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

Report classification of

- Medicines belonging to ATC group D04A
(Antipruritics, incl. Antihistamines, Anaesthetics, etc.)

- Medicines containing Naloxone (ATC: V03AB15)

(2022)

Table of Contents

INTRODUCTION

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

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

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

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

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

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

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

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

It is important to note that:

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

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

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

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

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

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

[3] https://goo.gl/at4RZo

[4] https://goo.gl/KvqKir

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

Pharmacopoeia, as well as national information about the classification status and supply conditions of medicines in these member states. The information is publicly available. Recommendations about 2100 medicines are published in the *Melclass* database.

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

GENERAL NOTE

This document is published for information only.

The reports included in this document have no legal status and no binding character.

They reflect the debates and conclusions of the reviews of scientific classifications of medicines that took place at the 2021 meetings of the CD-P-PH/PHO. The document was reviewed and endorsed by the CD-P-PH/PHO at the expert committee's biannual meetings held in 2022.

GLOSSARY OF TERMS USED IN THIS DOCUMENT

ATC	Anatomical Therapeutic Chemical classification [1]
CNS	Central nervous system
EDQM	European Directorate for the Quality of Medicines and HealthCare
EMA	European Medicines Agency
MDD	Maximal daily dose
MQP	Maximal quantity per pack
MS	Maximal strength
POM	Prescription only medicine
WHO	World Health Organization

Classification used throughout this document

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

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

1. Active substances in medicines subject to prescription

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

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

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

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

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

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

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Thonzylamine

1.2 ATC code: D04AA01

1.3 Therapeutic indications: antihistamine with antipruritic and local analgesic actions

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Mepyramine

1.2 ATC code: D04AA02

1.3 Therapeutic indications: mepyramine has analgesic, antihistaminic and antipruritic properties and is used for symptomatic relief of insect stings and bites and nettle rash.

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, medicines containing this active substance are not authorised in at least three member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Thenalidine

1.2 ATC code: D04AA03

1.3 Therapeutic indications: antihistamine with antipruritic and local analgesic actions

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Tripelennamine

1.2 ATC code: D04AA04

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Chloropyramine

1.2 ATC code: D04AA09

1.3 Therapeutic indications: skin reactions accompanied by itching due to insect bites and urticaria.

1.4 Posology and duration of treatment: chloropyramine ointment should be applied in a thin layer two to three times a day and rubbed into the affected part of the skin. Duration of treatment: if symptoms worsen or do not improve after 3 days, the patient should seek medical advice.

1.5 Pharmaceutical forms: ointment 1%

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients. The ointment should not be applied to infected or damaged skin, moist dermatoses or eczema.

1.7 Relevant warnings: the ointment should not be applied to large areas of skin. In case of skin hypersensitivity reaction, use should be discontinued immediately. If symptoms do not improve during 3 days of drug administration, it is necessary to consult a doctor. The medication should not be used in newborns (up to one month of age). When using the medication in infants and young children, special caution and consultation with a doctor is required. It is not recommended for application to large skin surfaces in infants and young children. Contact of the drug with the eyes and mucous membranes should be avoided. Exposure to the sun should be avoided during treatment. Chloropyramine ointment contains stearyl alcohol which may cause local skin reactions (e.g. contact dermatitis) and methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (delayed hypersensitivity reactions possible). No interaction studies have been conducted for topical chloropyramine.

Pregnancy: chloropyramine ointment is used during pregnancy only if necessary, in small amounts and for as short a duration as possible.

Breastfeeding: chloropyramine ointment should be used during breastfeeding only if necessary, in small amounts and for as short a duration as possible. Chloropyramine ointment should not be applied to the nipples during breastfeeding.

Fertility: no data is available on the effects of chloropyramine on fertility.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): photosensitivity and hypersensitivity reactions, especially skin (rash), are possible.

2.2 Indirect risks (incorrect use): overdoses of chloropyramine ointment have not been observed. If necessary, symptomatic treatment can be provided in specific settings.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
Armenia (AM)	Not subject to prescription	1%				
Austria (AT)	Not authorised					
Bosnia and Herzegovina	Not subject to prescription	1%				

(BA)						
Belgium (BE)	Not authorised					
Switzerland (CH)	Not authorised					
Czech Republic (CZ)	Not authorised					
Estonia (EE)	Not authorised					
Spain (ES)	Not authorised					
Finland (FI)	Not authorised					
France (FR)	Not authorised					
Germany (DE)	Not authorised					
Greece (GR)	Not authorised					
Croatia (HR)	Not subject to prescription	1%		20 g	Skin reactions with pruritus due to insect bites and urticaria	
Hungary (HU)	Not authorised					
Ireland (IE)	Not authorised					
Italy (IT)	Not authorised					
Lithuania (LT)	Not authorised					
Latvia (LV)	Not subject to prescription				Symptomatic therapy in the following cases: mild rashes and itching of allergic origin, contact dermatitis and localised dermatitis, insect bites	
North Macedonia (MK)	Not subject to prescription	1%		20 g	Insect bites, rash	
Netherlands (NL)	Not authorised					
Poland (PL)	Not authorised					
Portugal (PT)	Not subject to prescription	1%				
Romania (RO)	Not authorised					
Serbia (RS)	Not subject to prescription	1%			Skin reactions associated with pruritus due to insect bites and urticaria	
Sweden (SE)	Not authorised					
Slovenia (SL)	POM					
Türkiye (TR)	Not authorised					
United Kingdom (UK)	Not authorised					

No more data available from other member states.

Melclass database[1]:Currently not available

3.2 Social dimension of classification:

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

Proposed recommendation: **Not subject to prescription**

Criteria: no serious adverse reactions reported recently.

3.2.2 Paediatric use: not to be used in newborns (up to one month of age). When using the medication in infants and young children, special caution and consultation with a doctor is required.

3.2.3 Social dimension: -

[1]Available at: https://melclass.edqm.eu/ (NB: this is the CD-P-PH/PHO's recommendation at the time of the compilation of the evidence-based review.)

4. REFERENCES/COMMENTS

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

Agency for Medicines and Medical Devices (North Macedonia) – Available at: https://bit.ly/3mftU5h

Agency for Medicinal Products and Medical Devices of Croatia – Available at: https://bit.ly/3k01l96

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Promethazine

1.2 ATC code: D04AA10

1.3 Therapeutic indications: symptomatic treatment of pruritus, in particular associated with insect bites.

1.4 Posology and duration of treatment: it should be applied in a thin layer two to three times a day. It should not be used for more than 3-4 days without medical advice. Not for use in children under the age of 2 years.

1.5 Pharmaceutical forms: cream 2%

1.6 Contraindications: hypersensitivity to one of its components (promethazine, paraben, lanolin or wool fat); seeping dermatosis; infected dermatosis; eczema.

1.7 Relevant warnings: given the allergenic potential of the components of this drug, the risks incurred must be weighed against the expected benefit. There is a risk of a skin reaction and photosensitisation. In case of a skin reaction from the promethazine in the cream, cross-sensitisation may occur after a course of phenothiazines. Pregnant and breastfeeding women should use this drug with caution due to the atropinic and sedative effects of promethazine. Not to be applied to the breasts during breastfeeding.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): risk of sensitisation to the different components of the drug. Some studies conducted in 2013 showed that topical application of promethazine may cause systemic toxic effects, especially in young children. Photocontact dermatitis due to topical use of promethazine was the most frequent reaction observed in almost 15% of patients.

2.2 Indirect risks (incorrect use): signs of a promethazine overdose: convulsions (especially for babies and children), disorientation and coma.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
AM	Not authorised					
AT	Not authorised					
BA	Not authorised					
BE	Not authorised					
CH	Not authorised					
CZ	Not authorised					
DE	Not authorised					
EE	Not authorised					
ES	Not subject to prescription	2%		30 g	Local treatment of itching, in particular insect bites	
FI	Not authorised					
FR	Not subject to prescription	2%		30 g	Symptomatic treatment of pruritus, in particular associated with insect bites	

GR	Not subject to prescription	2%		30 g	Itching, in particular associated with insect bites	
HR	Not authorised					
HU	Not authorised					
IE	Not authorised					
IT	Not subject to prescription	2%				
LT	Not authorised					
LV	Not authorised					
MK	Not authorised					
NL	Not authorised					
PL	Not authorised					
PT	Not subject to prescription	2%		30 g		
RO	Not authorised					
RS	Not authorised					
SE	Not authorised					
SL	Not authorised					
TR	Not authorised					
UK	Not authorised					

No more data available from other member states.

Melclass database[1]: Not subject to prescription

3.2 Social dimension of classification:

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

Proposed recommendation: **Not subject to prescription (short-term treatment only), MS: 2%, MQP: 30g**

Criteria: promethazine for topical use is for short-term treatment.

3.2.2 Paediatric use: not for use in children under the age of 2 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

Websites of national regulatory authorities of member states

Cantisani C, Ricci S, Grieco T, Paolino G, Faina V, Silvestri E, *et al*. Topical promethazine side effects: Our experience and review of the literature. Biomed Res Int 2013

4.2 Comments: topical promethazine is not widely used. It is no longer available in member states where it was previously marketed. It has probably been replaced with new formulations with lower allergenic potential such as topical dimetindene, which is authorised in almost all European countries.

[1]Available at: https://melclass.edqm.eu/ (NB: this is the CD-P-PH/PHO's recommendation at the time of the compilation of the evidence-based review.)

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Tolpropamine

1.2 ATC code: D04AA12

1.3 Therapeutic indications: antihistamine with antipruritic and local analgesic actions.

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Dimetindene

1.2 ATC code: D04AA13

1.3 Therapeutic indications: treatment of pruritis associated with irritated skin conditions including dermatoses, urticaria, insect bites, sunburn and superficial burns.

1.4 Posology and duration of treatment: in adults and children older than 2 years: a thin layer should be applied two to four times a day on the affected parts of the skin and rubbed in gently.

In children younger than 2 years, the medicine should only be used with a doctor's prescription.

Special dosing instructions: in cases of very severe pruritus or extensive lesions, topical application of dimetindene should be followed by systemic antihistamine therapy.

1.5 Pharmaceutical forms: cream 0.1%, gel 0.1% - in most member states it is authorised as a gel.

1.6 Contraindications: hypersensitivity to dimetindene maleate or to any of the excipients; dimetindene gel must not be used for known allergies to insect bites (systemic antihistamines are available for this condition); dimetindene should not be used on open or inflamed wounds, in conditions that cause moist wounds on the skin, on mucous membranes or near the eyes, especially in infants and young children.

1.7 Relevant warnings: in children younger than 2 years, dimetindene for topical use can be used only if it is prescribed by a doctor. Dimetindene for topical use should not be applied to a large area of skin, especially in infants and young children. Prolonged exposure to sunlight should be avoided.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): the most commonly reported side effects during use of the drug are mild and transient skin reactions at the application site. Occasionally: dry skin, burning sensation. Very rare cases of allergic dermatitis have been observed.

2.2 Indirect risks (incorrect use): accidental ingestion of dimetindene maleate for topical use may result in poisoning similar to H1-antihistamine overdose. Symptoms include: central nervous system (CNS) depression with stupor (especially in adults), CNS stimulation and antimuscarinic effects (especially in children) with excitation, ataxia, hallucinations, tonic-clonic spasm, mydriasis, dry mouth, flushing, urinary retention and fever. Hypotension may also occur. There is no specific antidote. The usual emergency measures should be applied, including activated charcoal, saline laxatives, stabilisation of breathing and circulation. Stimulants should not be applied; vasopressors can be used to normalise blood pressure.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
AM	Not subject to prescription					
AT	Not subject to prescription					
BA	Not subject to prescription					
BE	Not subject to prescription					
CH	Not subject to prescription					

CZ	Not subject to prescription					
DE	Not subject to prescription					
EE	Not authorised					
ES	Not subject to prescription					
FI	Not authorised					
FR	Not subject to prescription					
HR	Not subject to prescription	0.1%		50 g	For short-term relief of itching due to dermatosis, urticaria (hives), insect bites, sunburn and superficial skin burns (first degree).	
HU	Not subject to prescription					
IE	Not authorised					
IT	Not subject to prescription					
LT	Not subject to prescription					
LV	Not subject to prescription					
MK	Not subject to prescription	0.1%		30 g	Pruritus associated with dermatoses, urticaria, insect bites, sunburn, superficial skin burns.	
PL	Not subject to prescription				Itching associated with dermatoses, urticaria, insect bites, sunburn, superficial skin burns (first degree).	
PT	Not subject to prescription	0.1%		30 g	Pruritus associated with dermatoses, urticaria, insect bites, sunburn.	
RO	Not subject to prescription					
RS	Not subject to prescription	0.1%		30 g	Pruritus associated with dermatoses, urticaria, insect bites, sunburn, superficial skin burns.	
SL	Not subject to prescription					
TR	Not subject to prescription	0.1%		30 g	Relief of itching skin, rashes, insect bites and skin burns.	
UK	Not subject to prescription	0.1%		30 g	Pruritus associated with dermatoses, urticaria, insect bites, sunburn and superficial skin burns.	

No more data available from other member states.

Melclass database[1]: Not subject to prescription

3.2 Social dimension of classification:

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

Proposed recommendation: **Not subject to prescription**

Criteria: a) Short-term treatment; b) no serious adverse reactions have been reported recently.

3.2.2 Paediatric use: in children younger than 2 years, topical dimetindene can be used only if it is prescribed by a doctor.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

[1]Available at: https://melclass.edqm.eu/ (NB: this is the CD-P-PH/PHO's recommendation at the time of the compilation of the evidence-based review.)

Medicines and Healthcare Products Regulatory Agency (UK) – Available at: https://bit.ly/3CZN456

Agency for Medicines and Medical Devices (North Macedonia) – Available at: https://bit.ly/3mftU5h

Agency for Medicinal Products and Medical Devices of Croatia – Available at: https://bit.ly/3k01l96

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Clemastine

1.2 ATC code: D04AA14

1.3 Therapeutic indications: antihistamine with antipruritic and local analgesic actions.

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Bamipine

1.2 ATC code: D04AA15

1.3 Therapeutic indications: antihistamine with antipruritic and local analgesic actions; symptomatic treatment of pruritus, in particular associated with insect bites.

1.4 Posology and duration of treatment: to be applied in a thin layer; the gel can also be carefully massaged in. Not recommended for paediatric use.

1.5 Pharmaceutical forms: gel 0.2%

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients. The gel should not be applied to infected or damaged skin, moist dermatoses or eczema. It should not be used during pregnancy and lactation.

1.7 Relevant warnings: in case of skin hypersensitivity reaction, use should be discontinued immediately. If symptoms persist after drug administration, it is necessary to consult a doctor. It is not recommended for application to large skin surfaces in infants and young children

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): skin and subcutaneous tissue disorders: very rare: hypersensitivity reactions (local allergic reactions, contact dermatitis, urticaria); slight burning sensation after application.

Nervous system disorders: when using bamipine over a large area, especially on areas of skin with inflammatory changes, there may be a systemic effect as a result of the absorption of larger amounts of bamipine. Very rare adverse effects: restlessness and confusion, as well as dilated pupils in children. Experience has shown that the side effects recede after treatment is discontinued completely.

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

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
AM	Not authorised					
AT	Not subject to prescription	0.2%		20 g		
BA	Not authorised					
BE	Not authorised					
CH	Not authorised					
CZ	Not authorised					
DE	Not subject to prescription					
EE	Not authorised					
ES	Not authorised					
FI	Not authorised					
FR	Not authorised					

GR	Not authorised					
HR	Not authorised				.	
HU	Not authorised					
IE	Not authorised					
IT	Not authorised					
LT	Not authorised					
LV	Not authorised					
MK	Not authorised					
NL	Not authorised					
PL	Not authorised					
PT	Not authorised					
RO	Not authorised					
RS	Not authorised					
SE	Not authorised					
SL	Not subject to prescription	0.2%		20 g		
TR	Not authorised					
UK	Not authorised					

No more data available from other member states.

Melclass database[1]: not in the database

3.2 Social dimension of classification:

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

Proposed recommendation: **Not subject to prescription**

Criteria: acceptable safety profile

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

Austrian Medicines and Medical Devices Agency - Available at: https://bit.ly/3swQ4kE

Agency for Medicinal Products and Medical Devices of the Republic of Slovenia- Available at: https://bit.ly/3iZwrOJ

4.2 Comments: -

[1]Available at: https://melclass.edqm.eu/ (NB: this is the CD-P-PH/PHO's recommendation at the time of the compilation of the evidence-based review.)

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Phenyramine

1.2 ATC code: D04AA16

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Isothipendyl

1.2 ATC code: D04AA22

1.3 Therapeutic indications: antihistamine with antipruritic and local analgesic actions.

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Diphenhydramine

1.2 ATC code: D04AA32

1.3 Therapeutic indications: symptomatic treatment of allergic conditions, e.g. urticaria, pruritus, allergic rashes, sunburn, stings and insect bites.

1.4 Posology and duration of treatment: it should be applied sparingly and infrequently (maximum twice daily) to the affected area. Short-term treatment only - not more than 3 days. Not recommended for children under 6 years old.

1.5 Pharmaceutical forms: gel 20 mg/g; gel 1%; ointment 12.5 mg/g; cream 2%; spray

1.6 Contraindications: known sensitivity to antihistamines and benzoates. It should not be applied to mucous membranes, eczematous conditions or where the skin is extensively broken or denuded, or in acute vesicular or exudative dermatoses. Do not use with any other product containing the same active ingredient.

1.7 Relevant warnings: it should be applied sparingly. Prolonged use or repeated applications, especially to large areas, should be avoided. If burning or rash develops, or if the condition persists, medical advice should be sought immediately. If necessary the medication should be removed by washing with soap and water. Hands should be washed after use, unless they are being treated.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): diphenhydramine applied externally has antihistaminic activity in conditions induced by allergic stimuli. Diphenhydramine is a histamine H1 receptor antagonist. External applications to largely intact skin results in minimal systemic absorption. It may give rise to sensitisation reaction and photosensitivity. Rarely eczematous reactions have been reported; if this occurs, treatment should be discontinued**.**

2.2 Indirect risks (incorrect use): accidental ingestion or excessive absorption may lead to dose-related signs of diphenhydramine toxicity, including drowsiness and sedation. Treatment is by gastric lavage and aspiration. In cases of acute poisoning, activated charcoal may be useful.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
AM	Not subject to prescription					
AT	Not subject to prescription					
BA	Not authorised					
BE	Not subject to prescription					
CH	Not subject to prescription					
CZ	Not subject to prescription					
DE	Not subject to prescription					
EE	Not authorised					
ES	Not subject to prescription					
FI	Not authorised					
FR	Not authorised					
HR	Not authorised					

HU	Not subject to prescription					
IE	Not authorised					
IT	Not subject to prescription					
LT	Not subject to prescription					
LV	Not subject to prescription					
MK	Not authorised					
NL	Not authorised					
PL	Not authorised					
PT	Not subject to prescription					
RO	Not subject to prescription					
RS	Not subject to prescription					
SE	Not authorised					
SL	Not authorised					
TR	Not subject to prescription					
UK	Not subject to prescription					

No more data available from other member states.

Melclass database[1]: Not subject to prescription

3.2 Social dimension of classification:

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

Proposed recommendation: **Not subject to prescription**

Criteria: short-term treatment that should be started as soon as possible; low systemic absorption.

3.2.2 Paediatric use: Not recommended for children under 6 years old.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

Medicines and Healthcare Products Regulatory Agency (UK): https://bit.ly/3CZN456

Mutual Recognition Information (MRI) Index: https://mri.cts-mrp.eu/Human/

4.2 Comments: -

[1] Available at: https://melclass.edqm.eu/ (NB: this is the CD-P-PH/PHO's recommendation at the time of the compilation of the evidence-based review.)

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Diphenhydramine methylbromide

1.2 ATC code: D04AA33

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

Mutual Recognition Information (MRI) Index: https://mri.cts-mrp.eu/Human/

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Chlorphenoxamine

1.2 ATC code: D04AA34

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, medicines containing this active substance are not authorised in at least three member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Lidocaine

1.2 ATC code: D04AB01 – *Note*: lidocaine is used for different therapeutic indications and therefore it appears in the ATC/DDD Index under different ATC codes. ATC group D04AB refers to local anaesthetics for dermatological use, such as treatment of pruritus, minor burns and insect stings. Other lidocaine-containing local anaesthetics used, for example, for dental and ophthalmological anaesthesia are classified under other ATC codes.

1.3 Therapeutic indications: a) Symptomatic treatment of allergic, pruritic or inflammatory skin diseases, e.g. mild sunburn, insect bites, mild allergic dermatitis, minor burns (first degree).

b) A vaginal cream is authorised in Italy and Spain and is indicated for short-term and local symptomatic relief of mild itching, burning and irritation of the external vaginal and perianal areas.

1.4 Posology and duration of treatment: a) Treatment of allergic, pruritic or inflammatory skin diseases: adults and children from 2 years: several applications daily on the area of skin irritation, in a thin layer. Infants and children under 2 years: only on prescription and under medical supervision.

b) Vaginal cream: the product is intended for use in adult patients only. It should be applied in a thin layer on the area to be treated and the application can be repeated up to three or four times a day, if necessary. It should only be used for short periods of treatment.

1.5 Pharmaceutical forms: various pharmaceutical forms are authorised: creams and ointments containing up to 5% lidocaine; lotions containing up to 1% lidocaine; vaginal creams containing 2% lidocaine. In Poland and Switzerland combination products are also authorised and classified under this ATC code (Poland: gels containing 1% lidocaine and 2% diphenhydramine; Switzerland: gel containing 1.5% lidocaine, 1.5% mepyramine and 5% dexpanthenol).

1.6 Contraindications: a) Treatment of allergic, pruritic or inflammatory skin diseases: the medication is contraindicated in patients with open skin lesions, exudative rashes, infected wounds or hypersensitivity to any of the medication components, and in children under 2 years of age.

b) Vaginal cream: contraindicated in patients with hypersensitivity to any of the medication components, the paediatric population, and during pregnancy and lactation.

1.7 Relevant warnings: a) Treatment of allergic, pruritic or inflammatory skin diseases: for external use only. Contact with eyes should be avoided as lidocaine may cause eye irritation. The product should not be used on large areas of skin, in large quantities or for prolonged periods. The product should not be used on wounds, mucous membranes or in patients with atopic dermatitis as no clinical data are available. The product is not indicated for children under 2 years of age without medical advice. If new skin reactions occur, use should be discontinued.

b) Vaginal cream: caution should be exercised in elderly and seriously ill patients. In cases of injury to the mucous membranes, the product should not be used and a physician should be consulted. The use, especially if prolonged, of products for topical use may give rise to sensitisation phenomena, in which case treatment should be discontinued and, if necessary, appropriate therapy should be administered. After a short period of treatment without appreciable results or in cases of suspected fungal infection, a physician should be consulted.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): a) Treatment of allergic, pruritic or inflammatory skin diseases: local (e.g. irritation at the application site and hypersensitivity reactions) and general allergic reactions up to anaphylactoid reactions may occur with lidocaine. The occurrence of systemic adverse reactions is rare and may result from high plasma levels due to overdose, rapid absorption, hypersensitivity or reduced tolerance. These reactions involve the central nervous system (CNS) and/or the cardiovascular system. Reactions at the CNS level are excitatory and/or depressive, whereas cardiovascular reactions are depressive.

Appropriate emergency measures must be taken in such cases.

b) Vaginal cream: rarely, in sensitive persons, irritation, stinging, oedema or allergic reactions may appear in the area of application. In this case, treatment must be discontinued and, if necessary, appropriate therapy should be started. After a short period of treatment without appreciable results or in cases of suspected fungal infection, a physician should be consulted.

2.2 Indirect risks (incorrect use): a) Treatment of allergic, pruritic or inflammatory skin diseases: although the bioavailability of lidocaine is low, cases of CNS toxicity have been reported after ingestion of topical solutions. The effects of acute overdose are mainly on the central nervous and cardiovascular systems (hypotension, asystole, bradycardia, apnoea, and possibly even coma and death). If signs of acute systemic toxicity occur, administration of the medication should be immediately discontinued. Severe neurological reactions (e.g. convulsions) require symptomatic treatment such as respiratory support and anticonvulsant therapy. In cases of chronic systemic absorption, a patient with symptoms of toxicity should be observed for several hours after treatment for these symptoms. Accidental oral ingestion of cream by children may cause toxicity symptoms, depending on the dose. There is no specific antidote for lidocaine.

b) Vaginal cream: given the pharmaceutical form and route of administration of the product, intoxication is very unlikely. However, excessive application of the product or accidental ingestion may cause local irritation, nausea, gastric discomfort, anxiety, nervousness, confusion, blurred vision, tinnitus and drowsiness. Systemic absorption, through application of preparations with high lidocaine concentration, for example, may cause more serious reactions, such as convulsions, irregular heartbeat, respiratory depression and, in very rare cases, anaphylaxis, especially if used on extensive areas of skin, with occlusive dressings or on irritated or wounded skin, or due to increased skin temperature. The usual measures should be applied in these cases (gastric emptying, use of adsorbents, etc.).

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
AM***	POM				Local anaesthesia (dental procedures and surgery, otorhinolaryngology, endoscopy and instrumental methods of examination, gynaecology and obstetrics, and dermatology)	
AT	Not authorised					
BA	Not authorised					
BE	Not authorised					
BG***	Not subject to prescription				Local anaesthesia	
CH	Not subject to prescription				Authorised medicinal products: a) combination product containing mepyramine, dexpanthenol and lidocaine; pharmaceutical form: gel for cutaneous use (MQP: 20 g); indication: symptomatic treatment of allergic, pruritic or inflammatory skin diseases, e.g. mild sunburn, insect bites, mild allergic dermatitis, minor burns (first degree) b) lotion for cutaneous use	Another medicinal product is authorised under this ATC code, i.e. medicated plasters indicated to relieve the pain following post-herpetic neuralgia. The product is classified as List II. However, given the indication, the ATC code might not be appropriate.

					containing lidocaine (MS: 1% and MQP: 85 mL); indication: minor injuries from sunburn, insect bites, skin erosions, irritant skin lesions and first degree burns (minor burns)	
CZ	Not authorised					
EE	Not authorised					
ES	Not subject to prescription				Vaginal cream indicated for short-term and local symptomatic relief of mild itching, burning and irritation of the external vaginal area	
FI	Not authorised					
FR	Not subject to prescription				Gel for cutaneous use containing lidocaine and magnesium sulphate. Indicated for short-term local treatment of benign trauma (e.g. sprains and contusions)	
GR	Not authorised					
HR	Not authorised					
HU***	POM + Exemption	Ex.: 5%		20 g	Ex.: local anaesthesia (e.g. dentistry, prior to proctological examination, post-herpetic neuralgia)	Other authorised products under this ATC code are classified as POM and indicated for anaesthesia of the skin or mucous membranes.
IE	Not authorised					
IT***	List II + Exemption				Ex.: authorised medicinal products not subject to prescription: a) cream for anaesthetic use (mucous membranes of the oropharyngeal cavity and mild skin lesions) and anorectal itching; b) vaginal cream indicated for vulvar and perianal itching	Other authorised products under this ATC code are classified as List II and indicated for local anaesthesia***
LT***	POM				Oropharyngeal use	
LV	Not authorised					
MK	Not authorised					
NL	POM + Exemption				Ex.: 50 mg/g ointment that can be used prophylactically and therapeutically for conditions of the skin and mucous membranes associated with pain, burning, itching and other unpleasant sensations, particularly pruritus, anal itch and haemorrhoids.	Other authorised products under this ATC code are classified as POM and indicated for rapid and reliable anaesthesia of mucous membranes, especially in procedures in ear, nose and throat surgery, obstetrics, oral surgery and traumatology (oromucosal use)***
PL	POM + Exemption				Ex.: indicated for symptomatic treatment of inflammatory and allergic lesions of the skin, accompanied by pruritus, as a result of insect bites as well as contact with plants (e.g. nettle)	Ex.: indicated in cases of premature ejaculation – ATC code not correct (correct ATC code: N01BB02) POM: medicinal product for local anaesthesia of superficial layers of skin***

PT	POM + Exemption				Ex.: cream containing 5% lidocaine and indicated for temporary relief from pain caused by minor burns and abrasions of the skin; anaesthesia of the mucous membranes; pain relief during some semiological and instrumental procedures; superficial anaesthesia of the gums before injection, deep cleaning and application of dental prostheses.	Ex.: cream for topical anaesthesia prior to a needle insertion procedure*** POM: spray for cutaneous, nasal and vaginal use***
RO***	List I				Local anaesthesia	
RS	Not authorised					
SE	POM + Exemption				Ex.: ointment containing 5% lidocaine indicated for painful wounds (e.g. burns and insect bites), various anal complaints (e.g. haemorrhoids and fissures) and after anorectal procedures or explorations.	Ex. and POM: cream containing 4% lidocaine and indicated for local anaesthesia***
SK***	POM				Cutaneous solution and cream indicated for short-term anaesthesia of the skin or mucous membranes	
SL	POM				Ointment and cream containing 4% and 5% lidocaine – no further details available	
UK***	Not subject to prescription				Lidocaine 4% w/w cream: local anaesthetic for topical use to produce surface anaesthesia of the skin	

******* The authorised medications are indicated for local anaesthesia. Therefore, the ATC code of these medicinal products may not be correct.

No more data available from other member states.

Melclass database[1]: Not subject to prescription

3.2 Social dimension of classification:

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

Proposed recommendation: **Not subject to prescription**

Criteria: a) indications are easy to self-diagnose and self-treat; b) important to have prompt access to medication; c) overall risks and potential for abuse and misuse are low for these indications, pharmaceutical forms, strengths and dosages.

3.2.2 Paediatric use: not indicated for children under 2 years of age without medical advice. Vaginal cream (external use) is contraindicated in children under 3 years of age and should be used under medical supervision in children between 3 and 12 years.

3.2.3 Social dimension: -

[1] Available at: https://melclass.edqm.eu/ (NB: this is the CD-P-PH/PHO's recommendation at the time of the compilation of the evidence-based review.)

4. REFERENCES/COMMENTS

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

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

National medicine registers in the different member states of the Council of Europe

4.2 Comments: as pointed out above, medications classified under this ATC code are indicated for dermatological use, e.g. treatment of pruritus, minor burns and insect stings. In some member states there are medicinal products that are classified under this ATC code but are indicated for local anaesthesia, oropharyngeal use and premature ejaculation. According to the CD-P-PH/PHO, the ATC code of these products may be incorrect and the above-mentioned indications are not taken into account in this evidence-based classification review.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Cinchocaine

1.2 ATC code: D04AB02

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, medicines containing this active substance are not authorised in at least three member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Oxybuprocaine

1.2 ATC code: D04AB03

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Benzocaine

1.2 ATC code: D04AB04

1.3 Therapeutic indications: symptomatic relief of pain from minor superficial burns and scalds where the skin is unbroken. The powder for cutaneous use is for the treatment of exudative and inflamed skin with painful and itchy eruptions. Incidental treatment and relief of symptoms such as eczema, childhood eczema, vesicular varicella rash, shingles, exudative blemishes, scabies, heat rash, urticaria, conditions after insect bites, juvenile acne.

1.4 Posology and duration of treatment: for topical administration.

Adults, the elderly and children: to reduce pain and blistering the medication should be used as quickly as possible. The nozzle should be held 5 inches (10 cm) from the skin and the product should be sprayed once for 2-3 seconds. Spraying should be immediately stopped if a white frost deposit appears. If necessary, the application may be repeated once only after 15 minutes. If pain persists medical advice should be sought. For cutaneous use. The product should be shaken before use.

Children: in children under 12 years of age, the product may be used only after consulting a doctor.

1.5 Pharmaceutical forms: 15 mg/g cutaneous powder; 1% w/w aerosol spray; 1% w/w cutaneous spray, solution.

1.6 Contraindications: the product should not be used if the patient is sensitive to benzocaine or any chemically related anaesthetics (butylcaine and tetracaine). Benzocaine should not be used if the patient is sensitive to any of the excipients or to PABA, parabens, paraphenylenediamine or to commercial hair dyes as there is cross sensitivity between these products. Benzocaine should not be used on broken or infected skin.

Hypersensitivity to the active substance or to any of the excipients contained in the product. Not to be used: a) on mucous membranes; b) on open wounds; c) for ulcers; d) on body surfaces devoid of epidermis; e) in patients treated with sulphonamides; f) in children under 12 years of age, the product may be used only after consulting a doctor.

1.7 Relevant warnings: patients with any known allergy should seek medical advice. Do not apply to large areas or to broken skin. Do not use in or near the mouth or eyes or under conditions in which significant inhalation is likely. Avoid freezing the skin by repeated or prolonged use. Seek medical advice immediately if burns are extensive (particularly in young children or if they affect fingers, toes or sensitive areas).

Pregnancy: there are limited data (less than 300 pregnancy outcomes) on the use of benzocaine in pregnant women. As a precautionary measure, it is preferable to avoid the use of benzocaine during pregnancy.

Lactation: there is insufficient information on the excretion of benzocaine or its metabolites in human milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from benzocaine therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother.

Fertility: there is no known effect on fertility.

Benzocaine should not be used for prolonged periods as allergic reactions may occur.

There is a risk of methaemoglobinaemia with the use of the product, especially in hypersensitive patients and in children.

Contact of the product with the eyes should be avoided.

In the event of a hypersensitivity reaction (e.g. increased itching, redness), discontinue use and consult a dermatologist.

Concomitant use of the product with: a) cationic substances: phenazone, camphor, resorcinol, glycols polyoxyethylene (ointments, suppositories), as the product may become discoloured; b) substances of a strongly acidic or alkaline nature and at elevated temperatures, because the breakdown of benzocaine can occur; c) sulfonamides or oxytetracycline, as benzocaine inhibits their antibacterial effect.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): benzocaine may cause allergic dermatitis in sensitive individuals. Hypersensitivity reactions are rare and generally limited to local anaesthetics of the ester type. There appears to be no cross-sensitivity between ester-and amide type local anaesthetics. Idiosyncrasy to local anaesthetics has been reported.

2.2 Indirect risks (incorrect use): an overdose is extremely unlikely with this type of preparation. There are no data available on overdose of the product when used as directed. In case of accidental ingestion of the product, general side effects such as gastrointestinal disorders, vomiting, cramps, tachycardia, loss of consciousness and methaemoglobinaemia may occur.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
AM	Not authorised					
AT	Not subject to prescription					
BA	Not authorised					
BE	Not authorised					
BG	Not authorised					
CH	Not authorised					
Cyprus (CY)	Not authorised					
CZ	Not authorised					
EE	Not authorised					
ES	Not authorised					
FI	Not authorised					
FR	Not authorised					
GR	Not authorised					
HR	Not authorised					
HU	Not authorised					
IS	Not authorised					
IE	Not subject to prescription					
IS	Not authorised					
IT	Not authorised					
LT	Not authorised					
LV	Not authorised					
MT	Not authorised					
MK	Not authorised					
NL	Not authorised					
Norway (NO)	Not authorised					
PL	Not subject to prescription					

PT	Not subject to prescription					
RO	Not authorised					
RS	Not authorised					
SE	Not authorised					
SK	No authorised					
SL	Not subject to prescription					
UK	Not subject to prescription					

No more data available from other member states.

Melclass database[1]: Not subject to prescription

3.2 Social dimension of classification:

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

Proposed recommendation: **Not subject to prescription**

Criteria: topical mode of action and well-known efficacy, acceptable safety profile, unlikely to cause severe side effects.

3.2.2 Paediatric use: not for use in children under 12 years of age.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

Health Products Regulatory Authority (Ireland) - Available at: https://bit.ly/2Uu1mt5

Medicines and Healthcare Products Regulatory Agency (UK): https://bit.ly/3CZN456

Medicinal Products Registry (Poland) - Available at: https://bit.ly/3svy7To

4.2 Comments: -

[1] Available at: https://melclass.edqm.eu/ (NB: this is the CD-P-PH/PHO's recommendation at the time of the compilation of the evidence-based review.)

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Quinisocaine

1.2 ATC code: D04AB05

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, medicines containing this active substance are not authorised in at least three member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Tetracaine

1.2 ATC code: D04AB06

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Pramocaine

1.2 ATC code: D04AB07

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, medicines containing this active substance are not authorised in at least three member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Doxepin

1.2 ATC code: D04AX01

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Naloxone

1.2 ATC code: V03AB15

1.3 Therapeutic indications: a) complete or partial reversal of CNS depressive effects, especially respiratory depression, caused by natural or synthetic opioids and partial agonist/antagonist opioids; b) diagnosis of suspected acute opioid overdose or intoxication; c) complete or partial reversal of respiratory depression and other CNS depressive effects in neonates, if the mother has received/taken opioids; d) immediate administration as emergency therapy for known or suspected opioid overdose as manifested by respiratory and/or CNS depression in both non-medical and healthcare settings in adults and adolescents aged 14 years and over.

1.4 Posology and duration of treatment: intravenous or intramuscular injection or via intravenous infusion. Nasal use. Both systemic – emergency preparation – and diagnostic, short-term use.

1.5 Pharmaceutical forms: solution for injection 0.4 mg/mL naloxone hydrochloride and nasal spray single dose 1.8 mg naloxone hydrochloride.

1.6 Contraindications: No specific contraindications.

1.7 Relevant warnings: naloxone should be given with caution to patients who have received high doses of opioids or are physically dependent on opioids (including neonates born to women who are opioid-dependent). In such cases a prompt and complete reversal of opioid effects by too high a dose of naloxone may precipitate acute withdrawal symptoms. Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest have been described. This also applies to newborn infants of such patients.

Patients who have responded satisfactorily to naloxone treatment must be carefully monitored. The effects of opioids can last longer than those of naloxone and new injections may be necessary.

Excessive doses of naloxone in post-operative patients may result in a clear reversal of analgesia, excitement and an elevation in blood pressure. A reversal of opioid effects achieved too rapidly may induce nausea, vomiting, sweating or tachycardia.

Naloxone is not effective in central nervous system depression caused by agents other than opioids. Reversal of buprenorphine-induced respiratory depression may be incomplete. If an incomplete response occurs respiration should be mechanically assisted.

Naloxone should be used with caution in patients with pre-existing cardiovascular disease or in patients who are taking relatively cardiotoxic drugs (e.g. calcium channel blockers, beta-blockers and digoxin).

Patients who respond satisfactorily to naloxone must be closely monitored. The effects of some opioids can last longer than those of naloxone.

Rapid reversal of the opioid effect can cause an acute withdrawal syndrome. Patients who are receiving opioids for the relief of chronic pain may experience pain and opioid withdrawal symptoms when naloxone is administered.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, hyperventilation, increased blood pressure, tremulousness and violent behaviour. In post-operative patients, higher than necessary doses of naloxone may result in significant reversal of analgesia and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, hyperventilation and pulmonary oedema have been associated with the use of naloxone post-operatively. Seizures have occurred on rare occasions following the administration of naloxone.

Description of selected adverse reactions

Drug withdrawal syndrome: signs and symptoms of drug withdrawal syndrome include restlessness, irritability, hyperaesthesia, nausea, vomiting, gastrointestinal pain, muscle spasms, dysphoria, insomnia, anxiety, hyperhidrosis, piloerection, tachycardia, increased blood pressure, yawning and pyrexia. Behavioural changes, including violent behaviour, nervousness and excitement, may also be observed.

Vascular disorders: in reports on intravenous/intramuscular administration of naloxone: hypotension, hypertension, cardiac arrhythmia (including ventricular tachycardia and fibrillation) and pulmonary oedema have occurred with the post-operative use of naloxone. Adverse cardiovascular effects have occurred more frequently in post-operative patients with a pre-existing cardiovascular disease or in those receiving other medicines that produce similar adverse cardiovascular effects.

2.2 Indirect risks (incorrect use): naloxone elicits a pharmacological response due to the interaction with opioids and opioid agonists. When administered to opioid-dependent subjects, naloxone can cause acute withdrawal symptoms in some individuals. Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest have been described, more typically when naloxone is used post-operatively. Naloxone may decrease the analgesic effects of opioids used primarily to provide pain relief, due to its antagonist properties. When administering naloxone to patients who have received buprenorphine as an analgesic, complete analgesia may be restored. It is thought that this effect is a result of the arch-shaped dose-response curve of buprenorphine with decreasing analgesia in the event of high doses. However, reversal of respiratory depression caused by buprenorphine is limited.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
AM	Not authorised					
AT	List I					
BA	Not authorised					
BE	POM					
BG	POM					
CH	List II					
CZ	POM					
DE	POM					
EE	POM					
ES	POM					
FI	POM					
FR	List I + Ex.	Ex.: 0.9 mg/0.1 mL		Ex.: 0.1 mL	Ex.: nasal spray solution in single-dose containers (MS: 0.9 mg/0.1 mL), indicated in adults and children aged one month and over for the emergency treatment of opioid overdose, manifested by respiratory depression, while awaiting treatment by a medical facility.	
GE	POM					
GR	POM					
HR	List I					
HU	POM					

IE	List I + Ex.				Ex.: in accordance with emergency medicines legislation – intramuscular and nasal use: respiratory depression secondary to known or suspected narcotic overdose in adults and children.	
IT	List II + Ex.	Ex. 0.4 mg		Ex. 1 mL		
LT	POM					
LV	POM					
MK	Not authorised					
NL	POM					
NO	POM					
PL	POM					
PT	POM					
RO	List I					
RS	Not authorised					
SE	POM					
SK	POM					
SL	POM					
UK	POM					

No more data available from other member states.

Melclass database[1]: POM

3.2 Social dimension of classification:

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

Proposed recommendation: **List I + Exemption** - Exemptions: immediate emergency therapy for known or suspected opioid overdose, administration by specially trained personnel.

Criteria:

List I: given the possibility of adverse effects due to rapid reversal of opioid effects (e.g. acute withdrawal syndrome) as well as incomplete reversal of respiratory depression, there is a need for patient monitoring and management after naloxone use.

Exemption: a wider availability of naloxone in emergency situations would prevent deaths due to opioid overdose in at-risk patients.

3.2.2 Paediatric use: List I for children under 14 years.

3.2.3 Social dimension: use of naloxone by specially trained people (emergency response personnel). 'Take-home naloxone' (THN) programmes, available in 11 EU countries and Norway, combine training on overdose risk and management with the distribution of naloxone to potential bystanders. The aim is to expand the availability of naloxone to opioid-using peers, family members and other trained laypeople.

4. REFERENCES/COMMENTS

4.1 References:

European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA): Take-home naloxone topic

[1] Available at: https://melclass.edqm.eu/ (NB: this is the CD-P-PH/PHO's recommendation at the time of the compilation of the evidence-based review.)

overviews - Available at: https://www.emcdda.europa.eu/publications/topic-overviews/take-home-naloxone_en

European Medicines Agency (EMA): European Public Assessment for Nyxoid 1.8 mg nasal spray, solution in a single-dose container - Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/nyxoid

4.2 Comments: -

LIST OF AUTHORS

Mrs Merjem HADJIHAMZA
Agency for Medicines and Medical Devices
St. Sv. Kiril i Metodij 54
1000 Skopje (North Macedonia)

Mr Markus PONGRATZ
Austrian Agency for Health and Food Safety
Traisengasse 5
1200 Vienna (Austria)

Ms Dovilė ZACHARKIENĖ
State Medicines Control Agency *(at the time of the compilation of this document)*
Žirmūnų st. 139A
09120 Vilnius (Lithuania)

SECRETARIAT
Department of Biological Standardisation, OMCL Network and HealthCare (DBO)
EDQM – Council of Europe
7 Allée Kastner
CS 30026 67081 Strasbourg (France)