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

Report classification of medicines belonging to ATC group R05DB (Other cough suppressants)

(2021)

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 Pharmacopoeia, as well as national information about the classification status and supply conditions of

[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/

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

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

GENERAL NOTE

This report focuses on the legal classification of medicines containing active substances belonging to ATC group R05DB - Other cough suppressants.

This ATC group was chosen for the following reasons: a) medicines containing some of these active substances are widely used in member states; b) their classification status is not harmonised across member states.

The classification reviews included in this document have no legal status and no binding character. They reflect the debates and conclusions of the reviews of scientific classifications of medicines that took place at the 2021 meetings of the CD-P-PH/PHO.

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

GLOSSARY OF TERMS USED IN THIS DOCUMENT

ATC	Anatomical Therapeutic Chemical classification [1]
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://goo.gl/KvqKir

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Benzonatate

1.2 ATC code: R05DB01

1.3 Therapeutic indications: cough suppressant

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 (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

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Benproperine

1.2 ATC code: R05DB02

1.3 Therapeutic indications: cough suppressant

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 (based on the available data, medicines containing this active substance are only authorised in Germany (classification status: POM)).

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

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Clobutinol

1.2 ATC code: R05DB03

1.3 Therapeutic indications: cough suppressant

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 (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

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Isoaminile

1.2 ATC code: R05DB04

1.3 Therapeutic indications: cough suppressant

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 (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

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Pentoxyverine

1.2 ATC code: R05DB05

1.3 Therapeutic indications: pentoxyverine is a centrally acting cough suppressant used for non-productive cough. Symptomatic treatment of irritable cough in adults and children from 6 years of age.

1.4 Posology and duration of treatment: children 6-15 years: body mass 20-26 kg: 6.75 mg three to four times a day; body mass 27-45 kg: 10.125 mg three to four times a day; body mass 46-60 kg: 20.25 mg three to four times a day.

Adolescents and adults with body mass over 60 kg: 20.25 mg three to four times a day.

1.5 Pharmaceutical forms: oral solution: 1.35 mg/mL; oral drops, solution: 19 mg/mL

1.6 Contraindications: respiratory failure or central nervous system depression, hepatic insufficiency, pregnancy and lactation, children under 6 years of age.

1.7 Relevant warnings: the combined use of secretolytics and cough suppressants may improve the treatment of the cough, with secretolysis recommended during the day and cough suppression during the night. However, in the case of a productive cough with considerable mucus production, a cough suppressant such as pentoxyverine should only be used after a careful assessment of the benefits and risks and with particular caution, since under these circumstances, suppression of the cough reflex is undesirable. In patients with asthma, cough suppressants such as pentoxyverine can be used in addition to the standard therapy, if the cough does not respond – or only responds inadequately – to the anti-asthmatic therapy. However, other causes must be excluded first. Because of the very rare occurrence of seizures and respiratory depression in infants, these must be particularly closely observed during treatment with pentoxyverine. Caution is advised in patients with renal insufficiency and in elderly patients, since for these patient groups there is not enough data available concerning the use of this medicinal product.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): common adverse events reported with the use of pentoxyverine are gastrointestinal disorders, including epigastric pain, diarrhoea, nausea and vomiting. Uncommon adverse events reported with the use of pentoxyverine are somnolence and fatigue. In very rare cases hypersensitivity reactions, including anaphylactic reactions, are reported, as well as angioedema, urticaria, exanthema and dyspnoea and respiratory depression (especially in infants).

2.2 Indirect risks (incorrect use): signs of intoxication are central nervous and gastrointestinal symptoms such as respiratory depression, sedation and vomiting, as well as anticholinergic effects (e.g. urinary retention, glaucoma, tachycardia, blurred vision, agitation, hallucinations).

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	Routes of Administration/ Indications	MS	MDD	MQP
Armenia (AM)	Not authorised				
Austria (AT)	Not subject to prescription	Symptomatic treatment of irritable cough in adults and children from 6 years of age			
Bosnia and Herzegovina (BA)	Not authorised				
Belgium (BE)	Not authorised				

Bulgaria (BG)	Not subject to prescription				
Switzerland (CH)	Not authorised				
Czech Republic (CZ)	Not authorised				
Germany (DE)	Not subject to prescription				
Estonia (EE)	Not authorised				
Spain (ES)	Not authorised				
Finland (FI)	Not subject to prescription				
France (FR)	Not subject to prescription				
Greece (GR)	Not subject to prescription				
Georgia (GE)	Not authorised				
Croatia (HR)	Not authorised				
Hungary (HU)	Not authorised				
Ireland (IE)	Not authorised				
Italy (IT)	Not subject to prescription				
Lithuania (LT)	Not authorised				
Latvia (LV)	Not authorised				
Montenegro (ME)	Not authorised				
North Macedonia (MK)	Not authorised				
Netherlands (NL)	Not subject to prescription	Dry cough treatment			
Poland (PL)	Not authorised				
Portugal (PT)	Not subject to prescription	Treatment of dry cough in adults and children 6 years	1.35 mg/mL	120 mg	256.5 mg
Romania (RO)	Not authorised				
Serbia (RS)	Not authorised				
Slovakia (SK)	Not subject to prescription				
Turkey (TR)	Not subject to prescription				
United Kingdom (UK)	Not authorised				

No more data available from other member states.

Melclass database[1]: List II + Exemption

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): Proposed recommendation: **Non-prescription medicine**

Criteria: the use of medicines containing pentoxyverine (under this ATC code) does not present a danger, either directly or indirectly, when used correctly. Conditions or symptoms for which the medication is indicated can be correctly diagnosed without medical supervision or can be easily recognised. No risk of misuse.

3.2.2 Paediatric use: contraindicated in children under 6 years of age. Children known to be predisposed to convulsions should be monitored during pentoxyverine therapy. In children, suppression of the cough reflex is undesirable if the cough is accompanied by significant hypersecretion.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

Martindale Complete Drug Reference - 40th edition, 2020

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

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Oxolamine

1.2 ATC code: R05DB07

1.3 Therapeutic indications: oxolamine is a cough suppressant with a mainly peripheral action that is administered to treat non-productive cough.

1.4 Posology and duration of treatment: oral doses of 100 to 200 mg three times daily. In children, the duration of treatment should not exceed 5 days, unless medically indicated otherwise.

1.5 Pharmaceutical forms: syrup 10 mg/mL

1.6 Contraindications: hypersensitivity to oxolamine citrate.

1.7 Relevant warnings: oxolamine should not be used in case of persistent chronic cough associated with respiratory pathology. Oxolamine should not be used in case of productive cough.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): gastrointestinal disorders (very rare): anorexia, epigastric pain, nausea, diarrhoea, heartburn.

General disorders: slight feeling of anaesthesia in the oral cavity that quickly disappears.

Nervous system disorders (very rare): insomnia. Hallucinations in children have been reported after oxolamine use.

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:

Country	Classification	Routes of Administration/ Indications	MS	MDD	MQP
AM	Not authorised				
AT	Not authorised				
BA	Not authorised				
BE	Not authorised				
BG	Not authorised				
CH	Not authorised				
CZ	Not authorised				
DE	Not authorised				
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 subject to prescription				
LT	Not authorised				
LV	Not authorised				
ME	Not authorised				
MK	Not authorised				
NL	Not authorised				

PL	Not authorised				
PT	Not subject to prescription	Treatment of dry cough in children (over 4 months) and adults	10 mg/mL	600 mg	2500 mg
RO	Not authorised				
RS	Not authorised				
RU	Not authorised				
SK	Not authorised				
TR	POM	Symptomatic antitussive			
UK	Not authorised				

No more data available from other member states.

Melclass database[1]: no entry in Melclass database.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): Proposed recommendation: **List I + Exemption** – Exemptions: short-term treatment of dry cough in adults; MS: 10 mg/mL; MDD: 600 mg

Criteria: given the consequence of incorrect use/misuse in some member states, it is advised to classify this medication as List I. Conditions or symptoms for which the medication is indicated can be correctly diagnosed without medical supervision or can be easily recognised (therefore, in this case, a non-prescription status is recommended).

3.2.2 Paediatric use: use in children over 4 months of age. Hallucinations in children have been reported after oxolamine use.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

[1] Melclass database - Available at: http://www.edqm.eu/melclass/ (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: Oxeladin

1.2 ATC code: R05DB09

1.3 Therapeutic indications: oxeladin is used orally as a centrally acting cough suppressant for non-productive cough.

1.4 Posology and duration of treatment: up to 50 mg daily in divided doses is administered orally. Higher doses of up to 120 mg daily are administered as a modified-release preparation.

1.5 Pharmaceutical forms: syrup: 2 mg/mL; prolonged-release hard capsules: 40 mg

1.6 Contraindications: hypersensitivity to oxeladin; productive cough.

1.7 Relevant warnings: it is not recommended to use an expectorant or mucolytic together with a cough suppressant. Before prescribing a cough suppressant, the causes of the cough that require specific treatment should be investigated. If the cough is resistant to a cough suppressant administered at the usual dosage, the dose should not be increased, but the clinical situation should be re-examined.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): hypersensitivity reactions have sometimes been reported (urticaria, rash, angioedema).

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:

Country	Classification	Routes of Administration/ Indications	MS	MDD	MQP
AM	Not authorised				
AT	Not authorised				
BA	Not authorised				
BE	Not authorised				
BG	Not authorised				
CH	Not authorised				
CZ	Not authorised				
DE	Not authorised				
EE	Not subject to prescription	Dry cough treatment			
ES	Not authorised				
FI	Not authorised				
FR	Not subject to prescription				
GR	Not authorised				
HR	Not authorised				
HU	Not authorised				
IE	Not authorised				
IT	Not authorised				
LT	Not subject to prescription				
LV	Not authorised				
ME	Not authorised				
MK	Not authorised				
NL	Not authorised				
PL	Not authorised				
PT	Not authorised				
RO	Not subject to prescription				
RS	Not authorised				

RU	Not authorised				
SK	Not subject to prescription				
TR	Not authorised				
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, MS, MDD, MQP, as applicable): Proposed recommendation: **Not subject to prescription**

Criteria: the use of medicines containing oxeladin (under this ATC code) does not present a danger, either directly or indirectly, when used correctly. Conditions or symptoms for which the medicine is indicated can be correctly diagnosed without medical supervision or can be easily recognised. No risk of misuse.

3.2.2 Paediatric use: oxeladin should not be given to children under 30 months of age in the absence of data to support its efficacy and safety in this age group.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

[1] Melclass database - Available at: http://www.edqm.eu/melclass/ (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: Clofedanol

1.2 ATC code: R05DB10

1.3 Therapeutic indications: cough suppressant

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 (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

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Pipazetate

1.2 ATC code: R05DB11

1.3 Therapeutic indications: cough suppressant

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 (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

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Bibenzonium bromide

1.2 ATC code: R05DB12

1.3 Therapeutic indications: cough suppressant

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 (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

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Butamirate

1.2 ATC code: R05DB13

1.3 Therapeutic indications: butamirate is a cough suppressant used in non-productive cough.

1.4 Posology and duration of treatment: the usual oral dose is up to 30 mg daily in 3 or 4 divided doses; some countries permit up to 90 mg daily in divided doses. Modified-release tablets containing 50 mg are administered two or three times daily.

1.5 Pharmaceutical forms: syrup: 4 mg/5 mL; syrup: 7.5 mg/5 mL; oral solution: 4 mg/5 mL; prolonged-release tablets: 20 mg; prolonged-release tablets: 50 mg

1.6 Contraindications: hypersensitivity to butamirate; productive cough.

1.7 Relevant warnings: butamirate should be used with caution in patients with severe renal impairment or severe hepatic impairment. Patients may be at higher risk of side effects due to accumulation of active substance and metabolites. Because butamirate inhibits the cough reflex, concomitant use with expectorants should be avoided as this may cause mucus retention in the respiratory system and thus increase the risk of bronchospasm and respiratory infections. It is necessary to consult a doctor or pharmacist if the cough lasts longer than 7 days.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): nervous system disorders (rare): dizziness, drowsiness.

Gastrointestinal disorders (uncommon): nausea, diarrhoea.

Skin and subcutaneous tissue disorders (rare): urticaria.

2.2 Indirect risks (incorrect use): symptoms of acute butamirate overdose are manifested as drowsiness, vomiting, ataxia, abdominal pain, diarrhoea, agitation and lowering of blood pressure. There is no need to treat mild cases of overdose.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	Routes of Administration/ Indications	MS	MDD	MQP
AM	Not subject to prescription	Symptomatic therapy of dry (unproductive) cough of various origins	50 mg	150 mg	500 mg
AT	Not authorised				
BA	Not authorised				
BE	Not subject to prescription	Symptomatic treatment of dry cough in adults and children aged 6 years and older	15 mg/10 mL	90 mg	300 mg
BG	Not subject to prescription				
CH	Not subject to prescription				
CZ	Not subject to prescription				
DE	Not authorised				
EE	Not authorised				
ES	Not authorised				
FI	Not authorised				
FR	Not authorised				
GR	Not subject to prescription				

HR	List I + Exemption	Ex.: symptomatic treatment of dry (unproductive) cough	Ex.: 4 mg/5 mL		Ex.: 160 mg
HU	POM	Symptomatic treatment of dry cough			
IE	Not authorised				
IT	Not subject to prescription				
LT	Not authorised				
LV	Not authorised				
ME	POM				
MK	Not subject to prescription				
NL	Not authorised				
PL	Not subject to prescription	Symptomatic treatment of dry cough			
PT	Not subject to prescription	Treatment of dry cough in adults and children 6 years and older	0.4 mg/mL	24 mg	50 mg
RO	Not subject to prescription				
RS	Not subject to prescription	Symptomatic therapy of dry (unproductive) cough of various origins	50 mg	150 mg	500 mg
SK	Not subject to prescription				
TR	POM	Symptomatic treatment of dry cough			
UK	Not authorised				

No more data available from other member states.

Melclass database[1]: List II + Exemption (Exemptions: oral use; treatment of dry cough including pertussis; not for children < 6 years of age; MS: 30 mg; MDD: 100 mg)

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: oral use; symptomatic short-term treatment of dry cough; not for children under 6 years of age; medical reassessment needed if cough does not resolve within 7 days; MS: 30 mg; MDD: 100 mg

Criteria: List I: medical examination needed in case of long-lasting dry cough in order to identify underlying cause.

Exemptions: the use of medicines containing butamirate (under this ATC code) does not present a danger, either directly or indirectly, when used correctly. Symptoms for which the product is indicated can be correctly diagnosed without medical supervision or can be easily recognised. No risk of misuse.

3.2.2 Paediatric use: not recommended for children under 6 years of age.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: websites of national regulatory authorities of member states

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

[1] Melclass database - Available at: http://www.edqm.eu/melclass/ (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: Fedrilate

1.2 ATC code: R05DB14

1.3 Therapeutic indications: cough suppressant

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 (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

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Zipeprol

1.2 ATC code: R05DB15

1.3 Therapeutic indications: cough suppressant

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 (based on the available data, medicines containing this active substance are only authorised in Greece (classification status: narcotic status)).

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

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Dibunate

1.2 ATC code: R05DB16

1.3 Therapeutic indications: cough suppressant

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 (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: Martindale Complete Drug Reference - 40th edition, 2020

Sevelius H. and Colmore J.P. Antitussive effect of ethyl dibunate in patients with chronic cough. *Clin Pharmacol Ther* (1967); 8(3): 381-384.

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Droxypropine

1.2 ATC code: R05DB17

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 (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: Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Prenoxdiazine

1.2 ATC code: R05DB18

1.3 Therapeutic indications: acute and chronic primarily non-productive cough of any origin (tracheobronchial, pulmonary, pleural and cardiac). It is beneficial in alleviating coughs associated with respiratory and gas exchange disorders, as it does not inhibit the functioning of the respiratory centre. Premedication for bronchoscopic or bronchographic examination.

1.4 Posology and duration of treatment: Adults: the recommended dose is 1 tablet three to four times a day (3-4 x 100 mg). In more severe cases, the dose is increased to 3-4 tablets twice a day or 3 tablets three times a day (3-4 x 200 mg or 3 x 300 mg). Children 1-14 years of age: the recommended dose is proportionally lower according to the age and body weight: 1/4-1/2 tablet three to four times a day (3-4 x 25-50 mg); children aged 1-6 years (body weight 10 kg to 20 kg): 1/2 tablet three times a day (3 x 50 mg); children aged 6-14 years (body weight > 20 kg): 1/2 tablet three to four times a day (3-4 x 50 mg).

Duration of use is limited to 7 days; if the patient's condition does not improve or worsens, a doctor's advice should be sought.

Preparation for bronchoscopic examination (use only after consultation with a doctor): 0.9-3.8 mg/kg prenoxdiazine hydrochloride, in combination with 0.5-1 mg atropine, 1 hour before the procedure.

1.5 Pharmaceutical forms: tablets (strength: 100 mg).

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients; diseases with high bronchial secretion; postoperative conditions (after inhalation anaesthesia).

1.7 Relevant warnings: in case of viscous secretions that are difficult to empty, administration of expectorant or mucolytic is also required. Use during pregnancy and lactation only after consultation with a doctor (limited data available; it is not known if prenoxdiazine is excreted in human milk). At higher doses, the drug may impair alertness, so caution is required before driving and using machinery. Use with caution in the elderly.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): side effects: gastrointestinal side effects: nausea, constipation, dry mouth; respiratory, thoracic and mediastinal disorders: bronchospasm; immune system disorders: allergic reactions.

Interactions with other medicinal products: no known clinically relevant interactions with other medicinal products.

2.2 Indirect risks (incorrect use): overdose: in case of overdose, sedation and fatigue may occur within a few hours of ingestion. No available information on antidote.

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	Routes of Administration/ Indications	MS	MDD	MQP
AM	Not subject to prescription	Oral use. Symptomatic therapy of dry (unproductive) cough of various origins	100 mg	400 mg	2000 mg
AT	Not authorised				
BA	Not authorised				

BE	Not authorised				
BG	Not subject to prescription				
CH	Not authorised				
CZ	Not authorised				
DE	Not authorised				
EE	Not authorised				
ES	Not authorised				
FI	Not authorised				
FR	Not authorised				
GR	Not authorised				
HR	Not authorised				
HU	Not subject to prescription	Oral use. Acute and chronic primarily non-productive cough of any origin. Premedication for bronchoscopic or bronchographic examination	100 mg		2000 mg
IE	Not authorised				
IT	Not authorised				
LT	Not authorised				
LV	Not authorised				
ME	Not authorised				
MK	Not authorised				
MT	Not subject to prescription		100 mg		2000 mg
NL	Not authorised				
PL	Not authorised				
PT	Not authorised				
RO	Not authorised				
RS	Not authorised				
SK	Not authorised				
TR	Not authorised				
UK	Not authorised				

No more data available from other member states.

Melclass database[1]: List II

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): Proposed recommendation: **List I + Exemption** - Exemptions: short-term relief of dry cough in adults, limited to 7 days.

Criteria: good tolerability profile; peripherally acting cough suppressant; use before bronchoscopic and bronchographic examinations only upon doctor's advice; use in small children and special populations only upon doctor's advice.

3.2.2 *Paediatric use:* use in children over 1 year of age.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Hungary National Institute of Pharmacy and Nutrition: SmPC of Libexin 100 mg tablets (Sanofi Aventis) (date of revision 19.08.2017) - Available at https://bit.ly/3AREoLZ

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

[1] Melclass database - Available at: http://www.edqm.eu/melclass/ (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: Dropropizine

1.2 ATC code: R05DB19

1.3 Therapeutic indications: dry, irritating, unproductive cough in respiratory diseases.

1.4 Posology and duration of treatment: syrup (3 mg/mL): adults: 5 mL six to eight times a day; children aged 6-13 years: 5 mL three to four times a day; children aged 3-6 years: 2.5 mL three to four times a day; children aged 6 months to 3 years: 1.25 mL three to four times a day.

Oral drops, solution (22 mg/mL): 1 mL of solution = 26 drops = 22 mg dropropizíne. Adolescents and adults: 52 drops three to four times a day; children aged 3-13 years: 26 drops three to four times a day; children aged 1-3 years: 13 drops three to four times a day; children aged 6-12 months: 6 drops three to four times a day.

Duration of use is limited to 5 to 7 days; if the patient's condition does not improve or worsens, a doctor's advice should be sought.

1.5 Pharmaceutical forms: oral drops, solution (strength 22 mg/mL), syrup (strength 3 mg/mL).

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients; patients with a disease associated with bronchial hypersecretion or mucociliary apparatus impairment (Kartagener syndrome, ciliary dyskinesia); pregnant and lactating women; children under 6 months.

1.7 Relevant warnings: caution should be taken in patients with impaired renal and hepatic function and in patients taking drugs with a sedative effect. At the recommended doses, dropropizine does not damage the bronchial mucosa or ciliated epithelium of the respiratory tract. The drug should not be used with sedatives to increase the sedative effect. Concomitant use of expectorants is not recommended. Dropropizine passes into human milk, thus it is contraindicated during pregnancy and lactation. It has a minor effect on the ability to drive and use machinery.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): side effects: gastrointestinal disorders (nausea, dyspepsia, vomiting, diarrhoea); nervous system disorders (asthenia, somnolence, headache); cardiac disorders (palpitations).

Interactions with other medicinal products: sedatives and expectorants.

2.2 Indirect risks (incorrect use): overdose: at higher doses, postural hypotension 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	Routes of Administration/ Indications	MS	MDD	MQP
AM	Not authorised				
AT	Not authorised				
BA	Not authorised				
BE	Not authorised				
BG	Not authorised				
CH	Not authorised				
CZ	Not subject to prescription	Dry cough treatment	22 mg/mL		50 mL
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 subject to prescription				
LT	Not authorised				
LV	Not authorised				
ME	Not authorised				
MK	Not authorised				
NL	Not authorised				
PL	Not authorised				
PT	Not subject to prescription	Treatment of dry cough in adults and children over 6 months	3 mg/mL	120 mg	600 mg
RO	Not authorised				
RS	Not authorised				
SK	Not subject to prescription				
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, MS, MDD, MQP, as applicable): Proposed recommendation: **Not subject to prescription**

Criteria: good safety profile (good tolerance and low sedative effect, minimal effect on respiratory centre); mostly peripheral action; use in small children (< 6 years of age) should be after doctor's advice.

3.2.2 Paediatric use: use in children over 6 months of age.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Republic State Institute for Drug Control (Czech Republic) - Available at: https://bit.ly/2UtBaie

National Authority of Medicines and Health Products (Portugal) - Available at https://bit.ly/37TlKXV

Banderali G., Riva E., Fiocchi A., Cordaro C.I., Giovannini M. Efficacy and tolerability of levodropropizine and dropropizine in children with non-productive cough. *J Int Med Res* 1995; 23(3):175-183

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

[1] Melclass database - Available at: http://www.edqm.eu/melclass/ (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: Combinations

1.2 ATC code: R05DB20

1.3 Therapeutic indications: cough suppressant

1.4. Posology and duration of treatment: posology and duration of treatment vary based on the qualitative and quantitative composition of the medications that are authorised and marketed in member states.

1.5 Pharmaceutical forms: various pharmaceutical forms for oral use.

1.6 Contraindications: contraindications vary based on the qualitative and quantitative composition of the medications that are authorised and marketed in member states.

1.7 Relevant warnings: warnings vary based on the qualitative and quantitative composition of the medications that are authorised and marketed in member states.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): adverse effects depend on the qualitative and quantitative composition of the medications that are authorised and marketed in member states.

2.2 Indirect risks (incorrect use): indirect risks depend on the qualitative and quantitative composition of the medications that are authorised and marketed in member states.

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	Routes of Administration/ Indications	MS	MDD	MQP
AM	POM	Treatment of inflammatory airway diseases			
AT	Not authorised				
BA	Not authorised				
BE	Not authorised				
BG	Not subject to prescription				
CH	Not subject to prescription				
CZ	Not authorised				
DE	Not authorised				
EE	Not authorised				
ES	Not authorised				
FI	Not authorised				
GR	Not authorised				
HR	Not authorised				
HU	Not authorised				
IE	Not authorised				
IT	Not subject to prescription				
LT	Not authorised				
LV	POM	Treatment of inflammatory airway diseases			
ME	Not authorised				
MK	Not authorised				
NL	Not authorised				
PL	Not authorised				
PT	Not subject to prescription	Traditional herbal medicine used for cough relief during the night.	(12.5 mg + 9.09	30 mL (375 mg +	120 mL (1500 mg + 1090.8

		Althaea officinalis L., *Tilia cordata* Miller, *Tilia platyphyllos* Scop., *Tilia x vulgaris* Heyne; *Plantago lanceolata* L.	mg + 10 mg)/mL	272.72 mg + 300 mg)	mg + 12000 mg)
RO	Not authorised				
RS	Not authorised				
SK	Not authorised				
TR	POM	Antitussive			

No more data available from other member states.

Melclass database[1]: -

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): Proposed recommendation: **Not to classify**

Criteria: the qualitative and quantitative composition of combination products classified under this ATC code is unclear.

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

Websites of national competent authorities

4.2 Comments: detailed information about the combination products classified under this ATC code are not available.

[1] Melclass database - Available at: http://www.edqm.eu/melclass/ (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: Cloperastine

1.2 ATC code: R05DB21

1.3 Therapeutic indications: symptomatic treatment of non-productive cough.

1.4 Posology and duration of treatment: adults and adolescents over 15 years: coated tablets: 3 to 8 tablets per day. The adapted average daily dose is 1 tablet in the morning, 1 tablet at midday and 2 tablets in the evening before bedtime. Syrup: 30 to 80 mL per day. The adapted average daily dose is: 15 mL in the morning, 15 mL at midday and 30 mL in the evening before bedtime.

Children from 6 years: dosage is calculated based on 1.77 mg to 3.54 mg cloperastine per kg of body weight per day, which corresponds to 0.5 to 1 mL of syrup per kg of body weight per day.

1.5 Pharmaceutical forms: coated tablet (strength: 10 mg), syrup (strength: 3.54 mg/mL).

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients, concomitant treatment with MAO inhibitors, children under 6 years.

1.7 Relevant warnings: caution should be taken in case of intraocular hypertension or prostatism. It is recommended not to use the drug during the first months of pregnancy, and with greatest caution during later stages. It is not known if cloperastine is excreted in human milk; therefore, it is advised not to take this drug during breastfeeding. Caution is required when driving or using machinery because cloperastine can cause somnolence.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): side effects: nervous system disorders (somnolence, dry mouth); immune system disorders (anaphylactic reaction, anaphylactoid reaction); skin disorders (urticaria); ocular disorders (accommodation disorders); gastrointestinal disorders (gastric disturbances).

Interactions with other medicinal products: concomitant use of cloperastine with alcohol, antihistamines, anticholinergics and sedatives is not recommended. Cloperastine may enhance the sedative effect of central nervous system depressants. Cloperastine, antihistamines and anticholinergics may reciprocally increase their effects.

2.2 Indirect risks (incorrect use): overdose: in case of overdose, typical antihistamine intoxication syndrome may occur (drowsiness, atropine disorders, hallucinations, excitement, ataxia, incoordination and convulsions). Supportive measures and benzodiazepines are recommended.

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	Routes of Administration/ Indications	MS	MDD	MQP
AM	Not authorised				
AT	Not authorised				
BA	Not authorised				
BE	Not subject to prescription	Symptomatic treatment of dry cough in adults and children aged 6 years and older	10 mg	80 mg	300 mg
BG	Not authorised				
CH	Not authorised				
CZ	Not authorised				
DE	Not authorised				

EE	Not authorised				
ES	Not subject to prescription	Non-productive cough	10 mg, 3.54 mg/ml		200 mg, 200 ml
FI	Not authorised				
GR	Not authorised				
HR	Not authorised				
HU	Not authorised				
IE	Not authorised				
IT	Not subject to prescription				
LT	Not authorised				
LV	Not authorised				
ME	Not authorised				
MK	Not authorised				
NL	Not authorised				
PL	Not authorised				
PT	Not authorised				
RO	Not authorised				
RS	Not authorised				
SK	Not authorised				
TR	Not authorised				
UK	Not authorised				

No more data available from other member states.

Melclass database[1]: -

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: **List II + Exemption** - Exemptions: short-term use in adults and children above 6 years of age

Criteria: dual action: antitussive (central and peripheral) and antihistaminic activity; good safety profile (good tolerance without acting on the central nervous system or the respiratory center); use in children > 6 years.

3.2.2 Paediatric use: use in children above 6 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Federal Agency for Medicines and Health Products (Belgium) - Available at https://bit.ly/3y17LtE

Catania M.A. and Cuzzocrea S. Pharmacological and clinical overview of cloperastine in treatment of cough. *Ther Clin Risk Manag* 2011; 7: 83-92

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

[1] Melclass database - Available at: http://www.edqm.eu/melclass/ (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: Meprotixol

1.2 ATC code: R05DB22

1.3 Therapeutic indications: cough suppressant

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 (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: Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Piperidione

1.2 ATC code: R05DB23

1.3 Therapeutic indications: cough suppressant

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 (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: Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Tipepidine

1.2 ATC code: R05DB24

1.3 Therapeutic indications: cough suppressant

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 (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: Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Morclofone

1.2 ATC code: R05DB25

1.3 Therapeutic indications: treatment of dry, irritating coughs of various origins.

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 (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: websites of national regulatory authorities of member states

Swiss Agency for Therapeutic Products - Available at: https://bit.ly/3mfIRUP

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Nepinalone

1.2 ATC code: R05DB26

1.3 Therapeutic indications: Cough sedative

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 (based on the available data, medicines containing this active substance are only authorised in Italy (classification status: List II)).

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

Italian Medicines Agency - Available at: https://bit.ly/3AWVQPw

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.2 Active ingredient: Levodropropizine

1.3. ATC code: R05DB27

1.4 Therapeutic indications: symptomatic treatment of dry non-productive cough. Before bronchoscopic examination.

1.5 Posology and duration of treatment: Tablet: adults and children over 12 years: 1 tablet (60 mg) up to 3 times a day with dose interval at least of 6 hours.

Syrup: adults and children over 12 years: 10 ml (60 mg) up to 3 times a day with dose interval at least of 6 hours; children over 2 years (body weight from 10 – 20 kg): 3 ml up to 3 times a day; children over 2 years (body weight 20 – 30 kg): 5 ml up to 3 times a day. Minimal dose interval of 6 hours.

Oral drops, solution: 1 ml = 20 drops = 60 mg. Adults and children over 12 years: 1 ml (60 mg) up to 3 times a day with dose interval at least of 6 hours; children over 2 years: 1 mg/kg up to 3 times a day with minimal interval between doses of 6 hours.

Duration of treatment without doctor's advice is 14 days (2 weeks).

1.6 Pharmaceutical forms: tablet (strength: 60 mg), syrup (strength: 6 mg/ml), oral drops (solution) (60 mg/ml).

1.7 Contraindications: hypersensitivity to the active substance or to any of the excipients, patients with bronchial hypersecretion, in case of reduced mucociliary function (Kartagener's syndrome, ciliary dyskinesia), in case of marked hepatic impairment, during pregnancy and lactation.

1.8 Relevant warnings: caution is advised in patients with severe renal impairment (creatinine clearance less than 35 ml/min), in patients with hepatic impairment (possible dose reduction should be considered due to reduced drug clearance), in the elderly (as there is evidence that pharmacodynamic sensitivity to many drugs changes with age). Symptomatic treatment with levodropropizine should be used only short-term, on case of pending diagnosis of underlying disease or pending the effect of treatment on the underlying disease. Caution is advised when administering sedatives concomitantly in highly sensitive patients. Caution is advised when driving and using machines, as this drug can cause drowsiness.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): side effects (from postmarketing experience) of unknown frequency:

Immune system disorders: allergic and anaphylactic reactions, eyelid oedema, angioneurotic oedema, urticaria.

Psychiatric disorders: nervousness, somnolence, personality change or personality disorder.

Nervous system disorders: syncope (fainting), dizziness, vertigo, shakiness, paraesthesia, epilepsy with tonic-clonic seizures and epilepsy with absence seizures, hypoglycaemic coma, numbness, headache.

Eye disorders: pupil dilatation, bilateral blindness.

Cardiac disorders: palpitations, tachycardia, supraventricular extrasystole.

Vascular Disorders: hypotension.

Respiratory, thoracic and mediastinal disorders: dyspnoea, cough, respiratory tract edema.

Gastrointestinal disorders: stomach pain, abdominal pain, nausea, vomiting, diarrhoea, heartburn, dyspepsia.

Hepatobiliary disorders: cholestatic hepatitis.

Skin and subcutaneous tissue disorders: urticaria, erythema, spotted fever disorders, pruritis, angioedema, rash, pneumonia and stomatitis aphtosa (aphthous ulcers), epidermolysis.

Muscle, joint and connective tissue disorders: lower extremity weakness.

General disorders and administration site conditions: general malaise, generalized oedema, asthenia, fatigue.

Interactions with other medicinal products: non-clinical studies have shown that levodropropizine does not potentiate the pharmacological effects of substances that affect the central nervous system (such as benzodiazepines, alcohol, phenytoin and imipramine). Also, nonclinical studies have shown that product has no effect on the activity of oral anticoagulants or on the hypoglycaemic action of insulin. In clinical studies, co-administration of β2 agonists, methylxanthine and derivatives, corticosteroids, antibiotics, muco-regulators and antihistamines, have not shown any interactions. The possibility of interaction with other drugs that are also cleared via hepatic metabolism should be considered.

Pregnancy and lactation: in animal studies, levodropropizine has been shown to be harmful and that is excreted in human milk, therefore must not be used during pregnancy and lactation.

2.2 Indirect risks (incorrect use): overdose: no cases of levodropropizine overdose have been reported. No significant side effects were observed after a single dose up to 240 mg or after a dose of 120 mg three times daily for 8 consecutive days. In the event of an overdose, a transient and mild form of tachycardia can be expected. If this occurs, the usual measures should be taken to avoid intoxication.

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	Routes of Administration/ Indications	MS	MDD	MQP
AM	POM	Symptomatic treatment of cough			
AT	Not authorised				
BA	Not authorised				
BE	POM				
BG	Not authorised				
CH	Not authorised				
CZ	Not subject to prescription	Treatment of irritating dry cough. Before bronchoscopic examination	60 mg; 6 mg/ml; 60 mg/ml	180 mg	1200 mg
DE	POM				
EE	POM				
ES	Not subject to prescription	Treatment of unproductive cough	6 mg/ml	180 mg	1200 mg
FI	Not authorised				
FR	Not authorised				
GR	POM + Exemption	Ex.: symptomatic treatment of dry, non-productive cough	Ex.: 30 mg/5 mL		Ex.: 200 mL (1200 mg)
HR	Not authorised				
HU	Not subject to prescription	Short-term symptomatic treatment of non-productive dry cough	6 mg/mL and 60 mg/mL	180 mg	1200 mg
IE	Not authorised				
IT	List II (oral drops) + Exemption (tablets and syrup)				
LT	Not authorised				
LV	Not authorised				
ME	List I	Symptomatic treatment of dry, non-productive cough	6 mg/mL	30 mL (180 mg)	200 mL (1200 mg)
MK	Not authorised				
NL	POM				

PL	Not subject to prescription	Symptomatic treatment of dry cough			
PT	Not subject to prescription	Treatment of cough in adults and children	60 mg; 6 mg/mL; 60 mg/mL		1200 mg
RO	List II	Symptomatic treatment of dry cough			
RS	POM	Symptomatic treatment of dry, non-productive cough	6 mg/mL		
SK	Not authorised				
TR	POM	Antitussive			
UK	Not authorised				

No more data available from other member states.

Melclass database[1]: List II

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): Proposed recommendation: **List I + Exemption** – Exemptions: short-term symptomatic treatment of dry cough in adults, limited to 7 days, MQP: 1200 mg

Criteria: good tolerance, no effect on respiratory centre and low sedative effect; peripheral action; rapid absorption and short half-life; use in small children (< 6 years of age) should be upon doctor's advice.

3.2.2 Paediatric use: use in children above 2 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Republic State Institute for Drug Control (Czech Republic) - Available at: https://bit.ly/2UtBaie

Zanasi A., Lanata L., Fontana G. et al. Levodropropizine for treating cough in adult and children: a meta-analysis of published studies. *Multidiscip Respir Med* 2015; 10(1):19

Morice A. and Kardos P. Comprehensive evidence-based review on European antitussives. *BMJ Open Respir Res* 2016; 3

Banderali G., Riva E., Fiocchi A., Cordaro C.I., Giovannini M. Efficacy and tolerability of levodropropizine and dropropizine in children with non-productive cough. *J Int Med Res* 1995; 23(3):175-183

Catena E. and Daffonchio L. Efficacy and tolerability of levodropropizine in adult patients with non-productive cough. Comparison with dextromethorphan. *Pulm Pharmacol Ther* 1997; 10(2): 89-96

Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

[1] Melclass database - Available at: http://www.edqm.eu/melclass/ (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: Dimethoxanate

1.2 ATC code: R05DB28

1.3 Therapeutic indications: cough suppressant

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 (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: Martindale Complete Drug Reference - 40th edition, 2020

4.2 Comments: -

LIST OF AUTHORS

Mr Veljko JEREMIC
Medicines and Medical Devices Agency of Serbia (ALIMS)
458 Vojvode Stepe Street
11221 Belgrade (Serbia)

Ms Darija KOLARIĆ
Croatian Agency for Medicinal Products and Medical Devices (HALMED)
Ksaverska cesta 4
10 000 Zagreb (Croatia)

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