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

Report classification of

- Medicines belonging to ATC group R05DA
(Opium alkaloids and derivatives)

- Medicines containing Doxylamine (ATC: R06AA09)

(2021)

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INTRODUCTION

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

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

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

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

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

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

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

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

It is important to note that:

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

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

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

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

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

[2] 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 the ATC group R05DA (Opium alkaloids and derivatives) and medicines containing Doxylamine (ATC code: R06AA09).

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

AGEP	Acute generalised exanthematous pustulosis
ATC	Anatomical Therapeutic Chemical classification [1]
COPD	Chronic obstructive pulmonary disease
CNS	Central nervous system
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines and HealthCare
EMA	European Medicines Agency
MAOI	Monoamine oxidase inhibitor
MDD	Maximal daily dose
MQP	Maximal quantity per pack
MS	Maximal strength
POM	Prescription only medicine
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
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: Ethylmorphine

1.2 ATC code: R05DA01

1.3 Therapeutic indications: treatment of whooping cough.

1.4 Posology and duration of treatment: not for long-term treatment. The recommended dose should not be exceeded. Dosage: 5 mL = 12.5 mg of ethylmorphine. Adults (18 years and older): 5-10 mL three to four times daily. Adolescents 13-17 years (> 40 kg): 5 mL three to four times daily. Children: 11-12 years (30-40 kg): 3.5 mL three times daily. Children 6-10 years (20-30 kg): 2.5 mL three times daily. Children 3-5 years (15-20 kg): 2 mL three times daily. Children 2 years (13-15 kg): 1 mL three times daily. It should not be given to children under 2 years.

1.5 Pharmaceutical forms: oral solution - 2.5 mg/mL.

1.6 Contraindications: hypersensitivity to any of the active substances or to any of the excipients. Respiratory depression. Children (0-18 years) who have obstructive sleep apnoea syndrome and/or are scheduled to undergo tonsillectomy and/or adenoidectomy due to an increased risk of developing severe or life-threatening side effects. Patients who are known to be ultra-fast metabolisers of CYP2D6.

1.7 Relevant warnings: there is a certain risk of developing addiction at high doses and with long-term use.

The respiratory depressant effect of ethylmorphine should be taken into account in the treatment of patients with obstructive airway diseases such as sleep apnoea syndrome. Caution should also be exercised in acute bronchial asthma.

Concomitant use of ethylmorphine and barbiturates, benzodiazepines or other central nervous system (CNS) depressants (like other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, muscle relaxants, sedative antihistamines) can result in sedation, respiratory depression, coma and death. Because of these risks concomitant prescription of opioids and barbiturates, benzodiazepines or other CNS depressants should be restricted to patients for whom alternative treatment options are not possible. If the decision is taken to prescribe opioids concomitantly with barbiturates, benzodiazepines or other CNS depressants, the lowest effective dose should be used and the treatment should be as short as possible. Patients should be closely monitored for signs and symptoms of respiratory depression and sedation.

Children with impaired respiratory function: ethylmorphine is not recommended for children who may have impaired respiratory function, including neuromuscular diseases, severe heart or respiratory conditions, severe infections in upper respiratory tract or lungs, multiple trauma or extensive surgery. These factors may aggravate the symptoms of morphine intoxication.

CYP2D6 metabolism: if a patient is an ultra-fast metaboliser, there is an increased risk of morphine-related side effects even at normally prescribed doses. These patients rapidly convert ethylmorphine to morphine, which may result in higher than expected plasma levels of morphine.

General: symptoms of morphine intoxication include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and loss of appetite. In severe cases, this may include symptoms of circulatory and respiratory depression, which can be life-threatening and in very rare cases, fatal.

Pregnancy: no known risks from use during pregnancy.

Breastfeeding: ethylmorphine passes into breast milk. Therefore, it should not be used by breastfeeding women.

During treatment with ethylmorphine, reactions may be impaired. This should be taken into account when sharper attention is required, e.g. when driving or operating machinery.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): central and peripheral nervous system: uncommon: dizziness and

dysphoria, especially at high doses; unknown frequency: hallucinations, fatigue and drowsiness.

Respiratory, thoracic and mediastinal disorders: unknown frequency: angioedema, anaphylactic reaction.

Gastrointestinal tract: common: constipation, nausea and vomiting.

Liver and bile ducts: common: biliary dyskinesia; unknown frequency: hepatic reaction such as transaminase elevation.

Skin and subcutaneous tissue disorders: unknown frequency: exanthema, urticaria.

Kidneys and urinary tract: unknown frequency: urinary retention.

2.2 Indirect risks (incorrect use): toxicity is potentiated by barbiturates and alcohol. Infants are particularly sensitive to intoxication. The main risks are CNS effects (both excitation and depression) and respiratory depression, which may occur late in the process. Moderate dose causes lethargy, dizziness, ataxia, headache, excitation, tremor, motor anxiety, miosis and, in infants, affected breathing. At higher doses, erythema is seen, facial oedema (children), somnolence, decreased muscle tone, decreased reflexes, respiratory depression and coma, but also delirium, seizures, possibly hypotension, nausea, vomiting. In the case of severe poisoning, there are possible risks of rhabdomyolysis and renal failure.

Treatment: if possible, gastric emptying and charcoal are advised. Careful observation should be carried out with respect to breathing, degree of consciousness and blood circulation. Naloxone 0.4 mg iv can be administered to adults (children 0.01 mg/kg iv) in case of respiratory depression. The dose should be repeated until breathing is normalised. If needed, assisted breathing can be used. In case of cramps, diazepam is advised. Symptomatic therapy is advised.

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 authorised					
Austria (AT)	Not authorised					
Bosnia and Herzegovina (BA)	Not authorised					
Belgium (BE)	POM					
Bulgaria (BG)	Not authorised					
Switzerland (CH)	Not authorised					
Czech Republic (CZ)	Not authorised					
Germany (DE)	Not authorised					
Estonia (EE)	Not authorised					
Spain (ES)	Not authorised					
Finland (FI)	POM					
France (FR)	List II + Exemption	Ex.: 0.1 g/100 mL		Ex. 250 mL		Oral solutions containing 0.049 g/100 mL are List II
Greece (GR)	Not authorised					
Croatia (HR)	Not authorised					
Hungary (HU)	Not authorised					
Ireland (IE)	Not authorised					
Italy (IT)	Not authorised					
Lithuania (LT)	Not authorised					
Latvia (LV)	Not authorised					
Montenegro (ME)	Not authorised					

North Macedonia (MK)	Not authorised					
Netherlands (NL)	Not authorised					
Poland (PL)	Not authorised					
Portugal (PT)	Not authorised					
Romania (RO)	Not authorised					
Serbia (RS)	Not authorised					
Russia (RU)	Not authorised					
Sweden (SE)	POM					
Slovenia (SI)	Not authorised					
Slovakia (SK)	Not authorised					
Turkey (TR)	Not authorised					
United Kingdom (UK)	Not authorised					

No more data available from other member states.

Melclass database[1]: No data in Melclass

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: **List I** if exempted from Single Convention on Narcotic Drugs, 1961 ** Protocol of 25 March 1972 amending the Single Convention on Narcotic Drugs, 1961: when compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations, ethylmorphine is exempted from some provisions and included in schedule III of the above convention.

Criteria (rationale): opioid antitussive medicine: sedative, hypnotic and addictive effects; for short-term treatment.

3.2.2 Paediatric use: not under 12 years of age and not under 18 years in case of breathing problems.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Popa C., Beck O. and Brodin K. Morphine formation from ethylmorphine: implications for drugs-of-abuse testing in urine. J Anal Toxicol. 1998; 22(2): 142-147.

European Medicines Agency (EMA). Codeine-containing medicinal products for the treatment of cough or cold in paediatric patients, Article 31 referrals (EMEA/H/A-31/1394, CMDh position date: 22.04.2015) - Available at: https://bit.ly/3yXlJy1

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

Single Convention on Narcotic Drugs, 1961 ** Protocol of 25 March 1972 amending the Single Convention on Narcotic Drugs, 1961 – Available at: https://bit.ly/3xWDYlG

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: Hydrocodone

1.2 ATC code: R05DA03

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: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Codeine

1.2 ATC code: R05DA04

1.3 Therapeutic indications: a) Management of mild to moderate pain. Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen alone. b) As an antitussive for non-productive cough. c) Treatment of diarrhoea.

1.4 Posology and duration of treatment: *Tablets:* a) As an analgesic: Adults: 30-60 mg every 4 hours, when necessary, to a maximum 240 mg daily. Elderly: dosage should be reduced in the elderly where there is impairment of hepatic or renal function.

b) As an antitussive: Adults: 15-30 mg three or four times daily. Elderly: dosage should be reduced in the elderly where there is impairment of hepatic or renal function.

c) For the symptomatic treatment of chronic diarrhoea: Adults: 15-60 mg every 4 to 6 hours. Elderly: dosage should be reduced in the elderly where there is impairment of hepatic or renal function.

Warnings: codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose of codeine should not exceed 240 mg. The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patient/carer should be advised to seek the advice of a physician.

Oral solutions: Adult dosage: the usual dose is 5 to 7.5 mL (15 mg to 22.5 mg) three to four times a day. Dosage should be reduced in elderly or debilitated patients. Dose may be repeated every 4-6 hours if required. Paediatric population: Children aged less than 12 years: codeine is contraindicated in children below the age of 12 years. Children aged 12 to 18 years: codeine is not recommended for use in children aged 12 to 18 years with compromised respiratory function.

1.5 Pharmaceutical forms: tablets 30 mg and oral solutions 15 mg/5mL.

1.6 Contraindications: codeine is contraindicated in patients with: a) hypersensitivity to the active substance or to any of the excipients; b) acute respiratory depression; c) obstructive airway disease (e.g. emphysema); d) asthma – opioids should not be administered during an asthma attack; e) hepatic failure; f) head injuries or conditions where intracranial pressure is raised; g) acute alcoholism; h) diarrhoea associated with either pseudomembranous colitis or poisoning; i) risk of paralytic ileus; j) all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions; k) children below the age of 12 years for the symptomatic treatment of cough and/or cold due to an increased risk of developing serious and life-threatening adverse reactions; l) women during breastfeeding; m) patients known to be CYP2D6 ultra-rapid metabolisers.

1.7 Relevant warnings: a) Drug dependence, tolerance and potential for abuse: for all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g. major depression). Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse. A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained online, and past and present medical and psychiatric conditions. Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient. Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else. Patients should be closely monitored for signs of misuse, abuse or addiction. The clinical need for analgesic treatment should be reviewed regularly.

b) Drug withdrawal syndrome: prior to starting treatment with any opioids, a discussion should be held with

patients to put in place a withdrawal strategy for ending treatment with codeine phosphate. Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months. Opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure and increased respiratory rate or heart rate. If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

c) Hyperalgesia: hyperalgesia may be diagnosed if a patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

d) CYP2D6 metabolism: codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate therapeutic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity, even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels. General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases, this may include symptoms of circulatory and respiratory depression, which may be life-threatening and, very rarely, fatal.

e) Post-operative use in children: there have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea led to rare, but life-threatening adverse events including death. All children received doses of codeine that were within the appropriate dose range; however, there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

f) Children with compromised respiratory function: codeine is not recommended for use in children in whom respiratory function might be compromised, including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

g) Codeine phosphate should be used with caution in the following conditions: convulsions – they may be induced or exacerbated; myasthenia gravis; phaeochromocytoma – opioids may stimulate catecholamine release by inducing the release of endogenous histamine; adrenocortical insufficiency e.g. Addison's disease; hypothyroidism; hypotension and shock; history of cardiac arrhythmias; reduced respiratory function or history of asthma; inflammatory bowel disease – codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure, therefore should be used with caution in diverticulitis, acute colitis, diarrhoea associated with pseudomembranous colitis or after bowel surgery; gastrointestinal surgery – use with caution after recent gastrointestinal surgery as opioids may alter gastrointestinal motility; gall bladder disease or gall stones – opioids may cause biliary contraction (to be avoided in biliary disorders); hepatic impairment – avoid if severe; renal impairment; urinary tract surgery – following recent surgery patients will be more prone to urinary retention caused directly by spasm of the urethral sphincter, and via constipation caused by codeine; prostatic hypertrophy; elderly patients may metabolise and eliminate opioid analgesics more slowly than younger patients.

h) Interaction with other medicinal products: CNS depressants, anticholinergics, hydroxyzine and methadone – concurrent use of these medicines may result in potentiation of effects. Codeine may antagonise the effects of metoclopramide on gastrointestinal motility. The sedative effect of hypnotics, sedatives, anxiolytics or alcohol may be potentiated by codeine. Hypertensive crisis may be caused by concurrent use of codeine and monoamine oxidase inhibitors.

i) Effects on ability to drive and use machinery: codeine may cause drowsiness. Patients receiving this medication should not drive or operate machinery unless it has been shown not to affect mental or physical ability.

j) Pregnancy and lactation: risk-benefit ratio should be considered before using codeine during pregnancy and it should only be used if considered essential by the physician. Codeine is contraindicated in women during breastfeeding.

The risk-benefit ratio of continued use should be assessed regularly by the prescriber.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): the following undesirable effects have been reported following use of codeine phosphate or opioid analgesics. The frequency of adverse effects cannot be estimated from available data.

Psychiatric disorders: hallucinations, dysphoria, euphoria, mood changes, restlessness, confusion.

Nervous system disorders: dizziness, drowsiness, seizures, addiction, tolerance, dependence, headache, vertigo, malaise, sleep disturbances.

Eye disorders: miosis, visual disturbances.

Cardiac disorders: palpitations, bradycardia, tachycardia.

Vascular disorders: postural hypotension, hypothermia, facial flushing, oedema.

Respiratory, thoracic and mediastinal disorders: respiratory depression.

Gastrointestinal disorders: nausea, vomiting, constipation, abdominal pain, anorexia, pancreatitis, dry mouth.

Hepatobiliary disorders: biliary spasm.

Skin and subcutaneous tissue disorders: rashes, urticaria, pruritis, sweating.

Musculoskeletal and connective tissue disorders: muscle fasciculation or rigidity.

Renal and urinary disorders: difficulty with micturition, ureteric spasm or retention.

Reproductive system and breast disorders: decreased libido or potency.

2.2 Indirect risks (incorrect use): in cases of overdosage supportive therapy is recommended. Gastric lavage should be carried out and a saline purgative may be given to reduce absorption from the gastrointestinal tract. Symptomatic treatment of respiratory depression should be given. If respiration is severely depressed intravenous naloxone may be required.

2.3 Recent cases at European level: see Pharmacovigilance Risk Assessment Committee (PRAC) assessment report for codeine-containing medicinal products indicated in the management of pain in children (2013) - https://bit.ly/2YPIV0p

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	POM					
BE	POM					
BG	Not authorised					
CH	List II + Exemption	Ex.: 3 mg				2019: switch to List II

						due to legislation change. Not yet finalised due to appeal procedures.
CZ	POM					
DE	Not authorised					
EE	Not authorised					
ES	POM					
FI	Not authorised					
FR	List II					
GR	Not authorised					
HR	List I					
HU	POM					
IE	List I + Exemption	Ex.: 15 g/5 mL				
IT	List I - suppositories for adults 40 mg List II - oral drops 6 mg/mL and suppositories for children 10 mg					
LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	POM					
NL	POM + Exemption	Ex.: syrup with MS 0.5 mg/mL – Ind.: antitussive POM: MS: 30 mg – Ind.: acute moderate pain; antitussive; diarrhoea				
PL	Not authorised					
PT	POM					
RO	List I					
RS	Not authorised					
RU	Not authorised					
SE	POM					
SI	POM					
SK	POM					
TR	List I					
UK	POM + Exemption	Ex. 15 mg/5 mL				

No more data available from other member states.

Melclass database[1]: List I

3.2 Social dimension of classification:

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

Criteria (rationale): short-term treatment; safety profile.

[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.)

3.2.2 Paediatric use: not under 12 years of age and not under 18 years in case of breathing problems.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

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

PRAC assessment report for codeine-containing medicinal products indicated in the management of pain in children (2013) - https://bit.ly/2YPIV0p

Single Convention on Narcotic Drugs, 1961 ** Protocol of 25 March 1972 amending the Single Convention on Narcotic Drugs, 1961 – Available at: https://bit.ly/3xWDYlG

Websites of national competent authorities

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Opium alkaloids with morphine

1.2 ATC code: R05DA05

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: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Normethadone

1.2 ATC code: R05DA06

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: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Noscapine

1.2 ATC code: R05DA07

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

1.4 Posology and duration of treatment: a) Tablets 15 mg: children under 6 years of age: only if prescribed by a medical doctor and in line with the doctor's instructions; children and adolescents 6-15 years of age: 1 tablet three to four times daily; adolescents 15 years and older and adults: 1 or 2 tablets three to four times a day. Tablets 50 mg: children 10-14 years: ½ tablet three times daily; adults and children over 14 years: 1 tablet three times daily.

b) Suppositories: 1 suppository up to four times daily. Children under 2 years: according to medical prescription; children from 2 to 6 years old: 7.5 mg suppository; children from 6 to 12 years old: 15 mg suppository; adolescents 12 years and older and adults: 30 mg suppository.

c) Syrup 1 mg/mL: children from 3 to 6 years old: 7.5 mL two to four times daily; children from 6 to 12 years old: 15 mL two to four times daily; adolescents 12 years and older and adults: 15-30 mL three to four times daily. Syrup 3 mg/mL: children from 2 to 6 years old: 2.5 mL every 5-6 hours; children from 6 to 12 years old: 5 mL every 5-6 hours; adolescents 12 years and older and adults: 10 mL every 5-6 hours.

d) Oral suspension: 2.5 mg/mL: children 2-4 years: 2.5 mL three to four times daily; children 4-10 years: 5 mL three to four times daily; children 10-14 years: 10 mL up to three times daily; adults and children over 14 years: 20 mL three times daily. Oral suspension 5 mg/mL: children 4-10 years: 2.5 mL three to four times daily; children: 10-14 years: 5 mL three times daily; adults and children over 14 years: 10 mL three times daily.

1.5 Pharmaceutical forms: tablets 15 mg (in Sweden: 50 mg, in Germany 25 mg); suppositories 7.5 mg, 15 mg and 30 mg; syrup 1 mg/mL and 3 mg/mL; oral drops/oral suspension: 2.5 mg/mL and 5 mg/mL.

1.6 Contraindications: diseases of the respiratory tract associated with an excessive production of mucus. Hypersensitivity to the active ingredient or to one of the excipients.

1.7 Relevant warnings: a) the indicated dosage should not be exceeded.

b) Noscapine is possibly porphyrinogenic, due to its inhibitory effect on the cytochrome P450 2C9 isoenzyme; patients with porphyria should therefore use noscapine only if no safer alternative is available.

c) Concomitant use of noscapine and sedative drugs such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant use of these sedative medications should be limited to patients for whom alternative treatment options are not possible. If the decision is made to prescribe noscapine concomitantly with sedative drugs, the lowest effective dose should be used and the duration of treatment should be as short as possible. Patients should be closely monitored for signs and symptoms of respiratory depression and sedation. In this regard, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms.

d) Simultaneous administration of a mucolytic and an expectorant is irrational and may lead to stasis of the bronchial secretions by inhibition of the cough reflex and self-cleansing of the airways and carries the risk of bronchospasm and respiratory tract infection.

e) Interaction with other medicinal products: data show that CYP3A4 and CYP2C9 are inhibited by noscapine. This may have a negative effect in case of concomitant use of drugs with a narrow therapeutic index, such as anticoagulants (e.g. warfarin, phenprocoumon and acenocoumarol), but this also concerns the antiepileptic drug phenytoin and drugs to prevent rejection of transplanted organs (e.g. tacrolimus and ciclosporin). Concomitant use of opioids with sedative medications such as benzodiazepines or related medications increases the risk of sedation, somnolence, respiratory depression, coma and death due to their CNS depressant effect. The dose and duration of these medications should be limited.

f) Effects on ability to drive and use machinery: noscapine may cause dizziness that impairs the ability to drive vehicles and operate machinery.

g) Pregnancy and lactation: there is insufficient data to confirm the safety of noscapine; therefore, it should not be administered during pregnancy and lactation.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): drowsiness, dizziness, exanthema, headache, nausea, non-seasonal allergic rhinitis, conjunctivitis, exanthema and urticaria are infrequent. Almost all of these reactions are of no significant importance.

2.2 Indirect risks (incorrect use): symptoms may include excitement, anxiety, rash, nausea, vomiting, dizziness, drowsiness and histamine effects such as bronchoconstriction, dyspnoea, flushing, tachycardia and hypotension. After ingestion of very high doses, convulsions, coma and respiratory depression may occur. Treatment consists initially of preventing absorption by inducing vomiting and then drinking water or lemonade containing activated charcoal (adsorbent). In case of large amounts, gastric lavage is indicated, leaving activated charcoal and sodium sulfate (laxative) behind. Convulsions should be treated as usual. Respiratory depression may be counteracted with naloxone. Histamine effects should be antagonised with adrenaline and/or antihistamine H1 receptor blocker. Fluid and electrolyte balance should be maintained. Further treatment is supportive and symptomatic.

2.3 Recent cases at European level: study performed by the Dutch Pharmacovigilance Centre Lareb and Uppsala Monitoring Centre on noscapine and abdominal pain, chest pain and headache: https://bit.ly/3cT2OMH

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings / Additional Info
AM	Not authorised					
AT	List II					
BA	Not authorised					
BE	Not subject to prescription	15 mg tablets/ syrup 1 mg/mL				
BG	Not authorised					
CH	Not subject to prescription					
CZ	Not authorised					
DE	POM					
EE	Not authorised					
ES	POM					
FI	Not authorised					
FR	Not authorised					
GE	POM					
GR	Not authorised					
HR	Not authorised					
HU	Not authorised					
IE	Not authorised					
IT	Not authorised					
LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	Not authorised					
NL	Not subject to prescription					
PL	Not authorised					
PT	Not authorised					

RO	Not authorised					
RS	Not authorised					
RU	Not authorised					
SE	Not subject to prescription					
SI	Not authorised					
SK	Not authorised					
TR	POM					
UK	Not authorised					

No more data available from other member states.

Melclass database[1]: List II + Exemption – Exemptions: oral use and MS: 50 mg

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** if exempted from Single Convention on Narcotic Drugs, 1961 ** Protocol of 25 March 1972 amending the Single Convention on Narcotic Drugs, 1961: when compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations, noscapine is exempted from some provisions and included in schedule III of the above convention.

Criteria (rationale): in contrast to the other opium alkaloids, noscapine lacks analgesic, sedative, hypnotic and addictive effects.

3.2.2 Paediatric use: use in children above 2 years

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: report from the Dutch Pharmacovigilance Centre Lareb and Uppsala Monitoring Centre: https://bit.ly/3cT2OMH

Websites of national competent authorities

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

Single Convention on Narcotic Drugs, 1961 ** Protocol of 25 March 1972 amending the Single Convention on Narcotic Drugs, 1961 – Available at: https://bit.ly/3xWDYIG

Sen E.F., Verhamme K.M., Felisi M., 't Jong G.W., Giaquinto C., Picelli G., Ceci A., Sturkenboom M.C. TEDDY European Network of Excellence. Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age. Br J Clin Pharmacol. 2011; 71(6): 943-950

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: Pholcodine - morphine derivative with antitussive central action. Its depressive action on the respiratory centres is less than that of codeine. Pholcodine is widely used in the treatment of dry unproductive cough. Pholcodine is a centrally acting cough suppressant and can relieve local irritation of the respiratory tract for about 4 to 5 hours. Pholcodine has less sedatory and depressant effects on respiration than morphine.

1.2 ATC Code: R05DA08

1.3 Therapeutic indications: indicated in the treatment of non-productive cough.

1.4 Posology and duration of treatment: a) Oral solution 5 mg/5 mL: adults: 10 mL every 3 to 4 hours as required; children (aged 6-12 years): 5 mL every 3 to 4 hours as required.

b) Oral solution 10 mg/5 mL: adults and children over 12 years: one 5 mL spoonful three times a day and at bedtime.

Pholcodine should not be given to children under 12 years of age.

1.5 Pharmaceutical forms: oral solution 5 mg/5 mL; oral solution 10 mg/5 mL; syrup 131 mg/100 mL

1.6 Contraindications: liver failure; patients in or at risk of developing respiratory failure or during an attack of asthma; patients with chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchiolitis or bronchiectasis due to sputum retention; patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment.

1.7 Relevant warnings: pholcodine may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis. It must be used with caution in patients with renal or hepatic disease. Caution is needed in patients with a history of drug abuse. Pholcodine is an opioid and addiction is observed with opioids as a class. Pholcodine should not be taken with any other cough or cold medicine. 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 reviewed. Severe cutaneous adverse reactions including acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in patients treated with pholcodine, most likely in the first week. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, this medicine should be withdrawn immediately.

Interaction with other medicinal products and other forms of interactions: pholcodine may enhance the sedative effects of CNS depressants including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquillisers (phenothiazines and tricyclic antidepressants). Not to be used in patients taking MAOIs or within 14 days of stopping treatment. Interaction with neuromuscular blocking agents (anaphylaxis) has been reported. Pholcodine may accentuate the hypotensive effects of antihypertensives. The same effect may be seen when administered with diuretics. Use of pholcodine with alcohol or other CNS depressants may increase the effect on the CNS, which may lead to greater drowsiness and sedation. Pholcodine should not be taken with any other cough or cold medicine.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): the following side effects may be associated with the use of pholcodine: occasional drowsiness, dizziness, excitation, confusion, sputum retention, vomiting, gastrointestinal disturbances (nausea and constipation), skin reactions including rash, acute generalised exanthematous pustulosis (frequency unknown). Immune system disorders have been noted including hypersensitivity reactions and anaphylaxis.

2.2 Indirect risks (incorrect use): it is thought to be of low toxicity, but the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. Symptoms: these include nausea, drowsiness, restlessness, excitement, ataxia and respiratory depression. Management: treatment of overdose should be symptomatic and supportive. Gastric lavage may be of use. In cases of severe poisoning the specific narcotic antagonist naloxone may be used.

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	POM					
BE	Not subject to prescription	15 mg	90 mg	200 mg		Short-term treatment
BG	Not authorised					
CH	Not authorised					
CZ	Not authorised					
EE	Not authorised					
ES	Not authorised					
FI	Not authorised					
FR	List I					
DE	Not authorised					
GE	Not authorised					
GR	Not authorised					
HR	List I					
HU	Not authorised					
IE	Not subject to prescription					
IT	Not authorised					
LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	POM					
NL	Not authorised					
PL	Not authorised					
PT	Not authorised					
RO	Not authorised					
RS	POM					
RU	Not authorised					
SE	Not authorised					
SI	Not authorised					
SK	Not authorised					
TR	Not authorised					
UK	Not subject to prescription					

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 I** if exempted from Single Convention on Narcotic Drugs, 1961 ** Protocol of 25 March 1972 amending the Single Convention on Narcotic Drugs, 1961: when compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations, pholcodine is exempted from some provisions and included in schedule III of the above convention.

Criteria (rationale): opioid antitussive medicine: sedative, hypnotic and addictive effects; for short-term treatment.

3.2.2 Paediatric use: use in children above 6 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/

Single Convention on Narcotic Drugs, 1961 ** Protocol of 25 March 1972 amending the Single Convention on Narcotic Drugs, 1961 – Available at: https://bit.ly/3xWDYIG

Chen Z.R., Bochner F., Somogyi A. Pharmacokinetics of pholcodine in healthy volunteers: single and chronic dosing studies. Br J Clin Pharmacol 1988; 26(4): 445-453.

Martindale Complete Drug Reference – 40th edition, 2020

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Dextromethorphan - 3-methoxy derivative of levorphanol. It has an antitussive effect, but in therapeutic doses it does not have an analgesic or depressive effect on the respiratory system or psychomimetic effect and has a low addictive potential. The fully synthetic D-isomer is free of the L-isomer with an opioid-like effect. Ciliary activity is not inhibited by therapeutic doses of dextromethorphan hydrobromide.

1.2 ATC Code: R05DA09

1.3 Therapeutic indications: cough suppressant for the relief of acute non-productive (dry, tickly) cough associated with respiratory tract infection.

1.4 Posology and duration of treatment: Tablets 2.5 mg: adults and children over 12 years: no more than 10 lozenges should be taken in one day; children 6 to 12 years: no more than 2 lozenges within any 4 hours and no more than 7 in any one day, not to be used for more than 5 days without the advice of a doctor.

Tablets 20 mg: children 12-15 years: 35-40 mg daily; adults over 15 years: 60-120 mg daily.

Syrup 3.75 mg/5 mL: children 2-6 years: 10 mL three to four times daily; children 2-6 years: 20 mL three to four times daily.

Syrup 7.5 mg/5 mL: adults, elderly and children over 12 years: 10 mL up to four times daily; children under 12 years: not to be used in this population group.

1.5 Pharmaceutical forms: tablets and syrup (different quantitative composition).

1.6 Contraindications: hypersensitivity to the active substance; bronchial asthma; chronic obstructive pulmonary disease (chronic bronchitis and emphysema); pneumonia; respiratory failure; respiratory depression; concomitant use of MAOIs or within 14 days of discontinuation of MAOIs; severe hepatic impairment.

1.7 Relevant warnings: Liver dysfunction: the drug should only be used after careful consideration of the risk-benefit ratio in case of decreased liver function.

Chronic and productive cough: for productive cough with significant coughing up of mucus, dextromethorphan should only be taken after careful consideration of the risk-benefit ratio and with special care. Chronic cough can be an early symptom of bronchial asthma; dextromethorphan is therefore not suitable for the relief of such cough, especially in children.

Central nervous system depressive effect: dextromethorphan has low addictive potential. However, in the case of heavy dosage, symptoms of overdose, including hallucinations, may occur. Use of dextromethorphan with alcohol or other centrally depressant drugs can potentiate the effects on the CNS and cause toxic effects during use of relatively low doses.

Drug tolerance, and mental and physical dependence may develop with long-term use. Therefore, in patients with a tendency to drug abuse or drug addiction, treatment with a medicinal product containing dextromethorphan should only be used for short periods and under very strict medical control. In addition, symptoms should be carefully monitored in such patients suggesting abuse or non-medical use to obtain the recreational effect.

Dextromethorphan abuse and dependence have been reported. Special caution is recommended in adolescents and young adults, as well as in patients with a history of drug or substance abuse or use of psychoactive substances. Cases of dextromethorphan abuse have been reported.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): in 2016, in view of the data presented in the periodic safety update report (PSUR) for dextromethorphan, the PRAC considered that changes to the product information of

medicinal products containing dextromethorphan were necessary. During the reporting period of this single assessment procedure, cases of drug abuse were reported in adolescents and young adults, as well as in patients with a history of drug abuse. It was therefore considered that a warning should be introduced in the product information leaflet to recommend caution in this patient population (see below).

Summary of product characteristics: *Section 4.4:* Cases of dextromethorphan abuse have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

Section 5.2: Metabolism: This section should read as follows: Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled *O*-demethylation (CYD2D6) is the main determinant of dextromethorphan pharmacokinetics in human volunteers. It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolised dextromethorphan, together with the three demethylated morphinan metabolites dextrorphan (also known as 3-hydroxy-*N*-methylmorphinan), 3-hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine. Dextrorphan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine. Dextromethorphan is known to be metabolised by hepatic cytochrome P450 2D6 (CYP2D6). Drug interactions with dextromethorphan may potentially occur with drugs and herbal substances which interact with CYP2D6 either as substrates, inhibitors or inducers. During the period covered by this procedure, new information concerning the interaction of dextromethorphan with CYP2D6 has become available. It is recommended that caution be exercised in patients who are slow metabolisers of CYP2D6 or use CYP2D6 inhibitors. In addition, further information should be provided on the metabolism of dextromethorphan and on the increased risk for toxic effects when dextromethorphan is used concomitantly with CYP2D6 enzyme inhibitors. Therefore, in view of the data presented in the reviewed PSURs, the PRAC considered that changes to the product information of medicinal products containing dextromethorphan were warranted.

2.2 Indirect risks (incorrect use): for all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g. major depression).

Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, somnolence, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal electrocardiogram including QT prolongation), ataxia, toxic psychosis with visual hallucinations, hyperexcitability. In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.

Management: a) activated charcoal can be administered to asymptomatic patients who have ingested overdoses of dextromethorphan within the preceding hour. b) For patients who have ingested dextromethorphan and are sedated or comatose, naloxone, in the usual doses for treatment of opioid overdose, can be considered. Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used.

2.3 Recent cases at European level: in 2017 in France it was decided to change the status of dextromethorphan from non-prescription to List I + Exemption as a result of reports of cases of dextromethorphan abuse, including 2 deaths. In 2017 in the Czech Republic it was also decided to change the status for dextromethorphan from non-prescription to POM as a result of reports of cases of dextromethorphan abuse. In 2019 in Switzerland a switch to List II was also proposed but has not been finalised due to appeal procedures. In Romania in 2017 a switch was proposed from List I to non-prescription status, but it was rejected.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings/Additional Info
AM	Not authorised					

AT	List II + Exemption	Ex.: 15 mg	Ex.: 45 mg			Exemption: MS 15 mg and in combination with substances that are not centrally active antitussive and narcotic analgesics. Not for children under 12 years, no longer than 5 days.
BA	Not authorised					
BE	POM + Exemption				Ex: small packages ‹ 360 mg of active substance	
BG	Not authorised					
CH	List II + Exemption	Ex.: 25 mg	Ex.: 100 mg	Ex.: 500 mg		2019: switch to list II due to legislation change. Not yet finalised due to appeal procedures.
CZ	POM + Exemption				Ex. Syrup with MS 2 mg/mL	
EE	Not subject to prescription					
ES	Not subject to prescription					
FI	Not subject to prescription					
FR	List I + Exemption	Ex.: 0.3%				
DE	Not subject to prescription					
GE	Not authorised					
GR	Not authorised					
HR	Not authorised					
HU	Not subject to prescription					
IE	Not subject to prescription					
IT	Not subject to prescription					
LT	POM + Exemption					
LV	POM + Exemption				Ex.: in combination with ascorbic acid (MS 15 mg)	
ME	Not authorised					
MK	Not authorised					
NL	POM				Tickly and dry cough	
PL	Not subject to prescription				MQP-360 mg dextromethorphan (base)	
PT	Not subject to prescription	2 mg/mL	30 mg	400 mg (200 mL of syrup)		
RO	List I					
RS	Not authorised					
RU	Not authorised					
SE	Not authorised					
SI	Not authorised					
SK	Not subject to prescription					
TR	List I					
UK	Not subject to prescription					

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 I + Exemption** - Exemptions: short-term treatment (5 days), not for children under 12, MS: 15 mg.

Criteria (rationale): short-term and acute treatment (List I); exempted for low dosage.

3.2.2 Paediatric use: serious adverse events may occur in children in case of overdose, including neurological disorders. Caregivers should be advised not to exceed the recommended dose. It should not be used 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/

Martindale Complete Drug Reference – 40th edition, 2020

Websites of national competent authorities

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: Thebacon

1.2 ATC Code: R05DA10

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: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Dimemorfan - dimemorfan phosphate is a sigma 1 receptor agonist, used as a potent antitussive.

1.2 ATC Code: R05DA11

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: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Acetyldihydrocodeine - acetyldihydrocodeine is an opiate derivative discovered in Germany in 1914 and used as a cough suppressant and analgesic. It is not commonly used, but has activity similar to other opiates. Acetyldihydrocodeine is a very close relative derivative of thebacon, where only the 6-7 bond is unsaturated. Acetyldihydrocodeine can be described as the 6-acetyl derivative of dihydrocodeine and is metabolised in the liver by demethylation and deacetylation to produce dihydromorphine. Since acetyldihydrocodeine has higher lipophilicity than codeine and is converted into dihydromorphine rather than morphine, it can be expected to be more potent and longer lasting. It also has a higher bioavailability than codeine. Side effects are similar to those of other opiates and include itching, nausea and respiratory depression.

1.2 ATC Code: R05DA12

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: websites of national regulatory authorities of member states

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Combinations

1.2 ATC Code: R05DA20

1.3 Therapeutic indications: symptomatic relief of colds, chills and influenza.

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: available combination products: a) Oral solution: dextromethorphan 10 mg/5 mL and pseudoephedrine 30 mg/5 mL; b) Oral solution: paracetamol, pseudoephedrine, diphenhydramine and pholcodine; c) Capsules: paracetamol 250 mg, pseudoephedrine 30 mg, dextromethorphan 10 mg; d) Syrup: paracetamol 160 mg, dextromethorphan 7.5 mg, pseudoephedrine 15 mg, chlorpheniramine 1 mg.

1.6 Contraindications: medicines containing combinations of the above active substances are contraindicated in patients who are receiving MAOIs or for two weeks after stopping the MAOI drug; with severe hypertension or coronary artery disease; with or at risk of developing respiratory failure (e.g. those with chronic obstructive airways disease or pneumonia, or during an asthma attack or an exacerbation of asthma); with severe renal impairment; with bronchiolitis or bronchiectasis due to sputum retention; who are receiving other sympathomimetics (such as decongestants, appetite suppressants and amphetamine-like psychostimulants); who are taking oxazolidinone antibiotics (including linezolid); who are taking beta-blockers and other antihypertensives.

1.7 Relevant warnings: chlorphenamine: in common with other drugs having anticholinergic effects, chlorphenamine should be used with caution in epilepsy; raised intra-ocular pressure including glaucoma; prostatic hypertrophy; severe hypertension or cardiovascular disease; bronchitis, bronchiectasis and asthma; hepatic impairment; renal impairment. Children and the elderly are more likely to experience neurological anticholinergic effects and paradoxical excitation (e.g. increased energy, restlessness, nervousness). Use in elderly patients with confusion should be avoided. The anticholinergic properties of chlorphenamine may cause drowsiness, dizziness, blurred vision and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery. Concurrent use with drugs which cause sedation such as anxiolytics and hypnotics may cause an increase in sedative effects, therefore medical advice should be sought before taking chlorphenamine concurrently with these medicines. The effects of alcohol may be increased and therefore concurrent use should be avoided. It should not be used with other antihistamine-containing products, including antihistamine-containing cough and cold medicines. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Diphenhydramine: it should be used with caution in patients with myasthenia gravis; epilepsy or seizure disorders; narrow-angle glaucoma; prostatic hypertrophy; urinary retention; asthma; bronchitis; restless leg syndrome and COPD. Diphenhydramine has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance there have been cases of QT interval prolongation and torsade de pointes associated with overdose. Treatment should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and patients should seek immediate medical attention. Patients should be advised to promptly report any cardiac symptoms. Diphenhydramine should be used for the shortest possible duration. Tolerance and/or dependence may develop with continuous use. It should not be taken for more than 7 consecutive nights without consulting a doctor. Medical advice should be sought if sleeplessness persists, as insomnia may be a symptom of serious underlying medical illness. In patients with moderate to severe hepatic impairment and moderate to severe renal impairment, a lower dose might be required. It should not be used in patients currently receiving MAOIs or those patients who have received treatment with MAOIs within the last two weeks. It may increase the effects of alcohol, therefore alcohol should be avoided. Use of other antihistamine-containing preparations, including topical antihistamines and cough and cold medicines, should be avoided while taking diphenhydramine. Use in the elderly is not recommended because of the greater risk of adverse reactions (e.g. anticholinergic effects). Use in elderly patients with confusion should be avoided. Cases of abuse and dependence were reported with diphenhydramine in adolescents or young adults for

recreational use and/or in patients with psychiatric disorders and/or history of abuse disorders. The onset of signs or symptoms suggesting abuse should be monitored.

Dextromethorphan: see evidence-based classification review on dextromethorphan.

Paracetamol: care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Where analgesics are used long-term (>3 months) with administration every 2 days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.

Pholcodine: see evidence-based classification review on pholcodine.

Pseudoephedrine: caution should be used when prescribing pseudoephedrine for patients with prostatic enlargement or bladder dysfunction. Also use with caution in patients with severe hepatic impairment or with mild to moderate renal impairment. If any of the following occur, use should be stopped: hallucinations, restlessness, sleep disturbances. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take pseudoephedrine. Severe skin reactions: severe skin reactions such as AGEP may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localised on the skin folds, trunk and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema or many small pustules are observed, administration of pseudoephedrine should be discontinued and appropriate measures taken if needed. Ischaemic colitis: some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): chlorphenamine: common adverse effects may include sedation, somnolence, disturbance in attention, abnormal coordination, dizziness, headache, blurred vision, nausea, dry mouth and fatigue.

Diphenhydramine: common adverse effects may include sedation, drowsiness, disturbance in attention, unsteadiness, dizziness, dry mouth and fatigue.

Dextromethorphan: see evidence-based classification review on dextromethorphan.

Paracetamol: adverse events of paracetamol from historical clinical trial data are both infrequent and from exposure of small numbers of patients. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are listed below by system class. Due to limited clinical trial data, the frequency of these adverse events is not known (it cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare. Blood and lymphatic system disorders: thrombocytopenia, agranulocytosis. Immune system disorders: anaphylaxis, cutaneous hypersensitivity reactions, including skin rashes, angioedema and Stevens–Johnson syndrome/toxic epidermal necrolysis. Respiratory, thoracic and mediastinal disorders: bronchospasm. Hepatobiliary disorders: hepatic dysfunction.

Pholcodine: see evidence-based classification review on pholcodine.

Pseudoephedrine: adverse effects may include dry mouth, anxiety, restlessness, tremor, insomnia, tachycardia, cardiac arrhythmias, palpitations, hypertension, nausea, vomiting, headache and occasionally urinary retention in males and skin rashes. Hallucinations have been reported rarely, particularly in children. Skin and subcutaneous tissue disorders: frequency unknown: severe skin reactions, including AGEP.

2.2 Indirect risks (incorrect use): chlorphenamine: the estimated lethal dose of chlorphenamine is 25 to 50 mg/kg body weight. Symptoms and signs include sedation, paradoxical excitation of the CNS, toxic psychosis, convulsions, apnoea, anticholinergic effects, dystonic reactions and cardiovascular collapse including arrhythmias. Treatment: management should be as clinically indicated or as recommended by

national poison centres, where available. Symptomatic and supportive measures should be provided with special attention to cardiac, respiratory, renal and hepatic functions and fluid and electrolyte balance. If overdosage is by the oral route, treatment with activated charcoal should be considered provided there are no contraindications for use and the overdose has been taken recently (treatment is most effective if given within an hour of ingestion). Treat hypotension and arrhythmias vigorously. CNS convulsions may be treated with iv diazepam. Haemoperfusion may be used in severe cases.

Diphenhydramine: overdose is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include mydriasis, fever, flushing, agitation, tremor, dystonic reactions, hallucinations and ECG changes, such as QT prolongation and torsades de pointes. Large overdose may cause rhabdomyolysis, convulsions, delirium, toxic psychosis, arrhythmias, coma and cardiovascular collapse. Management treatment should be supportive and directed towards specific symptoms. Convulsions and marked CNS stimulation should be treated with parenteral diazepam.

Dextromethorphan: see evidence-based classification review on dextromethorphan.

Paracetamol: liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors: if the patient is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes; he/she regularly consumes ethanol in excess of recommended amounts; he/she is likely to be glutathione-deplete, e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Pholcodine: see evidence-based classification review on pholcodine.

Pseudoephedrine: symptoms of overdosage include irritability, restlessness, palpitations, hypertension, difficulty in micturition, nausea, vomiting, thirst and convulsions. In severe overdosage gastric lavage and aspiration should be performed. Symptomatic and supportive measures should be undertaken, particularly with regard to cardiovascular and respiratory systems. Convulsions should be controlled with intravenous diazepam. Chlorpromazine may be used to control marked excitement and hallucinations. Severe hypertension may need to be treated with an alpha-adrenoreceptor blocking drug, such as phentolamine. A beta blocker may be required to control cardiac arrhythmias.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

Country	Classification	MS	MDD	MQP	Indications	Warnings/Additional Info
AM	Not authorised					
AT	Not authorised					
BA	Not authorised					
BE	Not authorised					
BG	Not authorised					
CH	List II					
CZ	Not authorised					
EE	Not authorised					
ES	POM + Exemption					Combination products containing pseudoephedrine, chlorphenamine and codeine are classified as POM
FI	Not authorised					
FR	List I					
DE	Not authorised					
GE	Not authorised					
GR	POM (narcotic status)					
HR	Not authorised					
HU	POM					
IE	Not subject to prescription					
IT	Not authorised					

LT	Not authorised					
LV	Not authorised					
ME	Not authorised					
MK	Not subject to prescription					Relief of the symptoms of cold or flu conditions associated with mild or moderate pain, fever and nasal congestion and secretion in adults and adolescents over 14 years of age
NL	Not subject to prescription					
PL	Not subject to prescription					
PT	Not authorised					
RO	Not authorised					
RS	Not authorised					
RU	Not authorised					
SE	Not authorised					
SI	Not authorised					
SK	Not authorised					
TR	Not authorised					
UK	Not subject to prescription					

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 (rationale): not clear which combination products are classified under this ATC code.

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: -

[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: Doxylamine

1.2 ATC code: R06AA09

1.3 Therapeutic indications: treatment of insomnia in terms of symptomatic short-term treatment of occasional sleep disorders in adults.

1.4 Posology and duration of treatment: 25 mg about 30 minutes to 1 hour before going to bed. In the case of more severe sleep disorders, a maximum dose of 50 mg doxylamine can be taken. In the case of acute sleep disorders, treatment should be limited to single doses as far as possible. The duration of the application must be as short as possible. In general, the duration of treatment can range from a few days to a week. If there is no improvement or even worsening after 7 days, a doctor should be consulted. The treatment must be stopped after 2 weeks of daily use at the latest.

1.5 Pharmaceutical forms: orodispersible tablets and solutions for oral use.

1.6 Contraindications: because of its anticholinergic effects, doxylamine should be used with caution in patients with prostatic hyperplasia, glaucoma, cardiovascular disease or bronchial asthma. Patients intolerant to other antihistamines may also be intolerant to doxylamine. Doxylamine can be dangerous if used with alcoholic beverages. To be used with special caution in pregnant or breastfeeding women, children and groups at increased risk such as hepatic insufficiency or epilepsy, concomitant use of MAOIs and potent inhibitors of CYP450 isoenzymes, and porphyria.

1.7 Relevant warnings: doxylamine should only be used with special caution in case of impaired kidney and liver function, previous cardiac damage and hypertension, chronic breathing difficulties and asthma, and gastroesophageal reflux. Particular caution is required in patients with neurologically recognisable brain damage in the cerebral cortex and a history of seizures, as grand mal seizures can be triggered by taking even small doses. Electrocardiogram (ECG) controls are recommended. Existing seizure therapy should not be interrupted during treatment with doxylamine. During therapy with antihistamines, ECG changes, in particular repolarisation disorders, have been reported, so regular monitoring of cardiac function is recommended. This especially applies to older patients and patients with previous cardiac disorders. Particular caution is also required in patients with arterial hypertension, as antihistamines can cause an increase in blood pressure. After taking doxylamine, a sufficiently long sleep period (a period of at least 8 hours) must be ensured to avoid impaired reactions the following morning. The effects of doxylamine and the following drugs can be mutually intensified: central depressant drugs (e.g. neuroleptics, tranquilisers, antidepressants, hypnotics, analgesics, anaesthetics, anti-epileptics, muscle relaxants, other antihistamines). The effect of the following drugs can be weakened: phenytoin and neuroleptics. Simultaneous use of doxylamine and antihypertensive drugs with an active ingredient that affects the CNS, such as guanabenz, clonidine or alpha-methyldopa, can lead to an increased sedation effect. Signs of incipient inner ear damage caused by ototoxic drugs (e.g. aminoglycosides, salicylates, diuretics) may be weakened. The results of skin tests can be incorrect (false negative). Doxylamine should not be used in concomitance with epinephrine, as the administration of epinephrine can paradoxically lead to a further drop in blood pressure (reversal of adrenaline); however, severe shock can be treated with norepinephrine. Concomitant use of MAOIs can cause hypotension and increased depression of the CNS and respiratory function; therefore, simultaneous therapy with both substances should be avoided. Doxylamine has a major influence on the ability to drive and use machinery - even when used as intended, this medicinal product can change the ability to react to such an extent that the ability to actively drive or operate machinery is impaired. This effect is exacerbated in combination with alcohol. Therefore, driving vehicles, operating machinery or other dangerous activities (at least during the first phase of treatment) must be completely avoided. Pregnancy: epidemiological studies with doxylamine have shown no evidence of congenital malformations in humans. Animal studies on reproductive toxicity are insufficient. As a precaution, it is advisable to avoid the use of doxylamine during pregnancy. Lactation: as the active ingredient passes into breast milk, breastfeeding should be interrupted for the duration of the treatment. Fertility: no data are available on the possible effects of doxylamine on human fertility. Animal studies have shown no effects on fertility, even when using doses much higher than those recommended for clinical practice.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): adverse reactions to doxylamine are, in general, mild and transient,

being more frequent in the first days of treatment. The most frequent are somnolence and those due to anticholinergic effects (1-9 %): dry mouth, constipation, blurred vision, urinary retention, bronchial hypersecretion, vertigo.

Frequent: Nervous system disorders: residual daytime drowsiness. Ear and labyrinth disorders: vertigo. Gastrointestinal disorders: dry mouth, constipation. Ocular disorders: blurred vision. Renal and urinary disorders: urinary retention. Respiratory, thoracic and mediastinal disorders: bronchial hypersecretion.

Infrequent: General disorders: asthenia, confusion. Gastrointestinal disorders: nausea, vomiting, diarrhoea. Skin and subcutaneous tissue disorders: exanthematous eruptions. Ear and labyrinth disorders: tinnitus. Vascular disorders: orthostatic hypotension, peripheral oedema. Ocular disorders: diplopia.

Rare: Psychiatric disorders: paradoxical excitation (especially in children and the elderly). Nervous system disorders: tremor, convulsions. Blood and lymphatic system disorders: haemolytic anaemia, thrombocytopenia, leukopenia, agranulocytosis.

2.2 Indirect risks (incorrect use): doxylamine poisoning is rarely life-threatening. Recovery is usually complete within 24 to 48 hours. Reactions in mild to moderate intoxication include drowsiness, depression or stimulation of the CNS, anticholinergic effects (mydriasis, fever, dry mouth and decreased intestinal tone), tachycardia, hypertension, nausea, vomiting, agitation, confusion and hallucinations. Severe intoxication may produce delirium, psychosis, hypotension, convulsions, respiratory depression, loss of consciousness, coma and death. A serious complication may be rhabdomyolysis, with subsequent renal failure. Since there is no specific antidote for antihistamine overdose, treatment is symptomatic and supportive, with possible use of the following: induction of emesis, gastric lavage, vasopressors to treat hypotension. However, epinephrine should not be used as it may further lower 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	15 mg	30 mg			
AT	Not subject to prescription	25 mg				
BA	Not subject to prescription					
BG	POM	25 mg	50 mg			
CH	List II					Under ATC code N05CM
CZ	POM					
DE	Not subject to prescription					
EE	POM					
ES	Not subject to prescription					
FI	POM					
FR	Not authorised					
HR	List I					
HU	POM					
IE	Not authorised					
IT	Not authorised					
LT	POM					
LV	POM					
MK	Not subject to prescription					
NL	Not authorised					
PL	POM					
PT	Not subject to prescription	25 mg				
RO	List I					

RS	POM					
SE	POM					
SI	POM					
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: **List II + Exemption** - Exemptions: MS: 25 mg, MDD: 50 mg; MQP: 250 mg; symptomatic short-term treatment of insomnia.

Criteria: safety profile; short-term use.

3.2.2 Paediatric use: no paediatric indications, contraindicated in the paediatric population.

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: -

[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.)

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