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

Evidence-based classification reviews of
medicines belonging to various ATC codes

2019

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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

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

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

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

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

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

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

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

DISCLAIMER

This document is published for information only.

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

They reflect the debates and conclusions of the reviews of scientific classifications of medicines that took place at the 2018-2019 meetings of the CD-P-PH/PHO. The document was reviewed and endorsed by the CD-P-PH/PHO at its 67th meeting (December 2019).

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

ADH	Antidiuretic hormone
ATC	Anatomical Therapeutic Chemical classification [1]
CNS	Central nervous system
CTTH	Chronic tension type headache
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines and HealthCare
EMA	European Medicines Agency
GSL	General sales list medication
INR	International Normalized Ratio
MAOI	Monoamine oxidase inhibitor
MDD	Maximal daily dose
MQP	Maximal quantity per pack
MRI	Magnetic resonance imaging
MS	Maximal strength
MS	Multiple sclerosis
P	Pharmacy-only medicine
PML	Progressive multifocal leukoencephalopathy
POM	Prescription only medicine
PSUSA	Periodic Safety Update Report Single Assessment
PT	Prothrombin time
SmPC	Summary of product characteristics
SNRI	Serotonin/noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
ULN	Upper limit of normal
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:

[1] World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology - https://goo.gl/KvqKir

- 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. THERAPEUTIC PROFILE

1.1 Active ingredient: Riboflavin (Vit B12)

1.2 ATC code: A11HA04

1.3 Therapeutic indications: riboflavin is an active ingredient used in multivitamin-containing medicines under other ATC codes.

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)

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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 under this ATC code).

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 under this ATC code: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Melclass database (https://melclass.edqm.eu/)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Phenprocoumon

1.2 ATC code: B01AA04

1.3 Therapeutic indications: vitamin K antagonist - treatment of thrombosis, embolism and myocardial infarction and prophylaxis of arterial and venous thrombosis and embolism.

1.4 Posology and duration of treatment: therapeutic response to anticoagulants varies between individuals and can also change during treatment. Therefore, regular monitoring of coagulation cascade and dosage adjustments are necessary. Outpatient treatment with phenprocoumon should be done under medical control.

Standard dosage: dose on 1st day: 4 tablets; dose on 2nd day: 2 tablets; dose on 3rd day: 1 tablet; 4th day: test.

Patients suffering from hepatic insufficiency/kidney insufficiency/poor general condition: dose on 1st day: 2 to 3 tablets; dose on 2nd day: 2 to 1 tablets; dose on 3rd day: 1 tablet; 4th day: test. In patients who are ill or in poor condition, caution is advised and one can start with a lower dosage.

Normally, on the fourth day, the prothrombin time (PT) can be determined and the dosage should be adjusted accordingly. In general, the aim is to achieve an International Normalized Ratio (INR) value between 2.5 and 4.0. After that, treatment is continued with lower doses of phenprocoumon. The maintenance dosage, generally between ½ and 2 tablets per day, varies greatly from patient to patient and can therefore only be achieved by regular monitoring of the coagulation parameters for each patient individually. The tablets should be taken without chewing, with a little liquid, and should not be dissolved in advance.

Thrombosis prophylaxis: in most patients, who are at risk of thrombosis, a prophylactic administration of phenprocoumon for 3-6 weeks is advised; the anticoagulant prophylaxis should be at least as long as the patient is immobilised. Early withdrawal of the medication increases the risk of thrombosis. After surgical interventions and deliveries, phenprocoumon should be used from the second or third day after the intervention/delivery. For a direct-acting anticoagulation effect and in cases of surgical operations, heparin is to be preferred.

Therapy for acute thrombosis and embolism: on the first day of the medication switch, the patient should, in addition to the regular daily dose of heparin, take the full initial dose of phenprocoumon, as heparin has no after-effects, whereas the anticoagulant effect of phenprocoumon only occurs after the latency period described above. The duration of treatment with heparin depends on the time required to achieve the desired anticoagulant levels. During this transition period, frequent and careful controls of the INR are necessary. The duration of treatment with phenprocoumon is determined by clinical needs and can last several months or even years.

Paediatric patients: there is little experience in paediatric patients with the use of anticoagulants, including phenprocoumon. Evaluations and more frequent monitoring of the INR are recommended.

Elderly people: elderly people (particularly those over 75 years of age) will generally require lower doses than younger patients to reach the desired INR value.

Patients with renal insufficiency: renal impairment has no clinically relevant influence on the elimination half-life. Since chronic kidney disease has been associated with an increased response to vitamin K antagonists a dose reduction should be considered and more frequent monitoring is required.

Patients with hepatic insufficiency: hepatic insufficiency has no significant influence on the clearance of phenprocoumon, but the response to vitamin K antagonists is higher in patients suffering from liver disease. Therefore, a dose reduction should be considered and more frequent monitoring is required.

Monitoring of phenprocoumon therapy: therapeutic response to anticoagulants varies between individuals and can also change during treatment. It is absolutely necessary to check the efficacy of phenprocoumon by means of the PT or any other methods. Coagulation times can be measured in seconds, ratios or percentages. The first check should be made before the start of the treatment. It is advised to check new patients several times

a week to ensure that they are stable. As soon as sufficient experience has been gained with the maintenance dose, it is possible to space out the checks to longer intervals (e.g. one determination every 4-6 weeks) if stability is maintained and as far as the patient's condition or other concomitant medications do not undergo any abrupt change. More frequent monitoring is required in the event of simultaneous administration of medications that alter or influence the effects of anticoagulants. In the case of severely increased INR values (INR: 6.0-8.0), treatment with phenprocoumon should be interrupted and continued with a reduced dosage. It is recommended to administer vitamin K to patients with an INR value higher than 8.0. The decrease in the INR value in response to the administration of vitamin K varies between individuals.

1.5 Pharmaceutical forms: tablets containing 3 mg of phenprocoumon.

1.6 Contraindications: phenprocoumon should not be used in the following situations: a) known hypersensitivity to phenprocoumon, related coumarin derivatives or any of the excipients according to composition; b) pregnancy. Phenprocoumon is also contraindicated in all pathological situations where the risk of haemorrhage outweighs the possible clinical benefit, e.g. moderate to severe haemorrhagic diathesis, severe injury to the liver parenchyma, gastrointestinal ulcer, overt bleeding of the gastrointestinal, genitourinary or respiratory tract, acute bacterial endocarditis, period before or after neurosurgical intervention, pericarditis, pericardial effusion, cerebrovascular haemorrhage during ophthalmologic procedures and traumatic procedures with extensive tissue exposure.

1.7 Relevant warnings: phenprocoumon should only be used after careful evaluation of the benefit-risk ratio. Particularly careful monitoring of the patient is required following procedures on the lungs, genitals, stomach and bile ducts due to increased fibrinolytic activity. Patients with heart failure, severe hypertension, diseases related to suspected damage to the cardiovascular system (e.g. advanced arteriosclerosis or severe hypertension), severe liver disease or renal failure should be closely monitored. Phenprocoumon has a narrow therapeutic range. Therefore, caution should be exercised and close monitoring of INR is necessary when switching from one drug to another. Possible interactions between phenprocoumon and other drugs should be carefully considered. In particular, any change in co-medications requires more frequent checking of the INR. The risk of bleeding is increased after an injury, e.g. after an accident. In people who usually drink a lot of alcohol, the anticoagulant effect may be reduced, but liver failure may lead to increased anticoagulation. Liver function in patients under long-term treatment with phenprocoumon should be carefully monitored. Close monitoring is necessary in elderly patients, children, alcoholics and patients with psychiatric conditions. Diseases or conditions which may reduce the binding of phenprocoumon to proteins and thus enhance the effects of phenprocoumon (e.g. diabetes mellitus, thyrotoxicosis, tumours, kidney diseases, infections or inflammations) require close medical supervision. Caution should be exercised in cases of hepatic insufficiency, due to a possible decrease in clotting factor synthesis or an underlying disorder of thrombocyte function. Intramuscular injections should not be given throughout the duration of anticoagulation therapy as they may cause bleeding or hematomas. This complication is rarely observed after subcutaneous or intravenous injections. As a precautionary measure out-of-hospital patients using phenprocoumon should carry with them medications containing vitamin K1 and receive instructions for use in case of emergency, as well as a doctor's certificate stating that they are on anticoagulant medication. When certain diagnostic and therapeutic procedures require a shortening of the PT (angiography, lumbar puncture, minor surgery, dental extractions, etc.), this must be carried out under close supervision. In the event of impaired absorption in the gastrointestinal tract, the anticoagulant effect of phenprocoumon may be altered. In cases of severe heart failure, the dosage of phenprocoumon should be set with extreme caution, as the activation or the gamma-carboxylation of the coagulation factors may be impaired in the presence of hepatic congestion. However, after recovery from hepatic congestion, an increase in dosage may be necessary. Caution should be exercised in the case of known or suspected protein C or protein S deficiency. A possible decrease in the effect of oral anticoagulants with concomitant administration of St. John's Wort (Hypericum) preparations has been reported (risk of insufficient anticoagulation). In the extremely rare case of skin necrosis (most often due to skin infarction) observed at the start of anticoagulant therapy, phenprocoumon should be discontinued and immediately replaced by heparin. Calciphylaxis is a rare syndrome of vascular calcification with skin necrosis which is associated with high mortality. It is primarily seen in dialysis patients with end-stage renal disease or in patients with known risk factors such as protein C or S deficiency, hyperphosphatemia, hypercalcemia or hypoalbuminemia. Rare cases of calciphylaxis have been reported in patients taking K antivitamins, including phenprocoumon, even if they did not have renal disease. When calciphylaxis is diagnosed, appropriate therapy should be administered and consideration should be given to discontinuing phenprocoumon. During anticoagulant therapy, patients should not be subjected to angiography or any other diagnostic or therapeutic procedures that may lead to uncontrollable bleeding. Phenprocoumon tablets often contain lactose: patients with hereditary galactose intolerance (a rare hereditary disease), Lapp lactase deficiency or glucose/galactose

malabsorption should not take phenprocoumon tablets. No information is available on the effects of phenprocoumon on fertility.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): haemorrhages involving different organs are possible due to the properties of phenprocoumon. In particular, life-threatening haemorrhages can occur in the cardiovascular system, central nervous system (CNS), gastrointestinal system (melena), respiratory system, urogenital system (macrohaematuria, microhaematuria), uterus (metrorrhagia, menorrhagia), hepatobiliary system (haemobilia) and eyes. If bleeding occurs in the presence of an INR in the therapeutic area, diagnostic tests are necessary (e.g. for ulcerations, tumours or endogenous coagulation disorders).

The evaluation of adverse reactions is based on the following frequencies: very frequent (≥1/10), frequent (<1/10 ≥1/100), occasional (<1/100 ≥1/1000), rare (<1/1000 ≥1/10000), very rare (<1/10000), unknown (frequency cannot be estimated from available data).

Immune system disorders: frequency unknown: hypersensitivity (e.g. rheumatoid purpura, allergic dermatitis).

Haematological and lymphatic system disorders: rare: haemorrhagic anaemia.

Endocrine disorders: occasional: haemorrhages in the pancreas and adrenal gland.

Nervous system disorders: occasional: haemorrhages in the spinal cord and brain; very rare: femoral nerve compression syndrome, due to retroperitoneal haemorrhage.

Eye conditions: occasional: retinal haemorrhages.

Cardiac conditions: occasional: haemorrhages in the pericardium.

Vascular conditions: very common: bruising from injuries; occasional: burning pain and abnormal colouring of the big toes (purple toes).

Respiratory, thoracic and mediastinal conditions: very common: epistaxis; occasional: haemorrhages in the pleural cavity.

Gastrointestinal disorders: very common: gum bleeding; occasional: gastrointestinal haemorrhages, haemorrhages in the intestinal wall, retroperitoneal haemorrhages; rare: gastrointestinal diseases; frequency unknown: gastrointestinal disorders such as vomiting, diarrhoea, nausea, reduced appetite.

Hepatobiliary disorders: very rare: hepatitis, with or without jaundice, usually reversible. However, cases of liver failure requiring liver transplantation or resulting in death have been reported in patients taking phenprocoumon. For this reason, the liver function of patients under long-term treatment with phenprocoumon should be carefully monitored.

Skin and subcutaneous tissue disorders: rare: alopecia; very rare: severe cutaneous necrosis (most often skin infarction), purpura fulminans (sometimes fatal) (treatment: cancel the effect of phenprocoumon by administering vitamin K1 and immediately switch to heparin. Prednisone may be given as a supplement); frequency unknown: allergic dermatitis, calciphylaxis.

Musculoskeletal and connective tissue disorders: occasional: haemorrhages in joints and muscles; frequency unknown: after prolonged treatment: osteopenia, osteoporosis.

Kidney and urinary tract disorders: very common: haematuria.

2.2 Indirect risks (incorrect use): overdosage is manifested by increased INR beyond the intended therapeutic range and possibly by bleeding. If the INR rises above the therapeutic threshold during phenprocoumon therapy, the drug dosage should be reduced and the coagulation values rechecked 2 days later. In the case of a slight overdose of phenprocoumon with clinically insignificant haemorrhages (e.g. transient nosebleed, microscopic haematuria, isolated small haematomas), it is usually sufficient to reduce or skip a dose. In such cases, it is preferable to avoid vitamin K1 administration, which would prevent effective

anticoagulation for several days. After taking high doses, the patient experiences mainly a toxic effect on the capillaries, causing cerebral oedema for the first 24 hours. This is followed by an increase in INR and haemorrhages. Other possible identifiable signs of acute overdose, depending on the extent of the overdose, are also possible: blood in the urine, petechiae in areas exposed to mechanical stress, spontaneous haemorrhages of the skin and mucous membranes, blood in the stools, confused states up to and including loss of consciousness. Loss of consciousness may be a sign of cerebral haemorrhage. This situation requires emergency medical treatment. In most cases, a less severe haemorrhage can be controlled by withholding anticoagulant treatment.

Treatment: specific antidote: vitamin K1. Mild haemorrhages can usually be controlled by administering 5-10 mg of vitamin K1 orally or by slow intravenous injection. If a sufficient increase in clotting activity or cessation of bleeding is not achieved within 8 to 12 hours, a second (possibly higher) dose of vitamin K1 should be given. Only in case of life-threatening bleeding: slow intravenous administration of 10-20 mg vitamin K1 (caution: risk of anaphylactoid reaction). If the INR does not decrease, administration should be repeated a few hours later. Unit doses of 20 mg or total doses of 40 mg of vitamin K1 should be considered the maximum dose. Excessively high doses, i.e. above 40 mg, should be avoided as they would make it difficult to continue phenprocoumon therapy. In particularly dangerous situations (e.g. suspected intracranial haemorrhage, massive gastrointestinal haemorrhage or emergency intervention), clotting factor levels may be increased or normalised by infusion of prothrombin complex concentrate, intravenous administration of fresh frozen plasma or vitamin K-dependent clotting factor concentrate. Oral administration of cholestyramine (4 g five times daily) may be optionally considered, as it may further accelerate the elimination of phenprocoumon. Close monitoring of coagulation parameters should be ensured.

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	Indications/Additional details	MS	MD	MQP
Armenia (AM)	Not authorised				
Austria (AT)	List II	Treatment of thrombosis, embolism and myocardial infarction. Prophylaxis of arterial and venous thrombosis and embolism.			
Bosnia and Herzegovina (BA)	Not authorised				
Belgium (BE)	POM	Oral anticoagulant	3 mg		75 mg
Switzerland (CH)	Not authorised				
Czech Republic (CZ)	Not authorised				
Germany (DE)	POM				
Estonia (EE)	Not authorised				
Spain (ES)	Not authorised				
Finland (FI)	Not authorised				
France (FR)	Not authorised				
Georgia (GE)	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				
Macedonia (MK)	Not authorised				
Netherlands (NL)	POM	Thromboembolic disease			

Poland (PL)	Not authorised				
Portugal (PT)	Not authorised				
Romania (RO)	Not authorised				
Serbia (RS)	Not authorised				
Sweden (SE)	Not authorised				
Slovenia (SI)	Not authorised				
United Kingdom (UK)	Not authorised				

Melclass database[1]: List I

No more data available from other member states.

3.2 Social dimension of classification:

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

Criteria: medical supervision and close monitoring needed (INR and dosage adjustment); safety profile (narrow therapeutic window and high risk of major bleeding).

3.2.2 Paediatric use: given the limited experience in the paediatric population, evaluations and more frequent monitoring of the INR are recommended.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: databases of national competent authorities (Austria, the Netherlands and Switzerland) and Melclass database (https://melclass.edqm.eu/)

4.2 Comments: -

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Silver Sulfadiazine

1.2 ATC code: D06BA01

1.3 Therapeutic indications: silver sulfadiazine cream is indicated for the prophylaxis and treatment of infection in burn wounds. Silver sulfadiazine may also be used as an aid to the short-term treatment of infection in leg ulcers and pressure sores, and as an aid to the prophylaxis of infection in skin graft donor sites and extensive abrasions. Silver sulfadiazine is also indicated for the conservative management of fingertip injuries where pulp, nail loss and/or partial loss of the distal phalanx has occurred.

1.4 Posology and duration of treatment: silver sulfadiazine should be applied topically.

Burns: the burn wound should be cleaned and the cream applied over all the affected areas to a depth of 3-5 mm. This application is best achieved with a sterile gloved hand and/or sterile spatula. Where necessary, the cream should be re-applied to any area from which it has been removed by patient activity. In burns, the cream should be re-applied at least every 24 hours, or more frequently if the volume of exudate is large.

Hand burns: the product can be applied to the burn and the whole hand enclosed in a clear plastic bag or glove, which is then closed at the wrist. The patient should be encouraged to move the hand and fingers. The dressing should be changed when an excessive amount of exudate has accumulated in the bag/glove.

Leg ulcers and pressure sores: the cavity of the ulcer should be filled with the cream to a depth of at least 3-5 mm. As the cream can cause maceration of normal skin on prolonged contact, care should be taken to prevent spread onto non-ulcerated areas. Application of the cream should be followed by an absorbent pad or gauze dressing, with further application of pressure bandaging as appropriate for the ulcer. The dressings should normally be changed daily but for wounds which are less exudative, less frequent changes (every 48 hours) may be acceptable. Cleansing and debriding should be performed before application of the cream. The cream is not recommended for use in leg or pressure ulcers that are very exudative.

Fingertip injuries: haemostasis of the injury should be achieved prior to the application of a 3-5 mm layer of the cream. A conventional finger dressing may be used. Alternatively the finger of a plastic or unsterile surgical glove can be used and fixed in place with waterproof adhesive tape. Dressings should be changed every 2-3 days.

1.5 Pharmaceutical forms: cream and ointment 10 mg/g.

1.6 Contraindications: as sulphonamides are known to cause kernicterus, this medicine should not be used at or near the term of pregnancy, on premature infants or on new-born infants during the first months of life. The product is also contraindicated in patients known to be hypersensitive to silver sulfadiazine or to other components of the preparation such as cetyl alcohol or propylene glycol.

1.7 Relevant warnings: prolonged use of an anti-infective may result in the development of superinfection due to organisms resistant to that anti-infective. Fungal colonisation may occur. This medicine should be used with caution in the presence of significant hepatic or renal impairment. Caution of use is required in patients known to be sensitive to systemic sulphonamides and in individuals known to have glucose-6-phosphate dehydrogenase deficiency. Use of the cream may delay separation of burn eschar and may alter the appearance of the burn wounds.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): Blood and lymphatic tissue disorders: common: leukopenia - leukopenia has been reported in 3-5% of burns patients treated with the medicine. This may be a drug related effect, and often manifests itself 2-3 days after treatment has commenced. It is usually self-limiting and therapy with the cream does not usually need to be discontinued, although the blood count must be monitored to ensure that it returns to normal within a few days.

General disorders and administration site conditions: common: application site burning.

Renal and urinary disorders: very rare: renal failure.

Skin and subcutaneous tissue disorders: common: pruritus and application site rash (including eczema and contact dermatitis); rare: argyria (there is evidence that in large area wounds and/or after prolonged application, systemic absorption of silver can occur causing clinical argyria).

2.2 Indirect risks (incorrect use): overdosage is not likely to occur with normal usage.

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	Indications/Additional details	MS	MDD	MQP
AM	Not subject to prescription	Treatment and prophylaxis of burn infections, of infections in pressure ulcers, leg ulcers, abrasions, minor traumatic wounds, in incisions and other clean wounds and on the skin graft donor site	10 mg/g	1-2 times a day	500 mg (10 mg/g in 50 mg tube)
AT	List II				
BA	Not subject to prescription	Treatment and prophylaxis of burn infections, of infections in pressure ulcers, leg ulcers, abrasions, minor traumatic wounds, in incisions and other clean wounds and on the skin graft donor site	10 mg/g		
BE	Not subject to prescription				
CH	List II + Exemption	Ex.: minor first-degree burns, minor skin infections, minor infected wounds	Ex.: 10 mg/g		Ex.: 200 mg (20 g of 10 mg/g)
CZ	Not authorised				
DE	POM				
EE	POM + Exemption	Ex.: treatment of mild infections up to 1% of the patient's body surface area. Short-term treatment (up to 7 days). Not to be used in children under the age of 3 months.			Ex.: 15 g
ES	POM				
FI	POM				
FR	List I				
GE	Not subject to prescription				
HR	List I		10 mg/g		
HU	Not subject to prescription	Treatment of burns and for the prevention of superinfection	10 mg/g	2-4 mm cream several times daily	2500 mg
IE	List I				
IT	Not subject to prescription				
LT	POM		10 mg/g		50 g
LV	POM				
MK	POM	Silver sulfadiazine cream is used to prevent and treat wound infections in patients with second- and third-degree burns.	1%		50 g
NL	POM				
PL	Not authorised				
PT	POM	Topical use, antibacterial medication	10 mg/g		

RO	Not subject to prescription	It is especially indicated for the treatment and prevention of burns, for the treatment and prevention of lesions of decubitus lesions, varicose ulcers, abrasions, minor traumatic lesions, incisions or other uninfected injuries, and skin grafts.	10 mg/g	2 mg/g	
RS	POM				
SE	Not authorised				
SI	POM				
UK	POM				

Melclass database[1]: -

No data are available from other member states.

3.2 Social dimension of classification:

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

Criteria: the degree of burn and the level of wound healing cannot be evaluated by the patient alone, without medical supervision; safety profile of silver sulfadiazine.

3.2.2 Paediatric use: since sulfonamides may cause kernicterus, sulfadiazine silver should not be used in late pregnancy, in premature infants or infants younger than 2 months unless the expected benefit outweighs the potential risk.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Health Products Regulatory Authority Ireland (HPRA) (https://www.hpra.ie/homepage/medicines)

Medicines and Healthcare products Regulatory Agency (MHRA) (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1489124841570.pdf)

Melclass database (https://melclass.edqm.eu/)

4.2 Comments: -

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Dimethyl Fumarate

1.2 ATC code: L04AX07 (old ATC code: N07XX09)

1.3 Therapeutic indications: indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

1.4 Posology and duration of treatment: treatment should be initiated under supervision of a physician experienced in the treatment of MS.

Posology: the starting dose is 120 mg twice a day. After 7 days, the dose should be increased to the recommended maintenance dose of 240 mg twice a day. If a patient misses a dose, a double dose should not be taken. The patient may take the missed dose only if they leave 4 hours between doses. Otherwise the patient should wait until the next scheduled dose. Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended maintenance dose of 240 mg twice a day should be resumed. Dimethyl fumarate should be taken with food. For those patients who may experience flushing or gastrointestinal adverse reactions, taking dimethyl fumarate with food may improve tolerability.

Elderly: clinical studies of dimethyl fumarate had limited exposure to patients aged 55 years and above, and did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Based on the mode of action of the active substance there are no theoretical reasons for any requirement for dose adjustments in the elderly.

Renal and hepatic impairment: dimethyl fumarate has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology studies, no dose adjustments are needed. Caution should be used when treating patients with severe renal or severe hepatic impairment.

Paediatric population: the safety and efficacy of dimethyl fumarate in children and adolescents aged 10 to 18 years have not yet been established. No recommendation on a posology can be made. There is no relevant use of dimethyl fumarate in children aged less than 10 years for the indication of relapsing remitting MS.

1.5 Pharmaceutical forms: oral gastro-resistant capsules – 120 mg and 240 mg.

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

1.7 Relevant warnings: Blood/laboratory tests: changes in renal laboratory tests have been seen in clinical trials in subjects treated with dimethyl fumarate. Drug-induced liver injury, including liver enzyme increase (≥ 3 upper limit of normal (ULN)) and elevation of total bilirubin levels (≥ 2 ULN) can result from treatment with dimethyl fumarate. Patients treated with dimethyl fumarate may develop severe prolonged lymphopaenia. Dimethyl fumarate has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients. Prior to initiating treatment with dimethyl fumarate, a current complete blood count, including lymphocytes, must be performed. If lymphocyte count is found to be below the normal range, thorough assessment of possible causes should be completed prior to initiation of treatment with dimethyl fumarate. After starting therapy, complete blood counts, including lymphocytes, must be performed every 3 months. Interruption of dimethyl fumarate should be considered in patients with lymphocyte counts $<0.5 \times 10^9$/L persisting for more than 6 months. The benefit/risk balance of the therapy should be reconsidered in discussion with the patient in the context of other therapeutic options available.

Magnetic Resonance imaging (MRI): before initiating treatment with dimethyl fumarate, a baseline MRI should be available (usually within 3 months) as a reference. The need for further MRI scanning should be considered in accordance with national and local recommendations. MRI imaging may be considered as part of increased vigilance in patients considered at increased risk of progressive multifocal leukoencephalopathy (PML). In case of clinical suspicion of PML, MRI should be performed immediately for diagnostic purposes.

PML: PML cases have occurred with dimethyl fumarate and other medicinal products containing fumarates in the setting of moderate to severe prolonged lymphopaenia.

Prior treatment with immunosuppressive or immunomodulating therapies: no studies have been performed evaluating the efficacy and safety of dimethyl fumarate when switching patients from other disease-modifying therapies to dimethyl fumarate. The contribution of prior immunosuppressive therapy to the development of PML in dimethyl fumarate-treated patients is unknown. When switching patients from another disease modifying therapy to dimethyl fumarate, the half-life and mode of action of the other therapy should be considered in order to avoid an additive immune effect while, at the same time, reducing the risk of reactivation of MS.

Severe renal and hepatic impairment: dimethyl fumarate has not been studied in patients with severe renal or severe hepatic impairment and caution should, therefore, be used in these patients.

Severe active gastrointestinal disease: dimethyl fumarate has not been studied in patients with severe active gastrointestinal disease and caution should, therefore, be used in these patients.

Flushing: in clinical trials, 34% of dimethyl fumarate-treated patients experienced flushing. In the majority of patients who experienced flushing, it was mild or moderate in severity.

Anaphylactic reactions: cases of anaphylaxis/anaphylactoid reaction have been reported following dimethyl fumarate administration in the post-marketing setting.

Infections: in phase III placebo-controlled studies, the incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with dimethyl fumarate or placebo, respectively. However, due to dimethyl fumarate's immunomodulatory properties, if a patient develops a serious infection, suspending treatment with dimethyl fumarate should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy.

Treatment initiation: dimethyl fumarate treatment should be started gradually to reduce the occurrence of flushing and gastrointestinal adverse reactions.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): the most common adverse reactions (incidence ≥10%) for patients treated with dimethyl fumarate were flushing and gastrointestinal events (i.e. diarrhoea, nausea, abdominal pain, upper abdominal pain). Flushing and gastrointestinal events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience flushing and gastrointestinal events, these events may continue to occur intermittently throughout treatment with dimethyl fumarate. The most commonly reported adverse reactions leading to discontinuation (incidence >1%) in patients treated with dimethyl fumarate were flushing (3%) and gastrointestinal events (4%).

Adverse reactions, which were more frequently reported in dimethyl fumarate versus placebo-treated patients, are presented in the table below. These data were derived from two pivotal Phase 3 placebo-controlled, double-blind clinical trials with a total of 1529 patients treated with dimethyl fumarate for up to 24 months with an overall exposure of 2371 person-years. The frequencies described in the table below are based on 769 patients treated with dimethyl fumarate 240 mg twice a day and 771 patients treated with placebo.

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Gastroenteritis	Common
	PML[1]	Not known
Blood and lymphatic system disorders	Lymphopaenia	Common
	Leucopenia	Common
	Thrombocytopenia	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylaxis[1]	Not known
	Dyspnoea[1]	Not known
	Hypoxia[1]	Not known
	Hypotension[1]	Not known

	Angioedema[1]	Not known
Nervous system disorders	Burning sensation	Common
Vascular disorders	Flushing	Very common
	Hot flush	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Nausea	Very common
	Abdominal pain upper	Very common
	Abdominal pain	Very common
	Vomiting	Common
	Dyspepsia	Common
	Gastritis	Common
	Gastrointestinal disorder	Common
Hepatobiliary disorders	Aspartate aminotransferase increased	Common
	Alanine aminotransferase increased	Common
	Drug-induced liver injury[1]	Not known
Skin and subcutaneous tissue disorders	Pruritus	Common
	Rash	Common
	Erythema	Common
Renal and urinary disorders	Proteinuria	Common
General disorders and administration site conditions	Feeling hot	Common
Investigations	Ketones measured in urine	Very common
	Albumin urine present	Common
	White blood cell count decreased	Common

[1] Adverse reactions derived only during post marketing experience.

Description of selected adverse reactions:

Flushing: In the placebo-controlled studies, the incidence of flushing (34% versus 4%) and hot flush (7% versus 2%) was increased in patients treated with dimethyl fumarate compared to placebo, respectively. Flushing is usually described as flushing or hot flush, but can include other events (e.g. warmth, redness, itching, and burning sensation). Flushing events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience flushing, these events may continue to occur intermittently throughout treatment with dimethyl fumarate. In patients with flushing, the majority had flushing events that were mild or moderate in severity. Overall, 3% of patients treated with dimethyl fumarate discontinued due to flushing. Serious flushing, which may be characterised by generalised erythema, rash and/or pruritus, was seen in less than 1% of patients treated with dimethyl fumarate.

Gastrointestinal: the incidence of gastrointestinal events (e.g. diarrhoea [14% versus 10%], nausea [12% versus 9%], upper abdominal pain [10% versus 6%], abdominal pain [9% versus 4%], vomiting [8% versus 5%] and dyspepsia [5% versus 3%]) was increased in patients treated with dimethyl fumarate compared to placebo, respectively. Gastrointestinal events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience gastrointestinal events, these events may continue to occur intermittently throughout treatment with dimethyl fumarate. In the majority of patients who experienced gastrointestinal events, it was mild or moderate in severity. Four per cent (4%) of patients treated with dimethyl fumarate discontinued due to gastrointestinal events. Serious gastrointestinal events, including gastroenteritis and gastritis, were seen in 1% of patients treated with dimethyl fumarate.

Hepatic function: based on data from placebo-controlled studies, the majority of patients with elevations had hepatic transaminases that were <3 times the ULN. The increased incidence of elevations of hepatic transaminases in patients treated with dimethyl fumarate relative to placebo was primarily seen during the first 6 months of treatment. Elevations of alanine aminotransferase and aspartate aminotransferase ≥3 times ULN, respectively, were seen in 5% and 2% of patients treated with placebo and 6% and 2% of patients treated with dimethyl fumarate. Discontinuations due to elevated hepatic transaminases were <1% and similar in patients treated with dimethyl fumarate or placebo. Elevations in transaminases ≥3 times ULN with concomitant elevations in total bilirubin >2 times ULN were not observed in placebo-

controlled studies. Increase of liver enzymes and cases of drug-induced liver injury (elevations in transaminases ≥3 times ULN with concomitant elevations in total bilirubin >2 times ULN), have been reported in post-marketing experience following dimethyl fumarate administration, which resolved upon treatment discontinuation.

Lymphopaenia: in the placebo-controlled studies most patients (>98%) had normal lymphocyte values prior to initiating treatment. Upon treatment with dimethyl fumarate, mean lymphocyte counts decreased over the first year with a subsequent plateau. On average, lymphocyte counts decreased by approximately 30% of baseline value. Mean and median lymphocyte counts remained within normal limits. Lymphocyte counts $<0.5 \times 10^9$/L were observed in <1% of patients treated with placebo and 6% of patients treated with dimethyl fumarate. A lymphocyte count $<0.2 \times 10^9$/L was observed in one patient treated with dimethyl fumarate and in no patients treated with placebo. In clinical studies (both controlled and uncontrolled), 9% of patients had lymphocyte counts $\geq 0.5 \times 10^9$/L and $<0.8 \times 10^9$/L for at least 6 months; 2% of patients experienced lymphocyte counts $<0.5 \times 10^9$/L for at least 6 months, and in this group the majority of lymphocyte counts remained $<0.5 \times 10^9$/L with continued therapy. PML has occurred in the setting of moderate to severe prolonged lymphopaenia.

Laboratory abnormalities: in the placebo-controlled studies, measurement of urinary ketones (1+ or greater) was higher in patients treated with dimethyl fumarate (45%) compared to placebo (10%). No untoward clinical consequences were observed in clinical trials. Levels of 1,25-dihydroxyvitamin D decreased in dimethyl fumarate-treated patients relative to placebo (median percentage decrease from baseline at 2 years of 25% versus 15%, respectively) and levels of parathyroid hormone (PTH) increased in dimethyl fumarate-treated patients relative to placebo (median percentage increase from baseline at 2 years of 29% versus 15%, respectively). Mean values for both parameters remained within normal range. A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.

Paediatric population: the safety of dimethyl fumarate in paediatric patients with MS below the age of 18 has not yet been established. In a small 24-week open-label uncontrolled study in paediatric patients with RRMS aged 13 to 17 years (120 mg twice a day for 7 days followed by 240 mg twice a day for the remainder of treatment; safety population, n=22), followed by a 96-week extension study (240 mg twice per day; safety population n=20), the safety profile appeared similar to that observed in adult patients.

2.2 Indirect risks (incorrect use): cases of overdose with dimethyl fumarate have been reported. The symptoms described in these cases were consistent with the known adverse reaction profile of dimethyl fumarate There are no known therapeutic interventions to enhance elimination of dimethyl fumarate nor is there a known antidote. In the event of overdose, it is recommended that symptomatic supportive treatment be initiated as clinically indicated.

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	Indications/Additional information	MS	MDD	MQP
AM	Not authorised				
BA	POM				
BE	POM				
BG	Not authorised				
CH	List II				
CZ	POM				
DE	POM				
ES	POM				
ES	POM				
FI	POM				
FR	POM				
HR	List I				

HU	POM				
IE	List I				
IT	List II				
LT	POM				
LV	POM				
MK	POM				
NL	POM				
PL	POM				
PT	POM				
RO	POM				
RS	POM				
SE	POM				
SI	POM				
UK	POM				

Melclass database[1]: List I

No more data available from other member states.

3.2 Social dimension of classification:

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

Criteria: this medicinal product should be used under medical supervision.

3.2.2 Paediatric use: no data available.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: SmPC of Tecfidera® (https://bit.ly/2OpeWbg) and Melclass database (https://melclass.edqm.eu/)

4.2 Comments: centrally authorised medicinal product (EMA).

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Benzocaine

1.2 ATC code: N01BA05

1.3 Therapeutic indications: symptomatic relief of toothaches, teeth and gums in adults and children over 6 years. Topical use for dental pain.

1.4 Posology and duration of treatment: adults and teenagers from 12 years old: the product should be applied to the area to be treated at most 3 or 4 times a day. Each application is equivalent to approximately 3 mg of benzocaine. If necessary, the administration can be repeated up to 4 times a day.

Paediatric population: children 6-12 years old: only under adult supervision; children 2-6 years: under medical supervision; children under 2 years of age: the benefit-risk ratio should be evaluated by the paediatrician.

The treatment should be as short as possible. If after 2 days of treatment, the conditions worsen or the symptoms persist, the clinical situation should be evaluated. Due to the anaesthesia caused by this medication, it should not be used before eating or drinking.

1.5 Pharmaceutical forms: oral spray solution, 50-200 mg of benzocaine.

1.6 Contraindications: hypersensitivity to benzocaine, other p-aminobenzoic acid-derived local anaesthetics (PABA) or any of the excipients.

1.7 Relevant warnings: patients should not eat or drink while the numbness persists, because of the risk of biting your tongue or oral mucosa and choking. This medicine can cause contact dermatitis and dysgeusia. Patients should be advised to immediately report symptoms and signs of methaemoglobinaemia (i.e. headache, dizziness, shallow breathing, nausea, fatigue or tachycardia). Contact with eyes should be avoided. The medication should not be ingested or inhaled. In no cases should this medicine be applied more than 4 times a day. In people with asthma, bronchitis, emphysema the use of this medicine may increase the risk of complications due to methaemoglobinaemia. In people over 65 and in debilitated patients the risk of developing methaemoglobinaemia is increased. In patients with birth defects, such as glucose-6-phosphodiesterase deficiency, haemoglobin M disease, antidiuretic hormone (ADH) deficiency, methaemoglobulin reductase and pyruvate kinase deficiency, the risk of developing methaemoglobinaemia is increased.

Warnings about excipients: this medicine contains 42.9% ethanol (alcohol) which corresponds to an amount of 171.6 mg per dose and, therefore, it is harmful to people suffering from alcoholism. The alcohol content should be taken into consideration in the case of pregnant or nursing women, children and high-risk populations such as patients with liver disease or epilepsy.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): during the period of benzocaine use, the following adverse effects have been reported (frequency not accurately established):

Disorders of the blood and lymphatic system: methaemoglobinaemia mainly due to prolonged use and also in case of overdose. In patients with birth defects including glucose-6-phosphodiesterase deficiency, haemoglobin M disease, ADH-methaemoglobulin reductase deficiency and pyruvate kinase deficiency, the risk of developing methaemoglobinaemia is increased.

Disorders of the immune system: rare: urticaria, oedema, anaphylactoid reaction (contact dermatitis), cross-reactions with other sterile local anaesthetics, photosensitivity.

Gastrointestinal disorders: prolonged use has been reported to cause dysgeusia, bad taste in the mouth, dehydration of the mucous membranes and difficulty in swallowing.

General disorders and alterations in the place of administration: burning sensation in the mouth. Prolonged contact of benzocaine with the mucous membranes may cause dehydration of the epithelium and hardening

of the mucous membranes.

2.2 Indirect risks (incorrect use): benzocaine overdose can produce methaemoglobinaemia, characterised by blue colouring of skin and mucous membranes. The clinical manifestations of methaemoglobinaemia depend on the concentration of methaemoglobin in blood: between 15 and 20%, cyanosis occurs; with a methaemoglobin level above 20%, fatigue and headaches have been observed; nausea and vomiting with a level higher than 40%. When methaemoglobin levels are above 55% increased sweating, atrial fibrillation, tachycardia, hypotension and myocardial infarction, alterations in the level of consciousness may occur. Methaemoglobinaemia can be treated, among others, by intravenous infusion of 1% methylene.

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	Indications/Additional details	MS	MDD	MQP
AM	Not authorised				
AT	Not authorised				
BA	Not authorised				
BE	POM				
CH	Not authorised				
CZ	Not authorised				
DE	Not authorised				
EE	Not authorised				
ES	Not subject to prescription	Symptomatic relief of toothaches, teeth and gums in adults and children over 6 years			
FI	Not authorised				
FR	Not subject to prescription				
GE	Not authorised				
HR	Not authorised				
HU	Not authorised				
IE	Not authorised				
IT	Not authorised				
LT	Not authorised				
LV	Not authorised				
MK	Not authorised				
NL	Not authorised				
PL	Not authorised				
PT	Not subject to prescription	Topical use for dental pain			
RO	Not authorised				
RS	Not authorised				
SI	Not authorised				
UK	Not authorised				

Melclass database[1]: Currently not available.

No more data available from other member states.

3.2 Social dimension of classification:

3.2.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable): proposed recommendation: **Not subject to prescription** (children > 3 years; duration: max 48 hours).

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

Criteria: easy self-assessment; short-term treatment; well-established use.

3.2.2 Paediatric use: children above 3 years of age.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: databases of national competent authorities (France, Portugal and Spain) and Melclass database (https://melclass.edqm.eu/)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Amitriptyline

1.2 ATC code: N06AA09

1.3 Therapeutic indications: treatment of major depressive disorder in adults; treatment of neuropathic pain in adults; prophylactic treatment of chronic tension type headache (CTTH) in adults; prophylactic treatment of migraine in adults; treatment of nocturnal enuresis in children aged 6 years and above when organic pathology, including spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including antispasmodics and vasopressin-related products. This medicinal product should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis.

1.4 Posology and duration of treatment: *major depressive disorder:* dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerability.

Adults: initially 25 mg twice daily (50 mg daily). If necessary, the dose can be increased by 25 mg every other day up to 150 mg daily divided into two doses. The maintenance dose is the lowest effective dose.

Elderly patients over 65 years of age and patients with cardiovascular disease: initially 10-25 mg daily. The daily dose may be increased up to 100-150 mg divided into two doses, depending on individual patient response and tolerability. Doses above 100 mg should be used with caution. The maintenance dose is the lowest effective dose.

Paediatric population: amitriptyline should not be used in children and adolescents aged less than 18 years, as long-term safety and efficacy have not been established.

Duration of treatment: the antidepressant effect usually sets in after 2-4 weeks. Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time, usually up to 6 months after recovery in order to prevent relapse.

Neuropathic pain, prophylactic treatment of CTTH and prophylactic treatment of migraine prophylaxis: patients should be individually titrated to the dose that provides adequate analgesia with tolerable adverse drug reactions. Generally, the lowest effective dose should be used for the shortest duration required to treat the symptoms.

Adults: recommended doses are 25-75 mg daily in the evening. Doses above 100 mg should be used with caution. The initial dose should be 10-25 mg in the evening. Doses can be increased by 10-25 mg every 3-7 days as tolerated. The dose can be taken once daily, or be divided into two doses. A single dose above 75 mg is not recommended. The analgesic effect is normally seen after 2-4 weeks of dosing.

Elderly patients over 65 years of age and patients with cardiovascular disease: a starting dose of 10-25 mg in the evening is recommended. Doses above 75 mg should be used with caution. It is generally recommended to initiate treatment in the lower dose range as recommended for adults. The dose may be increased depending on individual patient response and tolerability.

Paediatric population: amitriptyline should not be used in children and adolescents aged less than18 years, as safety and efficacy have not been established.

Duration of treatment: treatment is symptomatic and should therefore be continued for an appropriate length of time. In many patients, therapy may be needed for several years. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

Prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine in adults. Treatment must be continued for an appropriate length of time. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

Nocturnal enuresis: the recommended doses for: a) children aged 6 to 10 years: 10-20 mg. A suitable dosage form should be used for this age group. b) children aged 11 years and above: 25-50 mg daily.

The dose should be increased gradually. Dose to be administered 1-1½ hours before bedtime. The maximum period of treatment course should not exceed 3 months. If repeated courses of amitriptyline are needed, a medical review should be conducted every 3 months. When stopping treatment, amitriptyline should be withdrawn gradually.

Special populations: a) Renal impairment: this medicinal product can be given in usual doses to patients with renal failure. b) Hepatic impairment: careful dosing and, if possible, a serum level determination is advisable. c) Cytochrome P450 inhibitors of CYP2D6: depending on individual patient response, a lower dose of amitriptyline should be considered if a strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to amitriptyline treatment. d) Known poor metabolisers of CYP2D6 or CYP2C19. These patients may have higher plasma concentrations of amitriptyline and its active metabolite nortriptyline. Consider a 50% reduction of the recommended starting dose.

Discontinuation of treatment: when stopping therapy the drug should be gradually withdrawn during several weeks.

1.5 Pharmaceutical forms: 25 mg tablets; 10 mg/5 mL, 25 mg/5 mL, 50 mg/5 mL oral solution.

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients. Recent myocardial infarction. Any degree of heart block or disorders of cardiac rhythm and coronary artery insufficiency. Concomitant treatment with monoamine oxidase inhibitors (MAOIs) is contraindicated. Simultaneous administration of amitriptyline and MAOIs may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia). Treatment with amitriptyline may be instituted 14 days after discontinuation of irreversible non-selective MAOIs and minimum one day after discontinuation of the reversible moclobemide. Treatment with MAOIs may be introduced 14 days after discontinuation of amitriptyline. Severe liver disease. In children under 6 years of age.

1.7 Relevant warnings: Cardiovascular: cardiac arrhythmias and severe hypotension are likely to occur with high dosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

Suicide/suicidal thoughts or clinical worsening: depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and care givers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. The risk of suicide remains during treatment of depressed patients and until significant remission occurs. Such patients require careful supervision. In manic-depressives, a shift towards the manic phase may occur; should the patient enter a manic phase amitriptyline should be discontinued. As described for other psychotropics, amitriptyline may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients; in addition the depressive illness itself may affect patients' glucose balance. Hyperpyrexia has been reported with tricyclic antidepressants when administered with anticholinergic or with neuroleptic medications, especially in hot weather. After prolonged administration, abrupt cessation of therapy may produce withdrawal symptoms such as headache, malaise, insomnia and irritability. Amitriptyline should be used with caution in patients receiving selective serotonin reuptake inhibitors (SSRIs).

QT interval prolongation: cases of QT interval prolongation and arrhythmia have been reported during the post-marketing period. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure or in patients concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to increase the proarrhythmic risk. Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk

of arrhythmias and hypotension. If possible, discontinue this medicinal product several days before surgery; if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being so treated. Great care is necessary if amitriptyline is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop. Elderly patients are particularly susceptible to orthostatic hypotension. This medical product should be used with caution in patients with convulsive disorders, urinary retention, prostatic hypertrophy, hyperthyroidism, paranoid symptomatology and advanced hepatic or cardiovascular disease, pylorus stenosis and paralytic ileus. In patients with the rare condition of shallow anterior chamber and narrow chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked.

Nocturnal enuresis: an electrocardiogram (ECG) should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome. Amitriptyline for enuresis should not be combined with an anticholinergic drug. Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed when treating patients with depression should therefore be followed when treating patients with enuresis.

Paediatric population: long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): amitriptyline may induce side effects similar to other tricyclic antidepressants. Some of the below mentioned side effects e.g. headache, tremor, disturbance in attention, constipation and decreased libido may also be symptoms of depression and usually attenuate when the depressive state improves.

In the listing below the following convention is used: Very common (> 1/10); Common (> 1/100 < 1/10); Uncommon (> 1/1000 < 1/100); Rare (> 1/10000 < 1/1000); Very rare (<1/10000); Not known (it cannot be estimated from the available data).

Blood and lymphatic system disorders: rare: bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia.

Metabolism and nutrition disorders: rare: decreased appetite. Not known: anorexia, elevation or lowering of blood sugar levels.

Psychiatric disorders: very common: aggression. Common: confusional state, libido decreased, agitation. Uncommon: hypomania, mania, anxiety, insomnia, nightmare. Rare: delirium (in elderly patients), hallucination, suicidal thoughts or behaviour*. Not known: paranoia.

Nervous system disorders: very common: somnolence, tremor, dizziness, headache, drowsiness, speech disorder (dysarthria). Common: Disturbance in attention, dysgeusia. paraesthesia, ataxia. Uncommon: convulsion. Very rare: akathisia, polyneuropathy. Not known: extrapyramidal disorder.

Eye disorders: very common: accommodation disorder. Common: mydriasis. Very rare: acute glaucoma. Not known: dry eye.

Ear and labyrinth disorders: uncommon: tinnitus.

Cardiac disorders: very common: palpitations, tachycardia. Common: atrioventricular block, bundle branch block. Uncommon: collapse conditions, worsening of cardiac failure. Rare: arrhythmia. Very rare: cardiomyopathies, torsades de pointes. Not known: hypersensitivity myocarditis.

Vascular disorders: very common: orthostatic hypotension. Uncommon: hypertension. Not known: hyperthermia.

Respiratory, thoracic, and mediastinal disorders: very common: congested nose. Very rare: allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Loffler’s syndrome).

Gastrointestinal disorders: very common: dry mouth, constipation, nausea. Uncommon: diarrhoea, vomiting, tongue oedema. Rare: salivary gland enlargement, ileus paralytic.

Hepatobiliary disorders: rare: jaundice. Uncommon: hepatic impairment (e.g. cholestatic liver disease). Not known: hepatitis.

Skin and subcutaneous tissue disorders: very common: hyperhidrosis. Uncommon: rash, urticaria, face oedema. Rare: alopecia, photosensitivity reaction.

Renal and urinary disorders: common: micturition disorders. Uncommon: urinary retention.

Reproductive system and breast disorders: common: erectile dysfunction. Uncommon: galactorrhoea. Rare: gynaecomastia.

General disorders and administration site conditions: common: fatigue, feeling thirst. Rare: pyrexia.

Investigations: very common: weight increased. Common: ECG abnormal, ECG QT prolonged, ECG QRS complex prolonged, hyponatraemia. Uncommon: intraocular pressure increased. Rare: weight decreased. Liver function test abnormal, blood alkaline phosphatase increased, transaminases increased.

*Case reports of suicidal thoughts or behaviour were reported during the treatment or after conclusion of the treatment with amitriptyline.

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and tricyclic antidepressants. The mechanism leading to this risk is unknown.

2.2 Indirect risks (incorrect use): the following symptoms can be experienced in case of overdosage: anticholinergic symptoms: mydriasis, tachycardia, urinary retention, dry mucous membranes, reduced bowel motility, convulsions, fever, sudden occurrence of CNS depression, lowered consciousness progressing into coma, respiratory depression.

Cardiac symptoms: arrhythmias (ventricular tachyarrhythmias, torsade de pointes, ventricular fibrillation). The ECG characteristically shows prolonged PR interval, widening of the QRS complex, QT prolongation, T-wave flattening or inversion, ST segment depression and varying degrees of heart block progressing to cardiac standstill. Widening of the QRS complex usually correlates well with the severity of the toxicity following acute overdoses. Heart failure, hypotension, cardiogenic shock. Metabolic acidosis, hypokalaemia, hyponatraemia.

Ingestion of 750 mg or more by an adult may result in severe toxicity. The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropics. There is considerably individual variability in response to overdose. Children are especially susceptible to cardiotoxicity, seizures and hyponatraemia. During awakening possible confusion, agitation and hallucinations and ataxia.

Treatment: a) Admission to hospital (intensive care unit) if required - treatment is symptomatic and supportive. b) Assessment and treatment of airway, breathing and circulation as appropriate; IV access to be secured; close monitoring even in apparently uncomplicated cases. c) Examination for clinical features (i.e. urea and electrolytes, arterial blood gases, electrocardiograph). d) Flumazenil should not be given to reverse benzodiazepine toxicity in mixed overdoses. e) Gastric lavage to be considered only if within one hour of a potentially fatal overdose. f) 50 g of charcoal to be given if within one hour of ingestion. g) Patency of the airway is maintained by intubation, where required; treatment in respirator is advised to prevent a possible respiratory arrest; continuous ECG-monitoring of cardiac function for 3-5 days; treatment of the following will be decided on a case-by-case basis: circulatory failure, hypotension, hyperthermia, convulsions, metabolic acidosis. h) Unrest and convulsions may be treated with diazepam. i) Patients who display signs of toxicity should be monitored for a minimum of 12 hours. j) Rhabdomyolysis should be monitored if the patient has been unconscious for a considerable time. k) Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase: deaths by deliberate or accidental overdosage have occurred with this class of medicament.

2.3 Recent cases at European level:

1. PSUSA (Periodic Safety Update Report Single Assessment) review in 2015: amendments to be included in the relevant sections of the Summary of Product Characteristics (SmPC):

Section 4.4 – Precautions and warnings: a warning should be added: i.e. QT interval prolongation: Cases of QT interval prolongation and arrhythmia have been reported during the post-marketing period. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure or in patients concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the proarrhythmic risk.

Section 4.8 – Undesirable effects: the following adverse reaction should be added under the SOC Investigations with a frequency common: ECG QT prolonged.

2. PSUSA review in 2018: amendments to be included in the relevant sections of the Product Information:

Section 4.5: amitriptyline plasma concentration can be increased by sodium valproate and valpromide. Clinical monitoring is therefore recommended.

Section 4.8: the following adverse reaction under the SOC 'Psychiatric disorders' with a frequency rare, should be amended as follows: hallucination (in schizophrenic patients).

Section 4.9: cardiac symptoms: metabolic acidosis, hypokalaemia, hyponatraemia.

In the part about overdose in children: children are especially susceptible to cardiotoxicity, and seizures and hyponatraemia.

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	Indications/Additional details	MS	MDD	MQP
AM	POM				
AT	List I	Severe depression, neuropathic pain in adults, prophylaxis of CTTH in adults, prophylaxis of migraine, enuresis nocturna in children aged 6 years or older.			
BA	POM				
BE	POM	Severe depression, neuropathic pain in adults, prophylaxis of CTTH in adults, prophylaxis of migraine, enuresis nocturna in children aged 6 years or older.			
CH	List II				
CZ	POM				
DE	POM				
EE	POM				
ES	POM	Treatment of major depressive disorder in adults; treatment of neuropathic pain in adults; prophylactic treatment of CTTH in adults; prophylactic treatment of migraine in adults; treatment of night enuresis in children aged 6 years or older.			
FI	POM				
FR	List I				
HR	List II				
HU	POM				
IE	List I				
IT	List II				
LT	POM	Major depressive disorder in adults; management of neuropathic pain in adults; prophylactic treatment of CTTH in adults; prophylactic treatment of migraine in adults; treatment of nocturnal enuresis in children aged 6 years and above.	25 mg	150 mg	1500 mg
LV	POM				

MK	POM				
NL	POM	Major depressive disorder in adults; management of neuropathic pain in adults; prophylactic treatment of CTTH in adults; prophylactic treatment of migraine in adults; treatment of nocturnal enuresis in children aged 6 years and above.			
PL	POM				
PT	POM		25 mg		1500 mg
RO	List I				
RS	POM				
SI	POM				
UK	POM				

Melclass database[1]: List I

No more data available from other member states.

3.2 Social dimension of classification:

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

Criteria: pharmacological profile; medical supervision required.

3.2.2 Paediatric use: amitriptyline should not be used in children below 6 years of age.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: SmPC of amitriptyline 25 mg film coated tablets (https://bit.ly/2Wy0lvL) and Melclass database (https://melclass.edqm.eu/)

4.2 Comments: -

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Duloxetine

1.2 ATC code: N06AX21

1.3 Therapeutic indications: adults: treatment of major depressive disorder; treatment of diabetic peripheral neuropathic pain; treatment of generalised anxiety disorder.

1.4 Posology and duration of treatment: major depressive disorder: the starting and recommended maintenance dose is 60 mg once daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day have been evaluated from a safety perspective in clinical trials. However, there is no clinical evidence suggesting that patients not responding to the initial recommended dose may benefit from dose up-titrations. Therapeutic response is usually seen after 2-4 weeks of treatment. After consolidation of the antidepressive response, it is recommended to continue treatment for several months, in order to avoid relapse. In patients responding to duloxetine, and with a history of repeated episodes of major depression, further long-term treatment at a dose of 60 to 120 mg/day could be considered.

Generalised anxiety disorder: the recommended starting dose in patients with generalised anxiety disorder is 30 mg once daily with or without food. In patients with insufficient response the dose should be increased to 60 mg, which is the usual maintenance dose in most patients. In patients with co-morbid major depressive disorder, the starting and maintenance dose is 60 mg once daily (please see also dosing recommendation above). Doses up to 120 mg per day have been shown to be efficacious and have been evaluated from a safety perspective in clinical trials. In patients with insufficient response to 60 mg, escalation up to 90 mg or 120 mg may therefore be considered. Dose escalation should be based upon clinical response and tolerability. After consolidation of the response, it is recommended to continue treatment for several months, in order to avoid relapse.

Diabetic peripheral neuropathic pain: the starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability. Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose. Response to treatment should be evaluated after 2 months. In patients with inadequate initial response, additional response after this time is unlikely. The therapeutic benefit should be reassessed regularly (at least every 3 months).

Special populations: elderly: no dosage adjustment is recommended for elderly patients solely on the basis of age. However, as with any medicine, caution should be exercised when treating the elderly, especially with duloxetine 120 mg per day for major depressive disorder or generalised anxiety disorder, for which data are limited.

Hepatic impairment: duloxetine must not be used in patients with liver disease resulting in hepatic impairment.

Renal impairment: no dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 mL/min). Duloxetine must not be used in patients with severe renal impairment (creatinine clearance <30 mL/min).

Paediatric population: duloxetine should not be used in children and adolescents under the age of 18 years for the treatment of major depressive disorder because of safety and efficacy concerns. The safety and efficacy of duloxetine for the treatment of generalised anxiety disorder in paediatric patients aged 7-17 years have not been established. The safety and efficacy of duloxetine for the treatment of diabetic peripheral neuropathic pain has not been studied. No data are available.

Discontinuation of treatment: abrupt discontinuation should be avoided. When stopping treatment with duloxetine the dose should be gradually reduced over a period of at least 1 to 2 weeks in order to reduce the risk of withdrawal reactions. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

1.5 Pharmaceutical forms: capsules, strength: 20 to 60 mg.

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients. Concomitant use of duloxetine with non-selective, irreversible MAOIs is contraindicated. Liver disease resulting in hepatic impairment. Duloxetine should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e. potent CYP1A2 inhibitors) since the combination results in elevated plasma concentrations of duloxetine. Severe renal impairment (creatinine clearance <30 mL/min). The initiation of treatment with duloxetine is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis.

1.7 Relevant warnings: Mania and seizures: duloxetine should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Mydriasis: mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine to patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate: duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism. For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered. In patients with uncontrolled hypertension duloxetine should not be initiated.

Renal impairment: increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 mL/min). For patients with severe renal impairment, see Contraindications.

Serotonin syndrome: as with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with duloxetine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, serotonin/noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants or triptans), with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter system. Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations and coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). If concomitant treatment with duloxetine and other serotonergic agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

St John’s Wort: adverse reactions may be more common during concomitant use of duloxetine and herbal preparations containing St John’s Wort (Hypericum perforatum).

Suicide - Major depressive disorder and generalised anxiety disorder: depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Other psychiatric conditions for which duloxetine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to

placebo in patients less than 25 years old. Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Close supervision of patients and in particular those at high risk should accompany medicinal product therapy, especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Diabetic peripheral neuropathic pain: as with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Concerning risk factors for suicidality in depression, see above. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Use in children and adolescents under 18 years of age: duloxetine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Haemorrhage: there have been reports of bleeding abnormalities, such as ecchymosis, purpura and gastrointestinal haemorrhage with SSRIs and SNRIs, including duloxetine. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g. non-steroidal anti-inflammatory drugs or acetylsalicylic acid), and in patients with known bleeding tendencies.

Hyponatraemia: hyponatraemia has been reported when administering duloxetine, including cases with serum sodium lower than 110 mmol/L. Hyponatraemia may be due to a syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics.

Discontinuation of treatment: withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. In clinical trials adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with duloxetine and 23% of patients taking placebo. The risk of withdrawal symptoms seen with SSRIs and SNRIs may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed below. Generally these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs.

Elderly: data on the use of duloxetine 120 mg in elderly patients with major depressive disorder and generalised anxiety disorder are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage.

Akathisia/psychomotor restlessness: the use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hepatitis/increased liver enzymes: cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine. Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly

hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Sexual dysfunction: SSRIs/SNRIs may cause symptoms of sexual dysfunction. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): a) Summary of the safety profile: the most commonly reported adverse reactions in patients treated with duloxetine were nausea, headache, dry mouth, somnolence and dizziness. However, the majority of common adverse reactions were mild to moderate, they usually started early in therapy, and most tended to subside even as therapy was continued.

b) Tabulated summary of adverse reactions: adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials:

Very common	Common	Uncommon	Rare	Very rare
Infections and infestations				
		Laryngitis		
Immune system disorders				
			Anaphylactic reaction Hypersensitivity disorder	
Endocrine disorders				
			Hypothyroidism	
Metabolism and nutrition disorders				
	Decreased appetite	Hyperglycaemia (reported especially in diabetic patients)	Dehydration Hyponatraemia SIADH[5]	
Psychiatric disorders				
	Insomnia Agitation Libido decreased Anxiety Orgasm abnormal Abnormal dreams	Suicidal ideation [4,6] Sleep disorder Bruxism Disorientation Apathy	Suicidal Behaviour[4,6] Mania Hallucinations Aggression and anger[3]	
Nervous system disorders				
Headache Somnolence	Dizziness Lethargy Tremor Paraesthesia	Myoclonus Akathisia[6] Nervousness Disturbance in attention Dysgeusia Dyskinesia Restless legs syndrome Poor quality sleep	Serotonin syndrome[5] Convulsion[1] Psychomotor restlessness[5] Extrapyramidal symptoms[5]	
Eye disorders				
	Blurred vision	Mydriasis Visual impairment	Glaucoma	
Ear and labyrinth disorders				
	Tinnitus[1]	Vertigo Ear pain		
Cardiac disorders				
	Palpitations	Tachycardia Supraventricular arrhythmia, mainly atrial fibrillation		
Vascular disorders				
	Blood pressure increase[3] Flushing	Syncope[2] Hypertension [2, 6] Orthostatic hypotension[2] Peripheral coldness	Hypertensive crisis[2,5]	
Respiratory, thoracic and mediastinal disorders				
	Yawning	Throat tightness Epistaxis	Interstitial lung disease[9] Eosinophilic pneumonia[5]	

Gastrointestinal disorders				
Nausea Dry mouth	Constipation Diarrhoea Abdominal pain Vomiting Dyspepsia Flatulence	Gastrointestinal haemorrhage[6] Gastroenteritis Eructation Gastritis Dysphagia	Stomatitis Haematochezia Breath odour Microscopic colitis[8]	
Hepato-biliary disorders				
		Hepatitis Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury	Hepatic failure[5] Jaundice[5]	
Skin and subcutaneous tissue disorders				
	Sweating increased Rash	Night sweats Urticaria Dermatitis contact Cold sweat Photosensitivity reactions Increased tendency to bruise	Stevens–Johnson Syndrome[5] Angioneurotic oedema[5]	Cutaneous vasculitis
Musculoskeletal and connective tissue disorders				
	Musculoskeletal pain Muscle spasm	Muscle tightness Muscle twitching	Trismus	
Renal and urinary disorders				
	Dysuria Pollakiuria	Urinary retention Urinary hesitation Nocturia Polyuria Urine flow decreased	Urine odour abnormal	
Reproductive system and breast disorders				
	Erectile dysfunction Ejaculation disorder Ejaculation delayed	Gynaecological haemorrhage Menstrual disorder Sexual dysfunction Testicular pain	Menopausal symptoms Galactorrhoea Hyperprolactinaemia Postpartum haemorrhage[5]	
General disorders and administration site conditions				
	Falls[7] Fatigue	Chest pain[7] Feeling abnormal Feeling cold Thirst Chills Malaise Feeling hot Gait disturbance		
Investigations				
	Weight decrease	Weight increase Blood creatine phosphokinase increased Blood potassium increased	Blood cholesterol increased	

[1] Cases of convulsion and cases of tinnitus have also been reported after treatment discontinuation.
[2] Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.
[3] Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.
[4] Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation.
[5] Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.
[6] Not statistically significantly different from placebo.
[7] Falls were more common in the elderly (≥65 years old).
[8] Estimated frequency based on all clinical trial data.
[9] Estimated frequency based on placebo-controlled clinical trials.

2.2 Indirect risks (incorrect use): cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia. No specific antidote is known for duloxetine but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. A free airway should be established. Monitoring of cardiac

and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion and exchange perfusion are unlikely to be beneficial.

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	Indications/Additional details	MS	MDD	MQP
AM	POM				
AT	List I	Treatment of major depression, pain in diabetic neuropathy, anxiety			
BA	POM				
BE	POM	Depressive disorder; diabetic neuropathic pain, anxiety			
CH	List II				
CZ	POM				
DE	POM				
EE	POM				
ES	POM	Major depressive disorder; diabetic peripheral neuropathic pain; generalised anxiety disorder.			
FI	POM				
FR	List I				
HR	List II				
HU	POM				
IE	List I				
IT	List II				
LT	POM	Major depressive disorder; generalised anxiety disorder	60 mg	120 mg	30 g
LV	POM				
MK	POM				
NL	POM	Major depressive disorder; generalised anxiety disorder			
PL	POM				
PT	POM		60 mg		3360 mg
RO	List I				
RS	POM				
SI	POM				
UK	POM				

Melclass database[1]: POM

No more data available from other member states.

3.2 Social dimension of classification:

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

Criteria: pharmacological profile; medical supervision required.

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

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: SmPC of duloxetine 60 mg capsules (https://bit.ly/30csLh9) and Melclass database (https://melclass.edqm.eu/)

4.2 Comments: this classification is consistent with that of other similar active substances within the same ATC code, e.g. mirtazapine, venlafaxine, agomelatine, trazodone, mianserin.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Varenicline

1.2 ATC code: N07BA03

1.3 Therapeutic indications: indicated for smoking cessation in adults.

1.4 Posology and duration of treatment: the recommended dose is 1 mg varenicline twice daily following a 1-week titration as follows: days 1 to 3: 0.5 mg once daily; days 4 to 7: 0.5 mg twice daily; day 8 to end of treatment: 1 mg twice daily. Patients should be treated for 12 weeks.

1.5 Pharmaceutical forms: tablets; strength: 0.5-1 mg.

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

1.7 Relevant warnings: neuropsychiatric symptoms; history of psychiatric disorders; seizures; treatment discontinuation symptoms; cardiovascular events; hypersensitivity reactions; cutaneous reactions.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): product information does not distinguish between symptoms associated with smoking cessation and adverse reactions associated with varenicline.

Adverse reactions, which occurred at an incidence greater than placebo, are listed below by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100) and rare (≥ 1/10000 to < 1/1000)).

Infections and infestations: very common: nasopharyngitis; common: bronchitis, sinusitis; uncommon: fungal infection, viral infection.

Blood and lymphatic system disorders: rare: platelet count decreased.

Metabolism and nutrition disorders: uncommon: weight increased, decreased appetite, increased appetite, hyperglycaemia; rare: diabetes mellitus, polydipsia.

Psychiatric disorders: very common: abnormal dreams, insomnia; rare: suicidal ideation, aggression, panic reaction, thinking abnormal, restlessness, mood swings, depression*, anxiety*, hallucinations*, libido increased, libido decreased, psychosis, somnambulism, abnormal behaviour, dysphoria, bradyphrenia.

Nervous system disorders: very common: headache; common: somnolence, dizziness, dysgeusia; uncommon: seizure, tremor, lethargy, hypoaesthesia; not known: cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder, transient loss of consciousness.

Eye disorders: rare: conjunctivitis, eye pain, scotoma, scleral discolouration, mydriasis, photophobia, myopia, lacrimation increased.

Ear and labyrinth disorders: uncommon: tinnitus.

Cardiac disorders: uncommon: myocardial infarction, angina pectoris, tachycardia, palpitations, heart rate increased; rare: atrial fibrillation, ECG ST segment depression, ECG T-wave amplitude decreased.

Vascular disorders: uncommon: blood pressure increased, hot flush.

Respiratory, thoracic and mediastinal disorders: rare: dyspnoea, cough, upper respiratory tract inflammation, respiratory tract congestion, dysphonia, rhinitis allergic, throat irritation, sinus congestion, upper airway cough syndrome, rhinorrhoea, laryngeal pain, snoring.

Gastrointestinal disorders: very common: nausea; common: gastrooesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, toothache, dyspepsia, flatulence, dry mouth; rare: haematochezia, gastritis, change of bowel habit, eructation, aphthous stomatitis, gingival pain, haematemesis, abnormal faeces, tongue coated.

Skin and subcutaneous tissue disorders: uncommon: rash, pruritus, erythema, acne, hyperhidrosis, night sweats; rare: severe cutaneous reactions, including Stevens–Johnson syndrome and erythema multiforme, angioedema.

Musculoskeletal and connective tissue disorders: rare: arthralgia, myalgia, back pain, muscle spasms, musculoskeletal chest pain, joint stiffness, costochondritis.

Renal and urinary disorders: rare: pollakiuria, nocturia, glycosuria, polyuria.

Reproductive system and breast disorders: rare: menorrhagia, vaginal discharge, sexual dysfunction.

General disorders and administration site conditions: common: chest pain, fatigue; rare: chest discomfort, influenza-like illness, pyrexia, asthenia, malaise, feeling cold and cyst.

Investigations: common: liver function test abnormal; rare: semen analysis abnormal, c-reactive protein increased, blood calcium decreased.

* Frequencies are estimated from a post-marketing, observational cohort study.

2.2 Indirect risks (incorrect use): no cases of overdose were reported in pre-marketing clinical trials. In case of overdose, standard supportive measures should be instituted as required. Varenicline has been shown to be dialysed in patients with end-stage renal disease; however, there is no experience in dialysis following overdose.

2.3 Recent cases at European level: none.

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	Indications/Additional details	MS	MDD	MQP
AM	POM				
AT	List I	Smoking cessation in adults			
BA	Not authorised				
BE	POM	Smoking cessation in adults			
CH	List II				
CZ	POM				
DE	POM				
EE	POM				
ES	POM	Smoking cessation in adults		2 mg	
FI	POM				
FR	List I				
HR	List II				
HU	POM				
IE	List I				
IT	List II				
LT	POM	Smoking cessation in adults	1 mg	2 mg	140 mg
LV	POM				
MK	Not authorised				
NL	POM	Smoking cessation in adults			
PL	POM				

PT	POM		1 mg		56 mg
RO	List I				
RS	Not authorised				
SI	POM				
UK	POM				

Melclass database[1]: List I

No more data available from other member states.

3.2 Social dimension of classification:

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

Criteria: short-term treatment and not 1st line treatment for smoking cessation.

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: SmPC of Champix® 0.5 mg (https://bit.ly/2V9Gp0U) and Melclass database (https://melclass.edqm.eu/)

4.2 Comments: centrally authorised product (EMA).

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Cinnarizine, Combinations

1.2 ATC code: N07CA52

1.3 Therapeutic indications: indications vary depending on the combination product.

Cinnarizine in combination with cyclizine: prevention and treatment of motion sickness.

Cinnarizine in combination with dimenhydrinate: treatment of vertigo symptoms of various origins.

Cinnarizine in combination with piracetam: used to improve the metabolic processes occurring in the cerebral cortex in various diseases of the CNS, especially those related to vascular disorders and abnormal metabolic processes in the brain. Medicinal properties of piracetam are determined by its ability to enhance the integrative activity of the brain and intellectual activities, contribute to the consolidation of memory, improve learning processes, restore and stabilise the function of the brain, including in the elderly. Cinnarizine is an antihistamine prescribed to control nausea and vomiting due to motion sickness. It is also used for vertigo and brain disorder. It blocks the action of histamine, which reduces allergy symptoms.

1.4 Posology and duration of treatment: cinnarizine in combination with cyclizine: 1 tablet. With long-term travel, 1 tablet three times a day.

Cinnarizine in combination with dimenhydrinate: 1 tablet three times daily. The duration of treatment should not exceed 4 weeks.

Cinnarizine in combination with piracetam: the recommended dosage for adults is 1 or 2 capsules, taken three times each day. It can be taken for up to 3 months depending on the severity of the disease.

1.5 Pharmaceutical forms: cinnarizine in combination with cyclizine: 12.5 mg of cinnarizine and 25 mg of cyclizine.

Cinnarizine in combination with dimenhydrinate: 20 mg of cinnarizine and 40 mg of dimenhydrinate.

Cinnarizine in combination with piracetam: 25 mg of cinnarizine and 400 mg of piracetam.

1.6 Contraindications: cinnarizine in combination with cyclizine: hypersensitivity to the active substances or to any of the excipients; hypersensitivity to other (related) antihistamines; patients with Parkinson's disease and/or extrapyramidal disorders (such as muscle tension and postural changes, involuntary movements, e.g. parkinsonism); patients with angle-closure glaucoma.

Cinnarizine in combination with dimenhydrinate: hypersensitivity to the active substances, diphenhydramine or other antihistamines of similar structure. Diphenhydramine is completely excreted renally, and patients with severe renal impairment were excluded from the clinical development programme. Product should not be used by patients with a creatinine clearance of ≤25 mL/min (severe renal impairment). As both active components are extensively metabolised by hepatic cytochrome P450 enzymes, the plasma concentrations of the unchanged drugs and their half-lives will increase in patients with severe hepatic impairment. The product should therefore not be used by patients with severe hepatic impairment. It should not be used in patients with angle-closure glaucoma, convulsions, suspicion of raised intracranial pressure, alcohol abuse or urine retention due to urethroprostatic disorders.

Cinnarizine in combination with piracetam: hypersensitivity to piracetam, cinnarizine or to any of the excipients; severe renal impairment; bleeding in the brain; systemic lupus erythematosus.

1.7 Relevant warnings: cinnarizine in combination with cyclizine: the medicine should be used with caution in patients with disorders potentially exacerbated by anticholinergic therapy, e.g. increased eye pressure, obstructive disorders of the gastrointestinal system (e.g. pylorus stenosis), prostatic hypertrophy, asthma, epilepsy, hypertension, hyperthyroidism and cardiovascular diseases. Elderly people in particular are sensitive to the sedative effects of cinnarizine. In exceptional cases, the occurrence or exacerbation of extrapyramidal symptoms during prolonged treatment with cinnarizine has been observed. This has

mainly been seen in the elderly, in women and at doses above 150 mg per day. If these symptoms are observed, the dosage should be lowered and treatment should be stopped if the side effects persist. The suppressive effect on the CNS of alcohol, antipsychotics, hypnotics, sedatives, etc. and anxiolytics, opioids and other antihistamines can be enhanced by the simultaneous use of this combination product. Simultaneous use is not recommended. No data are available on the use of cinnarizine and cyclizine in patients with renal and/or hepatic impairment; therefore, the medication should be used with caution in patients with renal and/or hepatic impairment. Patients with rare hereditary conditions such as galactose intolerance, general lactase deficiency or glucose-galactose malabsorption or sucrase-isomaltase insufficiency, should not use this medicinal product.

Cinnarizine in combination with dimenhydrinate: the medicinal product does not reduce blood pressure significantly; however, it should be used with caution in hypotensive patients. Product should be taken after meals to minimise any gastric irritation. Product should be used with caution in patients with conditions that might be aggravated by anticholinergic therapy, e.g. raised intraocular pressure, pyloroduodenal obstruction, prostatic hypertrophy, hypertension, hyperthyroidism or severe coronary heart disease. Caution should be exercised when administering the product to patients with Parkinson's disease.

Cinnarizine in combination with piracetam: this medicinal product should be used with caution in patients with hepatic and/or renal impairment, arterial hypotension, severe coronary heart disease, severe heart failure, porphyria or epilepsy. In case of mild to moderate renal impairment, it is recommended to reduce the therapeutic dose or increase the dose interval, especially if creatinine clearance is less than 60 mL/min. Hepatic enzyme levels should be monitored in patients with hepatic impairment. Alcohol consumption should be avoided during therapy. Caution should be exercised in patients with increased intraocular pressure and in patients with Parkinson's disease. Caution should be exercised in patients with haemostatic disorders, major surgery or severe haemorrhage since piracetam has an effect on platelet aggregation. During long-term treatment of elderly patients, creatinine clearance should be regularly evaluated to adjust the dose as necessary. This medicinal product causes positive doping tests in athletes. This medicinal product also contains lactose monohydrate; patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): cinnarizine in combination with cyclizine: side effects associated with the use of this combination product are reported hereafter. Adverse reactions have been reported during clinical trials, or reported following routine use of the combination product or cinnarizine alone. Frequency: often: 1/100, <1/10; sometimes: 1/1000, <1/100; rarely: 1/10000, <1/1000. Nervous system disorders: often: sedation, drowsiness, poor coordination; rarely: insomnia, irritability, tremor, convulsions, Parkinsonism, extrapyramidal symptoms. Eye diseases: sometimes: accommodation problems. Heart disease: rare: chest tightness, tachycardia. Gastrointestinal disorders: often: dry mouth; sometimes: gastrointestinal discomfort. Liver and bile disorders: rarely: cholestatic jaundice. Kidney and urinary tract disorders: sometimes: urinary retention. In addition, the following side effects have been reported for cyclizine (although not reported during the use of the combination product): dizziness, nightmares, hallucinations, dry mouth, dysuria, skin irritations, generalised chorea, allergic hepatitis, agranulocytosis, haemolytic anaemia, aplastic anaemia, constipation, tachycardia and decreased appetite.

Cinnarizine in combination with dimenhydrinate: the most frequently occurring adverse effects are somnolence (including drowsiness, tiredness, fatigue, daze) occurring in about 8% of patients and dry mouth occurring in about 5% of patients in clinical trials. These reactions are usually mild and disappear within a few days even if treatment is continued.

Cinnarizine in combination with piracetam: in very rare cases (<1 / 10000), the following adverse reactions may occur: skin and hypersensitivity reactions: photosensitivity, rash, pruritus, urticaria, dermatitis, angioedema, anaphylactoid reactions. Gastrointestinal disorders: abdominal pain, diarrhoea, nausea, vomiting, dry mouth, increased salivation. Nervous system disorders: ataxia, progression of epilepsy, headache, insomnia, somnolence (especially at the beginning of therapy), disturbed balance, confusion, visual disturbances, fatigue. Psychiatric disorders: hallucinations, vertigo (ear and labyrinth disorders), agitation, anxiety. Metabolic and nutritional disorders: weight gain. Prolonged use in the elderly may cause

extrapyramidal symptoms.

2.2 Indirect risks (incorrect use): cinnarizine in combination with cyclizine: symptoms: children are more sensitive to overdose. Symptoms of acute toxicity are associated with the effects on the CNS and may include drowsiness, dizziness, coordination disorders, flaccidity, convulsions, hyperpyrexia and respiratory depression. Treatment: within one hour after taking an overdose, the treatment consists of gastric lavage. When stomach rinse is no longer possible, the treatment consists of the use of laxatives and active charcoal. Respiratory failure or circulatory failure can be treated with general support measures. Convulsive symptoms can be treated through careful administration of short-acting barbiturate.

Cinnarizine in combination with dimenhydrinate: symptoms of overdosage with this medication include drowsiness, dizziness and ataxia with anticholinergic effects such as dry mouth, flushing of the face, dilated pupils, tachycardia, pyrexia, headache and urinary retention. Convulsions, hallucinations, excitement, respiratory depression, hypertension, tremor and coma may occur, particularly in cases of massive overdosage.

Cinnarizine in combination with piracetam: this medicinal product is well tolerated and no serious side effects have been observed in the event of an overdose which would require discontinuation of the drug. Children are more sensitive to overdosage and may experience symptoms such as insomnia, anxiety, euphoria, agitation, tremor and, rarely, nightmares, hallucinations and convulsions. Treatment of overdose is symptomatic.

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	Indications/Additional details	MS	MDD	MQP
AM	POM	In combination with dimenhydrinate (vertigo of different origin)			
AT	List II	In combination with dimenhydrinate			
BA	Not authorised				
BE	POM	In combination with dimenhydrinate (vertigo of different origin)			
CH	List II	In combination with dimenhydrinate			
CZ	POM	In combination with dimenhydrinate (vertigo of different origin)			
DE	POM				
EE	Not authorised				
ES	Not authorised				
FI	POM	In combination with dimenhydrinate			
FR	Not authorised				
HR	List II	In combination with dimenhydrinate			
HU	POM	In combination with dimenhydrinate			
IE	List II	In combination with dimenhydrinate			
IT	List II	In combination with dimenhydrinate			
LT	POM	In combination with dimenhydrinate and in combination with piracetam			
LV	POM	In combination with dimenhydrinate and in combination with piracetam			
MK	POM	In combination with dimenhydrinate (vertigo of different origin)			
NL	POM + Exemption	In combination with dimenhydrinate (POM) and with cyclizine (non-prescr.) (motion sickness)	POM: 20 mg Ex.: 12.5 mg		
PL	POM	In combination with dimenhydrinate			
PT	POM	In combination with dimenhydrinate			
RO	List I	In combination with dimenhydrinate			

RS	Not authorised				
SI	POM	In combination with dimenhydrinate (vertigo of different origin)			
UK	Not authorised				

Melclass database[1]: Currently not available.

No more data available from other member states.

3.2 Social dimension of classification:

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

Criteria: recurrent use needed.

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: SmPC of the available combination products (databases of national competent authorities and Melclass database (https://melclass.edqm.eu/)

4.2 Comments: -

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Ipratropium Bromide

1.2 ATC code: R01AX03

1.3 Therapeutic indications: indicated for the symptomatic relief of rhinorrhoea in allergic and non-allergic rhinitis.

1.4 Posology and duration of treatment: adults: two sprays (42 micrograms) in each nostril administered 2-3 times a day. Children: the product has not been evaluated in children, and therefore is not recommended for use in patients below the age of 12 years.

1.5 Pharmaceutical forms: nasal spray, solution - 20 mcg/dose (IT); 21 mcg/dose (CH, ES, IE, SE and UK); 31 mcg/dose (BE); 42 mcg/dose (SE).

1.6 Contraindications: contraindicated in patients known to be hypersensitive to atropine or its derivatives.

1.7 Relevant warnings: immediate hypersensitivity reactions following the use of ipratropium bromide have been demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis. Caution is advocated in the use of anticholinergic agents in patients predisposed to narrow-angle glaucoma, or with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-outflow obstruction). As patients with cystic fibrosis may be prone to gastrointestinal motility disturbances, Ipratropium bromide, as with other anticholinergics, should be used with caution in these patients. There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, angle-closure glaucoma, eye pain) when aerosolised ipratropium bromide, either alone or in combination with an adrenergic beta-2 agonist, has come into contact with the eyes. Thus, patients must be instructed in the correct administration of ipratropium bromide. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): the most frequent side effects reported in clinical trials were epistaxis, nasal dryness, headache, nasal discomfort and throat irritation.

Immune system disorders: uncommon: hypersensitivity, anaphylactic reactions.

Nervous system disorders: common: headache; uncommon: dizziness.

Eye disorders: uncommon: vision blurred, mydriasis*, intraocular pressure increased*, glaucoma*, eye pain*, halo vision, conjunctival hyperaemia, corneal oedema.

Cardiac disorders: uncommon: supraventricular tachycardia, atrial fibrillation, heart rate increased; rare: palpitations.

Respiratory, thoracic and mediastinal disorders: common: epistaxis, nasal dryness, throat irritation, nasal discomfort; uncommon: dry throat, bronchospasm, laryngospasm, pharyngeal oedema.

Gastrointestinal disorders: uncommon: dry mouth, nausea, gastrointestinal motility disorder, stomatitis, oedema mouth.

Skin and subcutaneous tissue disorders: uncommon: rash, angioedema; rare: urticaria, pruritus.

Renal and urinary disorders: uncommon: urinary retention**

*Ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination

with an adrenergic beta-2 agonist, has come into contact with the eyes.

**The risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

2.2 Indirect risks (incorrect use): no symptoms specific to overdosage have been encountered. In view of the wide therapeutic window and topical administration of this medicinal product, no serious anticholinergic symptoms are to be expected. As with other anticholinergics, dry mouth, visual accommodation disturbances and tachycardia would be the expected symptoms and signs 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	Indications/Additional details	MS	MDD	MQP
AM	Not authorised				
AT	Not authorised				
BA	Not authorised				
BE	Not subject to prescription	Symptomatic treatment of rhinorrhoea in allergic or non-allergic rhinitis in adults and children above 6 years of age	0.6 mg/mL		9 mL
CH	List II				
CZ	Not authorised				
DE	Not authorised				
EE	Not authorised				
ES	POM	Symptomatic relief of rhinorrhoea in allergic and non-allergic rhinitis			
FI	POM				
FR	Not authorised				
GE	Not authorised				
HR	Not authorised				
HU	Not authorised				
IS	Not authorised				
IE	List II				
IT	List II				
LT	Not authorised				
LV	Not authorised				
MK	Not authorised				
NL	Not authorised				
PL	Not authorised				
PT	Not authorised				
RO	Not authorised				
RS	Not authorised				
SE	Not subject to prescription				
SI	Not authorised				
UK	POM				

Melclass database[1]: List II

No more data available from other member states.

3.2 Social dimension of classification:

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

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

recommendation: **List II**

Criteria: recurrent use needed.

3.2.2 Paediatric use: the use of this medicinal product has not been evaluated in children, and therefore is not recommended for use in patients below the age of 12 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: SmPC Rinatec 21 micrograms per metered dose (https://bit.ly/2Jdiso1)

4.2 Comments: -

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