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

Evidence-based classification reviews of
medicines belonging to the ATC group N02B
(Other analgesics and antipyretics)

2019

Table of Contents

INTRODUCTION

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

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

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

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

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

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

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

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

It is important to note that:

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

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

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

The CD-P-PH/PHO supervises a database (i.e. *Melclass*[5]), hosted by the EDQM, which stores the recommendations that the Committee of Experts issues twice a year to health authorities of the

[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/

Council of Europe member states which are parties to the Convention on the Elaboration of a European Pharmacopoeia, as well as national information about the classification status and supply conditions of 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 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

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification [1]
CBD	Cannabidiol
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CNS	Central nervous system
EDQM	European Directorate for the Quality of Medicines and HealthCare
EMA	European Medicines Agency
GI	Gastrointestinal
GSL	General sales list medication
HIV	Human immunodeficiency virus
IM	Intramuscular
INR	International normalised ratio
IT	Intrathecal
IV	Intravenous
MDD	Maximal daily dose
MQP	Maximal quantity per pack
MS	Maximal strength
NSAID	Non-steroidal anti-inflammatory drug
P	Pharmacy-only medication
POM	Prescription only medicine
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Prothrombin time
SmPC	Summary of product characteristics
THC	Delta-9-tetrahydrocannabinol
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.

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

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

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

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Acetylsalicylic Acid

1.2 ATC code: N02BA01

1.3 Therapeutic indications: prescription: 300 mg: acetylsalicylic acid has analgesic, antipyretic and anti-inflammatory actions.

Non-prescription: 500 mg: a) symptomatic relief of mild to moderate pain, including headache, migraine pain, neuralgia, toothache, sore throat, period pain, aches and pains. b) symptomatic relief of influenza, feverishness, feverish colds. c) symptomatic relief of sprains, strains, rheumatic pain, sciatica, lumbago, fibrositis, muscular aches and pains, joint swelling and stiffness

Pharmacy-only: 1000 mg: symptomatic treatment of fever and/or mild to moderate pain for adults and adolescents 16-65 years of age.

1.4 Posology and duration of treatment: children: do not give to children aged under 16 years unless specifically indicated (e.g. for Kawasaki's disease).

Prescription: 300 mg: analgesic, antipyretic and anti-inflammatory actions: the usual dose of acetylsalicylic acid is 300-900 mg repeated three to four times daily according to clinical needs. In acute rheumatic disorders the dose is in the range of 4-8 g daily, taken in divided doses.

Non-prescription: 500 mg: adults: 1 or 2 tablets dissolved in half a glass of water (100 mL) every 4 hours as required. Do not exceed 8 tablets in 24 hours.

Pharmacy-only: 1000 mg: 1 tablet in each administration, repeating as necessary after a period of minimum of 4-6 hours. The maximum daily dose should not exceed 3 tablets. Acetylsalicylic acid should not be taken for more than 3 days (for fever cases), or for more than 3-4 days (for pain cases) unless by medical advice.

1.5 Pharmaceutical forms: oral forms: prescription: 75 mg and 162.5 mg; non-prescription: 300 mg, 500 mg, 1000 mg; pharmacy-only: 1000 mg.

1.6 Contraindications: acetylsalicylic acid is contraindicated in the following cases: patients with active peptic ulceration or a history of peptic ulceration; haemophilia, haemorrhagic disease or a history of bleeding disorders; gout or a history of gout; hypersensitivity to acetylsalicylic acid (e.g. asthma, rhinitis, angioneurotic oedema or urticaria), other non-steroidal anti-inflammatory drugs (NSAIDs) or other tablet excipients; third trimester of pregnancy; breast feeding; children under 16 (except for the treatment of Still's disease); concurrent anticoagulant therapy; active or a history of peptic ulcers, haemorrhagic diathesis, severe renal failure, severe hepatic failure, severe cardiac failure.

1.7 Relevant warnings: acetylsalicylic acid should be used with particular caution in the following cases: hypersensitivity to analgesics/anti-inflammatory agents/anti-rheumatics and in the presence of other allergies, with concomitant treatment with anticoagulants, patients with impaired renal function or patients with impaired cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major haemorrhagic events), since acetylsalicylic acid may further increase the risk of renal impairment and impaired hepatic function. Acetylsalicylic acid may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are pre-existing asthma, hay fever, nasal polyps or chronic respiratory disease. This also applies to patients exhibiting allergic reactions (e.g. cutaneous reactions, itching) to other substances. Due to its inhibitory effect on platelet aggregation, which persists for several days after administration, acetylsalicylic acid may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions). At low doses, acetylsalicylic acid reduces the excretion of uric acid. This can possibly trigger gout attacks in predisposed patients. There is a possible association between acetylsalicylic acid and Reye's syndrome when given to children - Reye's syndrome is a very rare disease which affects the brain and liver and can be fatal.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): blood and lymphatic system disorders: in the context of bleeding: haemorrhagic anaemia, iron deficiency anaemia with the respective laboratory and clinical signs and symptoms. In the context of glucose-6-phosphate dehydrogenase deficiency: haemolysis, haemolytic anaemia.

Nervous system disorders: mental confusion, dizziness, cerebral and intracranial haemorrhage.

Ear and labyrinth disorders: hearing disturbances (such as tinnitus), vertigo.

Respiratory, thoracic and mediastinal disorders: acetylsalicylic acid may precipitate bronchospasm and induce asthma in susceptible patients. Dyspnoea has also been reported.

Immune system disorders: hypersensitivity, drug hypersensitivity, allergic oedema and angioneurotic oedema, anaphylactic reaction, anaphylactic shock with respective laboratory and clinical manifestations. Hypersensitivity reactions include skin rashes, urticaria and angioneurotic oedema. Respiratory, thoracic and mediastinal disorders. Epistaxis, analgesic asthma syndrome, rhinitis, nasal congestion.

Gastrointestinal disorders (GI): dyspepsia, GI pain, abdominal pain, gingival bleeding, GI inflammation, GI ulcer, GI haemorrhage, GI ulcer perforation with the respective laboratory and clinical signs and symptoms.

Hepatobiliary disorders: liver disorder, transaminases increased.

Skin and subcutaneous tissue disorders: rash, pruritus.

Renal and urinary disorders: impaired renal function.

2.2 Indirect risks (incorrect use): salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning. Symptoms: common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases. A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood-brain barrier. Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased prothrombin time (PT) and international normalised ratio (INR), intravascular coagulation, renal failure, and non-cardiac pulmonary oedema. Central nervous system (CNS) features including confusion, disorientation, coma and convulsions are less common in adults than in children. Management: activated charcoal should be given if an adult presents within 1 hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Metabolic acidosis should be corrected with intravenous (IV) 8.4% sodium bicarbonate. Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under 10 years or over 70 have an increased risk of salicylate toxicity and may require dialysis at an earlier stage.

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	Additional information			
		Routes of administration/ Indications	MS	MDD	MQP
Armenia (AM)	Not subject to prescription	Oral	500 mg	3000 mg	8000 mg
Austria (AT)	List II + Exemption	Oral	1 g		
Belgium (BE)	Not subject to prescription		1 g	3 g	50 g
Bosnia and Herzegovina (BiH)	Not subject to prescription		500 mg	4000 mg	
Switzerland (CH)	List II + Exemption		Ex.: 500 mg		Ex.: 1 g
Czech Republic (CZ)	Not subject to prescription				
Germany (DE)	Not subject to prescription				
Estonia (EE)	Not subject to prescription				
Spain (ES)	POM + Exemption	POM: IV Ex.: oral forms	Ex.: 500 mg		
Finland (FI)	Not subject to prescription		500 mg		
France (FR)	Not subject to prescription				
Georgia (GE)	Not subject to prescription				
Hungary (HU)	POM + Exemption	Oral Note: MS: 1000 mg is POM			
Ireland (IE)	Not subject to prescription				
Italy (IT)	List II + Exemption	Ex: oral forms	1 g	3 g	20 g
Lithuania (LT)	POM + Exemption				
Latvia (LV)	Not subject to prescription		500 mg		
North Macedonia (MK)	Not subject to prescription		500 mg		10 g
Netherlands (NL)	POM + Exemption	POM: IV use Ex: oral forms	Ex.: 500 mg		
Poland (PL)	Not subject to prescription		500 mg	4000 mg	50 g
Portugal (PT)	POM + Exemption	POM oral and IV Ex.: oral forms	Ex.: 1 g		
Romania (RO)	Not subject to prescription		1000 mg	3 g	24 g
Serbia (RS)	Not subject to prescription	Contraindicated in children < 16 years	500 mg	3 g	15 g
Sweden (SE)	Not subject to prescription				
Slovenia (SI)	Not subject to prescription				
United Kingdom (UK)	Non-prescription (Pharmacy and General Sales List)		500 mg		50 g

No data available from other member states.

Melclass database[1]: Not subject to prescription.

3.2 Social dimension of classification

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

Proposed recommendation: **Not subject to prescription** (oral use; adults and children > 16 years of age; MS: 500 mg; MDD: 3 g; MQP: 10 g; short-term treatment).

Criteria:
Well-known safety profile.
Continuous medical supervision not required.

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. COMMENTS/REFERENCES

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

4.1 References: Product information available at the following databases of medicines: Portugal (https://bit.ly/2XrNLPx), Ireland (https://bit.ly/2UeYZFr) and United Kingdom (https://bit.ly/2VkzGSn)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Aloxiprin

1.2 ATC code: N02BA02

1.3 Therapeutic indications: aloxiprin is a polymeric condensation product of aluminium oxide and acetylsalicylic acid. It has actions similar to those of acetylsalicylic acid (aloxiprin 600 mg is equivalent to about 500 mg of acetylsalicylic acid). Aloxiprin has been used as an analgesic and anti-inflammatory in musculoskeletal and joint disorders. It has also been used in the treatment and prevention of thromboembolic disorders.

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Micromedex (https://bit.ly/2tCGq23)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Choline Salicylate

1.2 ATC code: N02BA03

1.3 Therapeutic indications: for the relief of pain, discomfort and inflammation caused by common mouth ulcers, cold sores, denture and sore spots, as well as mouth ulcers, and sore spots due to orthodontic devices. To help to fight minor mouth infection and aid healing of sore spots and ulcers due to dentures and orthodontic devices.

1.4 Posology and duration of treatment: adults and children over the age of 16: using a clean finger massage approximately half an inch of the gel onto the sore area, not more than once every 3 hours. There is no indication that dosage need be modified in the elderly. Denture irritation: apply and leave at least 30 minutes before reinsertion of the dentures. Do not apply this product directly to the dentures. The maximum duration of treatment is 7 consecutive days.

1.5 Pharmaceutical forms: oromucosal gel (choline salicylate: 87 mg per 1 gram).

1.6 Contraindications: not to be used in children and adolescents under the age of 16. This is because there is a possible association between salicylates and Reye's syndrome when given to children. Reye's syndrome is a very rare disease which affects the brain and liver and can be fatal. Not to be used in patients suffering from active peptic ulceration. Not to be used in patients with hypersensitivity to salicylates, acetylsalicylic acid or other NSAIDs, or to any of the excipients.

1.7 Relevant warnings: a doctor or dentist should be consulted before use if the patient is in the first or second trimester of pregnancy or when symptoms persist for more than 7 days.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): bronchospasm, and asthma. There have been a few cases of contact dermatitis and methaemoglobinaemia.

2.2 Indirect risks (incorrect use): salicylate toxicity can result if the stated dose is exceeded. Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning. Patients should be given supportive therapy or treatment for salicylate poisoning as necessary. This may include treatment like activated charcoal, urinary alkalinisation and in severe cases haemodialysis.

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	Additional information			
		Routes of administration/ Indications	MS	MDD	MQP
AM	Not authorised				
AT	Not authorised				
BE	Not authorised				
BiH	Not authorised				
CH	Not authorised				
CZ	Not authorised				
ES	Not authorised				
FI	Not authorised				

HU	Not authorised				
IE	Not subject to prescription				
IT	Not authorised				
LV	Not authorised				
MK	Not authorised				
NL	Not authorised				
PL	Not authorised				
PT	Not subject to prescription	Topical use for pain in oral and nasal cavities		87 mg/g	870 mg/g
RO	Not authorised				
RS	Not authorised				
SE	Not authorised				
SI	Not authorised				
UK	Not subject to prescription			87 mg/g	15 g

No data available from other member states.

Melclass database[1]: Not subject to prescription.

3.2 Social dimension of classification:

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

Proposed recommendation: **Not subject to prescription**

Criteria:
Well-known safety profile.
Continuous medical supervision not required.

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. COMMENTS/REFERENCES

4.1 References: product information available at the following databases of medicines: Portugal (https://bit.ly/2XrNLPx), Ireland (https://bit.ly/2UeYZFr) and United Kingdom (https://bit.ly/2VkzGSn)

4.2 Comments: in Ireland this medicinal product is also indicated for soothing relief from the pain and discomfort of teething. It is contraindicated in infants under four months.

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

1.2 ATC code: N02BA04

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, medicines containing this active substance are only authorised in 1 member state: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Republic State Institute for Drug Control of the Czech Republic (https://bit.ly/33vM3Am).

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Salicylamide

1.2 ATC code: N02BA05

1.3 Therapeutic indications: in the past, salicylamide tablets contained either 300 or 600 mg; however, these preparations are no longer available.

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Micromedex (https://bit.ly/2tCGq23)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Salsalate

1.2 ATC code: N02BA06

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Ethenzamide

1.2 ATC code: N02BA07

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Micromedex (https://bit.ly/2tCGq23)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Morpholine Salicylate

1.2 ATC code: N02BA08

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Dipyrocetyl

1.2 ATC code: N02BA09

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Benorilate

1.2 ATC code: N02BA10

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Diflunisal

1.2 ATC code: N02BA11

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Potassium Salicylate

1.2 ATC code: N02BA12

1.3 Therapeutic indications: potassium salicylate is a salicylic acid derivative that has been used for its analgesic effects.

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Micromedex (https://bit.ly/2tCGq23)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Guacetisal

1.2 ATC code: N02BA14

1.3 Therapeutic indications: guacetisal has been used in respiratory disorders as an expectorant. It has also been used as an antipyretic to reduce fever. It has been given orally and rectally.

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Micromedex (https://bit.ly/2tCGq23)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Carbasalate Calcium

1.2 ATC code: N02BA15

1.3 Therapeutic indications: 300 mg: headache, toothache, fever and pain in flu and cold, fever and post-vaccination pain, rheumatic pain, nerve pain, low back pain, muscle aches and menstrual pain.

600 mg: headache, toothache, fever and pain in flu and cold, fever and post-vaccination pain, rheumatic pain, nerve pain, low back pain, muscle aches and menstrual pain. Symptomatic treatment of migraine attacks in the presence of nausea and vomiting, in combination with metoclopramide.

1.4 Posology and duration of treatment: 300 mg: children aged between 7 and 11 years: the contents of 1 sachet at a time, up to 4-6 sachets; children aged 12 years and over: the contents of 2 sachets at a time, up to 6-8 sachets - the administration interval in children should be at least 4 hours. Adults: the content of 2-4 sachets at a time, up to 16 sachets

600 mg: the content of 1-2 sachets (600-1200 mg), up to 8 sachets (4800 mg). In migraine: after the onset of a migraine attack, 2 sachets (1200 mg) should be taken with 1 tablet of metoclopramide 10 mg. If necessary, this dose may be repeated after a few hours to a maximum of 6 sachets (3600 mg) and 3 tablets of metoclopramide at 10 mg per day.

1.5 Pharmaceutical forms: oral forms: 300 mg and 600 mg.

1.6 Contraindications: carbasalate calcium should be used with particular caution in the following cases: hypersensitivity to carbasalate calcium or acetylsalicylic acid; history of asthma caused by the administration of salicylates or similar effects, in particular NSAIDs; any congenital or acquired haemorrhagic disease; bleeding risks; severe liver impairment; severe renal impairment; erosive gastritis and stomach pain during previous use; severe untreated heart failure; concomitant use with methotrexate at a dose of more than 15 mg per week; concomitant use with oral anticoagulants when salicylates are used in high doses, especially in the treatment of rheumatic diseases; dosages up to 128 mg of carbasalate calcium per day, corresponding to 100 mg of acetylsalicylic acid per day, during the third trimester of pregnancy.

1.7 Relevant warnings: during prolonged treatment with high doses of analgesic, headache may occur, which should not be treated with higher doses. In general, the use of common analgesics, especially the combination of different analgesics, can lead to persistent kidney damage and risk of renal failure. Reye's syndrome has been observed in children with symptoms of viral infections after ingestion of acetylsalicylic acid.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): GI disorders: abdominal pain, occult GI bleeding (which may cause an iron deficiency anaemia), GI ulcer and perforation.

Nervous system disorders: headache, dizziness, feeling of hearing loss.

Blood and lymphatic system disorders: haemorrhagic syndromes (epistaxis, gum bleeding, purpura, etc.) with an increase in bleeding time. This action remains 4 to 8 days after stopping carbasalate calcium. This can lead to a risk of bleeding during surgery.

Skin and subcutaneous tissue disorders: urticaria, skin reactions, anaphylactic reactions, Quincke's oedema.

Respiratory, thoracic and mediastinal disorders: asthma.

Nervous system disorders/Hepatobiliary disorders: Reye's syndrome.

2.2 Indirect risks (incorrect use): in the elderly and especially in young children attention should be paid to the danger of potentially fatal intoxication. The following symptoms may occur if the stated dose is exceeded: moderate intoxication: tinnitus, impression of hearing loss, headache, vertigo and mental confusion are signs of overdose and these can be reduced by a dose reduction. Severe intoxication: fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular shock, respiratory insufficiency, severe hypoglycaemia.

Emergency treatment: immediate hospitalisation; gastrointestinal lavage and administration of activated charcoal; control of acid/base equilibrium; maintenance of adequate diuresis; alkalinisation of the urine through the administration of bicarbonate while monitoring the plasma and urine pH. In cases of severe intoxication (salicylate concentrations > 600-800 mg/L) haemodialysis may be used. This also serves to correct disturbances in the fluid and electrolyte balance and acid-base equilibrium. Symptomatic treatment should also be considered.

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	Additional information			
		Routes of administration/ Indications	MS	MDD	MQP
AM	Not authorised				
AT	Not subject to prescription				
BE	Not authorised				
BiH	Not authorised				
CH	Not authorised				
CZ	Not authorised				
DE	Not subject to prescription				
ES	Not authorised				
FI	Not authorised				
FR	Not authorised				
HU	Not authorised				
IE	Not authorised				
IT	Not authorised				
LT	Not authorised				
LV	Not authorised				
MK	Not authorised				
NL	Not subject to prescription				
PL	Not authorised				
PT	Not authorised				
RO	Not authorised				
RS	Not authorised				
SE	Not authorised				
SI	Not authorised				
UK	Not authorised				

No data available from other member states.

Melclass database[1]: Currently not available.

3.2 Social dimension of classification

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

Recommendation: **Not subject to prescription**

Criteria:
Well-known safety profile.

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

Continuous medical supervision not required.

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. COMMENTS/REFERENCES

4.1 References: product information available in the Dutch Medicines Data Bank (https://bit.ly/2NA8ht6)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Imidazole Salicylate

1.2 ATC code: N02BA16

1.3 Therapeutic indications: imidazole salicylate is a salicylic acid derivative that has been used in the treatment of fever and inflammatory respiratory tract and otorhinolaryngeal disorders. Imidazole salicylate has been given in oral doses of up to 2.25 g daily in divided doses. It has also been given as a rectal suppository and has been applied topically as a 5% gel for the relief of muscular and rheumatic pain.

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Micromedex (https://bit.ly/2tCGq23)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Acetylsalicylic Acid, Combinations excl. Psycholeptics

1.2 ATC code: N02BA51

1.3 Therapeutic indications: *codeine 8 mg + acetylsalicylic acid 400 mg (oral use):* short-term treatment of acute moderate pain which is not considered to be relieved by other analgesics (e.g. paracetamol, ibuprofen or acetylsalicylic acid) alone, such as: headache, migraine, neuralgia, toothache, period pain and rheumatic pains.

Caffeine 15 mg + acetylsalicylic acid 325 mg (oral use): relief of pain of headache, neuralgia, rheumatic pain, period pain, dental pain, toothache and the relief of symptoms of the common cold.

Pseudoephedrine hydrochloride 30 mg + acetylsalicylic acid 500 mg (oral use): symptomatic treatment of nasal congestion associated with the common cold and cold-related pain and fever. The fix combination should only be used when nasal congestion appears together with pain and/or fever.

Ascorbic acid 240 mg + acetylsalicylic acid 400 mg (oral use): short-term treatment of acute moderate pain: headaches, toothaches, rheumatic pains, menstrual pains. Cold and flu-related pain and fever.

Acetylsalicylic acid 500 mg + ascorbic acid 100 mg + caffeine 50 mg (oral use): symptomatic treatment of pain and fever related to cold and flu.

Acetylsalicylic acid 500 mg + caffeine 30 mg (oral use): symptomatic relief of colds and flu; relief of mild to moderate pain: headache, migraine, sore throat, dysmenorrhoea, muscle and rheumatic pain.

Acetylsalicylic acid 250 mg + paracetamol 250 mg + caffeine 65 mg (oral use): acute treatment of headache and migraine attacks with or without aura.

Acetylsalicylic acid 300 mg + paracetamol 200 mg + caffeine 45 mg (oral use): symptomatic relief of colds and flu; relief of mild to moderate pain: headache, migraine, sore throat, dysmenorrhoea, muscle and rheumatic pain.

1.4 Posology and duration of treatment: *codeine 8 mg + acetylsalicylic acid 400 mg (oral use):* adults over 18 years: 1 to 2 tablets. This dose may be taken up to 4 times a day at intervals of not less than 4 hours. Children aged 16 years to 18 years: 1 to 2 tablets every 6 hours when necessary up to a maximum of 8 tablets in 24 hours. It should not be given to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease). Children aged less than 12 years: codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine. Elderly: the normal adult dose is appropriate in the elderly. It should not be taken for more than 3 days continuously without medical review.

Caffeine 15 mg+ acetylsalicylic acid 325 mg (oral use): adults and adolescents over 16 years: 2 tablets every 4 hours if necessary. The maximum dose of 12 tablets in any 24-hour period should not be exceeded. It should not be given to children and adolescents aged under 16 years, except on medical advice, where the benefit outweighs the risk.

Pseudoephedrine hydrochloride 30 mg + acetylsalicylic acid 500 mg (oral use): adults: 1-2 sachets as a single dose. If necessary, there may be further administration of the single dose at intervals of 4-8 hours. The maximum daily dose of 6 sachets must not be exceeded.

Ascorbic acid 240 mg + acetylsalicylic acid 400 mg (oral use): adults: 1-2 tablets in each administration. The maximum daily dosage should not exceed 8 tablets. Children from 12 years: 400 mg of acetylsalicylic acid as an individual dose, which corresponds to 1 tablet in each administration.

Acetylsalicylic acid 500 mg + ascorbic acid 100 mg + caffeine 50 mg (oral use): adults: 1 tablet every 4 hours, if necessary, not to exceed the maximum dose of 6 tablets per day. Children 6 to 10 years: 1 tablet every 8 hours, if necessary, without exceeding the maximum dose of 3 tablets per day. Children 10 to 15 years: 1 tablet every 4 hours, if necessary, without exceeding the maximum dose of 4 tablets per day.

Acetylsalicylic acid 500 mg + caffeine 30 mg (oral use): adults (including the elderly) and children over 16 years of age: 1 to 2 tablets. These doses may be repeated within 4 to 6 hours as necessary. Maximum daily dose: 8 tablets (acetylsalicylic acid 4000 mg/caffeine 240 mg) in 24 hours.

Acetylsalicylic acid 250 mg + paracetamol 250 mg + caffeine 65 mg (oral use): adults: headache: the usual recommended dose is 1 tablet; 1 further tablet can be taken after an additional 4 to 6 hours. Migraines: 2 tablets to be taken when symptoms appear. If necessary, 2 further tablets may be taken after 4 to 6 hours.

Acetylsalicylic acid 300 mg + paracetamol 200 mg + caffeine 45 mg (oral use): adults and adolescents over 16 years: 1-2 tablets every 4 hours with a maximum of 6 in any 24-hour period. Do not give to children and adolescents aged under 16 years, except on medical advice, where the benefit outweighs the risk.

1.5 Pharmaceutical forms: Oral forms.

1.6 Contraindications: related to acetylsalicylic acid: acetylsalicylic acid is contraindicated in patients with active peptic ulceration or a history of peptic ulceration; haemophilia, haemorrhagic disease or a history of bleeding disorders; gout or a history of gout; hypersensitivity to acetylsalicylic acid (e.g. asthma, rhinitis), other NSAIDs or other tablet excipients; third trimester of pregnancy; breast feeding; children under 16 (except for the treatment of Still's disease); concurrent anticoagulant therapy; active or a history of peptic ulcers; haemorrhagic diathesis; severe renal failure; severe hepatic failure; severe cardiac failure.

1.7 Relevant warnings: related to acetylsalicylic acid: acetylsalicylic acid should be used with particular caution in the following cases: hypersensitivity to analgesics/anti-inflammatory agents/anti-rheumatics and in the presence of other allergies; patients with concomitant treatment with anticoagulants; patients with impaired renal function or patients with impaired cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major haemorrhagic events), since acetylsalicylic acid may further increase the risk of renal impairment; patients with impaired hepatic function. Acetylsalicylic acid may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are pre-existing asthma, hay fever, nasal polyps and chronic respiratory disease. This also applies to patients exhibiting allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances. Due to its inhibitory effect on platelet aggregation, which persists for several days after administration, acetylsalicylic acid may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions). At low doses, acetylsalicylic acid reduces the excretion of uric acid - this can possibly trigger gout attacks in predisposed patients. There is a possible association between acetylsalicylic acid and Reye's syndrome when given to children. Reye's syndrome is a very rare disease which affects the brain and liver and can be fatal. Factors that may increase the risk of haemolysis include high dosage, fever and acute infections.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): *Possible adverse reactions of acetylsalicylic acid*: Blood and lymphatic system disorders: increase of risk of bleeding. Immune system disorders: rare: hypersensitivity reactions (dyspnoea, anaphylaxis, skin reactions), especially in patients with asthma. Nervous system disorders: not known: dizziness. Ear and labyrinth disorders: vertigo and tinnitus may be symptoms of overdose. GI disorders: common: gastroduodenal complaints (gastralgia, dyspepsia, gastritis), nausea, vomiting, diarrhoea; rare: GI bleeding (hematemesis, melena, erosive gastritis) that may cause iron deficiency anaemia in isolated cases; gastrointestinal ulcers that may cause perforation in isolated cases. Hepatobiliary disorders: very rare: increase of transaminases.

Possible adverse reactions of ascorbic acid: large doses of ascorbic acid may cause diarrhoea. Patients known to be at risk of hyperoxaluria should not ingest ascorbic acid in doses exceeding 1 gram daily, as there may be increased urinary oxalate excretion. However such a risk has not been demonstrated in normal, non-hyperoxaluric individuals. Ascorbic acid has been implicated in precipitating haemolytic anaemia in certain individuals with a deficiency of glucose-6-phosphate dehydrogenase. Increased intake of ascorbic acid over a prolonged period may result in an increase in renal clearance of ascorbic acid, and deficiency may result if the intake is reduced or withdrawn rapidly. Doses of more than 600 mg have a diuretic effect.

Possible adverse reactions of caffeine: caffeine may produce nervousness, anxiety, irritability, restlessness, excitability and dizziness. When the recommended acetylsalicylic acid-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.

Possible adverse reactions of codeine: codeine can produce typical opioid effects including constipation, nausea, vomiting, dizziness, confusion, drowsiness and urinary retention. The frequency and severity are determined by dosage, duration of treatment and individual sensitivity. Tolerance and dependence can occur especially with prolonged high dosage of codeine. There have been very rare occurrences of pancreatitis.

Possible adverse reactions of paracetamol: liver damage in association with therapeutic use of paracetamol has been documented; most cases have occurred in conjunction with chronic alcohol abuse. There have been some reports of blood dyscrasias, thrombocytopenia and argranulocytosis with the use of paracetamol-containing products, but the causal relationship has not been established. Serious skin reactions have been reported in very rare cases.

Possible adverse reactions of pseudoephedrine: Nervous system disorders: uncommon: stimulation of the CNS (e.g. insomnia); rare: hallucinations. Cardiac disorders: rare: tachycardia, coronary spasms (potentially resulting in myocardial infarction). Vascular disorders: not known: blood pressure increase, although not in controlled hypertension. Skin and subcutaneous tissue disorders: uncommon: skin reactions (e.g. rash, urticaria, pruritus). Renal and urinary disorders: uncommon: urinary retention, especially in patients suffering from prostatic hyperplasia.

2.2 Indirect risks (incorrect use): overdosage may occur if the stated dose is exceeded.

Acetylsalicylic acid: common features of overdosage include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases. A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years old. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood-brain barrier. Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased PT/INR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema. CNS features including confusion, disorientation, coma and convulsions are more common in children than adults.

Ascorbic acid: at doses of over 3 grams per day unabsorbed ascorbic acid is chiefly excreted unmetabolised in the faeces. Absorbed ascorbic acid additional to the body's needs is rapidly eliminated. Large doses of ascorbic acid may cause diarrhoea and the formation of renal oxalate calculi. Symptomatic treatment may be required

Caffeine: common features of overdosage include CNS stimulation: anxiety, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, convulsions. Cardiac symptoms include tachycardia, cardiac arrhythmia. Gastric symptoms include abdominal or stomach pains. Other symptoms of overdosage associated with the caffeine component include diuresis and facial flushing.

Codeine: the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. Symptoms: CNS depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

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

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after administration and clinical symptoms generally culminate after 4 to 6 days. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Pseudoephedrine: the symptoms of overdose include irritability, nervousness, tremor, palpitations, convulsions, urinary retention, hypertension, restlessness, dry mouth, anxiety, insomnia, nausea, vomiting, whistling breathing, dyspnoea, chest pain, tachycardia, cardiac arrhythmias, convulsions, hallucinations and possible tolerance to pseudoephedrine.

Management

Acetylsalicylic acid: activated charcoal should be administered if an adult presents within 1 hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Metabolic acidosis should be corrected with IV 8.4% sodium bicarbonate. Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations > 700 mg/l (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under 10 years or over 70 years have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

Caffeine: treatment of caffeine overdose is primarily symptomatic and supportive. Diuresis should be treated by maintaining fluid and electrolyte balance and CNS symptoms can be controlled by IV administration of diazepam.

Codeine: This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg. Naloxone should be given if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. The patient should be monitored for at least 4 hours after ingestion, or 8 hours if a sustained release preparation has been taken.

Paracetamol: immediate treatment is essential in the management of paracetamol overdose. Despite a lack of clinically significant early symptoms, patients should be referred urgently to hospital for immediate medical attention. This is because early symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines. As concentrations soon after paracetamol ingestion are unreliable, plasma paracetamol concentration should be measured at 4 hours or later after the initial administration. Treatment with N-acetylcysteine may be used for up to 24 hours after administration of paracetamol; however, the maximum protective effect is only obtained up to 8 hours post-administration. The effectiveness of this antidote declines sharply after this 8 hour time period. If required, the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, then oral methionine may be a suitable alternative for remote areas, outside hospital. Management of those patients presenting with serious hepatic dysfunction 24 hours after paracetamol administration should be discussed with the national poisons information centres or a liver unit.

Pseudoephedrine: overdose should be treated by general supportive measures. Respiratory and circulatory function should be maintained by supportive measures. Catheterisation of the bladder may be required. The benefit of gastric decontamination is uncertain. Activated charcoal (charcoal dose: 50 g for adults; 1g/kg for children) can be considered. Optimal effects are within 1 hour of ingestion of more than a toxic dose. Volunteer studies suggest that there is reduced absorption within 2 hours and efficacy declines thereafter. Alternatively, gastric lavage could be considered in adults within 1 hour of a potentially life-threatening overdose. Pulse, blood pressure and cardiac rhythm should be monitored. Any hypertension or convulsions should be treated as necessary. Asymptomatic patients should be observed for 4 hours or 8 hours if a slow release product has been taken.

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	Additional information			
		Routes of administration/ Indications	MS	MDD	MQP
AM	Not subject to prescription	Oral use	acetylsalicylic acid: 400 mg	acetylsalicylic acid: 2400 mg	acetylsalicylic acid: 5000 mg
AT	Not subject to prescription				
BE	POM				
BiH	Not subject to prescription				
CH	List II + Exemption	Ex.: oral use	Ex.: acetylsalicylic acid: 500 mg		
CZ	Not subject to prescription				
ES	POM + Exemption	Ex.: oral use	Ex.: acetylsalicylic acid 250 mg + paracetamol 250 mg + caffeine 65 mg		
FI	Not subject to prescription				
HU	POM				
IE*	Not subject to prescription				
IT	Not subject to prescription				
LV	Not subject to prescription		acetylsalicylic acid: 500 mg		
MK	Not subject to prescription		acetylsalicylic acid 500 mg + ascorbic acid 250 mg		acetylsalicylic acid: 10 g
NL	POM + Exemption	POM: IV use Ex: oral use	Ex: combination products containing acetylsalicylic acid (500 mg) + ascorbic acid; acetylsalicylic acid (500 mg) + paracetamol + caffeine		
PL	Not subject to prescription	Oral use	available combination products: acetylsalicylic acid 300 mg + ethenzamide 100 mg + caffeine 50 mg; acetylsalicylic acid 250 mg + paracetamol 250 mg + caffeine 65 mg	acetylsalicylic acid: 1.8 g	acetylsalicylic acid: 3 g
PT	Not subject to prescription	Oral use	acetylsalicylic acid 400 mg + ascorbic acid 240 mg; acetylsalicylic acid 500 mg + ascorbic acid 100 mg + caffeine 50 mg; acetylsalicylic acid 500 mg + caffeine 30 mg; acetylsalicylic acid 250 mg + paracetamol 250 mg + caffeine 65 mg		
RO	Not subject to prescription				
RS	Not subject to prescription		acetylsalicylic acid 500 mg + ascorbic		acetylsalicylic acid: 2400 mg

			acid 300 mg; acetylsalicylic acid 300 mg + ibuprofen 200 mg		
SE	POM + Exemption POM: combination products with MQP 37.5 g acetylsalicylic acid	Oral use			
SI	Not subject to prescription				
UK**	POM + Exemption	Ex.: oral use			

* IE: Retail sale through pharmacies only in blister packs containing not more than 24 unit dosage forms. Not more than two such packs should be supplied in the course of any one retail transaction unless a valid prescription exists. The indications should be appropriate for self-diagnosis and self-treatment. Packs containing more than 24 unit dosage forms may be supplied to pharmacies for use by pharmacists provided the label states that they are for dispensing purposes only. Packs containing more than 50 unit dosage forms are prescription only. Promotion to the general public for packs containing not more than 24 unit dosage forms. Aspirin-containing medicinal products should not be administered to subjects under 16 years of age unless specifically indicated by a healthcare professional. Promotion to healthcare professionals only for packs containing more than 24 unit dosage forms.

** UK: acetylsalicylic acid with codeine can be sold to the public (as a pharmacy medicine) provided packs contain no more than 32 capsules or tablets.

No data available from other member states.

Melclass database[1]: Currently not available.

3.2 Social dimension of classification

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

Recommendation: **Not subject to prescription** (oral use, short-term treatment, not to be used in children under age of 16 years).

Criteria:
Known safety profile.
Continuous medical supervision not required.
Good accessibility to medications required for prompt pain management.

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. COMMENTS/REFERENCES

4.1 References: Product information available at the following databases of medicines: Portugal (https://bit.ly/2XrNLPx), Ireland (https://bit.ly/2UeYZFr) and United Kingdom (https://bit.ly/2VkzGSn).

4.2 Comments: -

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Salicylamide, Combinations excl. Psycholeptics

1.2 ATC code: N02BA55

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, a combination product containing 300 mg of salicylamide, 200 mg of ascorbic acid, 50 mg of rutoside and 5 mg of zinc is authorised in Poland (classification status: Not subject to prescription). No medications containing salicylamide in combination with other active substances are authorised in the rest of the member states.

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, medicines containing salicylamide in combination with other active substances are not authorised in at least 3 member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Micromedex (https://bit.ly/2tCGq23)

Product information available in the Polish Medicinal Products Registry (https://bit.ly/2EyuvZi)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Ethenzamide, Combinations excl. Psycholeptics

1.2 ATC code: N02BA57

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing ethenzamide in combination with other active substances are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Dipyrocetyl, Combinations excl. Psycholeptics

1.2 ATC code: N02BA59

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing dipyrocetyl in combination with other active substances are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Carbasalate Calcium, Combinations excl. Psycholeptics

1.2 ATC code: N02BA65

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: no data (based on the available data, no medicines containing carbasalate calcium in combination with other active substances are authorised in member states).

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing carbasalate calcium in combination with other active substances are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Acetylsalicylic acid, Combinations with Psycholeptics

1.2 ATC code: N02BA71

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, a combination product containing 300 mg of acetylsalicylic acid, 100 mg of ethenzamide and 50 mg of caffeine is authorised in Poland (classification status: Not subject to prescription). No medications containing acetylsalicylic acid in combination with psycholeptics are authorised in 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: based on the available data, medicines containing acetylsalicylic acid in combination with psycholeptics are not authorised in at least 3 member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Micromedex (https://bit.ly/2tCGq23)

Product information available in the Polish Medicinal Products Registry (https://bit.ly/2EyuvZi)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Salicylamide, Combinations with Psycholeptics

1.2 ATC code: N02BA75

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing salicylamide in combination with psycholeptics are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Micromedex (https://bit.ly/2tCGq23)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Ethenzamide, Combinations with Psycholeptics

1.2 ATC code: N02BA77

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing ethenzamide in combination with psycholeptics are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Dipyrocetyl, Combinations with Psycholeptics

1.2 ATC code: N02BA79

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing dipyrocetyl in combination with psycholeptics are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Phenazone

1.2 ATC code: N02BB01

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Metamizole Sodium

1.2 ATC code: N02BB02

1.3 Therapeutic indications: pain and fever not responding to other treatments.

1.4 Posology and duration of treatment: dose not stated. Maximum daily dose varies across countries (see table). Short-term treatment.

1.5 Pharmaceutical forms: oral, rectal, intramuscular (IM) and IV.

1.6 Contraindications: metamizole sodium is contraindicated in the following cases: hypersensitivity to the active substance, pyrazolones or pyrazolidines, e.g. medicinal products containing metamizole sodium, propyphenazone, phenazone or phenylbutazone (this also includes patients who have, for example, developed agranulocytosis after the use of these substances) or to any of the excipients; in patients with known analgesic asthma syndrome or known analgesic intolerance of the urticaria/angioedema type, i.e. patients who react with bronchospasm or other anaphylactoid types of reaction to salicylates, paracetamol or other non-narcotic analgesics, such as diclofenac, ibuprofen, indomethacin or naproxen; disturbances of bone marrow function (e.g. after treatment with cytostatic medicinal products) or haematopoietic disorders; hereditary glucose-6-phosphate dehydrogenase deficiency; acute hepatic porphyria; third trimester of pregnancy; breastfeeding; infants during the first 3 months of life or weighing less than 5 kg, as there are no scientific data available on the safety of use.

1.7 Relevant warnings: risk of anaphylaxis, agranulocytosis, pancytopenia, severe skin reactions and hypotensive reactions.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): the main undesirable effects of metamizole sodium are derived from hypersensitivity reactions. The most significant are shock and agranulocytosis. These reactions occur rarely or very rarely, but are life-threatening and may also occur if metamizole sodium was previously given without complications.

2.2 Indirect risks (incorrect use): overdosage can result if the stated dose is exceeded. Acute overdose is followed by nausea, vomiting, abdominal pain, renal impairment/acute renal failure (e.g. with the clinical picture of interstitial nephritis) and, more rarely, CNS symptoms (dizziness, somnolence, coma, convulsions) and a fall in blood pressure, sometimes including shock and tachycardia. Following very high doses, elimination of rubazonic acid may cause a red discolouration of the urine.

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	Additional information			
		Route of Administration/Indications	MS	MDD	MQP
AM	POM + Exemption	Treatment of pains of different origin and variable intensity; high fever, not responding to other drugs.	Ex.: 500 mg (oral) POM: IV solution		10 g
AT	List I				
BE	POM				

BiH	POM				
CH	List II				
CZ	POM				
DE	POM				
ES	POM				
HR	POM				
HU	POM	Treatment of fever and/or moderate or severe pain.	500 mg	4000 mg	25000 mg
IE	Not authorised				
IT	List II	Severe or severe febrile or feverish states. IM or iV forms should be used only when it is not possible to use oral or rectal forms; infants only IM administration.	Oral and rectal use: 500 mg IV: 1000 mg		
LV	POM				
MK	POM + Exemption	Pain of different origin, treatment of severe pain in patients with cancer, pain after surgery.	POM: 2.5 g/5 mL for parenteral use Ex.: 500 mg (oral use)		
NL	POM				
PL	POM + Exemption	Short-term treatment of severe pain and fever, where other measures are inappropriate or ineffective. Adults only.	Ex.: oral use: 500 mg POM (IV/IM): 500 mg/mL sol. for injection	Ex.: oral use: 500 mg POM (IV/IM): 500 mg/mL sol. for injection	Ex.: 3000 mg POM: 250 g
PT	Not authorised				
RO	List I				
SE	Not authorised				
UK	Not authorised				

No more data available from other member states.

Melclass database[1]: List I.

3.2 Social dimension of classification:

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

Proposed recommendation: information on the Melclass database indicates that this substance is **List I**. Given the pharmacological profile of this active substance and the fact that medications containing metamizole sodium are not first-line treatment in the management of pain and fever, no change in the classification is proposed.

4. REFERENCES/COMMENTS

4.1 References: Product information available in the databases of the Austrian Medicines and Medical Devices Agency (https://bit.ly/2VFphks), Italian Medicines Agency (https://bit.ly/2Udlg6o) and Spanish Agency for Medicines and Health Products (https://bit.ly/2GpiFCV).

4.2 Comments: -

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Aminophenazone

1.2 ATC code: N02BB03

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, medications containing aminophenazone are authorised in Hungary (classification status: POM). No medications containing this active substance are authorised in the rest of the member states.

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, medicines containing this active substance are not authorised in at least 3 member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Propyphenazone

1.2 ATC code: N02BB04

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Nifenazone

1.2 ATC code: N02BB05

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing this active substance are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Phenazone, Combinations excl. Psycholeptics

1.2 ATC Code: N02BB51

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, medications containing phenazone in combination with other active substances are authorised in Sweden (classification status: POM + Exemptions; Exemptions: oral use: MS: 400 mg of phenazone + 50 mg of caffeine). No medications containing phenazone in combination with other active substances are authorised in the rest of the member states.

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, medicines containing phenazone in combination with other active substances are not authorised in at least 3 member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: product information available in the database of the Swedish Medical Products Agency (https://bit.ly/2BZwxzZ).

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Metamizole Sodium, Combinations excl. Psycholeptics

1.2 ATC Code: N02BB52

1.3 Therapeutic indications: strong pain in gastric or intestinal colic, renal colic in nephrolithiasis, spastic dyskinesia of the biliary tract, dysmenorrhoea (AM).
Treatment of severe headache; treatment of mild or moderate migraine (HU).
Severe or resistant headache, the initial phase of mild and moderate migraine attacks (RO).

1.4 Posology and duration of treatment: maximum daily dose: 1500 mg to 3000 mg (AM).

1.5 Pharmaceutical forms: oral and IV

1.6 Contraindications: medications containing metamizole sodium in combination with other active substances are contraindicated in the following cases: hypersensitivity to the active substances, other pyrazolone derivatives (including patients with a history of agranulocytosis following the use of such medicinal products) and/or any of the excipients; acute liver porphyria; glucose-6-phosphate dehydrogenase deficiency (risk of haemolysis); severe liver and/or kidney problems; bone marrow dysfunction or haematological disorders, including aplastic anaemia, agranulocytosis and leukopenia; pregnancy and breastfeeding period; children under 16 years of age; hypotension with systolic blood pressure less than 100 mmHg.

1.7 Relevant warnings: metamizole should only be used temporarily and only when the benefit of the medicine exceeds the risk of possible side effects or when there is no alternative to the medicine. The risk of agranulocytosis increases with prolonged use of metamizole and, therefore, blood counts should be monitored regularly, including a differentiated white blood cell count. Caution should be exercised when prescribing this medicine to patients with allergic diseases (e.g. bronchial asthma, chronic upper respiratory tract inflammation), and in patients with a history of hypersensitivity reactions, known hypersensitivity to analgesic and antirheumatic agents, other medicines and food, because there is an increased risk of allergic reactions and asthma attacks. Metamizole may cause hypotensive reactions - these reactions are dose-dependent and are observed in parenteral therapy. Nevertheless, caution should be exercised when using metamizole in tablet form, especially in patients with hypotension, fluid depletion or dehydration as well as unstable blood circulation. Metamizole should not be taken with alcohol, as the effect of the medicine is increased in this case. In addition, it should be used with caution in patients with liver and kidney disease.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): possible side effects are mainly due to metamizole sodium.

Blood and lymphatic system disorders: agranulocytosis, leukopenia, aplastic anaemia, haemolytic anaemia, thrombocytopenia. The risk of agranulocytosis cannot be predicted. This is also possible when metamizole has been used in the past without any complications. The risk of agranulocytosis is higher with prolonged (longer than 1 week) use of metamizole.

GI disorders: nausea, vomiting; abdominal pain and abdominal pain, ulcers and bleeding (which may be clinically manifested as haematemesis, melena).

Renal and urinary disorders: proteinuria, oliguria, polyuria, anuria, interstitial nephritis. Renal impairment may occur at high doses.

Metabolism and nutrition disorders: decreased appetite.

Cardiac dysfunction: palpitations, tachycardia, cyanosis.

Vascular disorders: hypotension.

Immune system disorders: drug-induced exanthema, maculopapular rash, anaphylactic or anaphylactoid reactions.

Hypersensitivity reactions: itching, hives, oedema (generalised or localised), erythema, angioedema, vasomotor disorders, bronchospasm. Asthma attacks, Stevens–Johnson syndrome, Lyell's syndrome, anaphylactic shock (mainly after parenteral administration or after oral administration of metamizole at high doses in sensitive patients).

Nervous system disorders: headache, dizziness.

Hepatobiliary system disorders: Increased liver enzymes, cholestasis, hyperbilirubinaemia.

2.2 Indirect risks (incorrect use): overdosage can result if the stated dose is exceeded. The following symptoms may occur in case of overdose: GI disorders: nausea, vomiting, hematemesis, and melena. Toxic/allergic symptoms: vesicular-bullous skin lesions, urticaria, petechiae, sometimes with measles or typhoid-like rash, in some cases may develop toxic-allergic shock; cerebral symptoms: Ménière's syndrome-like symptoms, ringing in the ears, dizziness, drowsiness, apnoea, coma with hypotension, tonic-clonic seizures; metabolic disorders: metabolic alkalosis; haematological changes: agranulocytosis, aplastic anaemia or haemolytic anaemia, haemorrhagic diathesis. Acute renal and/or liver failure, oliguria, anuria, hypothermia and tachycardia are also possible. At very high doses, urine may be coloured red.

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	Additional information			
		Route of Administration/Indications	MS	MDD	MQP
AM	POM + Exemption	Strong pain in gastric or intestinal colic, renal colic in nephrolithiasis, spastic dyskinesia of the biliary tract, dysmenorrhoea. Ex.: oral forms POM: solution for injection		Ex.: 3000 mg (adults)/250-1500 mg (children)	Ex.: 50 g
AT	Not authorised				
BE	Not authorised				
CH	Not authorised				
CZ	Not authorised				
EE	Not authorised				
FI	Not authorised				
ES	Not authorised				
FR	Not authorised				
HR	Not authorised				
HU	POM	Treatment of severe headache; treatment of mild or moderate migraine Available combination products: metamizole sodium, drotaverine and caffeine; metamizole sodium and caffeine.	500 mg	1500 mg	8000 mg
IE	Not authorised				
IT	Not authorised				
LT	Not authorised				
LV	POM	Available combination product: metamizole sodium and triacetonamini-4-toluensulfon			
MK	Not authorised				

NL	Not authorised				
NO	Not authorised				
PL	Not authorised				
PT	Not authorised				
RO	List I	Severe or resistant headache, the initial phase of mild and moderate migraine attacks. Available combination product: metamizole sodium, drotaverine and caffeine.	400 mg	1200 mg	4000 mg
SE	Not authorised				
SI	Not authorised				
RS	Not authorised				
UK	Not authorised				

No more data available from other member states.

Melclass database[1]: Currently not available.

3.2 Social dimension of classification:

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

Proposed recommendation: **List I**

Criteria: not first-line treatment for pain relief.

4. REFERENCES/COMMENTS

4.1 References: Product information available in the databases of the Latvian State Agency of Medicines (https://bit.ly/2UfaXyw) and Hungarian National Institute of Pharmacy and Nutrition (https://bit.ly/2Xzpyar).

4.2 Comments: -

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Aminophenazone, Combinations excl. Psycholeptics

1.2 ATC code: N02BB53

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing aminophenazone in combination with other active substances are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Propyphenazone, Combinations excl. Psycholeptics

1.2 ATC code: N02BB54

1.3 Therapeutic indications: relief of mild or moderate pain (ES).
Relief of pain; treatment of fever and pain associated with cough and cold (BiH).
Inflammatory conditions of the upper airways (sinusitis, tonsillitis, pharyngitis, laryngitis, tracheobronchitis) also associated with cough and fever (IT).

1.4 Posology and duration of treatment: maximum daily dose is 1050 mg of propyphenazone.

1.5 Pharmaceutical forms: oral and suppositories.

1.6 Contraindications: hypersensitivity to the active substances or to any of the excipients; children under 6 months; granulocytopaenia; acute intermittent porphyria; glucose-6-phosphate dehydrogenase insufficiency.

1.7 Relevant warnings: due to the presence of propyphenazone, high doses and prolonged treatments with this medicinal product can cause, in hypersensitive subjects, blood system disorders. Periodic blood tests are recommended during prolonged treatments.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): side effects are not usually observed at the recommended doses. In hypersensitive subjects skin allergic reactions have been rarely observed. Occasionally, dizziness, nausea, nervousness, rapid heartbeat, or gastrointestinal irritation have been reported. Exceptionally (< 1%), agranulocytosis, aplastic anaemia, leukopenia, thrombocytopenia, anaphylactic reactions and dyspnoea have been observed.

2.2 Indirect risks (incorrect use): overdosage can result if the stated dose is exceeded. The following symptoms may occur in case of overdose: abdominal pain, nausea, vomiting, drowsiness or insomnia, excitement, irregular heartbeat, respiratory depression, seizures, coma with hypotension, shock and oliguria. The treatment is symptomatic. The medication should be eliminated as soon as possible from by means of gastric lavage, forced diuresis or dialysis.

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	Additional information			
		Route of Administration/Indications	MS	MDD	MQP
AM	Not authorised				
AT	Not authorised				
BE	Not authorised				
BiH	Not subject to prescription	Oral use Short-term treatment (3 days) Adults only			
CH	Not authorised				
CZ	Not authorised				
DE	Not authorised				

EE	Not authorised				
FI	Not authorised				
ES	Not subject to prescription	Available combination product: propyphenazone and caffeine.	Available combination products: tablets: propyphenazone 175 mg and 25 mg caffeine; suppositories: propyphenazone 500 mg and caffeine 75 mg		
FR	Not authorised				
HR	Not authorised				
HU	Not authorised				
IE	Not authorised				
IT	Not subject to prescription	Inflammatory conditions of the upper airways (sinusitis, tonsillitis, pharyngitis, laryngitis, tracheobronchitis) also associated with cough and fever. Rectal use. Available combination product: propyphenazone and oxolamine.	Adults: propyphenazone 350 mg and oxolamine Children: propyphenazone 150 mg and oxolamine 250 mg	Adults: propyphenazone: 1050 mg Children: 375 mg	
LT	Not authorised				
LV	Not authorised				
MK	Not authorised				
NL	Not authorised				
NO	Not authorised				
PL	Not authorised				
PT	Not authorised				
RO	Not authorised				
SE	Not authorised				
SI	Not authorised				
RS	Not authorised				
UK	Not authorised				

No more data available from other member states.

Melclass database[1]: Currently not available.

3.2 Social dimension of classification:

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

Proposed recommendation: **Not subject to prescription** (oral and rectal use; short-term use).

Criteria:
Well-known safety profile.
Continuous medical supervision not required.

4. REFERENCES/COMMENTS

4.1 References: Product information available in the databases of the Italian Medicines Agency (https://bit.ly/2Udlg6o) and Spanish Agency for Medicines and Health Products (https://bit.ly/2GpiFCV).

4.2 Comments: -

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Phenazone, Combinations with Psycholeptics

1.2 ATC code: N02BB71

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing aminophenazone in combination with psycholeptics are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Metamizole Sodium, Combinations with Psycholeptics

1.2 ATC code: N02BB72

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, medications containing metamizole sodium in combination with other active substances are authorised in Armenia (classification status: not subject to prescription; oral use: MS: 500 mg of metamizole and 20 mg of triacetonamine 4-toluenesulfonate). No medications containing metamizole sodium in combination with psycholeptics are authorised in the rest of the member states.

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, medicines containing metamizole sodium in combination with psycholeptics are not authorised in at least 3 member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: product information available in the database of the Armenian Scientific Center of Drug and Medical Technology Expertise (https://bit.ly/2P6DIiJ).

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Aminophenazone, Combinations with Psycholeptics

1.2 ATC code: N02BB73

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, medications containing aminophenazone in combination with other active substances are authorised in Hungary (classification status: POM; oral use: MS: 100 mg of aminophenazone and 20 mg of phenobarbital). No medications containing aminophenazone in combination with psycholeptics are authorised in the rest of the member states.

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, medicines containing aminophenazone in combination with psycholeptics are not authorised in at least 3 member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: product information available in the database of the Hungarian National Institute of Pharmacy and Nutrition (https://bit.ly/2Xzpyar).

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Propyphenazone, Combinations with Psycholeptics

1.2 ATC code: N02BB74

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, medications containing propyphenazone in combination with other active substances are authorised in Italy (classification status: List II; rectal use: MS: 375 mg of propyphenazone + 150 mg of butalbital + 75 mg of caffeine; oral use: MS: 125 mg of propyphenazone + 50 mg of butalbital + 25 mg of caffeine). No medications containing propyphenazone in combination with psycholeptics are authorised in the rest of the member states.

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, medicines containing propyphenazone in combination with psycholeptics are not authorised in at least 3 member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: product information available in the database of the Italian Medicines Agency (https://bit.ly/2Udlg6o).

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Paracetamol

1.2 ATC code: N02BE01

1.3 Therapeutic indications: prescription: mild to moderate pain; pyrexia; mild to moderate pain in patients with risk factors for hepatotoxicity; pyrexia in patients with risk factors for hepatotoxicity; pain; pyrexia with discomfort; prophylaxis of post-immunisation pyrexia following immunisation with meningococcal group B vaccine; post-immunisation pyrexia in infants.

Non-prescription: for the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains, aches and pains, symptomatic relief of rheumatic aches and pains and of influenza, feverishness and feverish colds.

1.4 Posology and duration of treatment: mild to moderate pain and pyrexia: oral use: adults: 0.5-1 g every 4-6 hours, maximum 4 g per day. IV infusion: adults (body weight up to 50 kg): 15 mg/kg every 4-6 hours, dose to be administered over 15 minutes, maximum 60 mg/kg per day; adults (body weight 50 kg and above): 1 g every 4-6 hours, dose to be administered over 15 minutes; maximum 4 g per day. Rectal use: adults: 0.5-1 g every 4-6 hours, maximum 4 g per day.

Mild to moderate pain in patients with risk factors for hepatotoxicity and pyrexia in patients with risk factors for hepatotoxicity: IV infusion: adults (body weight up to 50 kg): 15 mg/kg every 4-6 hours, dose to be administered over 15 minutes, maximum 60 mg/kg per day; adults (body weight 50 kg and above): 1 g every 4-6 hours, dose to be administered over 15 minutes, maximum 3 g per day.

Pain and pyrexia with discomfort: oral use: children 3-5 months: 60 mg every 4-6 hours, maximum 4 doses per day; children 6 months-1 year: 120 mg every 4-6 hours, maximum 4 doses per day; children 2-3 years: 180 mg every 4-6 hours, maximum 4 doses per day; children 4-5 years: 240 mg every 4-6 hours, maximum 4 doses per day; children 6-7 years: 240-250 mg every 4-6 hours, maximum 4 doses per day; children 8-9 years: 360-375 mg every 4-6 hours; maximum 4 doses per day; children 10-11 years: 480–500 mg every 4-6 hours, maximum 4 doses per day; children 12-15 years: 480-750 mg every 4-6 hours, maximum 4 doses per day; children 16-17 years: 0.5-1 g every 4-6 hours, maximum 4 doses per day. Rectal use: children 3-11 months: 60-125 mg every 4-6 hours as required, maximum 4 doses per day; children 1-4 years: 125-250 mg every 44-6 hours as required, maximum 4 doses per day; children 5-11 years: 250–500 mg every 4-6 hours as required, maximum 4 doses per day; children 12-17 years: 500 mg every 4-6 hours.

Prophylaxis of post-immunisation pyrexia following immunisation with meningococcal group B vaccine: oral use: children 2 months: 60 mg, first dose to be given at the time of vaccination, then 60 mg after 4-6 hours, then 60 mg after a further 4-6 hours; children 4 months: 60 mg, first dose to be given at the time of vaccination, then 60 mg after 4-6 hours, then 60 mg after a further 4-6 hours.

Post-immunisation pyrexia in infants: oral use: children 2-3 months: 60 mg for 1 dose, then 60 mg after 4-6 hours if required; children 4 months: 60 mg for 1 dose, then 60 mg after 4-6 hours, maximum 4 doses per day.

1.5 Pharmaceutical forms: tablet (500 mg), suppository (60 mg, 80 mg, 120 mg, 125 mg, 240 mg, 250 mg, 500 mg, 1 g), oral suspension (120 mg/5 mL, 250 mg/5 mL), effervescent tablet (500 mg), solution for infusion (1 g/100 mL, 500 mg/50 mL), oral solution (120 mg/5 mL, 500 mg/5 mL), powder (650 mg/sachet), capsule (500 mg), orodispersible tablet (250 mg).

1.6 Contraindications: hypersensitivity to paracetamol or any of the constituents.

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

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): adverse events with paracetamol from historical clinical trial data are both infrequent and from exposure of small numbers of patients. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare.

Blood and lymphatic system disorders: thrombocytopenia, agranulocytosis.

Immune system disorders, anaphylaxis, cutaneous hypersensitivity reactions, including skin rashes, angioedema and Stevens–Johnson syndrome/toxic epidermal necrolysis

Respiratory, thoracic and mediastinal disorders: bronchospasm (there have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs).

Hepatobiliary disorders: hepatic dysfunction.

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

Symptoms: symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after administration and clinical symptoms generally culminate after 4 to 6 days. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management: immediate treatment is essential in the management of paracetamol overdose. Despite a lack of clinically significant early symptoms, patients should be referred urgently to hospital for immediate medical attention. This is because early symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines. As concentrations soon after paracetamol ingestion are unreliable, plasma paracetamol concentration should be measured at 4 hours or later after the initial administration. Treatment with N-acetylcysteine may be used for up to 24 hours after administration of paracetamol; however, the maximum protective effect is only obtained up to 8 hours post-administration. The effectiveness of this antidote declines sharply after this 8 hour time period. If required, the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, then oral methionine may be a suitable alternative for remote areas, outside hospital. Management of those patients presenting with serious hepatic dysfunction 24 hours after paracetamol administration should be discussed with the national poisons information centres or a liver unit.

2.3 Recent cases at European level: following a review, the European Medicines Agency (EMA) experts in medicine safety have recommended that modified-release or prolonged-release paracetamol products (designed to release paracetamol slowly over a longer period than the usual immediate-release products) should be suspended from marketing. This is in view of the risks to patients from the complex way these medicines release paracetamol into the body after an overdose. The review of modified-release paracetamol has been carried out by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), following a request from the Swedish medicines authority (Medical Products Agency), which had noted problems in managing overdose with such products since marketing approval. The PRAC evaluated published studies and reports of overdose with these medicines, consulted experts in the management of poisoning and assessed how overdose with paracetamol is managed in the EU and other

parts of the world. Experience has shown that in overdose (particularly at high doses), because of the way the paracetamol in modified-release products is released in the body, the usual treatment procedures developed for immediate-release products are not appropriate. If doctors are not aware modified-release paracetamol has been taken, which affects decisions such as when and for how long to give an antidote, overdose might result in severe liver damage or death. In modified-release products that also contain the painkiller tramadol, this could be complicated further because of the additional effects of overdose with tramadol. In many cases, it may not be known whether an overdose of paracetamol involves immediate-release or modified-release products, making it difficult to decide what type of management is needed. The committee could not identify means to minimise the risk to patients, or a feasible and standardised way to adapt the management of paracetamol overdose across the EU to allow for treatment of cases that involve modified-release preparations. It concluded on balance that the risk following overdose with these medicines outweighs the advantage of having a longer-acting preparation. The PRAC therefore recommended that marketing of modified-release paracetamol medicines should be suspended. Immediate-release paracetamol products, which are not affected by this review, will continue to be available as before. When used appropriately and in recommended doses the benefits of paracetamol outweigh its risks. It remains important that patients seek medical advice quickly if they have taken, or think they may have taken, more than the recommended amount of any paracetamol-containing product. Patients should also consult a healthcare professional if they have any other concerns about their medication.

On 13 December 2017 the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) endorsed by majority the PRAC's recommendation that the marketing authorisations for medicines containing modified-release paracetamol, alone or combined with the opioid medicine tramadol, should be suspended. The medicines will remain suspended unless the companies that hold the marketing authorisations can provide evidence of appropriate and practical EU-wide measures to help prevent overdose with these products and adequately reduce its risks. Because the CMDh decision was agreed by majority vote it was sent to the European Commission which issued a final legally binding decision valid throughout the EU on 19 February 2018.

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	Additional information			
		Routes of administration/Indications	MS	MDD	MQP
AM	POM + Exemption	Ex.: oral and rectal use	Ex.: 325 mg suppositories; 500 mg tablets POM: 150 mg/mL solution for infusion	Ex.: 325 mg suppositories; 4000 mg tablets POM: 150 mg/mL solution for infusion	Ex.: 3250 mg suppositories; 500000 mg tablets; POM: 3015 mg solution for infusion
AT	List II + Exemption	Ex.: oral use	650 mg	2 g	
BE	POM + Exemption	Ex.: oral use	1 g	4 g	10.5 g
BiH	Not subject to prescription	Oral use	600 mg	4000 mg	
CH	List II + Exemption		Ex.: 500 mg	1000 mg	
CZ	POM + Exemption		Ex.: oral and rectal use: 500 mg	15 g	
ES	POM + Exemption		Ex.: oral use: 1 g Ex.: rectal use:600 mg		
FI	POM + Exemption		Ex.: oral use: 500 mg Ex.: rectal use: 250 mg		
FR	List I + Exemption	Ex.: oral use	Ex.: 1 g		
HU	Not subject to prescription		1000 mg	4000 mg	10000 mg
IE*	Not subject to prescription		1000 mg		

	(supply through general sales)				
IT	List II + Exemption	Ex. oral and rectal use	Ex: 1000 mg		16 g
LT	POM + Exemption	Ex.: oral and rectal use	Ex.: 500 mg		10 g
LV	POM + Exemption		Ex.: oral use: 500 mg Ex.: rectal use: 150 mg		
MK	POM + Exemption	Ex.: oral and rectal use	Ex.: 500 mg		
NL	POM + Exemption		Ex.: oral and rectal use: 1000 mg		
PL	POM + Exemption		Ex.: 1000 mg (oral and rectal use) POM: 1 g (IV)		Ex.: 25 g (oral and rectal use) POM: 10 g (IV)
PT	POM + Exemption		Ex.: oral and rectal use: 500 mg POM: oral and rectal use: 1000 mg; parenteral use; 150 mg/mL		
RO	Not subject to prescription		1000 mg	4000 mg	10000 mg
RS	Not subject to prescription		500 mg	4 g	12 g
SE	POM + Exemption	Ex.: oral and rectal	Ex.: oral use: 500 mg Rectal use: 1 g		
SI	POM + Exemption	Ex.: oral and rectal use	Ex.: 500 mg		
UK	Not subject to prescription (Pharmacy-only and General Sales List)		500 mg	4 g	P: 16 g GSL: 8 g

*IE: General Sale: maximum pack size: 12 items (500 mg). Contains only paracetamol as analgesic. Maximum one pack per sale. Pharmacy-only: maximum pack size: 24 items. Maximum two packs per sale. Prescription only: Pack size greater than 24 items. Product not supplied in blister packs. Promotion to the public: Pack size not more than 24 items. Healthcare professionals: Pack size greater than 24 items.

No more data available from other member states.

Melclass database[1]: List I + Exemption (exemptions: oral use; MS: 1 g; MDD: 4 g; MQP: 10 g).

3.2 Social dimension of classification:

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

Proposed recommendation: **No change.** Paracetamol is classified under List I + Exemption. The exemption is as follows: oral treatment with MS 1 g, MDD: 4 g, MQP 10 g. Paracetamol is a well-known active substance and its use is well established. In addition, the conditions applicable to paracetamol across countries are consistent with this information.

3.2.2 Paediatric use: for use in children 2 months old and over.

3.2.3 Social dimension: no comment.

4. REFERENCES/COMMENTS

4.1 References: Modified-release paracetamol-containing products to be suspended from EU market (link: https://bit.ly/2gpAjqW).

Summary of product characteristics (SmPC) available in the UK database of medicines (http://www.mhra.gov.uk/spc-pil/index.htm)

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

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4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Phenacetin

1.2 ATC code: N02BE03

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing phenacetin are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Bucetin

1.2 ATC code: N02BE04

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing bucetin are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Propacetamol

1.2 ATC code: N02BE05

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing propacetamol are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Paracetamol, Combinations excl. Psycholeptics

1.2 ATC code: N02BE51

1.3 Therapeutic indications: there are many different combination products containing paracetamol in combination with caffeine, chlorphenamine, ibuprofen, pseudoephedrine, phenylephrine, pheniramine, propyphenazone, diphenhydramine, dextromethorphan, guaifenesin and ascorbic acid available as non-prescription medicines. These are for the symptomatic relief of colds and flu.

NOTE: combinations of paracetamol with opioids should be classified in N02AJ - Opioids in combination with non-opioid analgesics. This includes combinations with codeine (N02AJ06) and dihydrocodeine (N02AJ01).

1.4 Posology and duration of treatment: the maximum daily dose of paracetamol is these combinations is limited to 4 g.

1.5 Pharmaceutical forms: forms for oral use (tablet, powder, capsule).

1.6 Contraindications: hypersensitivity to paracetamol or any of the constituents.

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

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): adverse events of paracetamol from historical clinical trial data are both infrequent and from exposure of small numbers of patients. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class. Due to limited clinical trial data, the frequency of these adverse events is not known (it cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare.

Blood and lymphatic system disorders: thrombocytopenia, agranulocytosis.

Immune system disorders: anaphylaxis, cutaneous hypersensitivity reactions, including skin rashes, angioedema and Stevens–Johnson syndrome/toxic epidermal necrolysis

Respiratory, thoracic and mediastinal disorders: Bronchospasm*

Hepatobiliary disorders: hepatic dysfunction.

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

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

2.3 Recent cases at European level: nothing specific for paracetamol in combination products. However, see the evidence-based review specifically for paracetamol.

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	Additional information			
		Route of Administration/Indications	MS	MDD	MQP
AM	Not subject to prescription	Note: available combination products: paracetamol, phenylephrine, pheniramine; paracetamol, pheniramine, phenylephrine, ascorbic acid; paracetamol, caffeine, phenylephrine, terpin hydrate, ascorbic acid; paracetamol, chlorphenamine, ascorbic acid	paracetamol: 1000 mg	paracetamol: 4000 mg	paracetamol: 10 g
AT	List II + Exemption	Note: combination products not subject to prescription (exemptions): paracetamol and caffeine; paracetamol, ascorbic acid and acetylsalicylic acid; paracetamol, caffeine and acetylsalicylic acid; paracetamol and pseudoephedrine; paracetamol and phenylephrine; paracetamol and ascorbic acid			
BiH	Not subject to prescription	Note: available combination product: paracetamol and ascorbic acid	paracetamol: 500 mg		
BE	POM + Exemption depending on quantity paracetamol in package				
CH	List II + Exemption	Ex.: oral use	Ex: paracetamol: 500 mg		
CZ	POM + Exemption	Note: Ex.: different combination products available	Ex.: paracetamol: 1 g		
EE	Not authorised				
ES	POM + Exemption	Note: POM: some combination products containing phenylephrine are POM. All the other available products are not subject to prescription.			
FI	Not subject to prescription	Note: available combination products: paracetamol and caffeine; paracetamol and ascorbic acid.			
FR	Not subject to prescription				
GE	Not subject to prescription				
HR	Not subject to prescription				
HU	Not subject to prescription	Note: available combination products: paracetamol in combination with propyphenazone, caffeine, phenylephrine, ibuprofen, ascorbic acid	paracetamol: 1000 mg	paracetamol: 4000 mg	paracetamol: 10000 mg

IE	Not subject to prescription	Note: GSL: maximum pack size: 12 items. It contains only paracetamol as analgesic. Maximum one pack per sale. Pharmacy-only: maximum pack size: 24 items. Maximum two packs per sale. Promotion to the public: pack size not more than 24 items. P: Combination of paracetamol and dextromethorphan for night-time pain; Pharmacy-only: maximum pack size: 24 items. Maximum two packs per sale. Promotion to the public: pack size not more than 24 items.			
IT	List II + Exemption	Note: combination products not subject to prescription (exemptions): paracetamol and caffeine; paracetamol and chlorphenamine. List II: paracetamol (MS: 2400 g) and chlorphenamine (MS: 15 mg); paracetamol (MS: 1000 g) and caffeine (MS: 130 mg); paracetamol (MS: 500 mg) and ibuprofen (MS: 150 mg)	Ex.: paracetamol: 1000 mg		Ex.: paracetamol: 20 g
LT	POM + Exemption	Note: POM: combination products containing paracetamol MQP: 50 g + caffeine: MQP: 6.5 g			
LV	Not subject to prescription				
MK	Not subject to prescription	Available combination product: paracetamol, propyphenazone, caffeine and codeine	paracetamol: 250 mg		
NL	POM + Exemption	Note: Ex.: different combination products available Combination products with codeine are POM	Ex.: paracetamol: 500 mg		
PL	POM + Exemption	Ex.: available combination products: paracetamol in combination with pseudoephedrine, phenylephrine, caffeine, dextromethorphan, acetylsalicylic acid, ascorbic acid, pheniramine, chlorpheniramine. Note: combination products with codeine (MS: 60 mg) are POM	Ex.: paracetamol: 1000 g		
PT	POM + Exemption	Ex.: available combination products: paracetamol and chlorphenamine; paracetamol and caffeine; paracetamol and pseudoephedrine; paracetamol and ibuprofen; paracetamol and diphenhydramine. Note: combination products with codeine (MS: 60 mg) are POM.			
RO	Not subject to prescription	Available combination products: paracetamol, phenylephrine and caffeine; paracetamol, codeine and caffeine.			
RS	Not subject to prescription				
SE	POM				
SI	POM + Exemption	Note: some combination products containing phenylephrine are POM.			
UK	Not subject to prescription				

No more data available from other member states.

Melclass database[1]: currently not available.

3.2 Social dimension of classification:

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

Proposed recommendation: given the large variation of combination products classified under this ATC code, the Committee of Experts CD-P-PH/PHO decided not to issue any recommendation for the legal classification of these preparations.

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: SmPC available in the UK database of medicines (http://www.mhra.gov.uk/spc-pil/index.htm).

Martindale: The Complete Drug Reference – 38th Edition.

4.2 Comments: -

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

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Phenacetin, Combination excl. Psycholeptics

1.2 ATC code: N02BE53

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, medications containing phenacetin in combination with other active substances are authorised in Hungary (classification status: POM; oral use: MS: 300 mg of phenacetin, 200 mg of aminophenazone and 50 mg of caffeine). No medications containing phenacetin in combination with other active substances are authorised in the rest of the member states.

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, medicines containing phenacetin in combination with other active substances are not authorised in at least 3 member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: product information available in the database of the Hungarian National Institute of Pharmacy and Nutrition (https://bit.ly/2Xzpyar).

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Bucetin, Combination excl. Psycholeptics

1.2 ATC code: N02BE54

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing bucetin in combination with other active substances are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Paracetamol, Combinations with Psycholeptics

1.2 ATC code: N02BE71

1.3 Therapeutic indications: different combination products are available containing paracetamol with caffeine and acetylsalicylic acid; paracetamol with carbasalate calcium and caffeine; paracetamol with pseudoephedrine and dextromethorphan; paracetamol, codeine and caffeine; paracetamol with ascorbic acid and pseudoephedrine; paracetamol with pseudoephedrine, ascorbic acid and dextromethorphan. These are for the symptomatic treatment of mild to moderate pain, and for the symptomatic relief of colds and flu.

1.4 Posology and duration of treatment: the maximum daily dose of paracetamol in these combinations is limited to 4 g.

1.5 Pharmaceutical forms: tablets for oral use.

1.6 Contraindications: hypersensitivity to paracetamol or any of the constituents.

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

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): adverse events of paracetamol from historical clinical trial data are both infrequent and from exposure of small numbers of patients. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare.

Blood and lymphatic system disorders: thrombocytopenia, agranulocytosis.

Immune system disorders: anaphylaxis, cutaneous hypersensitivity reactions, including skin rashes, angioedema and Stevens–Johnson syndrome/toxic epidermal necrolysis

Respiratory, thoracic and mediastinal disorders: bronchospasm*

Hepatobiliary disorders: hepatic dysfunction.

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

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

2.3 Recent cases at European level: nothing specific for paracetamol in combination products. However, see the evidence-based review specifically for paracetamol.

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	Additional information			
		Route of Administration/Indications	MS	MDD	MQP
AM	Not subject to prescription	Note: available combination product: paracetamol, acetylsalicylic acid and caffeine			
AT	Not subject to prescription	Note: available combination product: paracetamol and carbasalate calcium			
BA	Not subject to prescription	Note: available combination product: paracetamol, pseudoephedrine and dextromethorphan	paracetamol: 325 mg		
BE	Not authorised				
CH	Not authorised				
CZ	Not authorised				
DE	Not authorised				
EE	Not authorised				
ES	Not authorised				
FI	Not authorised				
FR	Not authorised				
GE	POM				
HR	Not authorised				
HU	Not authorised				
IE	Not authorised				
IT	Not authorised				
LT	Not subject to prescription	Note: available combination product: paracetamol, codeine and caffeine	paracetamol: 500 mg		
LV	Not subject to prescription	Note: available combination product: paracetamol, pseudoephedrine and dextromethorphan	paracetamol: 325 mg		
MK	Not subject to prescription	Note: available combination product: paracetamol, pseudoephedrine and ascorbic acid	paracetamol: 500 mg		
NL	Not authorised				
PL	Not authorised				
PT	Not authorised				
RO	Not authorised				
RS	Not authorised				
SE	Not authorised				
SI	Not subject to prescription	Note: available combination products: paracetamol, pseudoephedrine, ascorbic acid and dextromethorphan; paracetamol, pseudoephedrine and dextromethorphan	paracetamol: 500 mg		
RS	Not authorised				
UK	Not authorised				

No more data available from other member states.

Melclass database[1]: currently not available.

3.2 Social dimension of classification:

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

Proposed recommendation: given the variation of combination products classified under this ATC code, the Committee of Experts CD-P-PH/PHO decided not to issue any recommendation for the legal classification of these preparations.

3.2.2 Paediatric use: -

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

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Product information available at the following databases of medicines: Armenia (https://bit.ly/2P6DIiJ), Austria (https://bit.ly/2VFphks), Latvia (https://bit.ly/2UfaXyw), Lithuania (https://bit.ly/2J4KWRk), North Macedonia (https://bit.ly/2TkZn8V) and Slovenia (https://bit.ly/2EPKUZx).

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Phenacetin, Combination with Psycholeptics

1.2 ATC code: N02BE73

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing phenacetin in combination with psycholeptics are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Bucetin, Combination with Psycholeptics

1.2 ATC code: N02BE74

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing bucetin in combination with psycholeptics are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Rimazolium

1.2 ATC code: N02BG02

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing rimazolium are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Glafenine

1.2 ATC code: N02BG03

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing glafenine are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Floctafenine

1.2 ATC code: N02BG04

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing floctafenine are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Viminol

1.2 ATC code: N02BG05

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, no medicines containing viminol are authorised in member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: -

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Nefopam

1.2 ATC code: N02BG06

1.3 Therapeutic indications: nefopam is indicated for the relief of acute and chronic pain, including post-operative pain, dental pain, musculoskeletal pain, acute traumatic pain and cancer pain.

1.4 Posology and duration of treatment: adults: dosage may range from 1 to 3 tablets three times daily depending on response. The recommended starting dosage is 2 tablets three times daily.

Elderly: elderly patients may require reduced dosage due to slower metabolism. It is strongly recommended that the starting dose does not exceed 1 tablet three times daily as the elderly appear more susceptible to, in particular, the CNS side effects of nefopam and some cases of hallucinations and confusion have been reported in this age group.

Paediatric population: the safety and efficacy of nefopam have not been evaluated in children under 12 years; no dosage recommendation can be given for patients under 12 years.

Renal impairment: patients with end-stage renal disease might experience increased serum peak concentrations during treatment with nefopam. In order to avoid that, it is recommended the daily dose should be reduced not only for the elderly, but also for patients with terminal renal insufficiency.

1.5 Pharmaceutical forms: solution for injection: 20 mg/2 mL, oral forms: tablets: 30 mg.

1.6 Contraindications: hypersensitivity to the active substance. Nefopam is contraindicated in patients with a history of convulsive disorders and should not be given to patients taking monoamine oxidase inhibitors.

1.7 Relevant warnings: the side effects of nefopam may be additive to those of other agents with anticholinergic or sympathomimetic activity. It should not be used in the treatment of myocardial infarction since there is no clinical experience in this indication. Hepatic and renal insufficiency may interfere with the metabolism and excretion of nefopam. Nefopam should be used with caution in patients with angle closure glaucoma. Cases of nefopam dependence and abuse have been reported with nefopam use. Nefopam should be used with caution in patients with, or at risk of, urinary retention. Rarely a temporary, harmless pink discolouration of the urine has occurred.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance):

The following undesirable effects have been reported with the following frequency: not known (cannot be estimated from the available data)

System organ class	Frequency	Undesirable effects
Immune system disorders	Not known	Allergic reaction, anaphylactic reactions
Psychiatric disorders	Not known	Nervousness, convulsions, confusional state, hallucination, insomnia
Nervous system disorders	Not known	Lightheadedness, syncope, dizziness, paraesthesia, tremor, drowsiness, headache, coma
Eye disorders	Not known	Blurred vision
Cardiac disorders	Not known	Palpitations, tachycardia
Vascular disorders	Not known	Hypotension
GI disorders	Not known	Nausea, vomiting, dry mouth, GI disturbances (including abdominal pain and diarrhoea)
Skin and subcutaneous tissue disorders	Not known	Angioedema, sweating

Renal and urinary disorders	Not known	Urinary retention

2.2 Indirect risks (incorrect use): overdosage: the clinical pattern of nefopam toxicity in overdose is on the neurological (coma, convulsions, hallucinations and agitation) and cardiovascular systems (tachycardia with a hyperdynamic circulation). Routine supportive measures should be taken and prompt removal of ingested drug by gastric lavage or induced vomiting with syrup of ipecacuanha should be carried out. Oral administration of activated charcoal may help prevent absorption. Convulsions and hallucinations should be controlled (e.g. with intravenously or rectally administered diazepam). Beta-adrenergic blockers may help control the cardiovascular complications.

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	Additional information			
		Routes of administration/ Indications	MS	MDD	MQP
AM	POM				
AT	Not authorised				
BE	POM				
BiH	Not authorised				
Bulgaria (BG)	Not authorised				
CH	Not authorised				
CZ	Not authorised				
DE	Not authorised				
ES	Not authorised				
FI	Not authorised				
FR	List I				
HR	List I				
HU	Not authorised				
IE	List II				
IT	Not authorised				
LT	Not authorised				
LV	Not authorised				
MK	POM				
NL	Not authorised				
PL	POM				
PT	Not authorised				
RO	List I				
RS	POM				
SE	Not authorised				
SI	Not authorised				
UK	Not authorised				

No data available from other member states.

Melclass database[1]: Not to classify.

3.2 Social dimension of classification:

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

Proposed recommendation: **oral forms: List II; forms for parenteral use: List I**

Criteria: acute treatment under medical supervision (parenteral use); chronic treatment (oral use) – prescription could be renewed.

[1] Melclass database - Available at: http://www.edqm.eu/melclass/ (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: not to be used in children under 12 years of age. Parenteral use contraindicated in patients under 18 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Product information available in the databases of the French National Agency for the Safety of Medicine and Health Products (https://bit.ly/2Wvt1Zu) and Irish Health Products Regulatory Authority (https://bit.ly/2QwwwuM).

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Flupirtine

1.2 ATC code: N02BG07

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): -

2.2 Indirect risks (incorrect use): -

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions: based on the available data, a product containing flupirtine is authorised in Poland (classification status: POM). No medications containing flupirtine are authorised in the rest of the member states.

3.2 Social dimension of classification:

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

Proposed recommendation: based on the available data, medicines containing flupirtine are not authorised in at least 3 member states: **Not to classify**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Product information available in the Polish Medicinal Products Registry (https://bit.ly/2EyuvZi)

4.2 Comments: -

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Ziconotide

1.2 ATC code: N02BG08

1.3 Therapeutic indications: indicated for the treatment of severe, chronic pain in adults who require intrathecal (IT) analgesia.

1.4 Posology and duration of treatment: treatment with ziconotide should only be undertaken by physicians experienced in IT administration of medicinal products.

Adults (including the elderly ≥ 65 years of age): dosing of ziconotide should be initiated at 2.4 µg/day and titrated on an individual patient basis according to the patient's analgesic response and adverse reactions. Patients should be titrated in dose increments of ≤ 2.4 µg/day, up to a maximum dose of 21.6 µg/day. The minimal interval between dose increases is 24 hours; the recommended interval, for safety reasons, is 48 hours or more. If necessary the dose can be decreased by any amount (including stopping the infusion) for the management of adverse reactions. Approximately 75% of patients who respond satisfactorily to treatment require a dose of ≤ 9.6 µg/day.

Renal impairment: studies have not been conducted in patients with impaired renal function. Caution should be exercised when ziconotide is administered to patients with impaired renal function.
Hepatic impairment: studies have not been conducted in patients with impaired hepatic function. Caution should be exercised when ziconotide is administered to patients with impaired hepatic function.

Paediatric population: the safety and efficacy of ziconotide in children aged 0 to 18 years have not been established. No data are available.

Method of administration: IT use. Ziconotide must be administered as a continuous infusion via an intrathecal catheter, using an external or internally implanted mechanical infusion pump capable of delivering an accurate infusion volume. As the risk of meningitis secondary to prolonged catheterisation of the intrathecal space is greater with an external catheter infusion system, internal systems are recommended to administer ziconotide for prolonged periods. An external catheter system should only be used when an internal system cannot be implanted. When low doses of ziconotide are required, for example when initiating titration, ziconotide must be diluted before use with preservative-free sodium chloride 9 mg/mL (0.9%) solution for injection.

1.5 Pharmaceutical forms: solution for infusion 25 µg/mL.

1.6 Contraindications: hypersensitivity to the active substance and combination with IT chemotherapy.

1.7 Relevant warnings: long-term use: although ziconotide has been studied in long-term, open-label efficacy and safety clinical trials, controlled studies of longer than 3 weeks' duration have not been conducted. Possible long-term local toxic effects on the spinal cord have not been excluded and preclinical data in this respect are limited. Therefore, caution is needed during long-term treatment.

Risk of infection: the administration of medicinal products by the IT route carries the risk of potentially serious infections, such as meningitis, which may be life-threatening. Meningitis due to the entrance of organisms along the catheter track or inadvertent contamination of the infusion system is a known complication of intrathecal medicinal product administration, especially with external systems. Patients and physicians must be vigilant for typical symptoms and signs of meningitis. The optimal intrathecal placement of the catheter tip has not been established. Lower catheter tip placement, e.g. at the lumbar level, may reduce the incidence of ziconotide-related neurological adverse reactions. Therefore, catheter tip placement should be carefully considered to allow adequate access to spinal nociceptive segments whilst minimising medicinal product concentrations at cerebral levels. Only a small number of patients have received systemic chemotherapy and IT ziconotide. Caution should be exercised when ziconotide is administered to patients who are receiving systemic chemotherapy.

Elevations in creatine kinase: elevations in creatine kinase, which are usually asymptomatic, are common amongst patients on intrathecal ziconotide. Progressive elevation of creatine kinase is uncommon.

However, monitoring of creatine kinase is recommended. In the event of progressive elevation, or clinically significant elevation in association with clinical features of myopathy or rhabdomyolysis, discontinuation of ziconotide should be considered.

Hypersensitivity reactions: hypersensitivity reactions, including anaphylaxis, have not been observed during clinical trials and the immunogenicity of ziconotide administered by the IT route appears to be low. However, the potential for severe allergic reactions cannot be excluded and spontaneous reports of anaphylactic reactions have been received.

Cognitive and neuropsychiatric adverse reactions: cognitive and neuropsychiatric adverse reactions, particularly confusion, are common in patients treated with ziconotide. Cognitive impairment typically appears after several weeks of treatment. Episodes of acute psychiatric disturbances, such as hallucinations, paranoid reactions, hostility, aggressiveness, delirium, psychosis and manic reactions have been reported in patients treated with ziconotide. The ziconotide dose should be reduced or discontinued if signs or symptoms of cognitive impairment or neuropsychiatric adverse reactions develop, but other contributing causes should also be considered. The cognitive effects of ziconotide are typically reversible within 1-4 weeks after discontinuation of the medicinal product, but may persist in some cases. It is recommended that patients undergo a neuropsychiatric evaluation before and after starting intrathecal ziconotide. In patients with severe chronic pain there is a higher incidence of suicide and suicide attempts than in the general population. Ziconotide may cause or worsen depression with the risk of suicide in susceptible patients.

Depression of CNS: patients have experienced depressed levels of consciousness while receiving ziconotide. The patient usually remains conscious and breathing is not depressed. The event may be self-limited, but ziconotide should be discontinued until the event resolves. The re-introduction of ziconotide is not recommended in these patients. Withdrawal of concomitant CNS depressant medicinal products should also be considered as they may contribute to the reduced level of arousal.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): in clinical trials, 88% of patients experienced adverse reactions. The most common adverse reactions reported in long-term clinical trials were dizziness (42%), nausea (30%), nystagmus (23%), confusional state (25%), gait abnormal (16%), memory impairment (13%), vision blurred (14%), headache (12%), asthenia (13%), vomiting (11%), and somnolence (10%). Most adverse reactions were mild to moderate in severity and resolved over time. Ziconotide must not be used in patients at the same time as intrathecal chemotherapy.

Description of selected adverse reactions:

Meningitis: administration of medicinal products by the intrathecal route carries the risk of potential serious infections, such as meningitis, which may be life-threatening. Patients and physicians must be vigilant for typical symptoms and signs of meningitis.

Elevations of creatine phosphokinase: elevations in creatine phosphokinase were usually asymptomatic. Monitoring of creatine phosphokinase is recommended. Discontinuation of ziconotide should be considered in the event of progressive or significant elevation of creatine phosphokinase in association with clinical features of myopathy or rhabdomyolysis.

CNS adverse reactions: cognitive and neuropsychiatric adverse reactions are common in patients treated with ziconotide. Cognitive impairment typically appears after several weeks of treatment. Episodes of acute psychiatric disturbances, such as hallucinations, paranoid reactions, hostility, aggressiveness, delirium, psychosis and manic reactions have been reported in patients treated with ziconotide. The ziconotide dose should be reduced or discontinued if signs or symptoms of cognitive impairment or neuropsychiatric adverse reactions develop, but other contributing causes should also be considered. The cognitive effects of ziconotide are typically reversible within 1-4 weeks after discontinuation of the medicinal product, but may persist in some cases. It is recommended that patients undergo a neuropsychiatric evaluation before and after starting intrathecal ziconotide.

2.2 Indirect risks (incorrect use): overdose: in IV infusion studies, healthy male volunteers received

ziconotide at doses of up to 70,000 µg/day or 3,200 times the maximum recommended daily intrathecal infusion dose. Postural hypotension was observed in almost all subjects who received high intravenous doses of ziconotide. The maximum recommended intrathecal dose is 21.6 µg/day. The maximum intended intrathecal dose of ziconotide in clinical trials was 912 µg/day following upward titration over 7 days. Symptoms: In one clinical study a male cancer patient received an accidental IT ziconotide overdose of 744 µg over a 24-hour period (31 µg/hour) and resumed treatment at the intended dose after experiencing a reduction in Visual Analogue Scale of Pain Intensity (VASPI) from 82 to 2.5 mm. In some patients who received intrathecal doses greater than the maximum recommended dose, exaggerated pharmacological effects, e.g. ataxia, nystagmus, dizziness, stupor, depressed level of consciousness, muscle spasms, confusional state, sedation, hypotension, aphasia, speech disorder, nausea and vomiting were observed. There was no indication of respiratory depression. Most patients under observation recovered within 24 hours of withdrawal of the medicinal product. Management: general medical supportive measures should be administered to patients who receive an overdose until the exaggerated pharmacological effects of the medicinal product have resolved.

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	Additional information			
		Routes of administration/ Indications	MS	MDD	MQP
AM	Not authorised				
AT	List I				
BE	POM				
BiH	Not authorised				
CH	List II				
CZ	POM				
EE	POM				
ES	POM				
FI	POM				
FR	POM				
DE	POM				
HR	POM				
HU	POM				
IE	List I				
IT	List I				
LT	POM				
LV	POM				
MK	Not authorised				
NL	POM				
PL	POM				
PT	POM				
RO	POM				
RS	Not authorised				
SE	POM				
SI	POM				
UK	POM				

No data available from other member states.

Melclass database[1]: POM.

3.2 Social dimension of classification:

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

Proposed recommendation: **List I**

Criteria: indications and administration route require strict medical supervision.

3.2.2 Paediatric use: not recommended in patients under 18 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: EMA (link: https://www.ema.europa.eu/en/medicines/human/EPAR/prialt#product-information-section).

4.2 Comments: medicines containing this active substance are authorised via centralised procedure.

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

1.2 ATC code: N02BG09

1.3 Therapeutic indications: emergency relief of moderate to severe pain in conscious adult patients with trauma and associated pain.

1.4 Posology and duration of treatment: methoxyflurane should be self-administered under supervision of a person trained in its administration (physician, nurse, paramedic) using the hand-held methoxyflurane inhaler. It is inhaled through the custom-built inhaler.

Adults: one bottle of 3 mL methoxyflurane as a single dose, administered using the device provided. A second bottle should only be used where needed. The frequency at which methoxyflurane can be safely used is not established. The following administration schedule is recommended: no more than 6 mL in a single day, administration on consecutive days is not recommended, and the total dose to a patient in a week should not exceed 15 mL. Onset of pain relief is rapid and occurs after 6-10 inhalations. Patients should be instructed to inhale intermittently to achieve adequate analgesia. Patients are able to assess their own level of pain and titrate the amount of methoxyflurane inhaled for adequate pain control. Continuous inhalation of a bottle containing 3 mL provides analgesic relief for up to 25-30 minutes. Intermittent inhalation may provide longer analgesic relief. Patients should be advised to use the lowest possible dose to achieve pain relief.

Renal impairment: methoxyflurane may cause renal failure if the recommended dose is exceeded. Caution should be exercised for patients diagnosed with clinical conditions that would predispose to renal injury.

Hepatic impairment: cautious clinical judgement should be exercised when methoxyflurane is to be used more frequently than on one occasion every 3 months.

Paediatric population: methoxyflurane should not be used in children and adolescents under 18 years.

1.5 Pharmaceutical forms: inhalation vapour, liquid (methoxyflurane 99.9%).

1.6 Contraindications: use as an anaesthetic agent. Hypersensitivity to methoxyflurane, any fluorinated anaesthetic or to any of the excipients. Malignant hyperthermia: patients who are known to be genetically susceptible to malignant hyperthermia. Patients with a known family history of severe adverse reactions after being administered with inhaled anaesthetics. Patients who have a history of showing signs of liver damage after previous methoxyflurane use or halogenated hydrocarbon anaesthesia. Clinically significant renal impairment. Altered level of consciousness due to any cause including head injury, drugs or alcohol. Clinically evident cardiovascular instability. Clinically evident respiratory depression.

1.7 Relevant warnings: renal disease: to ensure the safe use of methoxyflurane as an analgesic the following precautions should be observed: a) use the lowest effective dose to control pain; b) use with caution in the elderly or other patients with known risk factors for renal disease; c) use with caution in patients diagnosed with clinical conditions which may predispose to renal injury. Methoxyflurane causes significant nephrotoxicity at high doses. Nephrotoxicity is thought to be associated with inorganic fluoride ions, a metabolic breakdown product. When administered as instructed for the analgesic indication, a single dose of 3 mL methoxyflurane produces serum levels of inorganic fluoride ions below 10 micromol/L. In the past when used as an anaesthetic agent, methoxyflurane at high doses caused significant nephrotoxicity, which was determined to occur at serum levels of inorganic fluoride ions greater than 40 micromol/L. Nephrotoxicity is also related to the rate of metabolism. Therefore factors that increase the rate of metabolism, such as drugs that induce hepatic enzymes, can increase the risk of toxicity with methoxyflurane as well as sub-groups of people with genetic variations that may result in fast metaboliser status.

Liver disease: methoxyflurane is metabolised in the liver, therefore increased exposures in patients with hepatic impairment can cause toxicity. Methoxyflurane must not be used in patients who have

a history of showing signs of liver damage after previous methoxyflurane use or halogenated hydrocarbon anaesthesia. Methoxyflurane should be used with care in patients with underlying hepatic conditions or with risks for hepatic dysfunction (such as enzyme inducers). It has been reported that previous exposure to halogenated hydrocarbon anaesthetics (including methoxyflurane when used in the past as an anaesthetic agent), especially if the interval is less than 3 months, may increase the potential for hepatic injury. Cautious clinical judgement should be exercised when methoxyflurane is to be used more frequently than on one occasion every 3 months.

Cardiovascular system depression/use in elderly: potential effects on blood pressure and heart rate are known class effects of high-dose methoxyflurane used in anaesthesia and other anaesthetics. They do not appear to be significant at the analgesic doses. There is no particular pattern to the patients' systolic blood pressure levels after methoxyflurane administration as an analgesic across age groups. However, as the risk may potentially be increased for older people with hypotension and bradycardia, caution should be exercised in the elderly due to possible reduction in blood pressure.

CNS effects: secondary pharmacodynamic effects including potential CNS effects such as sedation, euphoria, amnesia, altered ability to concentrate, altered sensorimotor co-ordination and change in mood are also known class effects. Self-administration of methoxyflurane in analgesic doses will be limited by occurrence of CNS effects, such as sedation. Whilst the possibility of CNS effects may be seen as a risk factor for potential abuse, reports are very rare in post-marketing use.

Frequent repeated use: due to the limitations on the dose of methoxyflurane and the duration of pain relief, methoxyflurane is not appropriate for providing relief of breakthrough pain/exacerbations in chronic pain conditions. Methoxyflurane is also not appropriate for relief of trauma-related pain in closely repeated episodes for the same patient.

Butylated hydroxytoluene: methoxyflurane contains the excipient butylated hydroxytoluene (E321) as a stabiliser. Butylated hydroxytoluene may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

Occupational exposure: healthcare professionals who are regularly exposed to patients using methoxyflurane inhalers should be aware of any relevant occupational health and safety guidelines for the use of inhalational agents. To reduce occupational exposure to methoxyflurane, the methoxyflurane inhaler should always be used with the activated carbon chamber which adsorbs exhaled methoxyflurane. Multiple use of methoxyflurane inhaler without the activated carbon chamber creates additional risk. Elevation of liver enzymes, blood urea nitrogen and serum uric acid have been reported in exposed maternity staff in delivery wards when methoxyflurane was used in the past in obstetric patients at the time of labour and delivery.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): the common non-serious reactions are CNS-type reactions, such as dizziness and somnolence, and are generally easily reversible.

Very common (≥1/10): dizziness

Common (≥1/100 to <1/10): euphoric mood, amnesia, dysarthria, dysgeusia, headache, somnolence, hypotension, cough, dry mouth, nausea, feeling drunk.

Uncommon (≥1/1,000 to <1/100): increased appetite, anxiety, depression, inappropriate affect, paraesthesia, peripheral sensory neuropathy, diplopia, flushing, oral discomfort, hyperhidrosis, fatigue, feeling abnormal, chills, feeling of relaxation.

Rare (≥1/10,000 to <1/1000): -

Very rare (<1/10,000): -

Not known (cannot be estimated from the available data): affect lability, agitation, confusional state, dissociation, restlessness, altered state of consciousness, nystagmus, vision blurred, blood pressure

fluctuation, choking, hypoxia, vomiting, hepatic failure, hepatitis, jaundice, liver injury, hepatic failure, hepatitis, jaundice, liver injury, hepatic enzymes increased, blood urea increased, blood uric acid increased, blood creatinine increased.

2.2 Indirect risks (incorrect use): overdosage: patients should be observed for signs of drowsiness, pallor and muscle relaxation following methoxyflurane administration. High doses of methoxyflurane cause dose-related nephrotoxicity. High output renal failure has occurred several hours or days after the administration of repeated high analgesic or anaesthetic doses of methoxyflurane.

2.3 Recent cases at European level: unknown.

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	Additional information			
		Routes of administration/ Indications	MS	MDD	MQP
AM	Not authorised				
AT	List I				
BE	POM				
BiH	Not authorised				
BG	POM				
CH	List II				
CZ	POM				
EE	POM				
ES	Not authorised				
FI	POM				
FR	POM				
DE	POM				
HR	List I				
HU	Not authorised				
IE	List I				
IT	List I				
LT	POM				
LV	POM				
MK	Not authorised				
NL	POM				
PL	POM				
PT	POM				
RO	List I				
RS	Not authorised				
SE	POM				
SI	POM				
UK	POM				

No data available from other member states.

Melclass database[1]: POM.

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

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: safety profile and medical supervision required.

3.2.2 Paediatric use: methoxyflurane should not be used in children and adolescents under 18 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Product information available in the databases of Irish Health Products Regulatory Authority (https://bit.ly/2QwwwuM) and UK database of medicines (http://www.mhra.gov.uk/spc-pil/index.htm).

4.2 Comments: medicines containing this active substance are authorised via decentralised procedure and are on the list of medicines under additional monitoring (black triangle).

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Cannabinoids

1.2 ATC code: N02BG10

1.3 Therapeutic indications: it is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.

1.4 Posology: oromucosal use only. It is intended to be used in addition to the patient's current anti-spasticity medication. Treatment must be initiated and supervised by a physician with specialist expertise in treating this patient population.

Adults: the spray container should be shaken before use and the spray should be directed at different sites on the oromucosal surface changing the application site each time the product is used. Patients should be advised that it might take up to 2 weeks to find the optimal dose and that undesirable effects can occur during this time, most commonly dizziness. These undesirable effects are usually mild and resolve in a few days. However, physicians should consider maintaining the current dose, reducing the dose or interrupting, at least temporarily, the treatment depending on seriousness and intensity. To minimise variability of bioavailability in the individual patient, administration of spray should be standardised as far as possible in relation to food intake. In addition, starting or stopping some concomitant medicinal products may require a new dose titration.

Titration period: a titration period is required to reach optimal dose. The number and timing of sprays will vary between patients. On day one of treatment, patients should take one spray during the morning and one spray during the afternoon/evening. The morning dose can be taken at any time between waking up and 12 noon and the afternoon dose can be taken at any time between 4 pm and bedtime. On subsequent days patients may gradually increase the total number of sprays by one spray each day, up to a maximum of 12 sprays per day, until they achieve optimum symptom relief. There should be at least a 15 minute gap between sprays. During initial titration, sprays should be evenly spread out over the day.

Maintenance period: following the titration period, patients are advised to maintain the optimum dose achieved. The median dose in clinical trials for patients with multiple sclerosis is 8 sprays per day. Once the optimum dose has been achieved, patients may spread the doses throughout the day according to individual response and tolerability. Re-titration upwards or downwards may be appropriate if there are any changes in the severity of the patient's condition, changes in their concomitant medication or if troublesome adverse reactions develop. Doses of greater than 12 sprays per day are not recommended.

Review by the physician: a thorough evaluation of the severity of spasticity-related symptoms and of the response to standard anti-spasticity medication should be performed prior to initiation of treatment. Spray is only indicated in patients with moderate to severe spasticity that have responded inadequately to other anti-spasticity medication. The patient's response to spray should be reviewed after 4 weeks of treatment. If a clinically significant improvement in spasticity related symptoms is not seen during this initial trial of therapy, then treatment should be stopped. In the clinical trials this was defined as at least a 20% improvement in spasticity related symptoms on a 0-10 patient reported numeric rating scale. The value of long-term treatment should be re-evaluated periodically.

Elderly: no specific studies have been carried out in elderly patients, although patients up to 90 years of age have been included in clinical trials. However, as elderly patients may be more prone to develop some CNS adverse reactions, care should be taken in terms of personal safety such as preparation of hot food and drinks.

Patients with significant hepatic or renal impairment: no data with multiple dosing are available in subjects with hepatic impairment. Spray can be administered to patients with mild hepatic impairment without any dose adjustment. Administration to patients with moderate or severe hepatic impairment is not advised due to the lack of information on the potential for accumulation of delta-9-

tetrahydrocannabinol (THC) and cannabidiol (CBD) with chronic dosing. There are no studies in patients with impaired renal function. However, in these sub-populations the effects of spray may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in these patient populations.

1.5 Pharmaceutical forms: oromucosal spray, solution. Each single 100 microlitre spray contains: 2.7 mg THC and 2.5 mg CBD (from *Cannabis sativa L*.).

1.6 Contraindications: contraindicated in patients: a) with hypersensitivity to cannabinoids or to any of the medication excipients; b) with any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition; c) who are breast feeding (in view of the considerable levels of cannabinoids likely in maternal breast milk and the potential adverse developmental effects in infants).

1.7 Relevant warnings: mild or moderate dizziness is commonly reported. This most frequently occurs in the first few weeks of treatment. Spray is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data. Alterations in pulse rate and blood pressure have been observed following initial dose introduction so caution during initial dose titration is essential. Fainting episodes have been observed with use of medication. Use of spray is not recommended in patients with serious cardiovascular disease. However, following dosing in healthy volunteers with the medication up to 18 sprays twice daily, there were no clinically relevant changes in QTc, PR or QRS interval duration, heart rate or blood pressure. Until further information is available, caution should be taken when treating patients with a history of epilepsy or recurrent seizures. Psychiatric symptoms such as anxiety, illusions, changes in mood and paranoid ideas have been reported during treatment with spray. These are likely to be the result of transient CNS effects and are generally mild to moderate in severity and well tolerated. They can be expected to remit on reduction or interruption of medication. Disorientation (or confusion), hallucinations and delusional beliefs or transient psychotic reactions have also been reported and in a few cases a causal association between spray administration and suicidal ideation could not be ruled out. In any of these circumstances, medication should be stopped immediately and the patient monitored until the symptom has completely resolved. No specific studies have been carried out in patients with significant hepatic or renal impairment. THC and CBD are metabolised in the liver, and approximately one third of the parent drugs and their metabolites are excreted in the urine (the remainder via the faeces). Several THC metabolites may be psychoactive. Thus, the systemic exposure and the effects of spray are dependent on both renal and hepatic function and in patients with significant impaired hepatic or renal function; the effects of medication may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in these patient populations. Spray contains approximately 50% v/v of ethanol. Each actuation contains up to 0.04 g of ethanol. A small glass of wine (125 mL) of nominal ethanol content 12% v/v would contain approximately 12 g ethanol. Most patients respond at doses up to and including 12 sprays a day which would contain less than 0.5 g of ethanol. There is a risk of an increase in incidence of falls in patients whose spasticity has been reduced and whose muscle strength is insufficient to maintain posture or gait. In addition to an increased risk of falls, the CNS adverse reactions of medication, particularly in elderly patients, could potentially have an impact on various aspects of personal safety, such as with food and hot drink preparation. Although there is a theoretical risk that there may be an additive effect with muscle-relaxing agents such as baclofen and benzodiazepines, thereby increasing the risk of falls, this has not been seen in clinical trials with the medication. However, patients should be warned of this possibility.

Women of childbearing potential: spray may reduce the effectiveness of hormonal contraceptives. Women of childbearing potential must use highly effective contraception while taking the medication. It is currently unknown whether spray may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should use an additional method of contraception for the duration of therapy and for 3 months after discontinuation of therapy.

Substance abuse: patients who have a history of substance abuse may be more prone to abuse of this medication. The abrupt withdrawal of long-term treatment has not resulted in a consistent pattern or time profile of withdrawal-type symptoms and the likely consequence will be limited to transient disturbances of sleep, emotion or appetite in some patients. No increase in daily dosage has been observed in long-term use, and patient self-reported levels of 'intoxication' are low. For these reasons, dependence on medication is unlikely.

Adverse reactions have been reported which could be associated with the route of administration of the medicine. Application site type reactions consisted of mainly mild to moderate stinging at the time of application. Common application site reactions include application site pain, oral pain and discomfort, dysgeusia, mouth ulceration and glossodynia. Two cases of possible leukoplakia were observed but neither was confirmed histologically; a third case was unrelated. In view of this, patients who observe discomfort or ulceration at the site of application of the medicine are advised to vary the site of application within the mouth and should not continue spraying onto sore or inflamed mucous membrane. Regular inspection of the oral mucosa is also advised in long-term administration. If lesions or persistent soreness are observed, medication should be interrupted until complete resolution occurs.

Patients should be advised that if they travel to another country it may not be legal for them to take this medicine into some countries. They should be encouraged to check the legal status before travelling with medication.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance): Very common (≥ 1/10): dizziness, fatigue.

Common (≥ 1/100 to < 1/10): anorexia (including appetite decreased), appetite increased, depression, disorientation, dissociation, euphoric mood, amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment somnolence, vision blurred, vertigo, constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort, oral pain, vomiting, application site pain, asthenia, feeling abnormal, feeling drunk, malaise, fall.

Uncommon (≥ 1/1000 to < 1/100): pharyngitis, hallucination (unspecified, auditory, visual), illusion, paranoia, suicidal ideation, delusional perception, syncope, palpitations, tachycardia, hypertension, throat irritation, abdominal pain (upper), oromucosal discolouration, oromucosal disorder, oromucosal exfoliation, stomatitis, tooth discolouration, application site irritation.

2.2 Indirect risks (incorrect use): there is no experience of deliberate overdose with this medication in patients. However, in a thorough QT study in 257 subjects, with 18 sprays taken over a 20-minute period twice daily, signs and symptoms of overdose/poisoning were observed. These consisted of acute intoxication produced CB1 agonism-type reactions including dizziness, hallucinations, delusions, paranoia, tachycardia or bradycardia with hypotension. In three of 41 subjects dosed at 18 sprays twice a day, this presented as a transient toxic psychosis which resolved upon cessation of treatment. Twenty-two subjects who received this substantial multiple of the recommended dose successfully completed the 5-day study period. In the case of overdose, treatment should be symptomatic and supportive.

2.3 Recent cases at European level: unknown.

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	Additional information			
		Routes of administration/ Indications	MS	MDD	MQP
AM	Not authorised				
AT	Special medical prescription - Narcotics				
BE	POM				
BiH	Not authorised				
CH	List I				
CZ	POM				
EE	Not authorised				

ES	POM				
FI	POM				
FR	List I				
DE	POM				
HR	Not authorised				
HU	Not authorised				
IE	List I				
IT	Hospital prescription				
LT	Not authorised				
LV	Not authorised				
MK	Not authorised				
NL	POM				
PL	POM				
PT	POM				
RO	Not authorised				
RS	Not authorised				
SE	POM				
SI	Not authorised				
UK	POM				

No more data available from other member states.

Melclass database[1]: currently not available

3.2 Social dimension of classification:

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

Proposed recommendation: **Not to classify**

Criteria: Narcotics (Vienna Convention – Yellow list).

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References: Product information available in the databases of Irish Health Products Regulatory Authority (https://bit.ly/2QwwwuM) and UK database of medicines (http://www.mhra.gov.uk/spc-pil/index.htm).

4.2 Comments: patients going abroad should be advised to check the legal status of medicinal products containing cannabinoids in the country to which they are travelling. These are controlled medicinal products and their legal status may vary between countries.

[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)

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