiovascular:

Syncope has been reported as an adverse effect of ketotifen therapy (Szczeklik *et al.*, 1980).

Dermatologic:

Case report - A patient developed contact dermatitis after treatment with ketotifen ophthalmic drops (Niizeki *et al.*, 1994).

Rash, contact dermatitis and other skin eruptions have occurred with therapeutic ketotifen therapy. Rash has been reported following ketotifen fumarate ophthalmic solution therapy.

Gastrointestinal:

Dry mouth has been reported in patients during therapeutic ketotifen therapy.

Ophthalmic:

Mild conjunctival injection (blood shot eyes) has been reported with an incidence of 10-25% with the application of ophthalmic ketotifen. Other events that have been reported with an incidence of less than 5% were: allergic reactions, burning or stinging, conjunctivitis, discharge, dry eyes, eye pain, eyelid disorder, itching, keratitis, lacrimation disorder, mydriasis, and photophobia.

Other:

Pharyngitis and flu-like symptoms have been reported with ophthalmic use of ketotifen fumarate solution.

Mild rhinitis has been reported, with an incidence of 10-25%, after cutaneous application of ketotifen fumarate solution.

1.1. Indirect risks (incorrect use)

Overdose:

No toxic effects have been reported after ingestion of up to 20 mg ketotifen fumarate.

2. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution Recap(2007) ¹ , annually revised appendices (recommendations)	I(1)	Ophthalmic use				
A	Not marketed	Ophthalmic use				
BIH	Not marketed	Ophthalmic use				
F	II	Ophthalmic use				
H	OTC	Ophthalmic use				
HR	Not marketed	Ophthalmic use				
LV	II	Ophthalmic use				
MK	Not marketed	Ophthalmic use				
N	OTC	Ophthalmic use				
RO	II	Ophthalmic use				
SLO	I	Ophthalmic use				

2.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

Ketotifene, S01GX08, Ophthalmic administration
MS 0.025%, MQP 5ml

2.2. Paediatric use:

Safety and efficacy have not been established for use in children less than 3 years of age.

The recommended classification: List II

Criteria:

The safety profile of the drug is good, no serious adverse reactions such as systemic reactions have been reported after ophthalmic use, but there are many localised ADRs, e.g. mild conjunctival injection (blood shot eyes), which has been reported with an incidence of 25% with the application of ophthalmic ketotifen.

Not widely distributed in Member States. Insufficient data on prescription status.

Note: The prescription status of Ketotifen ophthalmic solution 0.025% in the USA is OTC (Prod Info Zaditor(TM)).

3. References:

- <http://www.micromedex.com/products/hcs/>
- <http://www.rxlist.com/ketotifen-drug.htm>
- <http://www.micromedex.com/products/pdrlibrary>
- Martindale ,Thompson Healthcare 2009

Active ingredient: KETOTIFEN

ATC Code: R06AX17
Anti-histamines for systemic use – Other anti-histamines for systemic use.

S01GX08
Decongestants and anti-allergics - Other anti-allergics.

Therapeutic indications:

- FDA (USA) approved indication:
 - Allergic conjunctivitis, itching, prophylaxis of allergic reactions.
- EU approved indications:
 - prevention of asthma attacks.
 - allergic rhinitis.
 - urticaria.
 - conjunctivitis.
 - symptomatic treatment of allergic conditions including rhinitis and conjunctivitis in adults and children over 6 months of age.

Posology/duration of treatment:

- oral, local application.

MICROMEDEX Dosing Information

Adult:

- Ophthalmic route:
 - 1 drop in the affected eye(s) twice daily (every 8 to 12 hours) for temporary prevention of itching of the eye due to allergic conjunctivitis.
- Oral route:
 - doses from 1 to 2 mg twice daily - 4 mg Ketotifen daily is the maximum recommended dose for treating asthma.

Paediatric:

- Ophthalmic route:
 - 1 drop in the affected eye(s) twice daily (every 8 to 12 hours) for temporary prevention of itching of the eye due to allergic conjunctivitis in children 3 years of age and older.
- Oral route
 - doses of 0.5 to 2 mg twice daily.
 - The total dose, however, is lower in children than in adults.

Pharmaceutical forms: tablets, syrup, eye drops.

Contraindications - relevant warnings:

a) Contraindications:

- hypersensitivity to ketotifen products or benzoate compounds.

b) Precautions:

- not for contact lens-related irritation.
- Ketotifen may lower the seizure threshold and it should be used with caution in patients with a history of epilepsy (Romania).

- A reversible decrease in the thrombocyte count of patients receiving ketotifen concomitantly with oral anti-diabetic agents has been observed in a few cases. This combination of drugs should, therefore, be avoided until this phenomenon has been satisfactorily explained (Romania).

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

- U.S. FDA Pregnancy Category C
- syncope, contact dermatitis, rash, weight gain, dry mouth, xerostomia, dizziness, headache, drowsiness, sedation, somnolence, burning or stinging, conjunctivitis, discharge, dry eyes, eye pain, eyelid disorder, itching, keratitis, lacrimation disorder, mydriasis, and photophobia.

1.2. Interactions with (MICROMEDEX):

- No information available.

1.3. Adverse drug reactions

1.3.1. Recent case reports (UMC database)

In the period from the 1st of January 2005 up to the 7th of February 2009, the Uppsala Monitoring Centre received 195 reports of ketotifen with 374 ADRs. Reports came from Armenia, Australia, Canada, Chile, Cuba, **Germany, Denmark**, France, India, Iran, **Italy**, Japan, Mexico, **The Netherlands**, Peru, **Poland, Portugal**, Romania, Thailand, **Turkey**, Ukraine, the USA and Venezuela. The most common ADR was somnolence (18 cases), followed by “drug ineffective” (11 cases), and “condition aggravated (10 cases). A reversible decrease in the thrombocyte count of patients receiving ketotifen concomitantly with oral anti-diabetic agents has been observed in a few cases. This combination of drugs should, therefore, be avoided until this phenomenon has been satisfactorily explained. For localised application to the eyes, most reports refer to eye irritation, *i.e.* about 80 eye ADRs. Four cases of medication error were also reported from the USA, all of which were cases of self-medication with eye drops.

1.4. Indirect risk

Overdose with oral tablets of ketotifen has produced CNS depression, headache, dyspnoea, respiratory depression, hypotension, bradycardia, tachycardia, and two reports of seizures. Patients have survived ingestions of up to 120 mg; although seizures, coma and hypotension have been reported after ingestions of more than 20 mg/day in adults. No serious toxic effects have been reported after the ingestion of up to 20 mg of ketotifen fumarate (ophthalmic solution).

2. Discussion

The main therapeutic area of this drug is symptomatic treatment of allergic conditions, including rhinitis and conjunctivitis in adults and children over 6 months of age.

Safety profile of the drug: No deaths or coma have been reported to the UMC database in the past three years. The most common ADR is somnolence when given orally, as with other anti-histamines from this group.

Ketotifen cutaneous presentations (gel, solutions, and plasters) were found to be phototoxic. Cutaneous use should be prescribed by a physician.

There is a wide range of classification for the drug among Member States.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

KETOTIFEN, anti-histamines for systemic use – Other anti-histamines for systemic use; Oral administration.

Criteria:

- Ketotifen is an OTC drug in most Member States or the prescription status is List II. Safety profile of the drug Ketotifen cutaneous presentations (gel, solutions, plasters) were found phototoxic; no serious ADRs such as coma or death were reported, possibly because the oral drug is classified as List II prescription status in a majority of Member States.
- Recommendation for OTC prescription status:
 - o Indication: allergic rhinitis or conjunctivitis.
 - o MS corresponds to 1 mg, MDD corresponds to 4 mg, MQP corresponds to 50 mg.
 - o Only short-term use for seasonal allergic rhinitis, conjunctivitis.
 - o Only for children > 6 years of age.

KETOTIFEN, Decongestants and anti-allergics - Other anti-allergics; Localised application in eye

List I

Criteria:

- The safety profile of the drug is good, with no serious ADRs reported, such as systemic reactions, after localised application of the eye drops, but with many localised eye reactions.
- A few reports of medication error have been received at the UMC database following self-medication of eye-drops, meaning that there is a possibility for misuse if a diagnosis is not made by a physician.

3.2. Paediatric use

In some countries also authorised for children > 3 month of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/98A2D8/DUPLICATNSHIELDSYNC/3C5EDB/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/7RTTtI2PZr7U5/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/0398/ContentSetId/31/SearchTerm/ketotifen%20/SearchOption/BeginWith#secN109C6
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: LEVOCABASTINE

ATC Code: R01AC02

Therapeutic indications:

Symptomatic treatment of perennial and seasonal allergic rhinitis.

Posology/ duration of treatment:

2-4 puffs twice daily into each nostril (1 puff~0.05 mg).
Treatment should last while the symptoms persist.

Pharmaceutical forms: nasal spray

Contraindications - relevant warnings:

- hypersensitivity to levocabastine products (contraindicated).
- the use of levocabastine nasal spray is not recommended in those with significant renal impairment because it is excreted through the kidneys (warning).

1. List of direct/indirect risks (safety profile)

Levocabastine is a piperidine derivative; a long-acting and potent second-generation anti-histamine with a rapid onset of action.

The most common adverse effects reported with levocabastine nasal use were headache, nasal irritation and, rarely, somnolence and fatigue.

1.1. Direct risks (Pharmacovigilance)

Nasal irritation, somnolence and fatigue after administration of the nasal spray.

The subsequent plasma concentrations following administered doses of cutaneous levocabastine are low and, thus, the risk of systemic adverse events is expected to be minimal.

With normal dosages, no clinically relevant sedations were observed.

1.1.1 Teratogenicity/Effects in Pregnancy/Breastfeeding:

Not known if it crosses the placenta, therefore, it should only be used during pregnancy if the benefits to the mother exceed the risks to the foetus.

Trace amounts of levocabastine have been found in breast milk after nasal use, but it did not have an adverse effect on the nursing child.

1.1.2 Elderly

No dose modification is needed.

1.1.3 Recent cases in Europe

None

1.2. Indirect risks (incorrect use)

None

2. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
A	II					
BG	II					
FIN	II					
IRL	II					
LT	II					
NL	II					
RO	II					
SLO	II					
Resolution ResAP(2007)1, annually revised appendices (recommendations)	II exemption +					
E	II exemption +					
GB	II exemption +					
LV	II exemption +					
Publication	II exemption +					
A	List II					
B	OTC					
BIH	Not marketed					
CH	OTC					
CZ	OTC					
D	OTC					
DK	OTC					
H	OTC					
HR	Not marketed					
I	OTC					
N	OTC					
P	OTC					
PL	Not marketed					
S	II exemption +					

2.1. The proposed classification:

List of classification: **OTC**

- Symptomatic treatment of perennial and seasonal allergic rhinitis.

Rationale:

- Low risk of systemic adverse effects.
- No sedative effect with nasal route.
- Can be used safely for long-term treatment and relief of symptoms.

2.2. Paediatric use

Recommended for children. No dose modification is needed.

3. References:

- Sweetman, S. (2007) Martindale: The Complete Drug Reference (35th Edition). Pharmaceutical Press.
- Micromedex 2.0, Healthcare Series
- Noble S, McTavish D. (1995) Levocabastine. An update of its pharmacology, clinical efficacy and tolerability in the cutaneous treatment of allergic rhinitis and conjunctivitis. *Drugs*, Dec; 50(6):1032-49.
- Okubo K, Uchida E, Nogami S. (2010) Levocabastine nasal spray significantly improves perennial allergic rhinitis: A single-blind placebo-controlled study. *Auris Nasus Larynx.*, Aug; 37(4):436-42.
- Hampel FC Jr, Martin BG, Dolen J, Travers S, Karcher K, Holton D. (1999) Efficacy and safety of levocabastine nasal spray for seasonal allergic rhinitis. *Am J Rhinol.*, Jan-Feb; 13(1):55-62.
- Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition.

Active ingredient: LEVOCETIRIZINE

ATC Code: R06AE09
Anti-histamines for systemic use – Piperazine derivatives.

Therapeutic indications:

- FDA (USA) approved indication :
 - Idiopathic urticaria, chronic or uncomplicated skin manifestations.
 - Perennial allergic rhinitis with seasonal variation.
 - Seasonal allergic rhinitis.

- EU approved indications:
 - Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis).
 - Chronic idiopathic urticaria.

Posology/duration of treatment:

- oral

MICROMEDEX Dosing Information

Adult:

- A once-daily dose of 5 mg (mg) in the evening is recommended. However, a dosage of 2.5 mg, once daily, in the evening may be adequate.

Dosage in cases presenting with Renal Failure

In patients 12 years and older with impaired renal function:

CREATININE CLEARANCE (ml/min)	DOSAGE
50 to 80	2.5 mg (mg) daily
30 to 50	2.5 mg once every other day
10 to 30	2.5 mg twice weekly (every 3 to 4 days)
less than 10	not recommended
patients undergoing dialysis	not recommended

Elderly:

- Because geriatric patients frequently have impaired renal function, dosage should be based on renal function with periodic monitoring.

Paediatric:

- In children 12 years and older, a once-daily dose of 5 mg (mg) in the evening. However, a dosage of 2.5 mg, once daily, in the evening may be adequate.
- In children 6 to 11 years of age, a once daily dose of 2.5 mg in the evening. The recommended dosage for children 6 to 11 years of age must not be exceeded.

Pharmaceutical forms: Solution/Tablets

Contraindications - relevant warnings:

a) Contraindications:

- haemodialysis patients.
- hypersensitivity to levocetirizine, cetirizine, or any component of the product.
- end-stage renal disease (creatinine clearance less than 10 ml/min).
- renally-impaired paediatric patients aged between 6 and 11 years.

b) Precautions:

- concurrent alcohol use should be avoided due to a potential increase in CNS depression and sedation.
- concurrent use of other CNS depressants should be avoided due to a potential increase in CNS depression.
- increased risk of adverse reactions in patients with impaired renal function; dosage adjustment required.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

There is a direct risk of toxicity in patients with renal impairment if the dose is not accordingly adjusted.

1.2. Interactions with (MICROMEDEX):

- Interaction can only theoretically occur with ritonavir, which could lead to increased exposure to levocetirizine and, thereby, symptoms of levocetirizine toxicity may occur.

1.3. Adverse reactions (ADRs)

- Rash
- Hepatitis
- Increased liver enzymes
- Hypersensitivity reaction
- Asthenia
- Headache
- Somnolence
- Cough
- Epistaxis
- Nasopharyngitis
- Pharyngitis
- Xerostomia
- Angioedema
- Fatigue
- Fever

1.3.1. Recent case reports (UMC database)

In the period from the 1st of January 2005 up to the 7th of February 2009, the Uppsala Monitoring Centre received 345 reports of levocetirizine with 734 ADRs. Reports came from **Austria, Chile, Czech Republic, Germany, Denmark, Spain, Finland, United Kingdom, Hungary, Ireland, Italy, Mexico, The Netherlands, Norway, Portugal, Slovakia, Thailand, Turkey, the USA and South Africa.** In the System Organ Class (SOC) *Blood and lymphatic system disorders*, 12 reports of blood diskriasias were received and from the SOC *Cardiac disorders*, 27 cases of cardiac arrhythmia were reported. An additional three cases of QT interval prolongation were

observed. The most common ADR was somnolence (36 cases), with an additional three cases of coma and five cases of lethargy reported from France, the Czech Republic, Germany, Switzerland, Hungary, Spain, Ireland, The Netherlands, and the USA. In most cases, other medicinal products, such as anti-histamines, anti-depressants, anti-psychotics and benzodiazepines, were given simultaneously. However, in a few cases only levocetirizine was administered. The database shows an increased risk of somnolence in the age group 5-14 years and also in the group aged over 45 years, and this relative risk increased with the time the drug has been on the market (from 2002 to 2009).

1.4. Indirect risk

Symptoms of overdose may include drowsiness in adults and initially agitation and restlessness, followed by drowsiness in children. There is no known specific antidote to levocetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following short-term ingestion.

Levocetirizine is not removed effectively by haemodialysis.

2. Discussion

The main therapeutic area of this drug is the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and chronic idiopathic urticaria in children aged over 6 years and adults.

From the safety profile there are recent reports of somnolence, coma and lethargy in adults and the elderly, mostly when the drug is given with anti-depressants, anti-psychotics, benzodiazepines and other antihistamines. Also, because of the pharmacokinetic characteristics of the drug, renal impairment leads to high plasma concentrations of the drug that results in drug toxicity and related ADRs.

Also, there are reported cases of cardiac arrhythmia and QT interval prolongation, which demands caution when prescribing the drug.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II	Oral use				
Publication	II	Oral use				
A	II	Oral use	Indications: allergic rhinitis, idiopathic urticaria, atopic dermatitis.	2 mg	4 mg	
CZ	I + exemption	Oral use	Indications: allergic rhinitis, urticaria. Warnings: only for adults and children > 6 years.	5 mg	5 mg	35 mg
D	Currently not available	Oral use				
E	I (1)	Oral use				
F	II	Oral use	Not marketed.			

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
H	II	Oral use	Not marketed.			
HR	I (1)	Oral use				
I	I	Oral use				
LV	II	Oral use				
NL	II	Oral use				
MK			Not marketed			
RO	II	Oral use				
SLO	I	Oral use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

LEVOCETIRIZINE, anti-histamines for systemic use – Piperazine derivatives; Oral administration.

List I

Criteria:

- concurrent use of other CNS depressants can lead to potential increases in CNS depression.
- cases of somnolence and coma have recently been reported in Europe.
- increased risk of adverse reactions in patients with impaired renal function; dosage adjustment required.

No exemption from prescription-only status is proposed.

3.2. Paediatric use

Not recommended in children younger than 6 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/5027DC/DUPLICATIO SHIELDSYNC/F1C565/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/7RTTtI2PZVTy9/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2262/ContentSetId/31/SearchTerm/levocetirizine%20/SearchOption/BeginWith#secN11088
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: LOPERAMIDE

ATC Code: A07DA03

Therapeutic indications: Treatment of acute diarrhoea for adults.

Posology/ duration of treatment:

The starting dose is 2 mg; then doses of 1 mg, if necessary, without taking more than 6 mg/day. The duration of treatment cannot exceed 2 days.

Pharmaceutical forms: Different pharmaceutical forms for oral route of administration exist (tablets, hard capsules, oral powder).

Contraindications - relevant warnings:

Contraindications:

- Children (variable age limits from a country to another).
- Acute haemorrhagic proctocolitis.
- Hypersensitivity to the active substance or to any of the excipients.

Special warnings:

If diarrhoea continues after 2 days, the patient must visit a doctor.

The treatment is not adequate for diarrhoea linked to anti-biotic treatment.

The product should not be used during pregnancy.

1. List of direct/ indirect risks (safety profile)

1.1 . Direct risks (Pharmacovigilance)

The direct risks of taking loperamide are not major. Risks mainly concern gastrointestinal disorders (primarily constipation, dyspepsia, vomiting, nausea), nervous system disorders (dizziness, fatigue, somnolence) and, rarely, allergic reactions.

1.1.1 Recent cases in Europe

Unknown

1.2. Indirect risks (incorrect use)

In case of overdosing, nervous system disorders, urine retention or ileus can occur, but fatalities are not likely.

Generally, there are no cases of abusing because of undesirable gastro-intestinal undesirable.

2. Discussion

Conditions of use of loperamide as non-prescription medicine are the same in most European countries. Differences lie mainly in age limits for paediatric use. After discussion, it was recommended that loperamide as an OTC medicine must be contra-indicated for children under 8 years of age and that specific posology for this population exists, requiring medical prescription.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Indications / Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	OTC	Oral Use		2 mg		40 mg
A	II + exemption	Oral Use	OTC only for solid oral forms. Exemption R80: OTC for solid oral presentation up to 2mg per dose and 12 mg/day. Contraindicated for children aged < 8 years.	2 mg	12 mg	
B	II + exemption	Oral Use	Suspensions are on prescription only.			
BG	II	Oral Use	No conditions or details of supply status.			
CH	II + exemption	Oral Use		2 mg		40 mg
CZ	I + exemption	Oral Use	Indications: acute diarrhée.	2 mg	16 mg	40 mg
D	I + exemption	Oral Use	Indications: acute diarrhoea. Firm preparation for oral use. Only allowed for adults and children aged >12 years.	0 mg	12 mg	24 mg
DK		Oral Use	No conditions or details of supply status.			
E	II + exemption	Oral Use	Not for use in children aged under 12 years. Maximum treatment period: 2 days. Harmonisation is on-going to classify all available loperamide medicines as OTC.	2 mg	16 mg	
F	II + exemption	Oral Use	All forms with more than 24mg/pack are List II.	2 mg		24 mg
FIN	II + exemption	Oral Use		2 mg		32 mg
GB	OTC	Oral Use	For the symptomatic treatment of acute diarrhoea in adults and children aged over 12 years.	2 mg	12 mg	12 mg
H	I + exemption	Oral Use	Chewing tablets for adults and children aged > 12 years.	2 mg	16 mg	12 mg
HR	I (1)	Oral Use		2 mg	16 mg	40 mg
I	OTC		No OTC details.			
IRL	II + exemption	Oral Use	Treatment of acute diarrhea.			
LT	OTC	Oral Use	No OTC details.			
LV	II + exemption	Oral Use	For adults and children aged 5 years and older.	2 mg		48 mg
MK	POM	Oral Use	Symptomatic treatment of acute and chronic diarrhoea of non-infectious origin (e.g. after bowel resection, in chronic inflammatory bowel disease, large bowel neoplasia, diarrhoea of hormonal origin or irritable bowel syndrome). Ileostomy.	2 mg	16 mg	
N	II + exemption	Oral Use	Mixture.			100 ml
NL	OTC	Oral Use	No OTC details.			
P	II	Oral Use	Specific posology for children aged between 2-5 years.		16 mg	
PL	I (1) + exemption	Oral Use	Acute diarrhoea. not for children aged < 6 years.	2 mg	16 mg	60 mg

Country	Prescription Status	Exemption				
		Routes of administration	Indications / Comments	MS	MDD	MQP
RO	I (1) + exemption	Oral Use	Only for oral solid pharmaceutical forms. Two-day treatments of acute diarrhoea. Only for adults and children aged over 8 years. (For children aged under 8 years only with medical prescription and adequate pharmaceutical forms).			20 mg
S	OTC	Oral Use	No OTC details.			
SLO	II	Oral Use	No conditions and details of supply status.			

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

Loperamide A07D A03, Treatment of acute diarrhoea, Oral administration.

List OTC

Conditions:

MS 2 mg

MDD 16 mg

3.2. Paediatric use

Loperamide, as an OTC medication, must not be used for children below 8 years of age. Specific posology for children below 8 years of age should exist and a medical prescription be required.

4. References:

« Répertoire des spécialités pharmaceutiques » de l'Agence française de sécurité sanitaire des produits de santé (Afssaps) : <http://afssaps-prd.afssaps.fr/php/ecodex/index.php>
<http://www.edqm.eu/melclass/>

Active ingredient: LORATADINE

ATC Code: R06AX13
Anti-histamines for systemic use – Other anti-histamines for systemic use.

Therapeutic indications:

- idiopathic chronic urticaria
- seasonal allergic rhinitis and conjunctivitis
- asthma

Posology/duration of treatment:

- Oral

MICROMEDEX Dosing Information

Adult:

- Asthma
 - 10-20 mg (mg), once daily. Treatment duration has ranged from 3 days to 8 weeks.
- Chronic idiopathic urticaria
 - 10 mg, once daily.
- Seasonal allergic rhinitis
 - 10 mg, once daily.
- **Dosage in cases presenting with Renal Failure**
 - patients with creatinine clearances of less than 30 ml/minute should be given a lower starting dose (10 mg, every other day).
- **Dosage in cases presenting with Hepatic Insufficiency**
 - oral loratadine dose of 10 mg every other day (the elimination half-life of loratadine and its active metabolite increases as hepatic function decreases).mg

Elderly:

There is extremely wide variability in the half-life data for the active metabolite in loratadine for elderly patients.

Paediatric:

- Asthma
 - 10-20 mg (mg). Once daily. The dose is based on body weight: 10 mg if weighing less than 30 kilograms (kg); 20 mg if weighing greater than 30 kg.
- Chronic idiopathic urticaria
 - 2 to 5 years of age: 5 mg (mg), or 5 ml (ml) of the syrup (1 mg/ml), once daily.
 - 6 years of age and older: 10 mg, or 10 ml of the syrup (1 mg/ml), once daily.

Seasonal allergic rhinitis

- 2 to 5 years of age: 5 mg (mg), or 5 ml (ml) of the syrup (1 mg/ml), once daily.
- 6 to 11 years of age: 10 mg, or 10 ml of the syrup (1 mg/ml), once daily.

Contraindications - relevant warnings:

a) Contraindications:

- hypersensitivity to loratadine or any of its ingredients.

b) Precautions:

- impaired liver function.
- impaired renal function.
- pregnancy.

In patients with impaired hepatic or renal function and for patients on haemodialysis, lower initial doses should be administered. Loratadine should be administered with caution to patients with disordered conductivity of the heart (Macedonia).

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Increased sweating, flushing, alopecia, dermatitis, dry hair, dry skin, urticaria, rash, pruritus, photo-sensitivity, erythema multiforme, and purpura have been reported rarely with the use of loratadine. Breast pain, breast enlargement, menorrhagia, dysmenorrhoea and vaginitis have also been reported infrequently. Rarely, abnormal hepatic function, jaundice, hepatitis, hepatic necrosis, arthralgia, myalgia, back pain and leg cramps have been reported with the use of loratadine. Other infrequent ADRs include: altered lacrimation, conjunctivitis, blurred vision, eye pain, blepharospasm, impotence, discoloured urine, altered micturition, anaphylaxis, nasal dryness, epistaxis, pharyngitis, dyspnea, nasal congestion, coughing, rhinitis, hemoptysis, sinusitis, sneezing, bronchospasm, bronchitis, laryngitis, Earache, tinnitus, asthenia, weight gain, malaise, rigors, fever, exacerbation of allergies, upper respiratory tract infection, angioneurotic oedema, anaphylaxis and peripheral edema.

Loratadine, alone or in combination with pseudoephedrine, has minimal gastrointestinal (GI) side-effects. In many studies, the reported incidence of GI side-effects from loratadine was similar to that of placebos. There have been rare post-marketing reports of mechanical upper GI obstruction in patients taking a 24-hour extended release formulation of loratadine/pseudoephedrine; in some cases requiring endoscopy to remove the tablet. The majority of the patients involved had a history of difficulty in swallowing tablets, upper GI narrowing, or abnormal oesophageal peristalsis. Headache is a common ADR. Driving should be avoided because of the possibility of sedation. FDA (USA) Pregnancy Category B.

1.2. Interactions with (MICROMEDEX):

- **Amiodarone**

Interaction Effect:

There is an increased and significant risk of QT interval prolongation and 'torsade de pointes'. Both amiodarone and loratadine are metabolised by CYP3A4 isozymes. Additionally, amiodarone is a CYP3A4 inhibitor. QT interval prolongation and 'torsades de pointes' have been reported with the co-administration of amiodarone and loratadine. Caution is advised if co-administration of these agents is being considered. Prior to using these agents concurrently, a baseline ECG should be obtained and repeated several hours after ingestion of the first dose. If QT interval prolongation or dispersion is observed, loratadine should be discontinued and monitoring of the heart rhythm should be initiated. Thus, this interaction should be considered severe.

1.3. Adverse reactions (ADRs)

- see under 1.1 Direct risks (Pharmacovigilance).

1.3.1. Recent case reports (UMC database)

In the period from the 1st of January 2005 to the 7th of February 2009, the Uppsala Monitoring Centre received 1,114 reports on loratadine with 2,617 ADRs. Reports came from Argentina, Australia, **Austria**, Canada, Chile, China, Columbia, **Germany Denmark, Spain, Finland, France, United Kingdom, Croatia, Hungary, Ireland**, Iran, **Italy, Japan, Mexico, The Netherlands, Norway**, New Zealand, Oman, Philippines, **Poland, Portugal, Russia**, Singapore, **Serbia, Sweden**, Thailand, Tunisia, **Turkey, Ukraine**, the USA, Venezuela and South Africa. In the SOC of *Cardiac disorders*, 103 reports of various cardiac arrhythmias and 10 cases of ECG QT interval prolongation are listed. In the SOC *Eye disorders*, there are some cases of blurred vision and glaucoma. One of the most common ADRs reported was gastrointestinal disturbances, particularly nausea and vomiting. There was no therapeutic response in 110 cases. The UMC database also received about 150 cases of “disturbances in consciousness”, with 96 cases of somnolence. Headache was also one of the most common ADRs (58 cases) in this period. In the SOC *Psychiatric disorders*, cases of confusion, aggression, insomnia, anxiety and depression were also reported.

There is a signal of congenital hypospadias in male babies arising in cases where mothers were taking loratadine during pregnancy. Cardiac arrhythmias, such as supra-ventricular tachycardia and ventricular arrhythmia, are also of concern.

2. Discussion

Loratadine is one of the most widely-used anti-histamines in the therapy of chronic idiopathic urticaria, seasonal allergic rhinitis, conjunctivitis and asthma.

The most common ADR is somnolence, especially in children, and in combination with anti-depressives, benzodiazepines and anti-psychotics in adults and the elderly. There is also a slight risk of cardiac arrhythmias, and caution is required in patients with a history of cardiac diseases. There is also a risk of congenital hypospadias in male offspring of mothers who take loratadine during pregnancy.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	Currently not available	Oral use				
Publication	II + exemption	Oral use		10 mg	10 mg	
A	II + exemption	Oral use	Indications: allergic rhinitis, idiopathic urticaria. Only in combination with warning (W10): For children aged < 12 years. POM.	10 mg	10 mg	
B	II + exemption	Oral use	Syrups are POM.			
BG	II	Oral use				
CH	II + exemption	Oral use		10 mg		140 mg

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
CZ	II + exemption	Oral use	Indications: allergic rhinitis, allergic conjunctivitis, urticaria, itching.	10 mg	10 mg	70 mg
D	OTC	Oral use				
DK	OTC	Oral use				
E	I + exemption	Oral use	Children aged 6-12 years. MDD=5 mg.	10 mg / 5 mg	10 mg / 5 mg	
F	II + exemption	Oral use	Indications: rhinitis.	10 mg	10 mg	70 mg
FIN	II + exemption	Oral use		10 mg		100 mg
GB	II + exemption	Oral use	This formulation became available as GSL in a maximum pack size of 7 tablets in 2002. The limit on pack/container size containing a maximum 100mg was removed for sales under the supervision of a pharmacist in 2002.		10 mg	
H	I + exemption	Oral use	Indications: symptoms of seasonal allergic rhinitis and chronic idiopathic urticaria. Loratadine 10mg tablets switched to non-prescription status in 2005. Warnings: severe hepatic impairment the dose needs to be decreased. If allergy is suspected and before confirmation through skin testing, the treatment has to be suspended.	10 mg	10 mg	100 mg
HR	I + exemption	Oral use	Indications: symptoms of seasonal allergic rhinitis.	10 mg	10 mg	70 mg
I	II	Oral use				
IRL	II + exemption	Oral use		10 mg	10 mg	
LT	II	Oral use				
LV	POM	Oral use	Indications: seasonally-related or long-lasting allergic rhinitis, allergic conjunctivitis, chronic idiopathic urticaria. Warnings: Lower initial doses should be administered to patients with impaired hepatic or renal function, and in patients on hemodialysis. To be administered with caution in patients with conductivity disorders of the heart.	10 mg		
N	II + exemption	Oral use	Pack size of up to 10 tablets to treat pollen allergies.			
NL	OTC	Oral use				
MK			Not marketed			
P	II	Oral use				
RO	OTC	Oral use	Indications: perennial rhinitis, seasonal allergic rhinitis and urticaria in adults and children aged > 2 years. Warnings: MS=1mg/ml syrup; MDD 10 mg for children 6-12 years (body mass >30mg) or 5mg for children 6-12 years (body mass <30 kg).	10 mg	10 mg	100 mg
S	II + exemption	Oral use		10 mg		300 mg
SLO	OTC	Oral use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

LORATADINE, anti-histamines for systemic use – Other anti-histamines for systemic use; Oral administration.

List II + exemption

Criteria:

- Prescription status is List II + exemption in most Member States.
- Safe profile, but some concerns about cardiac safety. An additional concern for hypospadias in male newborns (caution required during pregnancy).
- Caution required in the elderly and patients with renal impairment.
- Recommendation for OTC prescription status:
 - o Indication: seasonal allergic rhinitis or conjunctivitis.
 - o MS corresponds to 10 mg, MDD corresponds to 10 mg, MQP corresponds to 70 mg.
 - o Only short-term use for seasonal allergic rhinitis, conjunctivitis.
 - o Only for adults and children aged > 12 years.

3.2. Paediatric use

Not recommended for children less than 2 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/86C3D9/DUPLICATIONSHIELDSYNC/AFA053/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/7RTTtI2Q15E2J/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/0920/ContentSetId/31/SearchTerm/loratadine%20/SearchOption/BeginWith
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: MECLOZINE
Synonyms: Meclizine, Parachloramine

ATC Code: R06AE05
Anti-histamines for systemic use – Piperazine derivatives.

Therapeutic indications:

- Dyslexia
- Headache, motion sickness
- Radiation-induced nausea and vomiting
- Vertigo
- pregnancy-induced vomiting

In Romania, meclozine is also authorised for the symptomatic treatment of vertigo due to Ménière's Disease, labyrinthitis and nausea and vomiting from various causes.

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- Motion sickness; treatment and prophylaxis
 - 25-50 mg orally, 1 hour before departure; repeated, if necessary, at 24 hr intervals.
- Radiation-induced nausea and vomiting; treatment and prophylaxis
 - 50 mg orally, 2 to 12 h prior to radiotherapy.
- Vertigo
 - 25 to 100 mg a day orally divided in separate doses, depending on clinical response.

Paediatric:

- safety and effectiveness not established in children under 12 years of age.

In Romania, used for the symptomatic treatment of vertigo due to Ménière's Disease, labyrinthitis and other nausea and vomiting with a maximal daily dose of 100 mg for adults and children over 12 years of age.

Pharmaceutical forms: Tablets

Contraindications - relevant warnings:

a) Contraindications: hypersensitivity to meclozine.

b) Precautions:

additive CNS depressant effects can occur with the concomitant use of other CNS depressants.

asthma.

- drowsiness may impair the patient's ability to perform activities requiring alertness.
- prostatic hyperplasia.
- glaucoma.

- drowsiness may impair the patient's ability to perform activities requiring alertness.
- prostatic hyperplasia.
- glaucoma.

Meclozine should be used with caution in patients with raised intra-ocular pressure (including glaucoma), prostatic hypertrophy, bronchitis, bronchiectasis and asthma (Romania).

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

FDA (USA) Pregnancy Category B.

1.2. Interactions with:

- **Procarbazine**

Interaction Effect: CNS depression

To minimise CNS depression and possible potentiation, caution should be exercised in co-administering procarbazine and anti-histamines. The severity of the interaction is considered moderate, but the substantiation of the interaction is theoretical, and the probable mechanism is unknown.

1.3. Adverse reactions (ADRs)

- dryness of the mouth
- nausea and vomiting
- amnesia
- drowsiness
- fatigue
- headache and vertigo
- extrapyramidal disease
- blurred vision

1.3.1. Recent case reports (UMC database)

In the period from the 1st of January 2005 to the 7th of February 2009, the Uppsala Monitoring Centre received 122 reports on meclozine with 610 ADRs. Reports came from Canada, Cuba, **Germany**, **Norway**, New Zealand, **Sweden** and the USA. The most common ADR was dizziness (27 cases), headache (10 cases), and somnolence (9 cases). There have been two reports of death from the USA, involving other drugs such as anti-depressants and benzodiazepines.

The UMC ADR database suggests a slight indication for eventual weight gain, especially in women aged over 45 years old, as an ADR of meclozine.

2. Discussion

The main therapeutic area of this drug is treatment and prophylaxis of motion sickness, radiation-induced nausea and vomiting, and pregnancy-induced vertigo and vomiting. In Romania, additional indications for Ménière's Disease and labyrinthitis therapy exist. The safety profile is safe, which means that there have been no serious ADRs reported within the last three years in Europe. However, in combination with other CNS depressants, meclozine may cause somnolence and other CNS ADR symptoms. It is also indicated for vomiting during pregnancy and the drug is classified by the FDA (USA) as Pregnancy Category B. There no reports of serious birth malformations or other ADRs in the SOC *Pregnancy*.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II	Oral Use				
Publication	II	Oral Use				
A	II	Oral Use				
B	OTC	Oral Use				
CH	II + exemption	Oral Use		50 mg	100 mg	
CZ			Not marketed			
D	I (1)	Oral Use				
DK	OTC	Oral Use				
E	OTC	Oral Use	As an anti-emetic agent.			
F	II + exemption	Oral Use				
FIN	OTC	Oral Use				
GB	OTC	Oral Use	Information from the UMC Drug Dictionary.			
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LV			Not marketed			
N	OTC	Oral Use				
NL	OTC	Oral Use				
MK			Not marketed			
RO	II	Oral Use	Indication: vertigo due to Ménière's disease, labyrinthitis and other causes, for nausea and vomiting of various causes. Warning. caution in patients with raised intra-ocular pressure (including glaucoma), prostatic hypertrophy, bronchitis, bronchitis, bronchiectasis, and asthma. MDD=50 mg adults and children aged >12 years for vertigo (Ménière's disease).	30 mg	100 mg	300 mg

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

MECLOZINE, anti-histamines for systemic use – piperazine derivatives, Oral administration.

List II + exemption

Criteria:

- safe profile.
- only OTC prescription status for the indication of treatment and prophylaxis of motion sickness.
- for adults and children over 12 years of age.

3.2. Paediatric use

- safety and effectiveness not established in children aged less than 12 years.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/7C4A9C/DUPLICATIO SHIELDSYNC/6A5548/ND_PG/PRIH/ND_B/HCS/SBK/1/ND_P/Main/PFPUI/fX129jh2Q81auV/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/0544/ContentSetId/31/SearchTerm/meclozine/SearchOption/BeginWith
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: **MEPYRAMINE**

ATC Code: R06AC01
Anti-histamines for systemic use – substituted ethylene diamines.

D04AA02
Antipruritics, including anti-histamines, anaesthetics, *etc.* - Anti-histamines for cutaneous use.

Therapeutic indications:

- Pruritus, pain, minor burns and scalds, insect bites
- Allergic skin reactions

Pharmaceutical forms: Tablets, ointment, solution for injection

Contraindications - relevant warnings:

a) Contraindications:

- hypersensitivity to mepyramine.

b) Precautions:

- asthma.
- bladder neck obstruction.
- breast feeding.
- chronic bronchitis.
- concurrent use of alcohol or other CNS depressants.
- driving or performing other tasks that require alertness.
- narrow-angle glaucoma.
- not to be used for insomnia of duration greater than 2 weeks.
- pyloroduodenal obstruction.
- stenosing peptic ulcer.
- symptomatic prostatic hypertrophy.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

The most common adverse effect of sedating anti-histamines is CNS depression, with effects varying from slight drowsiness to deep sleep and including lassitude, dizziness, and lack of coordination (although, paradoxically, stimulation may occasionally occur, especially at high doses and in children or the elderly). These sedative effects, when they occur, may diminish after a few days of treatment.

Occasional gastrointestinal adverse effects include nausea, vomiting, diarrhoea and/or epigastric pain.

1.2. Interactions with:

No data available (MICROMEDEX).

1.3. Adverse reactions (ADRs)

- Common:
 - Neurologic: Somnolence

2. Discussion

Mepyramine, an ethylenediamine derivative, is a sedating anti-histamine with anti-muscarinic and sedative properties. Mepyramine maleate is used for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders. Mepyramine maleate is also a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold.

Mepyramine maleate has been given in an oral dose of 50 mg at night as a hypnotic for the short-term management of insomnia.

A cream containing 2% mepyramine maleate is used locally for insect bites or stings, and for hypersensitivity and pruritic skin conditions but, as with any anti-histamine, there is a risk of sensitisation. It has also been used in eye drops.

Mepyramine maleate is available for parenteral use in some countries. Mepyramine hydrochloride has also been given parenterally or administered rectally.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
A	OTC	Cutaneous Use				
		Oral Use				
B	OTC	Oral Use	Indication: used in combination with dextromethorphan, guaifenesin and phenylephrine for treatment of cough. Warning: can cause sedation.			
		Nasal Use	Only in combination preparations.			
CH	OTC	Cutaneous Use	Not marketed from 2008.			
CZ			Not marketed			
D	OTC	Oral Use				
DK	OTC	Cutaneous Use				
E	OTC	Oral Use	Common colds (for adults).		75 mg	
		Oral Use				
F			Not marketed			
GB	OTC	Cutaneous Use	General sale if maximum strength = 2% and if sold for symptomatic relief of insect stings and bites and nettle stings, for adults and children aged 2 years and over.			
H			Not marketed			
HR			Not marketed			
I			Not marketed			
IRL	OTC	Oral Use				
LV			Not marketed			
MK			Not marketed			
P	OTC	Oral use				
PL	II + exemption	Oral use	Prescription only: 24 tablets/ pack			
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

MEPYRAMINE, anti-histamines for systemic use – substituted ethylene diamines, Oral administration.

List II + exemption

Criteria:

- only OTC prescription status for short-term oral therapy of seasonal allergic symptoms.
- not widely marketed as a single active ingredient.
- MDD corresponds to 75 mg.

MEPYRAMINE anti-pruritics (including anti-histamines, anesthetics, *etc.*) - Anti-histamines for cutaneous use.

List OTC

Criteria:

- maximum strength is 2%.
- symptomatic relief of insect stings and bites and nettle stings, for adults and children aged 2 years and over.
- caution required as local anti-histamines can induce hypersensitivity.

3.2. Paediatric use

Not recommended for per-oral or parenteral use in children aged less than 12 years. Can be used topically in children aged over 2 years.

4. References:

- http://ovidsp.tx.ovid.com/spa/ovidweb.cgi?&S=HHEPFPDLODDGGAMMCGLIBOKKKONA00&Link+Set=S.sh.17%7c1%7csl_10
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: MIZOLASTINE

ATC Code: R06AX25
Anti-histamines for systemic use – Other anti-histamines for systemic use.

Therapeutic indications:

Mizolastine is a long-acting H₁- anti-histamine indicated for the symptomatic relief of seasonal allergic rhino-conjunctivitis (hay fever), perennial allergic rhino-conjunctivitis and urticaria.

Posology/duration of treatment: per os

MICROMEDEX Dosing Information

Adult:

- 10 mg daily.

Pharmaceutical forms: modified release tablets

Contraindications - relevant warnings:

a) Contraindications:

- Hypersensitivity to mizolastine.
- Concomitant administration with macrolide antibiotics or systemic imidazole anti-fungals.
- Significantly impaired hepatic function.
- Clinically significant cardiac disease or a history of symptomatic arrhythmias.
- Patients with known or suspected QT interval prolongation or with electrolyte imbalance, in particular hypokalaemia.
- Clinically significant bradycardia.
- Drugs known to prolong the QT interval, such as Class I and III anti-arrhythmics.

b) Precautions:

Mizolastine has a weak potential to prolong the QT interval in some individuals. The degree of prolongation is modest and has not been associated with cardiac arrhythmias.

The elderly may be particularly susceptible to the sedative effects of mizolastine and the potential effects of the drug on cardiac repolarisation.

Most patients taking mizolastine may drive or perform tasks requiring concentration. However, in order to identify sensitive people who have unusual reactions to drugs, it is advisable to check the individual response before driving or performing complicated tasks.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

- **Gastro-intestinal disorders:**
 - **Common:** dry mouth, diarrhea, abdominal pain (including dyspepsia), nausea.
- **CNS disorders and psychiatric disorders:**
 - **Common:** drowsiness (often transient), headache, dizziness.
 - **Uncommon:** anxiety and depression.
- **Liver disorders**
 - **Uncommon:** raised liver enzymes.
- **Haematological disorders**
- **Very rare:** low neutrophil count.

- **General**
 - **Common:** asthenia (often transient), increased appetite associated with weight gain.
 - **Very rare:** allergic reactions including anaphylaxis, angioedema, generalised rash/urticaria, pruritus and hypotension.
- **Cardiovascular disorders**
 - **Uncommon:** hypotension, tachycardia, palpitations.
 - **Very rare:** vasovagal attack.
- **Musculo-skeletal disorders**
 - **Uncommon:** arthralgia and myalgia.

There have been reports of bronchospasm and aggravation of asthma, but in view of the high frequency of asthma in the patient population being treated, a causal relationship remains unproven.

Treatment with certain anti-histamines has been associated with QT interval prolongation, increasing the risk of serious cardiac arrhythmias in susceptible subjects.

Minor changes in blood sugar and electrolytes have been rarely observed. The clinical significance of these changes in otherwise healthy individuals remains unclear. Patients at risk (*i.e.* diabetics and those patients susceptible to electrolyte imbalances and cardiac arrhythmias) should be monitored periodically.

The safety of mizolastine for use during pregnancy has not been established. The evaluation of experimental animal studies has not indicated direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and/or peri- and post-natal development. However, as with all drugs, mizolastine should be avoided in pregnancy, particularly during the first trimester.

Mizolastine is excreted into breast milk, therefore its use by lactating women is not recommended.

In Paediatric Use

Mizolastine is not recommended for children under 12 years of age.

1.2. Interactions

Although the bio-availability of mizolastine is high and the drug is principally metabolised by glucuronidation, systemically administered ketoconazole and erythromycin moderately increase the plasma concentration of mizolastine and, thus, their concurrent use is contraindicated.

Concurrent use of other potent inhibitors (*e.g.* cimetidine, ciclosporin, and nifedipine) or substrates (*e.g.* cytochrome P450 3A4) of hepatic oxidation with mizolastine should be approached with caution.

1.3. Adverse reactions (ADRs)

- See under 1.1 Direct risks (Pharmacovigilance).

1.3.1. Recent case reports (UMC database)

In the period from 1 January 2005 to 7 of February 2009, the Uppsala Monitoring Centre received 59 reports on mizolastine, with 119 ADRs. Reports came from **Germany, Spain, France, United Kingdom, Greece, Italy, the Netherlands** and Thailand. Most ADR reports came from Europe and no reports were received from the USA, from which more than 50% of all reports in the UMC database were received during this period, and explains the relatively low number of reports for mizolastine. There are four reports of cardiac arrhythmia and nine reports of somnolence. Of these nine cases of somnolence, five occurred after 10 mg of mizolastine was taken for about 14 days and, in the remaining cases, there were interactions between mizolastine and other anti-histamines or CNS depressants. Frequent, but not serious, reports of gastrointestinal ADRs have been received.

The combination database of the UMC ADR database shows that there is an increased risk for developing somnolence in women aged between 25 and 44 years.

2. Discussion

Mizolastine is an H₁ antagonist with minimal effect on the CNS at therapeutic doses (10 mg) but, as post-marketing data show, somnolence is the most frequently quoted ADR of the quite rare ADR reports. It has similar anti-histamine activity as other second-generation anti-histamines. Its pharmacokinetic profile allows for once-daily dosing with minimal distribution into the CNS. Therapeutic target areas for mizolastine include allergic rhinitis and urticaria. In addition to once-daily dosing and a favorable side-effect profile, the reduced propensity for arrhythmias associated with mizolastine will most likely favour the selection of this drug over other second generation anti-histamines in future. However, further studies and clinical usage of mizolastine will ultimately determine its relative therapeutic advantage.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II	Oral Use				
Publication	II	Oral Use				
A	II	Oral use	Indications: seasonal and perennial allergic rhinitis (with or without allergic conjunctivitis), perennial allergic urticaria. Not marketed	10 mg	10 mg	
B	POM					
BIH			Not marketed			
CZ			Not marketed			
F	I	Oral Use				
H			Not marketed			

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
HR			Not marketed			
I	II	Oral Use		10 mg	10 mg	
LV	II	Oral Use				
MK			Not marketed			
P	POM					
PL			Not marketed			
RO	II	Oral Use				
SLO	I	Oral Use				
UK			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

MIZOLASTINE, anti-histamines for systemic use – Other anti-histamines for systemic use, Oral administration.

List II

Criteria:

- new compound.
- the safety profile is good, but further data are needed to be entirely certain of its effect on cardiac arrhythmias.
- only for adults and children over 12 years of age.

No exemption from prescription-only status is proposed.

3.2. Paediatric use

Mizolastine is not recommended for children under 12 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/814B3F/DUPLICATIONSHIELDSYNC/8AF405/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/UI1aphB2Qp2Coc/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/1792/ContentSetId/31/SearchTerm/mizolastine%20/SearchOption/BeginWith#secN10591
- <http://emc.medicines.org.uk/medicine/19970/SPC/Mizollen+10+mg+modified+release+tablet>
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: OLOPATADINE

ATC Code: S01GX09

Posology/duration of treatment

Therapeutic indications:

Allergic conjunctivitis, itching (ophthalmic) (FDA approved indications).

Posology/ duration of treatment:

Dosing Information:

Olopatadine Hydrochloride

Adults: 1 drop of 0.1% solution in affected eye(s), twice daily (at 6-8 hour intervals) or 1 drop of 0.2% solution in affected eye(s) once daily.

Paediatric:

Aged 3 years and older: 1 drop of 0.1% solution in affected eye(s), twice daily (at 6-8 hour intervals) or 1 drop of 0.2% solution in affected eye(s) once daily.

Pharmaceutical form: ophthalmic solution

Contraindications:

Hypersensitivity to olopatadine products or benzoate compounds.

Precautions:

Not for contact lens-related irritation.

1. List of direct/indirect risks (safety profile)

Adverse Reactions:

Dermatologic:

Pruritus was reported in less than 5% of patients treated with olopatadine hydrochloride 0.1% ophthalmic solution.

Gastrointestinal:

Nausea and taste perversion were reported in 5% or less of patients treated with olopatadine hydrochloride 0.1% or 0.2% ophthalmic solution.

Hypersensitivity and infection were reported in 5% or less of patients treated with olopatadine hydrochloride 0.1% or 0.2% ophthalmic solution.

Neurologic:

Asthenia was reported in 5% or less of patients treated with olopatadine hydrochloride 0.1% or 0.2% ophthalmic solution. Headache was reported in 7% of patients treated with olopatadine hydrochloride 0.1% ophthalmic solution and in 5% or less of patients treated with olopatadine hydrochloride 0.2% ophthalmic solution.

Ophthalmic:

Blurred vision, burning sensations in the eye, eyelid oedema, foreign body sensations, keratitis, ocular hyperaemia and xerophthalmia have all been reported in 5% or less of patients treated with olopatadine hydrochloride 0.1% or 0.2% ophthalmic solution.

Drug interactions:

No information provided. (at least relating to ophthalmic use).

1.1. Indirect risks (incorrect use)

Overdosing: no information provided.

2. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	POM	Ophthalmic use				
BIH	Not marketed	Ophthalmic use				
CH	II	Ophthalmic use				
CZ	I	Ophthalmic use				
F	I	Ophthalmic use				
H	I	Ophthalmic use				
HR	HR	Ophthalmic use				
I	NA	Ophthalmic use				
MK	I	Ophthalmic use				
GB	II	Ophthalmic use				
P	I	Ophthalmic use				
RO	II	Ophthalmic use				
SLO	I	Ophthalmic use				

2.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

OLOPATADINE S01GX08

MS 0.1%, MDD 0.2%, MQP 5ml (ophthalmic solution).

The proposed classification: List I**2.2 Paediatric use:**

Safety and effectiveness in children under the age of 3 years have not been established.

3. References:

- <http://www.rxlist.com/patanol-drug.htm>
- <http://www.micromedex.com/products/hcs/>
- <http://www.micromedex.com/products/pdrlibrary>
- Martindale, Thompson Healthcare 2009
- http://www.edqm.eu/melclass/Expert/Expert_search.aspx

Active ingredient: OMEPRAZOLE

ATC Code: A02B C01
Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors.

Therapeutic indications: omeprazole is used in conditions where inhibition of gastric acid secretions may be beneficial, including aspiration syndrome, dyspepsia, gastro-oesophageal reflux disease, peptic ulcer disease and Zollinger-Ellison syndrome.

Posology/duration of treatment (2):
Oral dosage

The usual dose for the treatment of **gastro-oesophageal reflux disease** is 20 mg orally, once daily for 4 weeks, followed by a further 4 to 8 weeks if not fully resolved. In refractory oesophagitis, a dose of 40 mg/day may be used. Maintenance therapy after healing of oesophagitis is 20 mg, once daily, and for acid reflux it is 10 mg/day. In children over 1 year of age, UK licensed doses for oral treatment are 10 mg/day in those weighing 10-20 kg, and 20 mg/day in those weighing over 20 kg. These doses may be doubled if necessary. The British National Formulary for Children (BNFC) recommends a dose of 700 micrograms/kg/day in children aged 1 month to 2 years, increased if necessary to up to 3 mg/kg/day, or 20 mg/day, whichever is less. Similar initial doses are suggested for neonates.

In the management of **peptic ulcer disease** a single daily dose of 20 mg, or 40 mg in severe cases, may be given orally. Treatment can be continued for 4 weeks for duodenal ulcers and 8 weeks for gastric ulcers. Where appropriate, a dose of 10-20 mg, once daily, may be administered for maintenance.

For the eradication of *Helicobacter pylori* in peptic ulceration, omeprazole may be combined with anti-bacterials in dual or triple therapies. Effective **triple therapy** regimens incorporating omeprazole 20 mg taken twice daily include: amoxicillin 500 mg and metronidazole 400 mg (both three times daily); clarithromycin 500 mg and metronidazole 400 mg (or tinidazole 500 mg) (both twice daily); or with amoxicillin 1 g and clarithromycin 500 mg (both twice daily). These regimens are for 1 week duration. **Dual therapy** regimens, such as omeprazole 40 mg/day with either amoxicillin (750 mg to 1 g, twice daily) or clarithromycin (500 mg, three times daily), are less effective and must be administered for 2 weeks. Omeprazole treatment alone may be continued for a further 4 to 8 weeks.

Doses of 20 mg/day are used in the treatment of **NSAID-associated ulceration**. A dose of 20 mg/day may also be used for prophylaxis in patients with a history of gastro-duodenal lesions who require continued NSAID treatment.

The initial recommended dosage for patients with **Zollinger-Ellison syndrome** is 60 mg orally once daily, adjusted as required. The majority of patients are effectively treated by doses in the range of 20 to 120 mg/dly, but doses of up to 120 mg three times daily have been used. Daily doses above 80 mg should be given as divided doses.

Omeprazole is also used for the prophylaxis of **acid aspiration** during general anaesthesia, in a dose of 40 mg the evening before surgery and a further 40 mg two to six hours before the procedure.

Pharmaceutical forms: coated tablets, gastro-resistant coated tablets, capsules, gastro-resistant capsules, capsules containing enteric-coated pellets, granules, solution for injection.

Contraindications:

- known hypersensitivity to omeprazole or to any of the other constituents of the formulation.
- when gastric ulcer is suspected, the possibility of malignancy should be excluded before treatment with omeprazole is instituted, as treatment may alleviate symptoms and delay diagnosis.
- omeprazole like other proton-pump inhibitors should not be administered with atazanavir (see interactions).

Relevant warnings:

Decreased gastric acidity due to any cause, including the use of proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections such as by *Salmonella* and *Campylobacter*.

Some children with chronic illnesses may require long-term treatment, although this is not recommended.

The dose of omeprazole may need to be reduced in patients with hepatic impairment.

1. List of direct/indirect risks (safety profile)**1.1. Direct risks/pharmacovigilance*****General toxicity and relevant reproductive toxicity, genotoxic or carcinogenic properties***

Early toxicological studies in rats given high doses of omeprazole over 2 years identified carcinoid tumours of the gastric mucosa associated with complete blockage of gastric acid secretion, leading to hypergastrinaemia and hyperplasia of enterochromaffin-like cells (ECL) (2,3). Hypergastrinaemia can occur with both short- and long-term omeprazole therapy, and may be higher in patients with *Helicobacter pylori* infection(4).

Helicobacter pylori is also a cause of atrophic gastritis, another risk factor for stomach cancer, and one study found that omeprazole increased the risk of atrophic gastritis in *H. pylori*-positive patients with gastro-oesophageal reflux disease(5).

There are conflicting data on the risk and clinical implications of enterochromaffin-like cell hyperplasia in patients on long-term proton pump inhibitor therapy. These drugs now have a track record of more than 15 years of use worldwide, and no major new issues regarding safety have emerged (6)..

Proton pump inhibitors have not been associated with a major teratogenic risk when used during the first trimester of pregnancy, although caution is still warranted (6).

Risk of serious type A adverse reactions in the general population (those that result from exaggeration of a medicinal product's expected pharmacological actions when given in the usual therapeutic dose; normally dose-dependent).

Mechanism of action: Omeprazole belongs to a new class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anti-cholinergic or H₂-histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H⁺/K⁺ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterised as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion, irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more (2).

Anti-secretory activity: After oral administration, the onset of the anti-secretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of secretion is about 50% of maximum after 24 hours and the duration of inhibition lasts up to 72 hours. The anti-secretory effect thus lasts far longer than would be expected from the very short (less than one hour) plasma half-life, apparently due to prolonged binding to the parietal H⁺/K⁺ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

Results from numerous studies of the anti-secretory effect of multiple doses of 20 mg and 40 mg of omeprazole in normal volunteers and patients are shown below. The “max” value represents determinations at a time of maximum effect (2-6 hours after dosing), while “min” values are those 24 hours after the last dose of omeprazole (2).

Recent study: Recovery of acid secretion following inhibition by all PPIs, other than pantoprazole⁷, may depend on both protein turnover and reversal of the inhibitory disulfide bond.

In vivo, the rate of recovery of acid secretion varies depending on the PPI used. Acid secretion in humans returns in the case of omeprazole with a half-life of 27½ hours, after lansoprazole with a half-life of 12.9 hours.

In Paediatric use: On a per kilogram (weight) basis, children require higher doses of omeprazole than adults due to the different pharmacokinetics of omeprazole in children. The preferred dosage form for use in children is buffered PPI suspensions (8).

Interactions with commonly-used medicines that can produce serious adverse reactions

- absorption of ketoconazole or itraconazole may be reduced during omeprazole treatment.
- omeprazole can prolong the elimination of diazepam, phenytoin, warfarin and other vitamin K antagonists that are, in part, substrates for cytochrome P450.
- plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration. This is considered to be a useful interaction for *H. pylori* eradication.
- simultaneous treatment with omeprazole and digoxin in healthy subjects leads to a 10% increase in the bio-availability of digoxin.
- co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decreases in AUC (area under the plasma curve), C_{max} (maximum concentration), and C_{min} (minimum concentration)).
- concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.
- concomitant administration of omeprazole and a CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

For inefficient metabolisers

The major enzyme involved in omeprazole metabolism is cytochrome P450 isoenzyme CYP2C19. This enzyme is polymorphically expressed, and individuals who are deficient in the enzyme are inefficient metabolisers of omeprazole. This occurs in about 3% of Caucasians and 15% of the Chinese, Japanese and Korean populations. These individuals

have markedly higher plasma concentrations of omeprazole, and they may require dosage adjustment. Some omeprazole is metabolised by CYP3A to form omeprazole sulfone and hydroxyl-omeprazole, and some by CYP2D6 to form desmethylomeprazole (2).

The safety of a medicinal product

Adverse effects of omeprazole

The adverse effects reported most frequently with omeprazole have been headache, diarrhoea and skin rashes, some of which have been severe enough to require cessation of treatment. Other effects include pruritus, dizziness, fatigue, constipation, nausea and vomiting, flatulence, abdominal pain, arthralgia and myalgia, urticaria and dry mouth. Isolated cases of photosensitivity, bullous eruption, erythema multiforme, angioedema and anaphylaxis have been reported. Effects on the CNS include occasional insomnia, somnolence and vertigo. Reversible confusional states, agitation, depression and hallucinations have occurred in severely ill patients. Raised liver enzymes and isolated cases of hepatitis, jaundice and hepatic encephalopathy have been reported. Other adverse effects, reported rarely or in isolated cases, include paraesthesia, blurred vision, alopecia, stomatitis, sweating, taste disturbances, peripheral oedema, malaise, hyponatraemia, blood disorders (including leucopaenia, thrombocytopaenia, agranulocytosis) and interstitial nephritis).

Proton pump inhibitors may increase the risk of gastrointestinal infections because of their acid suppressive effects (2).

New data: On August 9, 2007, the FDA released an early communication about an on-going safety review for omeprazole and esomeprazole, regarding the preliminary review of new data from two small long-term clinical studies in patients with severe gastro-oesophageal reflux disease (GERD) as regards concerns that long-term use of omeprazole or esomeprazole may have increased the risk of heart attacks, heart failure, and heart-related sudden death in those patients taking either one of the drugs compared to patients who received surgery. The FDA's preliminary conclusion from the safety review is further supported by an additional analysis of 14 comparative studies of omeprazole, of which four were placebo-controlled. Patients in these studies were treated for up to two years. In these studies, there were fewer heart attacks or other heart problems reported in the patients treated with omeprazole compared to patients that were given a placebo. Although these studies were not specifically conducted to assess the risk of heart problems, and patient follow-up was incomplete, they do not suggest an increased risk of heart problems with the use of omeprazole. The FDA will continue its review of all available data (9). In the USA, omeprazole and esomeprazole are available by prescription; omeprazole is also sold OTC for frequent heartburn.

1.2. Indirect risks

Underlying condition requiring medical attention and supervision

Occasional heartburn is not dangerous, but chronic heartburn can indicate serious problems and can develop into gastro-oesophageal reflux disease (GERD). Also, other conditions such as hiatal hernia, pregnancy, diabetes and many auto-immune diseases such as CREST syndrome, Raynaud phenomenon and scleroderma, are related to heartburn.

The most frequent causes of heartburn/acid reflux are: coffee, tea, and other drinks that contain caffeine (caffeine can relax the lower oesophageal sphincter (LES), allowing stomach contents to reflux into the oesophagus), chocolate (which contains concentrations of theobromine - a compound that occurs naturally in many plants such as cocoa, tea and coffee plants, which relaxes the esophageal sphincter muscle, letting stomach acid squirt up into the esophagus), certain foods (such as fatty foods, spicy foods, onions, garlic, citrus fruits, tomato sauce, carbonated beverages and peppermint), alcohol, large meals, lying

down too soon after eating, stress (increases acid production), certain medications (including sedatives, anti-depressants and calcium channel blockers for high blood pressure), and cigarette smoking (relaxes the LES and stimulates stomach acid secretion).

Proton pump inhibitors relieve dyspeptic symptoms associated with gastric carcinoma and can therefore delay its diagnosis. In addition, there is some evidence that they may also endoscopically 'heal' early gastric carcinoma so that the diagnosis is missed (2).

Self-assessment

In the management of peptic ulcer disease, eradication of *Helicobacter pylori*, Zollinger-Ellison Syndrome and Non-Steroidal Anti-Inflammatory Drugs (NSAID)-associated ulceration are important considerations. However, due to the nature of these conditions, the duration of their symptoms and their reoccurrence and consequences, they cannot be correctly self-assessed.

In relation to gastro-oesophageal reflux disease, however, the symptoms are self-assessable in adults for short-term treatment.

2. Discussion

- Ranitidine and famotidine are listed as OTC in Resolution ResAP2007 1 for gastro-oesophageal reflux disease.
- Gastro-oesophageal reflux symptoms can be relieved with anti-acids and dietary habits.
- In January 2010, the European Medicines Agency (EMA) announced completion of a review of Losec products containing omeprazole to harmonise marketing authorisations in the EU. Indications for prescription availability were agreed by the Committee for Medicinal Products for Human Use (CHMP). The CHMP also recommended non-prescription availability for the treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

3. Conclusions – recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	II	Oral use				
A	II					
B	II + exemption	Oral use	Relief of reflux-like symptoms such as heartburn. Two week treatment only.	20 mg	20 mg	280 mg
BG	II					
BiH	I			20mg	Zollinger-Ellison: 120mg	560mg
CH	II					
CZ	I (1) + exemption	Oral use	Relief of reflux-like symptoms such as heartburn.	10 mg	20 mg	280 mg
D	I (1)					
DK	II					
E	II					

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
F	II					
FIN	II					
GB	II + exemption	Oral use	For the relief of reflux-like symptoms such as heartburn in adults aged 18 years and over. Maximum treatment period: 4 weeks.	10 mg	20 mg	280 mg
H	II					
HR	I + exemptions		Short-term treatment.	10mg	20mg	280 mg
I	II					
IRL	II					
LT	II					
LV	II					
N	II + exemption	Oral use	Tablets 10 mg.			
NL	II + exemption					
PL	I+ exemptions		2 week treatment.	10 mg	20 mg	280 mg
P	II + exemption		For short-term treatment of up to 14 days.	10 mg	10 mg	560 mg
RO	II					
S	II + exemption	Oral use, enterotablets	OTC status applies to treatment of symptoms of gastro-oesophageal reflux disease (e.g. heartburn, regurgitation) and for short-term treatment of up to 14 days.	10 mg		140 mg
SLO	I					

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

Omeprazole, proton pump inhibitors, oral administration.

Liste II + exemption

The recommended conditions for exemption are: MS 20 mg, MDD 20 mg, MQP 280 mg, for the relief of reflux-like symptoms such as heartburn and acid regurgitation in adults, and a maximum treatment period of up to 14 days.

Criteria for prescription availability:

- For long-term treatment and prevention of conditions such as duodenal ulcers, peptic ulcers, *H. pylori* eradication, Zollinger-Ellison Syndrome, symptomatic gastro-oesophageal disease and NSAID-associated ulcers.
- omeprazole may cause serious adverse reactions in a part of the population (*i.e.* elderly patients, those using other medicines, inefficient metabolisers) due to indirect dangers, even when the product is used correctly (*i.e.* according to the patient information)...
- the risk group is not clearly identifiable (no preventive action – endoscopic examination).
- use of omeprazole might delay diagnosis of an underlying disease.
- risk of adverse reactions, especially in a target population (the elderly).

Criteria for non-prescription availability:

- Treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults. MS 20mg; MDD 20mg; MQP 280mg.
- The symptoms are suitable for self-assessment, providing that there is suitable product information and advice from a pharmacist, where necessary.
- A short period of treatment is acceptable for non-prescription use, provided that patients are advised to consult a doctor if the symptoms persist long-term.
- The risk of side-effects can be minimised by suitable product information for the patient.

4. References:

1. A Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use. EC Rules governing medicinal products; Volume C Rev 01/2006.
2. Sweetman, S. (2007) Martindale: The Complete Drug Reference (35th Edition). Pharmaceutical Press.
3. Ekman, L. *et al.* (1985) Toxicological studies on omeprazole. *Scand J Gastroenterol.*, 20 (suppl 108): 53 – 69.
4. Sanduleanu, S., *et al.* (1999) Serum gastrin and chromogranin A during medium- and long-term acid suppressive therapy: a case-control study. *Aliment Pharmacol Ther.*, 13: 145 – 53.
5. Kuipers, E.J., *et al.* (1996) Atrophic gastritis and *Helicobacter pylori* infection in patient with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med.*, 334: 1018 – 22.
6. Brunton, L. (2001) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th edition, McGraw Hill, page 1009.
7. Shin, J.M. & Sachs, G. (2002) Restoration of acid secretion following treatment with proton inhibitors. *Gastroenterology*, 123(5): 1588-1597.
8. Litalien, C., Theoret, Y., Faure, C. (2005) Pharmacokinetics of proton pump inhibitors in children. *Clinical Pharmacokinetics* 44: 441-466.
9. http://www.fda.gov/cder/drug/early_comm/omeprazole_esomepazole_update.htm

Active ingredient: OXOMEMAZINE

ATC Code: R06AD08
Anti-histamines for systemic use – phenothiazine derivatives

Therapeutic indications:

- cough, common cold.
- anti-histamines for systemic use.
- symptomatic relief of hypersensitivity reactions and in pruritic skin disorders.
-

Posology/duration of treatment: per os, rectally

Adult:

- 5 to 13 mg daily, divided in separate doses.

Pharmaceutical forms: tablets, suppository

Contraindications - relevant warnings:

a) Contraindications:

- hypersensitivity to oxomemazine.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

1.2. Interactions

No data available.

1.3. Adverse reactions (ADRs)

1.3.1. Recent case reports (UMC database)

No reports on ADRs against oxomemazine were received by the Uppsala Monitoring Centre in the period from 1 January 2005 to 7 of February 2009.

2. Discussion

Oxomemazine is an H₁-histamine receptor antagonist.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II	Oral Use				
Publication	II	Oral Use				
B	POM		Indications: combination anti-cough syrup for children. Warnings: all medicines with phenothiazines present risk for sudden infant death syndrome.			
CH	OTC	Oral Use		4 mg	10 mg	50 mg
CZ			Not marketed			
D			Not marketed			
E			Not marketed			
F	OTC	Oral Use	- treatment of cough - for adults and children over than 12 months			
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LV			Not marketed			
MK			Not marketed			
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

OXOMEMAZINE, anti-histamines for systemic use – phenothiazine derivatives, Oral administration.

List II + exemptions

- for oral administration MS 4 mg, MDD 10 mg.
- only for adults and children aged 12 years and older.

Criteria:

- marketed in France for the treatment of cough and classified as OTC in Switzerland.
- no ADRs received by the UMC database within the last three years.
- **MS 4 mg**
- **MDD 10 mg**

3.2. Paediatric use

OXOMEMAZINE is not recommended for children under 12 years of age.

4. References:

- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: PHENIRAMINE (classification proposal adopted at 46th meeting)

ATC Code: R06AB05
Anti-histamines for systemic use – substituted alkylamines

Therapeutic indications:

- allergic conjunctivitis
- rhinitis

Posology/duration of treatment: per os

MICROMEDEX Dosing Information

Adult:

- 2-3 sprays of 0.2% nasal solution into each nostril, every 4 hours.
- 1-2 drops of 0.3% ophthalmic solution into each eye, every 3-4 hours.
- 5-15 mg orally, every 4 hours (in combination products).
- extended release tablets: 16-25 mg orally, every 8-12 hours or 12.5 mg orally, every 6-8 hours (in combination products).

Paediatric:

- aged 1-6 years: 3.125-3.25 mg orally, every 4-8 hours (in combination products).
- aged 6-12 years: 2.5-7.5 mg orally, every 4-8 hours (in combination products).

Pharmaceutical forms: nasal solution, eye drops, tablets, extended release tablets

Contraindications - relevant warnings:

a) Contraindications:

- hypersensitivity to pheniramine/alkylamine anti-histamines.

b) Precautions:

- angle-closure glaucoma.
- asthma or chronic obstructive pulmonary disease.
- balder neck obstruction.
- cardiovascular disease .
- discontinue at least 3 days prior to allergy skin tests.
- hypertension.
- hyperthyroidism.
- prostatic hypertrophy or history of urinary retention.
- pyloroduodenal obstruction.
- stenosing peptic ulcer.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

- **Cardiovascular Effects**
 - Palpitations and tightness of the chest may occur in some patients during pheniramine therapy.
- **Dermatologic Effects**
 - Allergic dermatitis may occur with alkylamine anti-histamines, although this is rare with oral therapy.
- **Gastrointestinal Effects**
 - Dry mouth (or nose or throat), anorexia, nausea, vomiting, abdominal discomfort, constipation, or diarrhea may occur with oral pheniramine, although all less frequently than sedation. Pheniramine may cause less dry mouth (due to anti-cholinergic effects) than ethanalamine anti-histamines (e.g. diphenhydramine, dimenhydrinate, clemastine) or promethazine. In contrast, the anti-cholinergic effects of pheniramine are greater than for terfenadine or astemizole.
- **Neurologic Effects**
 - CNS ADRs of pheniramine include dizziness, tiredness or lassitude, fatigue, tinnitus, lack of co-ordination, confusion, and headache. Confusion and dizziness may be more prevalent in elderly patients. Paradoxical adverse effects of pheniramine include nervousness, irritability, euphoria, nightmares, insomnia, tremors, and an increased tendency toward seizures. Paradoxical effects of the drug are more likely to occur in children and the elderly. Toxic psychoses can occur with high doses of pheniramine. The drug has been intentionally used as a hallucinogen.
 - Similar to other alkylamine anti-histamines, the most common adverse effect of pheniramine is drowsiness. However, tolerance to this effect is seen in most patients with continuous administration (within days or weeks). Pheniramine has a long elimination half-life and administration of the drug as a single dose at bedtime may reduce daytime sedation. However, this applies primarily to pheniramine monotherapy and not combination products.
 - Sedation with pheniramine may be less than with ethanalamine anti-histamines (e.g. diphenhydramine, dimenhydrinate, clemastine) and promethazine.
- **Ophthalmic Effects**
 - Blurred vision may occur with oral pheniramine due to anti-cholinergic effects, although this is rare if recommended doses are adhered to.
 - Stinging and burning may occur with cutaneous application of pheniramine/naphazoline ophthalmic preparations. Mydriasis may also occur with these formulations, and an acute attack of angle-closure glaucoma is possible with their use in predisposed patients.
- **Renal Effects**
 - Urinary retention or dysuria due to anti-cholinergic effects is typically rare complications of pheniramine. They are more likely to occur in the elderly.

Pheniramine is classified by the Australian Drug Evaluation Committee's (ADEC) as Category A, which means that it has been taken by a large number of pregnant women and women of child-bearing age, without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus.

Paediatric Use

Pheniramine is not recommended for children under 6 years of age.

1.2. Interactions

Theoretically with procarbazine (CNS depression).

1.3. Adverse reactions (ADRs)

Common ADRs:

- **Gastrointestinal:** xerostomia.
- **Neurologic:** somnolence.
- **Respiratory:** dry nasal mucosa, pharyngeal dryness, thick bronchial sputum.

1.3.1. Recent case reports (UMC database)

In the period from 1 January 2005 to 7 February 2009, the Uppsala Monitoring Centre received only 2 reports on pheniramine, with 3 ADRs, all of which were from Australia. There were no reports from European countries. The reported ADRs were not serious (pruritus, orbital oedema and decreased blood sugar).

The combination database of the UMC ADR database shows that there are no new risks associated with this early anti-histamine.

2. Discussion

Pheniramine is an early, well-known H₁ antagonist. Nowadays, it comes more often in combination preparations, than as a single active ingredient. It is available in tablet form, nasal solutions and eye solutions, mostly in combination with other cold medicines. The most common ADRs are the anti-cholinergic effects of the drug and CNS depression.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
A	II	Oral use		20 mg	60 mg	
CZ			Not marketed			
F			Not marketed			
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LV			Not marketed			
MK	POM	Oral use	Indications: allergic manifestations of skin and mucous membranes, itching of various origins (e.g. insect bites, contact with poison ivy). Warning: possible effect on psycho-physical abilities (drowsiness, reduced power of concentration, fatigue, nervousness). Warn of danger when operating machines or driving vehicles.	50 mg		
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

PHENIRAMINE, anti-histamines for systemic use – substituted alkylamines, Oral administration.

List II (adopted classification)

Criteria:

- indications: allergic rhinitis and conjunctivitis.
- early compound with sedating ADRs.
- marketed only in Austria and Macedonia as List II and POM, respectively.

Comment: available in combination with epinephrine or naphazoline only as nasal and eye drops.

3.2. Paediatric use

Pheniramine is not recommended for children under 6 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/C49F3E/DUPLICATIO SHIELDSYNC/AAD5F6/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/4E1exkk2QA7ULO/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2412/ContentSetId/31#secN106AA
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: PROMETHAZINE, a phenothiazine derivative.

Synonyms: Promethazine hydrochloride; Proazamine

ATC Code: D04AA10
Anti-histamines for cutaneous use.

Therapeutic indications:

Cutaneous use: "Promethazine has been used **topically** to provide relief in hypersensitivity disorders of the skin and for burns but, as with other antihistamines, it may produce skin sensitization (Sweetman, 2007).

Posology/duration of treatment: (PHENERGAN® Preparations Novartis Consumer Health)

Topical: Apply 2 or 3 times a day to affected area.
Avoid application to extensive skin areas. Do not exceed 10% of total body surface.

Pharmaceutical forms:

Cream: 2%

Contraindications - relevant warnings:

General: Cutaneous preparations containing anti-histamines should not be used on broken or eczematous skin.

Overdosage has been reported after use of the cream over extensive skin areas.

1. List of direct/indirect risks (safety profile) (see above)

1.1. Direct risks (Pharmacovigilance) (see above)

1.1.1 Recent cases in Europe

During 1 January 2007 to 22 February 2010, the Uppsala Monitoring Center received 46 reports on promethazine with a total of 63 ADRs. Route of administration: topical

2. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	II					
A			Not marketed			
B			Not marketed			
CH	OTC	cutaneous				
E	II + exemptions	cutaneous	Not for sunburn	2%		
HR			Not marketed			
HR			Not marketed			
I	OTC	cutaneous				
P	OTC	cutaneous	Indication: insect bites			
P	OTC					

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
PL			Not marketed			

No data available from other Member States

2.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

There is limited information from other Member States and from databases such as Micromedex or Martindale, and others listed below. No recommendation can be made.

3. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/609334/DUP...
- Sweetman, S. (2007) Martindale: The Complete Drug Reference (35th Edition). Pharmaceutical Press.
- <http://emc.medicines.org.uk/>
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- [http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20\(General%20Monographs-%20P\)/PHENERGAN%20PREPARATIONS.html](http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20(General%20Monographs-%20P)/PHENERGAN%20PREPARATIONS.html)

Active ingredient: **PROMETHAZINE**

ATC Code: R06AD02
Anti-histamines for systemic use – phenothiazine derivatives

Therapeutic indications:

- symptomatic treatment for allergic conditions of the upper respiratory tract and skin including allergic rhinitis, urticaria and anaphylactic reactions to drugs and foreign proteins.
- an adjunct in pre-operative sedation in surgery and obstetrics.
- an anti-emetic.
- for short-term sedation and treatment of insomnia in adults and as a Paediatric sedative.

Posology/duration of treatment: per os, parenteral, topical.

MICROMEDEX Dosing Information

Adult:

- Allergy:
 - 25 mg orally at bedtime or 12.5 mg orally, before meals and at bedtime.
 - 25 mg im or iv - may be repeated within 2 hours if needed.
- Anaesthesia (adjunct):
 - 25-50 mg im or iv, prior to surgery.
- Motion sickness (treatment and prophylaxis):
 - 25 mg orally, twice daily.
- Nausea and vomiting:
 - 12.5 to 25 mg (orally, rectally, im or iv), every 4 to 6 hours.
- Post-operative pain (adjunct):
 - 25-50 mg im or iv (combined with appropriately reduced doses of analgesics).
- Sedation:
 - 25-50 mg orally or 50 mg rectally.
- Sedation (obstetrical):
 - 25 to 75 mg (mean dose is 50 mg) im or iv. Maximum does is 100 mg/day.

Paediatric:

- *Not for use in children less than 2 years of age.*
- Allergy:
 - aged 2 years or older: 25 mg orally, at bedtime or 6.25-12.5 mg orally, three times daily.
- Motion sickness (treatment and prophylaxis):
 - aged 2 years or older: 12.5-25 mg (orally or rectally), twice daily.
- Nausea and vomiting:
 - aged 2 years or older: 12.5-25 mg or 1.1 mg/kg (orally or rectally), every 4 to 6 hours as needed.
- Post-operative pain (adjunct):
 - aged 2 years or older: 12.5-25 mg orally or rectally (combined with appropriately reduced doses of analgesics).
- Sedation:
 - aged 2 years or older: 12.5-25 mg (orally or rectally).

Pharmaceutical forms: tablets, solution for injection, syrup, suppository, gel

Contraindications - relevant warnings:

a) Contraindications:

- comatose states.
- hypersensitivity or history of an idiosyncratic reaction to promethazine or other phenothiazines.
- lower respiratory tract symptoms, including asthma.
- Paediatric patients (less than 2 years of age); increased risk for potentially fatal respiratory depression.
- subcutaneous or intra-arterial administration (injection only).

b) Precautions:

- concomitant use with other respiratory depressant medications. Avoid use in Paediatric patients.
- use lowest effective dose in Paediatric patients (2 years of age and older) due to increased risk for potentially fatal respiratory depression.
- use with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction due to anti-cholinergic effects
- bone-marrow depression, leukopenia and agranulocytosis have been reported.
- cardiovascular disease.
- increased risk of potentially fatal respiratory depression, so avoid use in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, sleep apnea).
- concomitant use with other medications that affect seizure thresholds (e.g. narcotics or local anaesthetics).
- liver function impairment.
- neuroleptic malignant syndrome has been reported and some cases have resulted in death.
- increased risk of dystonia in Paediatric patients with acute illness associated with dehydration.
- avoid use in Paediatric patients with signs and symptoms suggestive of Reye's syndrome or other hepatic diseases (e.g. encephalopathy).
- not recommended for Paediatric patients with uncomplicated vomiting. Limit use in cases of prolonged vomiting of unknown etiology.
- may lower the seizure threshold.
- severe injection-site reactions may occur (injection only). Severe tissue injuries (e.g. pain, paralysis, necrosis, and gangrene) have been reported with parenteral administration (intravenous, subcutaneous, or inadvertent intra-arterial routes), with some cases requiring surgical interventions such as fasciotomy, skin graft, and amputation. The risk is increased with concentrations above 25 mg/ml and with infusion rates greater than 25 mg/min.
- sulphite sensitivity - injection contains sodium metabisulphite.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Side-effects may be seen in some patients, including: drowsiness, dizziness, restlessness, headaches, nightmares, tiredness, and disorientation. Anti-cholinergic side-effects such as blurred vision, dry mouth and urinary retention occur occasionally. Infants are susceptible to the anti-cholinergic effects of promethazine, whilst other children may display paradoxical hyper-excitability. The elderly are particularly susceptible to the anti-cholinergic effects of promethazine (confusion). Other side-effects include urticaria, rash, pruritus, anorexia, gastric irritation, palpitations, hypotension, arrhythmias, extra-pyramidal effects, muscle spasms and tic-like

movements of the head and face. Anaphylaxis, jaundice and blood dyscrasias, including haemolytic anaemia, rarely occur. Photo-sensitive skin reactions have been reported. Strong sunlight should be avoided during treatment.

Paediatric Use

Mizolastine is not recommended for children under 2 years of age.

1.2. Interactions

Promethazine will enhance the action of any anti-cholinergic agent, tri-cyclic anti-depressant, sedative or hypnotic. Alcohol should be avoided during treatment. The drug may interfere with immunological urine pregnancy tests to produce false-positive or false-negative results. It should be discontinued at least 72 hours before the start of allergy skin tests, as it may inhibit the cutaneous histamine response, thereby producing false-negative results.

1.3. Adverse reactions (ADRs)

- See under direct risk.

1.3.1. Recent case reports (UMC database)

In the period from 1 January 2005 to 7 February 2009, the Uppsala Monitoring Centre received 1,047 reports of promethazine with 4,158 ADRs. Reports came from: Argentina, Australia, Brazil, Canada, Chile, China, **Germany, Denmark, France, United Kingdom, Ireland, Iran, Iceland, Italy**, Japan, Morocco, **The Netherlands, Norway**, New Zealand, **Poland, Portugal**, Singapore, Surinam, **Sweden**, Thailand, Tunisia, Uruguay and the USA. Most ADR reports came from the USA (over 90% of all reports). A few cases of blood disorders were reported, such as thrombocytopenia, agranulocytosis and leucopenia. From the SOC *Cardiac diseases*, there were 52 cases of cardiac arrest, followed by cardio-respiratory arrest (44 cases), and tachy- and bradycardia (more than 20 cases). The most common ADRs from the SOC *Gastrointestinal disorders* were diarrhea (69 cases) and nausea (82 cases). There were over 70 documented cases of medication error and intentional drug misuse and, in about 200 reports (mostly from the USA), there is evidence of overdose. In over 300 cases, disturbances in consciousness, which includes somnolence, sedation, dizziness and coma, were reported. There were also reports of anxiety (30 cases) and agitation (61 cases).

The combination database of the UMC ADR database shows that there is an increased risk for developing phlebitis, tissue necrosis, and gangrene when the drug is given as an injection.

2. Discussion

The Food and Drug Administration (FDA) have issued patient safety alerts regarding case reports of severe complications and tissue injury including burning, pain, paralysis, tissue necrosis, and gangrene associated with the parenteral administration of promethazine (inadvertent intra-arterial, intravenous, or subcutaneous routes). In some cases surgical intervention was required, including fasciotomy, skin graft, and amputation. It is recommended that promethazine is administered by deep intra-muscular injection into a large muscle. The use of promethazine via the intra-arterial, or subcutaneous routes is contraindicated.

If given orally in the treatment of allergies, caution is required when the drug is administered with other CNS depressants, and also extreme caution should be exercised when it is administered to children, because of the increased risk for potentially fatal respiratory depression. The lowest effective dose is always recommended for children.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	II + exemption	Oral Use		25 mg / 0.1 % / 2 %		
Publication	II + exemption	Oral Use		25 mg / 0.1 % / 2 %		
B	POM	IV				
BG	II	Oral use				
CH	II + exemption	Oral Use		25 mg		
CZ	I	Oral use	Intravenous use was withdrawn in 2008.			
D	II	Oral Use				
DK	II + exemption	Oral Use				
F	OTC	Oral Use	Indications: rhinitis, conjunctivitis, hives (for adults and children aged > 12 years)			
GB	OTC	Oral Use				
H	POM	Oral Use	Indications: symptomatic treatment of allergic reactions of various origins, adjuvant of anaphylactic reaction, peri-/post-operative sedation. During labour and post-operative nausea, increased analgetic and anaesthetic effect. MDD 150mg (nausea); MDD 50mg (vertigo, traveler's disease). Warnings: cardiovascular disease, hepatic impairment, asthma, severe pulmonary disease. Promethazine decreases the threshold of seizures and compounds narrow-angle glaucoma, gastric ulcer, bladder-neck obstruction and prostatic hypertrophy. Alcohol forbidden.	25 mg	50 mg	
		Parenteral Use	IV: as an adjunctive to narcosis and analgesia. MDD 150mg. IM: adjuvant treatment of anaphylactic reaction; conditions where oral treatment is not possible or contraindicated; pre- and post-operative sedation and sedation during labour to increase the effect of narcotics and analgesics. Suppositories were withdrawn from the market for commercial reasons.			
HR			Not marketed			
I	II	Oral Use		25 mg	16 mg	
	I	Parenteral Use	List I: administered by IV. MS=2ml, MDD=4ml. Warnings: not indicated for patients with glaucoma			

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
IRL	OTC	Oral Use				
LT	OTC	Oral Use				
LV			Not marketed			
MK			Not marketed			
N	II	Oral Use				
NL	II	Oral Use				
P	II	Oral Use				
RO	II	Oral Use	Indications: symptomatic treatment for allergic conditions of the upper respiratory tract and skin including allergic rhinitis, urticaria and anaphylactic reactions to drugs and foreign proteins; nausea and vomiting, as a Paediatric sedative. MDD 3 mg (children aged between 2-5 years), MDD 25 mg (children aged between 5-12 years). Warnings: use with care in patients with severe renal insufficiency. Caution: severe coronary artery disease, narrow-angle glaucoma, epilepsy, or hepatic and renal insufficiency.	1 mg		50 mg
S	II	Oral Use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

PROMETHAZINE, anti-histamines for systemic use – phenothiazine derivatives, Oral administration

List II

Criteria:

- for oral use.
- strong sedative effect.
- evidence of misuse, overdose and medication error.

Additional information: List I (i.v. administration)

Criteria:

- for parenteral use.
- reports of necrosis and severe ADRs at the injection site.
- severe CNS depression reported.

No exemption from prescription-only status is proposed.

3.2. Paediatric use

Promethazine is not recommended for children under 2 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/F2D4E4/DUPLICATIONSHIELDSYNC/238402/ND_PG/PRIH/ND_B/HCS/SBK/3/ND_P/Main/PFPUI/4E1exkk2QAomiy/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2421/ContentSetId/31#secN12FD5
- <http://emc.medicines.org.uk/medicine/15314/SPC/Phenergan+10mg+Tablets/>
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: RUPATADINE

ATC Code: R06AX28
Anti-histamines for systemic use – Other anti-histamines for systemic use

Therapeutic indications:

- allergic rhinitis
- chronic idiopathic urticaria

Posology/duration of treatment: per os

Adult:

- 10 mg/day

Pharmaceutical forms: Tablets

Contraindications - relevant warnings:

a) Contraindications:

- rupatadine hypersensitivity

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

1.2. Interactions

- It should not be administered concomitantly with known CYP3A4 inhibitors.

1.3. Adverse reactions (ADRs)

No adverse cardiovascular effects in pre-clinical or extensive clinical testing, nor negative significant effects on cognition or psychomotor performance (including a practical driving study).

1.3.1. Recent case reports (UMC database)

In the period from 1 January 2005 to 7 February 2009, the Uppsala Monitoring Centre received 6 reports on rupatadine, with 15 ADRs, all from either Portugal or Spain. The ADRs reported included: asthenia (2 cases), increased alanine aminotransferase, dry mouth, eyelid ptosis, increased gamma-glutamyltransferase, haemorrhage, hyperbilirubinaemia, hyperhidrosis, malaise, nausea, palpitations, polyarthritis, somnolence and swelling (all single cases).

The combination database of the UMC ADR database does not suggest any additional risks with rupatadine.

2. Discussion

Rupatadine is a new, once-daily, non-sedating, selective and long-acting drug with a strong antagonistic activity towards both histamine H₁ receptors and platelet-activating factor receptors. The use of rupatadine is indicated in adult and adolescent patients (> 12 years of age) suffering from intermittent and persistent allergic rhinitis and chronic idiopathic urticaria. It has a fast onset of action, producing rapid symptomatic relief, and it also has an extended duration of clinical activity that allows once-daily administration. Rupatadine is at least as effective as ebastine, cetirizine, loratadine and desloratadine in reducing allergic symptoms in adult/adolescent patients with seasonal, perennial or persistent allergic rhinitis. A very good safety profile of

rupatadine has been evidenced in various studies, including a long-term (1-year) safety study. Rupatadine does not present drug-drug interactions with azithromycin, fluoxetine and lorazepam, but should not be administered concomitantly with known CYP3A4 inhibitors.

It possesses a broader profile of anti-inflammatory properties, inhibiting both inflammatory cells and a range of mediators involved in the early- and late-phase inflammatory response, but the clinical relevance of these effects remain to be clarified.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007) 1, annually revised appendices (recommendations)	I(3)	Oral Use				
Publication	I(3)	Oral Use				
A	II	Oral Use	Indications: symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria.	10 mg	10 mg	
B	I	Oral Use				
CZ	I	Oral Use				
E	I(1)	Oral Use				
F	II	Oral Use				
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LV	II	Oral Use				
MK			Not marketed			
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

RUPATADINE, anti-histamines for systemic use – Other anti-histamines for systemic use, Oral administration.

List I

Criteria:

- a new medicinal product on the market.
- clinical data show a good safety profile of the drug but, as yet, there are not enough post-marketing safety data.

No exemption from prescription-only status is proposed.

3.2. Paediatric use

Only for adults and children aged over 12 years.

4. References:

- Mullol J. *et al.* (2008) Rupatadine in allergic rhinitis and chronic urticaria. *Allergy*, 63 Suppl 87:5-28.
- Kean SJ, Plosker GL. (2007) Rupatadine: a review of its use in the management of allergic disorders. *Drugs*, 67(3):457-74.
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: SPAGLUMIC ACID

ATC Code: R01AC05

Therapeutic indications:

Symptomatic treatment of perennial and seasonal allergic rhinitis.

Posology:

0.07 ml (~4.2 mg) spaglumic acid. 2 puffs four times a day to each nostril.

Duration of treatment:

Treatment duration is throughout the allergic season, but it is recommended to start the treatment a few days before allergens appear.

Pharmaceutical forms: nasal spray

Contraindications - relevant warnings:

Known hypersensitivity to spaglumic acid.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

No data available.

1.1.1 Teratogenicity/Effects in Pregnancy/Breast-feeding

It is not known if spaglumic acid exerts any effect on the baby if used during pregnancy or during breast-feeding.

1.1.2 Elderly

No data available.

1.1.3 Recent cases in Europe

No data available.

1.2. Indirect risks (incorrect use)

No data available.

2. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	II					
Publication	II					
A	Not marketed					
B	Not marketed					
F	OTC					
HR	Not marketed					
P	Not marketed					
Pt	Not marketed					

2.1. The proposed classification:

At present there are very few European countries where the medicine is registered and marketed. The committee decided to delete it from the annex.

List of classification:

No recommendation can be given.

Conditions of supply

None

2.2. Paediatric use:

Not applicable.

3. References:

-

Active ingredient: THIETHYLPERAZINE

ATC Code: R06AD03
Anti-histamines for systemic use - phenothiazine derivatives

Therapeutic indications:

- nausea and vomiting

Posology/duration of treatment:

MICROMEDEX Dosing Information

Adult:

- 10 mg (i.m., orally or rectally), 1-3 times a day.

Paediatric:

- Safety and efficacy have not been established in children.

Pharmaceutical forms: Tablets, solution for injection, suppository

Contraindications - relevant warnings:

a) Contraindications:

- children and adolescents with symptoms and signs suggestive of Reye's syndrome.
- hypersensitivity to thiethylperazine or to other phenothiazines.
- marked hypotension.
- severe CNS depression and comatose states.

b) Precautions:

- can potentiate the effects or actions of other CNS depressants such as alcohol, opiates, anesthetics, barbiturates and tranquilizers.
- drowsiness can be hazardous in individuals requiring alertness.
- injection contains sodium metabisulphite that may cause allergic reactions, including anaphylactic symptoms and life-threatening asthmatic episodes, in susceptible individuals.
- may accentuate a fall in blood pressure when given to patients who have received spinal or epidural anesthesia, or adrenergic blocking agents.
- may mask symptoms of organic disease, such as gastrointestinal or CNS disorders, as well as the toxic effects of other drugs.
- moderate hypotension has been occasionally observed within 30 minutes of administration of the drug in patients recovering from anesthesia.
- patients with a history of dyskinetic reactions.
- patients with moderate to severe hepatic dysfunction.
- pregnant women with preeclampsia, as these patients may have labile blood pressures and may experience a significant fall in blood pressure with the drug.
- restlessness and post-operative CNS depression during recovery from anesthesia have been observed.
- tablets contain tartrazine which may cause allergic reactions, including bronchial asthma, in susceptible individuals.

1. List of direct/indirect risks (safety profile)

1.1 . Direct risks (Pharmacovigilance)

1.2. Interactions

Thiethylperazine is contraindicated with Cisapride (probable), Grepafloxacin (probable) and Sparfloxacin (theoretical). Major interactions can occur if administered with Fentanyl (theoretical), Gatifloxacin (probable), Ibutilide (theoretical), Isradipine (theoretical), Levorphanol (theoretical), Methadone (theoretical), Metrizamide (theoretical), Morphine (theoretical), Morphine Sulfate Liposome (theoretical), Moxifloxacin (theoretical), Octreotide (theoretical), Oxycodone (theoretical), Pentamidine (theoretical), Procarbazine (probable) and Tramadol (theoretical). Minor interactions can occur with Belladonna (probable).

Belladonna Alkaloids (probable), Betel Nut (probable), Evening Primrose (probable), Meperidine (probable) and Phenylalanine (probable). (MICROMEDEX)

1.3. Adverse reactions (ADRs)

- Common:
 - **Neurologic:** dizziness, somnolence.
- Serious:
 - **Cardiovascular:** hypotension.
 - **Hematologic:** agranulocytosis (rare), leukopenia (rare), pancytopenia (rare), thrombocytopenia (rare).
 - **Hepatic:** cholestatic jaundice syndrome (rare).
 - **Neurologic:** seizure (rare).

1.3.1. Recent case reports (UMC database)

There is no data on Thiethylperazine in the UMC database.

2. Discussion

Thiethylperazine is an effective anti-emetic agent for the treatment of post-operative nausea and vomiting, for nausea and vomiting secondary to mildly emetic chemo-therapeutic agents, and vomiting secondary to radiation therapy and toxins. However, there are no adequate data comparing thiethylperazine with other piperazine anti-emetic agents (prochlorperazine, perphenazine, fluphenazine), although some sources suggest greater efficacy of thiethylperazine in the treatment of post-operative vomiting. Thus, the choice between these agents appears to be based primarily on individual preference. Thiethylperazine is preferred to chlorpromazine (and other aliphatic phenothiazines) by most clinicians due to the lower incidence of side-effects (e.g. hypotension, sedation, dry mouth), especially in the prevention of chemotherapy-induced nausea and vomiting. However, the incidence of extra-pyramidal reactions is greater with thiethylperazine, as opposed to aliphatic phenothiazine derivatives.

Thiethylperazine is only indicated for the treatment of nausea and vomiting, due to its higher ratio of anti-emetic to tranquilizing activity as compared to other phenothiazines. The anti-emetic effects of the drug are primarily related to direct actions on the chemo-receptor trigger zone. However, it also appears to inhibit peripheral, autonomic afferent impulses to the vomiting center via the vagus nerve. Thiethylperazine and other piperazine phenothiazines (fluphenazine, perphenazine, prochlorperazine), produce less drowsiness, orthostatic hypotension, nasal congestion, and dry mouth compared to aliphatic phenothiazines (chlorpromazine, triflupromazine and promazine). For these reasons, thiethylperazine is preferred for the treatment of nausea and vomiting. However, thiethylperazine is associated with a higher degree of extrapyramidal reactions compared to phenothiazines in the aliphatic group.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
Resolution ResAP(2007)1, annually revised appendices (recommendations)	II	Oral Use				
Publication	II	Oral Use				
CH	II	Oral Use				
CZ			Not marketed			
F			Not marketed			
H	POM	Oral Use	<p>Indication: prevention and treatment of nausea and vomiting of various origins (e.g. after surgical intervention or radiotherapy); Ménière syndrome; vertigo of various origins (arteriosclerosis in cerebral vessels, lesion in the vestibular system, traveler's disease, seasickness).</p> <p>Warnings: caution is required in cases of mild or moderate hepatic impairment. In asthma cases, the risk of allergic reactions of various severity is higher. Chronic treatment can result in disorders of the blood and lymphatic system. No information is available on safety or efficacy in children under the age of 12 years. Alcohol intake is forbidden during treatment.</p>	6,5 mg	19,5 mg	
HR	I	Oral use, Parenteral use				
I			Not marketed			
LV			Not marketed			
MK	POM	Oral use	<p>Indications: Thiethylperazine is used for the treatment and prophylaxis of nausea, vomiting and vertigo. It is effective in the suppression and prophylaxis of nausea and vomiting occurring after surgical procedures, cytotoxic chemotherapy, radiotherapy or therapy with certain substances having an emetic effect (opiates, ergot alkaloids, theophylline), after cranio-cerebral injuries, in intra-cranial hypertension, migraine and kinetoses, in uremia and in gastrointestinal and hepatobiliary disorders. Used for the treatment of vertigo in Ménière's syndrome and other vestibular disorders, after brain concussion, in post-concussion syndrome and in cerebrovascular atherosclerosis. With regard to prophylaxis and treatment of nausea and vomiting following chemotherapy, thiethylperazine is effective with drugs having a mild to medium emetic effect (fluorouracil), while it is relatively ineffective with drugs having a strong emetic effect (cisplatin).</p> <p>Warnings: like other anti-emetics, thiethylperazine can also mask the symptoms of some gastrointestinal and CNS diseases, as well as the toxic effects of other drugs. Thiethylperazine affects the psycho-physical abilities of patients and it may delay reaction speeds. The effect is more marked after injections, so patients receiving injections must</p>	6,5 mg		

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
			not drive motor vehicles or operate machines. Patients taking the tablets are advised to be extremely cautious. Because of the additive hypotensive effect of thiethylperazine, the drug should be given with caution to patients with spinal anesthesia or those concomitantly taking beta-blockers. The hypotensive effect is also dangerous for pregnant women with pre-eclampsia, as their blood pressure may decrease substantially. Thiethylperazine must never be injected intra-arterially. It is recommended that patients are in a supine position during parenteral administration (also for intra-muscular administration). They should be carefully monitored for at least one hour after administration. Thiethylperazine should be used with caution in patients with a history of dyskinesia and in those with moderate to severe hepatic dysfunction. Phenothiazines may cause malignant neuroleptic syndrome (clinically manifested as hyperpyrexia), muscular rigidity, altered psychic status and signs of autonomic nervous system instability. Therapy should be immediately discontinued in such cases. Treatment of limited duration is recommended in the elderly. Thiethylperazine solution for injection contains sodium metabisulphite, which may induce allergic-type reactions, including anaphylactic signs and bronchospasm, in susceptible people, especially those with a history of asthma and allergy.			
RO	I	Oral Use				
SLO	I	Oral Use				

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

THIETHYLPERAZINE, anti-histamines for systemic use – phenothiazine derivatives, Oral administration.

List I

Criteria:

- risk of serious adverse reactions due to interactions with CNS depressants and drugs that interact with Cytochrome P450 (coma, somnolence, neuroleptic malignant syndrome, confusional state and urinary retention) especially in the elderly.
- greater incidence of extra-pyramidal reactions than in other anti-emetics.
- caution required in hypotensive patients.
- only for treatment and prophylaxis of nausea and vomiting.

No exemption from prescription-only status is proposed.

3.2. Paediatric use

- Not recommended for children under 12 years of age.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/30E668/DUPLICATIONSHIELDSYNC/39008B/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/4E1exkk2QB0z7C/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/0422/ContentSetId/31#secN11060
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: THONZYLAMINE

ATC Code: R06AC06
Anti-histamines for systemic use – Substituted ethylene diamines

Recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
CZ			Not marketed			
F			Not marketed			
H			Not marketed			
HR			Not marketed			
I			Not marketed			
LV			Not marketed			
MK			Not marketed			
RO			Not marketed			

No data available from other Member States.

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

THONZYLAMINE, anti-histamines for systemic use – Substituted ethylene diamines, Oral administration

No recommendation is made because the medicine is not marketed in Member States.

Active ingredient: TRIPELENNAMINE

ATC Code: R06AC04
Anti-histamines for systemic use – Substituted ethylene diamines

Therapeutic indications:

- common cold
- cough

Posology/duration of treatment: per os

Pharmaceutical forms: tablets

Contraindications - relevant warnings:

a) Contraindications:

- angle-closure glaucoma.
- hypersensitivity to tripeleennamine products.

b) Precautions:

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Paediatric Use

Tripeleennamine is not recommended for children under 12 years of age.

1.2. Interactions

No data available.

1.3. Adverse reactions (ADRs)

Common ADRs:

- **Gastrointestinal:** xerostomia.
- **Neurologic:** sedation.
- **Respiratory:** dry nasal mucosa, pharyngeal dryness, thick bronchial sputum.

2. Discussion

Tripeleennamine, an ethylenediamine derivative, is a sedating anti-histamine with anti-muscarinic and moderate sedative properties. It has been used for the symptomatic relief of hypersensitivity reactions. It may also be used in compound preparations for the symptomatic treatment of coughs and the common cold.

Tripeleennamine has been given orally as citrate or hydrochloride. Tripeleennamine hydrochloride has also been applied topically to the skin, although, as with other anti-histamines, there is a risk of sensitisation.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
CZ			Not marketed.			
D	OTC	Oral Use				
E	OTC	Oral Use	Indications: in combinations for common colds.			
F			Not marketed			
H			Not marketed			
HR			Not marketed			
I	OTC	Oral Use				
LV			Not marketed			
MK			Not marketed			
NL	OTC	Oral Use				
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

TRIPELENNAMINE, anti-histamines for systemic use – Substituted ethylene diamines, oral administration.

List OTC

Criteria:

- indicated for short-term treatment of allergic rhinitis and symptomatic treatment of common cold in combination preparations.
- where marketed in Member States, prescription status is OTC.

3.2. Paediatric use

Not recommended for children aged under 12 years.

4. References:

- http://ovidsp.tx.ovid.com/spa/ovidweb.cgi?&S=HPNHFPOIIMDDGGNENCGLOACKFJALAA00&Link+Set=S.sh.17%7c1%7csl_10
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)
- http://www.edqm.eu/melclass/Expert/Expert_Search.aspx

Active ingredient: TRIPROLIDINE

ATC Code: R06AX07
Anti-histamines for systemic use – Other anti-histamines for systemic use

Therapeutic indications:

- allergic conjunctivitis
- common cold

Posology/duration of treatment: per os

MICROMEDEX Dosing Information

Adult:

- Allergic rhinitis:
 - alone or in combination with pseudoephedrine: 2.5 mg orally, every 4-6 hours. Maximum dose is 10 mg/day.
 - in combination with pseudoephedrine: 5 mg orally (sustained release tablet), every 12 hours. Maximum dose is 10 mg/day.
- Common cold:
 - alone or in combination with pseudoephedrine: 2.5 mg orally, every 4-6 hours. Maximum dose is 10 mg/day.
 - in combination with pseudoephedrine: 5 mg orally (sustained release tablet), every 12 hours. Maximum dose is 10 mg/day.

Paediatric:

- Not approved for children aged less than 6 years old.
- Allergic rhinitis:
 - aged 6-12 years (alone or in combination with pseudoephedrine): 1.25 mg orally, every 4-6 hours. Maximum dose is 5 mg/day.
 - aged 4-6 years: 0.938 mg orally, every 4-6 hours. Maximum dose is 3.744 mg/day.
 - aged 2-4 years: 0.625 mg orally, every 4-6 hours. Maximum dose is 2.5 mg/day.
 - aged 4 months-2 years: 0.313 mg orally, every 4-6 hours. Maximum dose is 1.25 mg/day.
- Common cold:
 - aged 6-12 years (alone or in combination with pseudoephedrine): 1.25 mg orally, every 4-6 hours. Maximum dose is 5 mg/day.
 - aged 4-6 years: 0.938 mg orally, every 4-6 hours. Maximum dose is 3.744 mg/day.
 - aged 2-4 years: 0.625 mg orally, every 4-6 hours. Maximum dose is 2.5 mg/day.
 - aged 4 months-2 years: 0.313 mg orally, every 4-6 hours. Maximum dose is 1.25 mg/day.

Pharmaceutical forms: tablets

Contraindications - relevant warnings:

a) Contraindications:

- angle-closure glaucoma.
- hypersensitivity to triprolidine products.
- neonates.

b) Precautions:

- asthma.
- bladder neck obstruction.
- children.
- chronic obstructive pulmonary disease.
- elevated intra-ocular pressure.
- geriatric patients.
- heart disease.
- hypertension.
- hyperthyroidism.
- prostatic hypertrophy.
- pyloric obstruction.
- stenosing peptic ulcer.

1. List of direct/indirect risks (safety profile)

1.1. Direct risks (Pharmacovigilance)

Paediatric Use

Triprolidine is not recommended for children under 6 years of age.

1.2. Interactions

Theoretically with procarbazine (CNS depression).

1.3. Adverse reactions (ADRs)

Common ADRs:

- **Gastrointestinal:** xerostomia.
- **Neurologic:** sedation.
- **Respiratory:** dry nasal mucosa, pharyngeal dryness, thick bronchial sputum.

2. Discussion

Triprolidine is a non-prescription alkylamine anti-histamine that is effective in the management of mild to moderate symptoms of allergic rhinitis. It is most commonly available in combination with the decongestant pseudoephedrine. The combination product is also useful in treating some symptoms associated with the common cold.

Because of the relatively short duration of action of triprolidine (4 to 6 hours), many patients find the commercial sustained-release combination product more convenient. Like all anti-histamines, triprolidine causes sedative effects in many patients. Due to the risk of paradoxical CNS stimulation effects, triprolidine should not be used in children under the age of six, except as directed by a physician.

Triprolidine is a member of the propylamine (alkylamine) chemical class of H₁ antagonist anti-histamines. As such, it is considered to be relatively less sedating than traditional anti-histamines of the ethanolamine, phenothiazine, and ethylenediamine classes of anti-histamines. Triprolidine has a shorter half-life and duration of action than most other alkylamine anti-histamines. Like all H₁ antagonist anti-histamines, the mechanism of action of triprolidine is believed to involve competitive blockading of H₁-receptor sites, resulting in the inability of histamine to combine with its receptor sites and exert its usual effects on target cells. Anti-histamines do not interrupt any effects of histamine that have already occurred. Therefore, these agents are used more successfully in prevention rather than treatment of histamine-induced reactions.

3. Conclusions - recommendations for legal classification

The recommendations take into account the legal classification of the active ingredient in Member States for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription Status	Exemption				
		Routes of administration	Comments	MS	MDD	MQP
B	II	Oral use				
CH	OTC	Oral Use	Not marketed from 2008.			
CZ	II	Oral use	Not marketed from 2008.			
D	OTC	Oral Use				
E	OTC	Oral Use	Indications: in combinations for common colds.			
F	OTC	Oral Use				
GB	OTC	Oral Use				
H			Not marketed			
HR			Not marketed			
I	OTC	Oral Use				
IRL	OTC	Oral Use				
LV	I	Oral Use				
MK			Not marketed			
P	II	Oral use				
RO			Not marketed			

No data available from other Member States.

3.1. Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

TRIPROLIDINE, anti-histamines for systemic use – Other anti-histamines for systemic use, Oral administration.

List OTC

Criteria:

- indicated for short-term treatment of allergic rhinitis and symptomatic treatment of common cold in combination preparations.
- most Member States classify it as OTC.

3.2. Paediatric use

Not recommended for children under 6 years of age due to the risk of paradoxical CNS stimulation effects.

4. References:

- http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/EB6867/DUPLICATIONSHIELDSYNC/97A9CF/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/UI1aphB2QFjQfh/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/0494/ContentSetId/31#secN107D4
- https://vigisearch.who-umc.org/dd_browser (UMC Drug Dictionary)
- <https://vigisearch.who-umc.org/vigisearch> (UMC ADR Database)

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