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

Evidence-based classification reviews of

- Medicines belonging to ATC group G01AF
(Imidazole derivatives)

- Medicines containing promethazine (ATC: R06AD02)

2017

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 interpreted and implemented differently by different states, and 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 ResAP(2007)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 annually issues 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 Whereas (32): "*It is therefore appropriate, as an initial step, to harmonize 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.

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

[2] http://go.edqm.eu/ResAP20071

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

- 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 (*Melclass*[5]), hosted by the EDQM, which stores the recommendations that the Committee of Experts annually issues to health authorities of the Council of Europe member states which are parties to the Convention on the Elaboration of a European Pharmacopoeia, as well as national information about the classification status and supply conditions of medicines in these member states. The information is publicly available. Recommendations for about 2300 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 ResAP(2007)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.

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

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

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 conclusions of the reports arising from reviews of scientific classifications of medicines and the rationale and debates on which the recommendations on the classification of medicines as regards their supply, taken by the CD-P-PH/PHO at its 60th meeting on 19-20 April 2016 and at its 61st meeting on 29-30 November 2016, were based. The document was reviewed and endorsed by the CD-P-PH/PHO at its 62nd meeting on 30-31 May 2017.

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

GLOSSARY OF TERMS USED IN THIS DOCUMENT

ATC	Anatomical Therapeutic Chemical classification[6]
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
EMA	European Medicines Agency
FDA	Food and Drug Administration
HMA	Heads of Medicines Agencies
IM	Intramuscular
IV	Intravenous
MS	Maximal strength
MDD	Maximal daily dose
MQP	Maximal quantity per pack
MRI	Mutual recognition information
OTC	Over-the-counter (medicine supplied without prescription)
PDR	Physicians' Desk Reference (www.pdr.net/)
PIL	Patient information leaflet
POM	Prescription only medicine
SmPC	Summary of product characteristics

Classification used throughout this document

Following the stipulations of Resolution ResAP(2007)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 of 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.

List II: The supply of a medicine containing one of the substances on this list may be repeated without the prescriber having specified so, provided that he/she did not explicitly forbid such repetition and that the amount supplied at renewals (and their frequency) is consistent with medical and pharmaceutical data (such as the prescribed daily dose, the duration of treatment, the degree of medical supervision required by the condition, etc.).

Exemptions from Lists I and II

For certain substances, exemptions from the "prescription only" requirement may appear in Lists I and II:

- In respect of a low dosage or concentration of the active substances and/or therapeutic indications of the medicines in which they are contained;

- According to the route of administration and the composition of the medicine;

[6] WHO Collaborating Centre for Drug Statistics Methodology - http://www.whocc.no/atc_ddd_index/

- According to the total content of the medicine per container;

- Active substances classified according to the conditions of supply of the medicines which contain them as supplied without prescription, i.e. over-the-counter (OTC) medicines.

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 are classified in the list “Medicines not subject to prescription (OTC medicines)”.

It is possible that a given active substance can be contained in both an OTC medicine and a medicine subject to prescription of the same ATC classification because of the particular conditions of use of the medicines in question.

General criteria for classification in the lists:

a. List I
1. 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;
2. Active substances of medicines administered for diagnostic purposes;
3. Active substances with a new pharmacological mechanism of action.

b. List II
Active substances of medicines indicated for conditions for which the patient may continue regular or intermittent treatment without new medical advice, and for which well-known undesirable effects do not call for frequent clinical examinations.

c. List of OTC medicines
(see above).

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Metronidazole

1.2 ATC code: G01AF01

1.3 Therapeutic indications: Adults: treatment of trichomoniasis (caused by *Trichomonas vaginalis*) and of bacterial vaginosis.

1.4 Posology and duration of treatment:

Adults:
Vaginal gel 0.75% (7.5 mg/g): 5 g of gel once daily at bedtime for 5 consecutive days
Vaginal tablets 500 mg: 1 vaginal tablet once daily at bedtime for 10 consecutive days
Vaginal pessaries 1000 mg: 1 vaginal tablet

Paediatric use: not recommended for use in children and adolescents under 18 years.

1.5 Pharmaceutical forms: vaginal gel 0.75% (7.5 mg/g), 37.5 mg/5 g for 5 days (USA, UK); vaginal gel 1.3% (13 mg/g), 65 mg/5 g for one application (USA); vaginal pessaries 1000 mg; vaginal tablets 500 mg.

1.6 Contraindications: hypersensitivity to the active substance or to other nitroimidazoles or parabens.

1.7 Relevant warnings: use during menses is not recommended.

Known or previously unrecognised candidiasis may present more prominent symptoms during therapy with metronidazole vaginal gel and may require treatment with a candicidal agent. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of a history of blood dyscrasias. As with all vaginal infections, sexual intercourse during the infection and during treatment with vaginal metronidazole is not recommended.
After vaginal administration of metronidazole, symptoms of intolerance to alcohol were observed. It is therefore necessary to warn the patient not to drink alcohol during or within 48 hours after application. Eye irritation: metronidazole may cause tearing of the eye; therefore, contact with the eyes should be avoided.

Pregnancy: data on a large number (several hundred) of exposed pregnancies **indicate no adverse effects of metronidazole on the foetus/newborn child.** There have been no formal studies with metronidazole vaginal gel in pregnant women. Caution should, therefore, be exercised when prescribing to pregnant women.

Breastfeeding: the ratio of serum concentrations of metronidazole vaginal gel/oral metronidazole is approximately 0.02. Metronidazole is excreted in milk at concentrations similar to those in maternal serum and the ratio of serum concentrations of metronidazole in the breastfed infant/mother is approximately 0.15. Caution should be exercised when prescribing to lactating women.

Interaction with other medicinal products and other forms of interaction: oral metronidazole has been associated with a disulfiram-like reaction in combination with alcohol. Acute psychotic reactions and confusion have occurred during concomitant use of disulfiram with oral metronidazole.

Oral metronidazole has been shown to increase the plasma concentrations of warfarin, lithium, cyclosporin and 5-fluorouracil. Similar effects after vaginal administration of

metronidazole are not expected due to the low plasma concentrations, but cannot be completely ruled out. Metronidazole may interfere with certain types of determination of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactic dehydrogenase (LDH), triglycerides and hexokinase glucose. Values of zero may be observed.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance):

Undesirable effects
Infections and infestations
Common (≥1/100, <1/10): vaginal candidiasis
Metabolism and nutrition disorders
Common (≥1/100, <1/10): decreased appetite
Psychiatric Disorders
Uncommon (≥1/1000, <1/100): depression, difficulty sleeping
Nervous system disorders
Common (≥1/100, <1/10): headache, dizziness
Uncommon (≥1/1000, <1/100): abnormal sensation of limbs, metallic taste
Gastrointestinal disorders
Common (≥1/100, <1/10): gastrointestinal discomfort/abdominal cramps, nausea and/or vomiting, unpleasant taste/unusual feeling on tongue
Uncommon (≥1/1000, <1/100): diarrhoea, constipation, abdominal bloating, dry mouth
Skin and subcutaneous tissue disorders
Uncommon (≥1/1000, <1/100): itching
Musculoskeletal and connective tissue disorders
Uncommon (≥1/1000, <1/100): cramp
Renal and urinary disorders
Uncommon (≥1/1000, <1/100): urine discolouration, urinary tract infection symptoms
Reproductive system and breast disorders
Common (≥1/100, <1/10): vaginal itching/irritation/burning/numbness, pelvic discomfort, vaginal discharge
Uncommon (≥1/1000, <1/100): vulval oedema, menstrual discomfort/irregularities, vaginal spotting/bleeding
General disorders and administration site conditions
Uncommon (≥1/1000, <1/100): fatigue, irritability

2.2 Indirect risks (incorrect use): there is no human experience of overdose with metronidazole vaginal gel. There is no specific treatment. Metronidazole is readily removed from the plasma by haemodialysis. After taking oral doses of up to 15 g of metronidazole, nausea, vomiting, hyperreflexia, ataxia, tachycardia, shortness of breath and mental confusion were observed. There were no deaths. No specific antidote is known. Complete resolution of symptoms was observed after a few days of symptomatic treatment.

2.3 Recent cases at European level: none

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Metronidazole has activity against anaerobic protozoans, such as *Entamoeba histolytica*, *Giardia lamblia* and *Trichomonas vaginalis*, for which the drug was first approved as an effective treatment. Anaerobic bacteria which are typically sensitive are primarily gram-negative anaerobes belonging to the *Bacteroides* and *Fusobacterium spp.* Gram-positive

anaerobes, such as *Peptostreptococcus* and *Clostridia spp*., are likely to test sensitive to metronidazole. Metronidazole has variable activity against the facultative anaerobes *Gardnerella vaginalis* and *Helicobacter pylori*. The mode of action of metronidazole is not entirely clear, but is thought to involve reduction by bacterial nitroreductases to an unstable intermediate which interacts with DNA, effectively preventing further replication. Absorption from vaginal pessaries is poor with a reported bioavailability of about 20 to 25%; absorption is gradual producing peak plasma concentrations of about 2 micrograms/mL after a dose of 500 mg. An intravaginal gel formulation providing a dose of 37.5 mg metronidazole produced peak plasma concentrations of 0.3 micrograms/mL at 8 hours, with a bioavailability of 56%. Vaginal forms are recommended for the treatment of trichomoniasis and bacterial vaginosis.

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/ Indication	MS	MDD	MQP
Database*	List II				
Austria (AT)	Not authorised				
Belgium (BE)	POM		500 mg	500 mg	5g
Switzerland (CH)	List II		500 mg	2 g	5 g
France (FR)	List I	Vaginal infections			
Croatia (HR)	List I	Trichomoniasis, bacterial vaginosis	1000 mg	1000 mg	5 g
Ireland (IE)	Not authorised				
Italy (IT)	POM	Bacterial vaginosis	500 mg vag. ovule 300 mg vag. gel	500 mg 7.5 mg	5000 mg 37.5 mg
Lithuania (LT)	POM	Bacterial vaginosis	1000 mg	1000 mg	2000 mg
Macedonia (MK)	POM	Trichomoniasis, Non-specific vaginosis	500 mg	500 mg	5 g
Poland (PL)	POM	Bacterial vaginosis, trichomoniasis	Vag. pessaries 1000 mg Vag. tablets 500 mg	1000 mg 500 mg	2 g (2 pcs) 5 g (10 pcs)
Portugal (PT)	POM	Local treatment of vaginitis, trichomoniasis	500 mg	500 mg	5000 mg (10 units)
Romania (RO)	Not authorised				
United Kingdom (UK)	POM	Bacterial vaginosis			

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

No data from other member states are 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:
- Difficult self-diagnosis
- Possible risk of systemic adverse effects
- Possible risk of sensitisation and development of resistance
- Possible risk of hypersensitivity and cross-sensitivity reactions.

Note: metronidazole is classified as a prescription-only medicine (POM) in most member states.

3.2.2 Paediatric use: not recommended for use in children and adolescents under 18 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale: The Complete Drug Reference - 35th and 37th Editions

electronic Medicines Compendium (eMC) - available at: https://www.medicines.org.uk/

Metronidazole – is it safe to use with breastfeeding - *Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals (20 March 2012)*

MRI Product Index: Zidoval, vaginal gel UK/H/0352/001 - available at: http://www.hma.eu/mriproductindex.html

Drugs@FDA: FDA approved medicines - available at: https://www.accessdata.fda.gov/scripts/cder/daf/

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Clotrimazole

1.2 ATC code: G01AF02

1.3 Therapeutic indications: treatment of candidal vaginitis and candidal vulvitis.

1.4 Posology and duration of treatment:

Adults: clotrimazole is given as vaginal pessaries/vaginal tablets in dosage regimens of 100 mg for 6 days, 200 mg for 3 days, or a single dose of 500 mg in the treatment of vulvovaginal candidiasis; similar doses are given as a 1, 2, or 10% vaginal cream. It may be necessary to treat balanitis in male partners concurrently.

Combinations:

1. Vaginal pessary 500 mg + vaginal cream 2%: pessaries are indicated for the treatment of candidal vaginitis, whereas creams are indicated for the treatment of candidal vulvitis. This treatment should be used as an adjunct to treatment of candidal vaginitis. Creams can also be used for treatment of the sexual partner's penis to prevent re-infection. The cream should be thinly applied to the vulva and surrounding area, two or three times daily and rubbed in gently. Treatment with the cream should be continued until symptoms of the infection disappear.

2. Vaginal cream 10% and external cream 2%: the internal cream is recommended for the treatment of candidal vaginitis. The external cream is recommended for the treatment of candidal vulvitis. This treatment should be used as an adjunct to treatment of candidal vaginitis. The internal cream should be administered intravaginally using the applicator supplied. The contents of the filled applicator (5 g) should be inserted as deeply as possible into the vagina, preferably at night. The external cream should be thinly applied to the vulva and surrounding area two or three times daily and rubbed in gently. Treatment with the external cream should be continued until symptoms of the infection disappear.

3. Cream 1%: in addition to the above treatments, this cream is thinly applied twice daily onto affected skin areas in the external genital region. The cream should be used for 1 week. Treatment may be continued for up to 2 weeks; however, if the symptoms do not improve within 7 days, the patient should consult a physician.

Children: not for use in children under 16.

1.5 Pharmaceutical forms: vaginal pessaries/tablets 100 mg, 200 mg and 500 mg; vaginal cream 10% (100 mg/g)

Combinations: vaginal pessary 500 mg and external cream 2%; vaginal pessary 500 mg and external cream 1%; vaginal cream 10% and external cream 2%.

1.6 Contraindications: hypersensitivity to clotrimazole.

1.7 Relevant warnings: medical advice should be sought if this is the first time the patient has experienced symptoms of candidal vaginitis.
Before using, medical advice must be sought if any of the following are applicable:
- more than two infections of candidal vaginitis in the last six months
- previous history of a sexually transmitted disease or exposure to partner with sexually transmitted disease

- pregnancy or suspected pregnancy
- aged under 16 or over 60 years
- known hypersensitivity to imidazoles or other vaginal antifungal products

Clotrimazole 100 mg pessaries should not be used if the patient has any of the following symptoms, whereupon medical advice should be sought:
- irregular vaginal bleeding
- abnormal vaginal bleeding or a blood-stained discharge
- vulval or vaginal ulcers, blisters or sores
- lower abdominal pain or dysuria
- any adverse events such as redness, irritation or swelling associated with the treatment
- fever or chills
- nausea or vomiting
- diarrhoea
- foul-smelling vaginal discharge

Treatment during the menstrual period should be avoided due to the risk of the cream/tablet being washed out by the menstrual flow. The treatment should be finished before the onset of menstruation. Do not use tampons, intravaginal douches, spermicides or other vaginal products while using this product. Vaginal intercourse should be avoided in cases of vaginal infection and while using this product because the partner could become infected.

Interaction with other medicinal products and other forms of interaction: laboratory tests have suggested that, when used together, this product may cause damage to latex contraceptives. Consequently the effectiveness of such contraceptives may be reduced. Patients should be advised to use alternative precautions for at least five days after using this product. Concomitant medication with vaginal clotrimazole and oral tacrolimus (immunosuppressant) might lead to increased tacrolimus plasma levels and similarly with sirolimus. Patients should thus be closely monitored for signs and symptoms of tacrolimus or sirolimus overdosage, if necessary by determination of the respective plasma levels.

Pregnancy: there is a limited amount of data from the use of clotrimazole in pregnant women. Animal studies with clotrimazole have shown reproductive toxicity at high oral doses. At the low systemic exposures of clotrimazole following vaginal treatment, harmful effects with respect to reproductive toxicity are not predicted. Clotrimazole can be used during pregnancy, but only under the supervision of a physician or midwife. During pregnancy the pessary should be inserted without using an applicator.

Lactation: available pharmacodynamic/toxicological data in animals have shown excretion of clotrimazole/metabolites in milk after intravenous administration. A risk to the child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from clotrimazole therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance):

Immune system disorders
allergic reaction (syncope, hypotension, dyspnoea, urticaria, pruritus)
Reproductive system and breast disorders
genital peeling, pruritus, rash, oedema, erythema, discomfort, burning, irritation, pelvic pain, vaginal haemorrhage
Gastrointestinal disorders

abdominal pain
Skin and subcutaneous tissue disorders
blisters, discomfort/pain, oedema, erythema, irritation, peeling/exfoliation, pruritus, rash, stinging/burning.

2.2 Indirect risks (incorrect use): no risk of acute intoxication is expected as it is unlikely to occur following a single vaginal application of an overdose (application over a large area under conditions favourable to absorption) or inadvertent oral ingestion. There is no specific antidote.

2.3 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Clotrimazole acts against fungi by inhibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the fungal cytoplasmic membrane. Clotrimazole has a broad antimycotic spectrum of action in vitro and in vivo, which includes dermatophytes, yeasts, moulds, etc. Primarily resistant variants of sensitive fungal species are very rare; the development of secondary resistance by sensitive fungi has so far only been observed in very isolated cases under therapeutic conditions. Pharmacokinetic investigations after vaginal application have shown that only a small amount of clotrimazole (3-10% of the dose) is absorbed. Due to the rapid hepatic metabolism of absorbed clotrimazole into pharmacologically inactive metabolites the resulting peak plasma concentrations of clotrimazole after vaginal application of a 500 mg dose were less than 10 ng/mL, reflecting that clotrimazole applied intravaginally does not lead to measurable systemic effects or side effects.

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
Database*	List II + exemption Annex III	Ex.: vaginal use	Ex.: 2%		
Armenia (AM)	POM + exemption Annex III	POM: vaginal tablets OTC: vag. suppositories	Ex.: 100 mg	Ex.: 100 mg	Ex.: 600 mg
AT	List II + exemption Annex III				
BE	OTC, see Annex III		500 mg	500 mg	600 mg
CH	List II + exemption Annex III	Ex.: vaginal use	Ex.: 200 mg	Ex.: 200 mg	Ex.: 600 mg
Czech Republic (CZ)	OTC, see Annex III				
FR	List I + exemption Annex III	Ex.: vaginal use	Ex.: 1%	Ex.: 200 mg	Ex.: 1200 mg
HR	List I + exemption Annex III	Ex.: vag. tablets and capsules 500 mg; internal cream 2% and external cream 1%			
HU	OTC, see Annex III	Mycosis			
IE	List II + exemption Annex III	Ex.: external use only			
IT	OTC, see Annex III	Vaginal tablets and vaginal cream	100 mg	100 mg	1200 mg (600 mg for cream prep.)
LT	POM + exemption Annex III	Ex.: vaginal use	Ex.: 200 mg	Ex.: 200 mg	Ex.: 600 mg
MK	OTC, see Annex III		500 mg	500 mg	600 mg
PL	POM	Candidal vaginitis and vulvitis			
PT	POM				
RO	Not authorised		100 mg	200 mg	1200 mg
Serbia (RS)	OTC, see Annex III		500 mg	500 mg	600 mg
UK	OTC, see Annex III	For external use only			

*Melclass database - available at: http://www.edqm.eu/melclass/ (NB: this is the CD-P-PH/PHO's recommendation at the time of

compilation of the evidence-based review)

No data from other member states are available.

3.2 Social dimension of classification:

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

Proposed recommendation: **OTC**

Additional information: vaginal use
short-term (1-3 days)
treatment of vaginal candidiasis (thrush)
not for children < 16 years old
MS 500 mg; MDD 500 mg; MQP 600 mg

Criteria:
- Self-diagnosis possible
- Clotrimazole applied intravaginally does not lead to measurable systemic effects or side effects
- Short period of the intravaginal treatment (1-3 days)

Note: registered as POM (List I or List II) + exemption or as OTC in most member states.

3.2.2 Paediatric use: not recommended in children < 16 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale: The Complete Drug Reference - 35th and 37th Editions

EMC - available at: https://www.medicines.org.uk/

Drug Information Online - available at: www.drugs.com

Mutual Recognition Procedure (MRP): DE_H_2307_001_FinalSPC. 08/06/2015, Vagisan Myko Kombi 500 mg pessary and 10 mg/g cream – combination of vaginal use and external cream (OTC) - available at: https://goo.gl/MM3B6q

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Miconazole

1.2 ATC Code: G01AF04

1.3 Therapeutic indications: treatment of mycotic vulvovaginitis and superinfections due to gram-positive bacteria.

1.4 Posology and duration of treatment: in the treatment of vaginal candidiasis, 5 g of a 2% intravaginal cream is inserted into the vagina once daily for 10 to 14 days or twice daily for 7 days. Miconazole pessaries may be inserted in dosage regimens of 100 mg once daily for 7 or 14 days, 100 mg twice daily for 7 days, 200 or 400 mg daily for 3 days or in a single dose of 1200 mg.

1.5 Pharmaceutical forms: vaginal tablets 100 mg; vaginal capsule 1200 mg; vaginal cream 2% (20 mg/g).

1.6 Contraindications: known hypersensitivity to miconazole/miconazole nitrate or other imidazole derivatives.

1.7 Relevant warnings: severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with miconazole formulations. If a reaction suggesting hypersensitivity or irritation should occur, the treatment should be discontinued. Appropriate therapy is indicated when the sexual partner is also infected. Avoid contact with eyes. The concurrent use of latex condoms or diaphragms with vaginal anti-infective preparations may decrease the effectiveness of latex contraceptive agents. Therefore miconazole cream and capsules should not be used concurrently with a latex condom or latex diaphragm.

Interaction with other medicinal products and other forms of interaction: Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to the **limited systemic availability after vaginal application, clinically relevant interactions occur very rarely.** In patients on oral anticoagulants, such as warfarin, caution should be exercised and anticoagulant effects should be monitored. The effects and side effects of other drugs metabolised by CYP2C9 (e.g. oral hypoglycaemics and phenytoin) and CYP3A4 (e.g. HMG-CoA reductase inhibitors such as simvastatin and lovastatin, and calcium channel blockers such as dihydropyridines and verapamil), when co-administered with miconazole, can be increased and caution should be exercised.

Pregnancy: although intravaginal absorption is limited, miconazole products should only be used in the first trimester of pregnancy if, in the judgment of the physician, the potential benefits outweigh the possible risks.

Breastfeeding: it is not known whether miconazole nitrate is excreted in human milk. Caution should be exercised when using vaginal capsules or cream during breastfeeding.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance):

Skin and Subcutaneous Tissue Disorders
Common: rash
Uncommon: rash pruritic, urticaria
Reproductive System and Breast Disorders
Very common: genital pruritus female, vaginal burning sensation, vulvovaginal discomfort
Common: dysmenorrhoea
Immune System Disorders
Not known: hypersensitivity including anaphylactic and anaphylactoid reactions
Skin and Subcutaneous Tissue Disorders
Not known: angioedema, pruritus
Reproductive System and Breast Disorders
Not known: vaginal irritation, pelvic cramps.

2.2 Indirect risks (incorrect use): there is little absorption through skin or mucous membranes when miconazole nitrate is applied topically. In case of accidental ingestion, no problems are expected. In the event of accidental ingestion of large quantities, use appropriate supportive care.

2.3 Recent cases at European level: none

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Miconazole is a synthetic imidazole antifungal agent with a broad spectrum of activity against pathogenic fungi (including yeasts and dermatophytes) and gram-positive bacteria (*Staphylococcus* and *Streptococcus* spp.). Miconazole inhibits the biosynthesis of ergosterol in fungi and changes the composition of other lipid components in the membrane, resulting in fungal cell necrosis. Systemic absorption of miconazole after intravaginal administration is limited, with a bioavailability of 1 to 2% following intravaginal administration of a 1200 mg dose. Plasma concentrations of miconazole are measurable within 2 hours of administration in some subjects, with maximal levels seen 12 to 24 hours after administration. Plasma concentrations decline slowly thereafter and were still measurable in most subjects 96 hours post-dose.

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
Database*	List II + exemption Annex III	Ex.: vaginal use	Ex.: 250 mg		
AM	Not authorised				
AT	Not authorised		0.1 g		
BE	OTC, see Annex III		1.2 g	1.2 g	1.4 g
CH	Not authorised				
FR	List I				
HR	List I	Vulvovaginal conditions and superinfections due to G+ bacteria	200 mg	200 mg	14 g (for 7 days)
HU	POM	mycosis			
IE	List II + exemption Annex III	Ex.: only external use for vaginal candidiasis			
IT	List II	Local treatment of vulvovaginal candidiasis, and superinfections due to G+ bacteria	1200 g	1200 g	2400 g
LT	Not authorised				
MK	POM	Local treatment of vulvovaginal candidiasis, and superinfections due to G+ bacteria	200 mg	200 mg	2400 mg
PL	POM	Fungal and yeast vaginal	100 mg	100 mg	1.5 g

		infections			
PT	Not authorised				
RO	Not authorised				
RS	POM		200 mg	200 mg	1.4 g
UK	POM				

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

No data from other member states are 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:
- Difficult self-diagnosis
- Possible risk of severe hypersensitivity reactions
- Short term treatment and doctor's supervision needed

Note: Miconazole is classified as POM (List I or List II) in most of member states.

3.2.2 Paediatric use: do not use in children and adolescents under the age of 18 years. The safety and efficacy of miconazole in children and adolescents has not been studied.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale: The Complete Drug Reference - 35th and 37th Editions

EMC – available at: https://www.medicines.org.uk/

MRI Product Index – available at: http://www.hma.eu/mriproductindex.html

Drugs@FDA: FDA approved medicines – available at:
https://www.accessdata.fda.gov/scripts/cder/daf/

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Econazole

1.2 ATC Code: G01AF05

1.3 Therapeutic indications: Econazole is indicated for the treatment of vulvovaginal mycoses and mycotic balanitis.

1.4 Posology and duration of treatment: Econazole is used in the treatment of vaginal candidiasis (vaginitis due to *Candida albicans* and other yeasts) as pessaries of 150 mg once daily at bedtime for 3 consecutive nights; a single dose of 150 mg in a long-acting formulation can also be used. Intravaginal administration of 5 g of a 1% cream once daily at night has been given for 2 weeks. A 1% cream may be used concurrently for the treatment of vulval infections or for the treatment of balanitis in a male partner (treatment of mycotic vulvovaginitis and mycotic balanitis).

Children: not indicated for use in children under the age of 16 years.

1.5 Pharmaceutical forms: vaginal cream 1% (10 mg/g); vaginal pessaries 50 mg and 150 mg.

1.6 Contraindications: hypersensitivity to any imidazole preparation or other vaginal antifungal products.

1.7 Relevant warnings: hypersensitivity has rarely been recorded; if it should occur administration should be discontinued. Contact between contraceptive diaphragms or condoms and this product must be avoided since the rubber may be damaged by the preparation. Patients using spermicidal contraceptives should consult their physician since any local vaginal treatment may inactivate the spermicidal contraceptive. Vaginal pessaries or cream should not be used in conjunction with other internal or external treatment of the genitalia.

Interaction with other medicinal products and other forms of interaction: Econazole is a known inhibitor of CYP3A4/2C9. **Due to the limited systemic availability after vaginal application**, clinically relevant interactions are unlikely to occur but have been reported with oral anticoagulants. In patients taking oral anticoagulants, such as warfarin or acenocoumarol, caution should be exercised and the anticoagulant effect should be monitored more frequently. Adjustment of the oral anticoagulant dosage may be necessary during and after treatment with econazole.

Pregnancy: in animals, econazole nitrate has shown no teratogenic effects but is foetotoxic at high doses. The significance of this to man is unknown as there is no evidence of an increased risk when taken in human pregnancy. However, because there is vaginal absorption, as with other imidazoles, econazole should be used in pregnancy only if the practitioner considers it to be necessary.

Lactation: following oral administration of econazole nitrate to lactating rats, econazole and/or metabolites were excreted in milk and were found in nursing pups. It is not known whether econazole nitrate is excreted in human milk. Caution should be exercised when using econazole vaginal pessaries if the patient is breast-feeding.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (pharmacovigilance):

Immune System Disorders
Not known: hypersensitivity including anaphylactic and anaphylactoid reactions
Skin and Subcutaneous Tissue Disorders
Common: pruritus, skin burning sensation
Uncommon: rash
Rare: erythema
Unknown: angioedema, urticaria, contact dermatitis, skin exfoliation
Reproductive System and Breast Disorders
Uncommon: vulvovaginal burning sensation
General Disorders and Administration Site Conditions
Unknown: application site pain, application site irritation, application site swelling.

2.2 Indirect risks (incorrect use): adverse events associated with overdose or misuse of vaginal pessaries are expected to be consistent with adverse drug reactions. In the event of accidental ingestion, nausea, vomiting and diarrhoea may occur. If necessary treat symptomatically.

2.3 Recent cases at European level: none

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Econazole nitrate has no anti-inflammatory action, no effect on the circulation, no central or autonomic nervous effects, no effect on respiration, no effect on α or β receptors and no anticholinergic or antiserotonic activity. A broad spectrum of antimycotic activity has been demonstrated against dermatophytes, yeasts and moulds. Clinically relevant activity against gram-positive bacteria has also been found. Econazole acts by damaging cell membranes, thereby increasing the permeability of the fungal cell. Sub-cellular membranes in the cytoplasm are also damaged. The site of action is most probably the unsaturated fatty acid acyl moiety of membrane phospholipids. Econazole nitrate is poorly absorbed after vaginal application. Using radiolabelling techniques, it has been determined that between 2.5% and 7% of vaginally applied econazole nitrate is absorbed. However, no antimycotic activity could be detected in the serum after vaginal application of 5 g or 1% econazole nitrate cream or a suppository containing 50 mg econazole nitrate.

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
Database*	List II				
AM	POM		150 mg	150 mg	450 mg
AT	List II + exemption Annex III	Ex.: vaginal use	Ex.: 150 mg		
BE	Not authorised				
CH	List II		150 mg	300 mg (modified release 150 mg)	450 mg vag. tablets; 750 mg cream
FR	List I + exemption Annex III	Ex.: vaginal infections	Ex.: 2%	Ex.: 300 mg	Ex.: 2 g
HU	POM + exemption Annex III	Ex.: treatment of vulvovaginal mycosis, dermatophytosis, candidiasis			
HR	Not authorised				
IE	Not authorised				
IT	OTC see annex III	Vulvovaginal mycosis, balanitis mycotic	150 mg	150 mg	900 mg
LT	POM	For the local treatment of fungal vulvovaginitis	150 mg	150 mg	450 mg
MK	Not authorised				

PL	POM	Fungal vulvovaginitis; also for male genital fungal infections	150 mg	150 mg	750 mg
PT	POM + exemption Annex III	Ex.: recurrent vaginal and male genital candidiasis			
RO	Not authorised				
RS	Not authorised				
UK	POM	Vaginal and vulval candidiasis			

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

No data from other member states are 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 + Exemption Annex III**

Exemptions: short-term treatment (3 days)
treatment of vaginal infections
MS: 150 mg, MDD: 150 mg
adults only

Criteria:
- Systemic absorption limited
- Hypersensitivity reactions rare

3.2.2 Paediatric use: not recommended in children < 18 years.

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale: The Complete Drug Reference - 35th and 37th Editions

EMC – available at: https://www.medicines.org.uk/

MRI Product Index - available at: http://www.hma.eu/mriproductindex.html

Drugs@FDA: FDA approved medicines – available at:
https://www.accessdata.fda.gov/scripts/cder/daf/

Heads of Medicines Agencies: EU Periodic Safety Update Report (PSUR) Work Sharing Summary Assessment Report; Econazole Nitrate and Econazole Nitrate with Triamcinolone acetonide HU/H/PSUR/0016/00 (P-RMS: Hungary) - available at: https://goo.gl/ncRKvJ

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Ornidazole

1.2 ATC Code: G01AF06

1.3 Therapeutic indications: there is no information on vaginal use of ornidazole in Europe

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

Ornidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazole and is used similarly in the treatment of susceptible protozoal infections and also in the treatment and prophylaxis of anaerobic bacterial infections. It is given by mouth after food, or intravenously. There is no information on vaginal use of ornidazole.

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
Database*	List II				
AT	Not authorised				
BE	Not authorised				
CH	Not authorised				
CZ	Not authorised				
Denmark (DK)	Not authorised				
Estonia (EE)	Not authorised				
Finland (FI)	Not authorised				
Spain (ES)	Not authorised				
FR	Not authorised				
HU	Not authorised				
HR	Not authorised				
IE	Not authorised				
IT	Authorised but not marketed				
Lithuania (LT)	Not authorised				
LV	Not authorised				
MK	Not authorised				
The Netherlands (NL)	Not authorised				
Norway (NO)	Not authorised				
PL	Not authorised				
PT	Not authorised				
RO	Not authorised				

Sweden (SE)	Not authorised				
Slovakia (SK)	Not authorised				
RS	Not authorised				
UK	Not authorised				

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

No data from other member states are 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**

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale: The Complete Drug Reference - 35th and 37th Editions (no information)

EMC - available at: https://www.medicines.org.uk/ (no information)

MRI Product Index - available at: http://www.hma.eu/mriproductindex.html (no information)

Drugs@FDA: FDA approved medicines - available at: https://www.accessdata.fda.gov/scripts/cder/daf/ (no information)

1. THERAPEUTIC PROFILE

1. 1 Active ingredient: Isoconazole

1.2 ATC Code: G01AF07

1.3 Therapeutic indications: treatment of vaginal mycoses

1.4 Posology and duration of treatment: Isoconazole is an imidazole antifungal used locally as the nitrate in the treatment of vaginal mycoses, particularly due to *Candida* spp. For vaginal infections, it is usually given as pessaries in a single dose of 600 mg or 300 mg daily for 3 days or as a 1% vaginal cream daily for 7 days.

1.5 Pharmaceutical forms: vaginal pessaries 300 mg and 600 mg; vaginal cream 1% and 2%.

1.6 Contraindications: hypersensitivity to isoconazole or other imidazole derivatives.

1.7 Relevant warnings: local reactions, including burning or itching, may occur following the application of isoconazole. Intravaginal preparations of azole antifungals may damage latex contraceptives and additional contraceptive measures are therefore necessary during local administration.

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

Isoconazole is an imidazole antifungal active against a wide spectrum of fungi including *Candida* spp., dermatophytes and *Malassezia furfur*. It is also active against some gram-positive bacteria.

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
Database*	List II + exemption Annex III	Ex.: vaginal use			
AM	POM	Vaginal yeast infections	600 mg	600 mg	600 mg
AT	Not authorised				
BE	Not authorised				
Bulgaria (BG)	Not authorised				
CH	Not authorised				
CZ	Not authorised				
DK	Not authorised				
EE	Not authorised				
ES	Not authorised				
FI	Not authorised				
FR	List I + exemption	Ex.: vaginal infections	Ex.: 2%	Ex.: 300 mg	Ex.: 2 g
HR	Not authorised				
HU	Not authorised				
IE	Not authorised				

IT	OTC see annex III	Vulvo-vaginal yeast infections, also with bacterial superinfections	600 mg	600 mg	600 mg
LT	Not authorised				
LV	Not authorised				
MK	Not authorised				
NL	Not authorised				
NO	Not authorised				
PL	Not authorised				
PT	POM	Vaginal cream 1% Treatment of vaginal mycoses including mixed infection with G+ bacteria	1%		400 mg
RO	List I	Candida vaginitis	600 mg	600 mg	1800 mg
RS	Not authorised				
SE	Not authorised				
SK	Not authorised				
UK	Not authorised				

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

No data from other member states are 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:
- Short-term treatment only
- Possible hypersensitivity

Note: limited information only, not available in most of the member states.

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale: The Complete Drug Reference - 35th and 37th Editions

EMC - available at: https://www.medicines.org.uk/

MRI Product Index - available at: http://www.hma.eu/mriproductindex.html

Drugs@FDA: FDA approved medicines - available at: https://www.accessdata.fda.gov/scripts/cder/daf/

Fazol G 300 mg, ovule - Résumé des caractéristiques du produit - available at: www.ansm.sante.fr

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Tioconazole

1.2 ATC Code: G01AF08

1.3 Therapeutic indications: recurrent vaginal candidiasis with previous medical diagnosis.

1.4 Posology and duration of treatment: used for the treatment of vaginal candidiasis as pessaries or vaginal ointment, usually as a single 300 mg dose.

1.5 Pharmaceutical forms: vaginal pessary 100 mg and 300 mg; vaginal cream 6.5% (USA).

1.6 Contraindications: -

1.7 Relevant warnings: local reactions to tioconazole, including burning, itching and erythema, have been reported. Intravaginal preparations of tioconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

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

Tioconazole is an imidazole antifungal with a broad spectrum of activity, including action against dermatophytes, *Malassezia furfur* and *Candida albicans*. Tioconazole is active *in vitro* against some gram-positive bacteria. Tioconazole is used in the treatment of superficial candidiasis, dermatophytoses and pityriasis versicolor.

Country	Classification	Additional information			
		Route of Administration/ Indications	MS	MDD	MQP
Database*	List II				
AT	Not authorised				
BE	Not authorised				
BG	Not authorised				
CH	Not authorised				
CZ	Not authorised				
DK	Not authorised				
EE	Not authorised				
ES	Not authorised				
FI	Authorised but not marketed (OTC)				
FR	List I				
HR	Not authorised				
HU	Not authorised				
IE	Not authorised				
IT	Not authorised				
LT	Not authorised				
LV	Not authorised				
MK	Not authorised				
NL	Not authorised				
NO	Not authorised				
PT	Authorised but not marketed (OTC)				

PL	Not authorised				
RO	Not authorised				
RS	Not authorised				
SE	Not authorised				
SK	Not authorised				
UK	Not authorised				

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

No data from other member states are available.

3.2 Social dimension of classification:

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

Proposed recommendation: **OTC**

Additional information: vaginal use
MS: 100 mg; MDD: 100 mg; MQP: 600 mg

Criteria:
- Short-term treatment for non-serious conditions
- Systemic absorption limited
- Adverse effects rare

3.2.2 Paediatric use: no data

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale: The Complete Drug Reference - 35th and 37th Editions

EMC - available at: https://www.medicines.org.uk/

MRI Product Index - available at: http://www.hma.eu/mriproductindex.html

Drugs@FDA: FDA approved medicines - available at:
https://www.accessdata.fda.gov/scripts/cder/daf/

Gyno Trosyd 300 mg, ovule SmPC - available at: www.ansm.sante.fr

Gyno Trosyd 100 mg, comprimidos vaginais SmPC - available at: http://www.infarmed.pt

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Ketoconazole

1.2 ATC Code: G01AF11

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

Ketoconazole is an imidazole antifungal administered topically or by mouth. It is given by mouth in chronic mucocutaneous or vaginal candidiasis, in fungal infections of the gastrointestinal tract, in dermatophyte infections of the skin and fingernails not responding to topical treatment and in systemic infections including blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis and paracoccidioidomycosis. Because of the risk of hepatotoxicity, the use of ketoconazole in non-systemic fungal infections tends to be restricted to serious infections resistant to other treatment. Ketoconazole is applied topically as a 2% cream in the treatment of candidal or dermatophyte infections of the skin, or in the treatment of pityriasis versicolor.

No data are available concerning vaginal treatment.

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
Database*	List II + exemption Annex III	Ex.: vaginal use			
Armenia	POM	Treatment of acute and chronic recurrent vaginal candidiasis	400 mg	400 mg	2 g
AT	Not authorised				
BE	Not authorised				
BG	Not authorised				
CH	Not authorised				
CZ	Not authorised				
DK	Not authorised				
ES	Not authorised				
FI	Not authorised				
FR	Not authorised				
HR	Not authorised				
HU	Not authorised				

IE	Not authorised				
IT	Not authorised				
LT	Not authorised				
LV	Not authorised				
MK	Not authorised				
NL	Not authorised				
PT	Not authorised				
PL	Not authorised				
RO	Not authorised				
RS	Not authorised				
SE	Not authorised				
SK	Not authorised				
UK	Not authorised				

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

No data from other member states are 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**

Ketoconazole is not authorised for vaginal use in the majority of the member states (Armenia only).

3.2.2 Paediatric use: -

3.2.3 Social dimension: -

4. REFERENCES/COMMENTS

4.1 References:

Martindale: The Complete Drug Reference - 35th and 37th Editions (no information)

EMC - available at: https://www.medicines.org.uk/ (no information)

MRI Product Index - available at: http://www.hma.eu/mriproductindex.html (no information)

Drugs@FDA: FDA approved medicines - available at: https://www.accessdata.fda.gov/scripts/cder/daf/ (no information)

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Promethazine

1.2 ATC code: R06AD02

1.3 Therapeutic indications: treatment of allergic conditions and reactions; antiemetic; tranquilliser. Other indications include: motion sickness; pre- and post-operative sedation; post-operative nausea and vomiting, and adjuvant treatment for pain; mild emotional disorders; radiation sickness.

1.4 Posology and duration of treatment: oral use.

Adults (including the elderly): the usual daily dose is 25-75 mg, either as a single daily dose at bedtime or in 3 divided doses, starting with the lower dose.

Children below 2 years: not recommended.

Children 2-5 years: use of Promethazine 5 mg/5 mL oral solution is recommended in this age group for the treatment of allergic conditions and reactions, and as an antiemetic (not as a tranquiliser). Posology: 1-3 × 5 mL spoonfuls (5-15 mg) once daily at bedtime. Alternatively, 5 mg twice daily. Maximum daily dose 15 mg.

Children 5-10 years: 2-5 × 5 mL spoonfuls (10-25 mg) once daily at bedtime. Alternatively: 5-10 mg twice daily. Maximum daily dose 25 mg. When two doses are required within 24 hours, the lower dose should be used.

As a tranquilliser: children 6-12 years: 25 mg (1 tablet) once daily at bedtime.

1.5 Pharmaceutical forms: film-coated tablet 25 mg; oral solution 5 mg/5 mL; solution for injection 2.5% w/v (25 mg/mL).

1.6 Contraindications: Promethazine should not be used in patients in pre-coma states. Promethazine should not be given to patients with a known hypersensitivity to promethazine or any of the excipients. Promethazine should be avoided in patients with blood dyscrasias and in patients taking monoamine oxidase inhibitors up to 14 days previously. Promethazine is contraindicated for use in children less than two years of age because of the potential for fatal respiratory depression. It must not be given to neonates or premature infants. Promethazine should not be used in pregnancy unless the physician considers it essential. Use is not recommended in the 2 weeks prior to delivery in view of the risk of irritability and excitement in the neonate. Available evidence suggests that the amount excreted in milk is insignificant. However, there are risks of neonatal irritability and excitement.

1.7 Relevant warnings: caution should be used in patients with pre-existing coronary insufficiency. Adjustment of dosage may be necessary to avoid postural hypotension, especially in the elderly. Since the drug is metabolised in the liver, promethazine should be used cautiously in patients with hepatic impairment. Prolonged treatment with this product may result in jaundice or blood dyscrasias necessitating regular monitoring of liver function and haemopoietic state. Particular attention should also be paid to the potential for inducing eye changes and myocardial conduction defects, especially if other concurrently administered drugs also have potential effects on these systems. Body temperature may fall during treatment with this product and special care should be exercised in this regard in the elderly. Promethazine should only be used cautiously in epileptic patients, since central nervous stimulation may sometimes occur. Caution should also be exercised in patients with narrow-angle glaucoma, renal insufficiency, or bladder neck or pyloroduodenal obstruction.

Promethazine may thicken or dry lung secretions and impair expectoration. It should be used with caution in patients with asthma, bronchitis or bronchiectasis. In the elderly, promethazine may delay the diagnosis of intestinal obstruction or increased intracranial pressure through the suppression of vomiting. Promethazine may mask the warning signs of ototoxicity caused by ototoxic drugs e.g. salicylates. There have been case reports of drug abuse with promethazine. The risk of abuse is greater in patients with a history of drug abuse.

Neuroleptic malignant syndrome (NMS): as with neuroleptics, NMS characterised by hyperthermia, extrapyramidal disorders, muscle rigidity, altered mental status, autonomic nervous instability and elevated creatine phosphokinase (CPK) may occur. As this syndrome is potentially fatal, promethazine must be discontinued immediately and intensive clinical monitoring and symptomatic treatment should be initiated.

Promethazine must not be used in children below two years of age due to the potential for fatal respiratory depression. Phenothiazines should be used with caution in patients with cardiac disease or cardiac arrhythmias. The use of promethazine should be avoided in children and in adolescents with signs and symptoms suggestive of Reye's syndrome.

Promethazine should not be used for longer than 7 days without seeking medical advice.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance): the following side effects have been observed: drowsiness or dizziness, restlessness, headaches, nightmares, tiredness or disorientation. Anticholinergic side effects, such as blurred vision, dry mouth and urinary retention, occur occasionally. Anaphylaxis, jaundice and blood dyscrasias, including haemolytic anaemia, rarely occur. Use of this product at high (relative or absolute) doses may induce extrapyramidal side effects, e.g. dyskinesia, akathisia or dystonia, especially in the presence of pre-existing brain damage. These are likely to be particularly severe in children. Children may display paradoxical hyperexcitability. Prolonged administration of this product may result in persistent or tardive dyskinesias, particularly in the elderly. Other side effects in the elderly include anorexia, gastric irritation, palpitations, hypotension, arrhythmias, extrapyramidal effects, muscle spasms and tic-like movements of the head and face. The effects of phenothiazines on the heart are dose related. Electrocardiogram (ECG) changes, with prolongation of the QT interval and T-wave changes, have been commonly reported in patients treated with moderate or high doses; they are reversible on reducing the dose. In a very small percentage of cases these have been reported to precede serious arrhythmias, including ventricular tachycardia and fibrillation, which have also occurred after overdosage. Sudden, unexpected and unexplained deaths have been reported in patients receiving phenothiazines. Frequency unknown: NMS. Very rare cases of allergic reactions, including urticaria, rash, pruritus and anaphylaxis have been reported. Photosensitive skin reactions have been reported. Strong sunlight should be avoided during treatment.

2.2 Indirect risks (incorrect use): symptoms of severe overdosage are variable. They are characterised in children by various combinations of excitation, ataxia, incoordination, athetosis and hallucinations, while adults may become drowsy and lapse into coma. Convulsions may occur in both adults and children. Coma may precede their occurrence. Tachycardia may develop. Cardiorespiratory depression is not uncommon. If the patient is seen soon enough after ingestion, it should be possible to induce vomiting with ipecacuanha, despite the antiemetic effect of promethazine; alternatively, gastric lavage may be used. Treatment is otherwise supportive with attention to maintenance of adequate respiratory and circulatory status. Convulsions should be treated with diazepam or another suitable anticonvulsant.

2.3 Recent cases at European level: the Health Products Regulatory Authority (HPRA) (formerly the Irish Medicines Board (IMB), 2011) and the Medicines and Healthcare products Regulatory Agency (MHRA) (2009) advised that cough and cold remedies containing certain ingredients – including first-generation H_1 antihistamines – should no longer be used in children under six because the balance of benefits and risks was not shown to be beneficial. The action applied to brompheniramine, diphenhydramine, doxylamine and triprolidine. Promethazine was not impacted by this action, as it is not present in cough and cold remedies in Ireland or the UK.

In 2010, the Global Allergy and Asthma European Network Task Force (GA^{2}LEN) published a position paper on the risk of first-generation H_1-antihistamines. The group raised concerns about the potential dangers of the indiscriminate use of first-generation H_1-antihistamines, including promethazine, purchased over the counter in the absence of appropriate medical supervision. It recommended that first-generation H_1-antihistamines should no longer be available over the counter as non-prescription medicines for self-medication of allergic and other diseases. GA^{2}LEN has also recommended that first-generation H_1-antihistamines, including promethazine, should no longer be used as initial therapy for urticaria, except in those countries where second-generation antihistamines are not available or where their use outweighs their risks (2009). The classification of two formulations of promethazine has been changed from over-the-counter to prescription-only in Denmark following a recent review by the Danish Health and Medicines Authority (DKMA) of the safety of the medicine. The prescription-only status, which took effect in December 2014, applies to both 25 mg film-coated tablets and 1 mg/mL oral solution for children aged ≥ 2 years.

The following four serious safety issues associated with promethazine use were identified by the DKMA and formed the basis for the change to prescription-only status:

1. Abuse of higher doses than recommended.
2. Serious adverse reactions at recommended doses.
3. Serious interactions with psychoactive drugs.
4. Heavy sedative effect compromising the ability to drive.

A Danish survey of antihistamine use and poisoning patterns (2016) showed an increasing tendency for antihistamine exposures during a 7-year period from 2007 to 2013. Promethazine use was noted to have increased significantly during this period, although there was no clear explanation for this. First-generation antihistamine exposures were more frequently involved in intentional overdose, and in adults, indicating a conscious choice of and a preference for first-generation antihistamines. The results of the survey support the action to limit promethazine to prescription-only supply, but the authors caution that replacement of promethazine with other first-generation antihistamines could occur.

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	Prescription status	Additional information				
		Routes of administration/ Indications	Comments	MS	MDD	MQP
Database*	List I	Oral and IV Oral: treatment for allergic conditions of the upper respiratory tract; adjunct in preoperative sedation in surgery and obstetrics; antiemetic, sedation and treatment of insomnia in				

		adults				
AM	POM	Oral	Not for children under 6 years old	25 mg	25-50 mg	500 mg
AT	Not authorised					
BE	POM	50 mg/2 mL, solution for injection		50 mg/2 mL (sol. for injection)	50 mg	250 mg
CH	Not authorised					
CZ	POM					
DE	List II					
DK	POM					
FR	List I + Exemption Annex III	List I: parenteral OTC: oral				
HR	Not authorised					
HU	List I					
IT	POM (List I: IV; List II: oral)			Par.: 50 mg vials Oral: 25 mg		
IE	List I + Exemption Annex III	Parenteral: IM or IV (List I) Oral: oral solution (OTC)	Promotion to healthcare professionals only			
LT	Not authorised					
MK	Not authorised					
PL	POM			1 mg/mL and 10 mg and 25 mg	60 mg	500 mg
PT	POM	Oral: oral solution (authorised but not marketed) Parenteral: IV		Oral: 1 mg/mL Parenteral: 50 mg/mL IV	Oral: 60 mg Parenteral: 50 mg/mL	Oral: 125 mg Parenteral: 500 mg
RO	List I	Oral		5 mg/5 mL	0.5 mg/kg/day b.i.d.	250 mg/250 mL
RS	Not authorised					
UK	POM + Exemption Annex III	POM: parenteral Non-prescription: oral		Non-prescription: 25 mg	Non-prescription: 60 mg	Non-prescription: 56 tablets

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

No data from other member states are available.

3.2 Social dimension of classification:

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

In July 2007, the Paediatric Working Party (PEG) of the Committee for Medicinal Products for Human Use (CHMP) (European Medicines Agency (EMA)) identified therapeutic areas and relevant medicines that should be the subject of further research and development. Promethazine was listed as one of these medicines. No further action has been taken.

PROMETHAZINE (ATC: R06AD02)	
Authorised indication	Treatment of agitation in psychiatric disorders
Authorised age group	Children and adolescents *(Germany)*
Authorised dose	Starting dose 0.5 mL (=10 mg) Maximum daily dose 0.5 mg/kg
Authorised formulation	Solution for injection Oral solution Tablets
Needs	Define lower age limit and investigate where needed (PK, safety and efficacy in younger children)

Proposed recommendation: promethazine is a first-generation H_1-antihistamine and a phenothiazine. It is a long-acting antihistamine that crosses the blood-brain barrier, with resultant antiemetic, sedative and anticholinergic effects. Promethazine is used in the treatment of allergic conditions, as an antiemetic, and as a tranquiliser. Other indications include motion-sickness and pre- and post-op sedation and nausea and vomiting. Promethazine is indicated for use in adults and children over 2 years. The product information includes a contraindication to use in children under 2 years of age because of the risk of fatal respiratory depression. There are warnings regarding use in patients with cardiac disease or cardiac arrhythmias, use in epilepsy due to the potential for central nervous system stimulation, and risk of abuse in patients with a history of drug abuse. Promethazine may potentiate the effect of alcohol or other central nervous system depressants. Because the duration of action may be up to 12 hours, patients are advised that if they feel drowsy they should not drive or operate heavy machinery.

Promethazine is classified under List I in Appendix 1 of Resolution ResAP(2007)1; however, oral formulations are available in some countries without prescription (OTC). Various publications have raised concerns about the potential for side effects, misuse and overdose and have recommended that the substance be subject to prescription. The potential role for first-generation H_1-antihistamines, such as promethazine, in the management of urticaria is acknowledged.

In conclusion, the current classification is List I. No change in the classification is proposed.

4. REFERENCES/COMMENTS

4.1 References:

HPRA SmPCs:
Phenergan 25 mg Film-Coated Tablets - available at: https://goo.gl/RfPDGY
Phenergan 5 mg/5 mL Oral Solution - available at: https://goo.gl/VJVN8p

Risk of first-generation H1-antihistamines: a GA^{2}LEN position paper: Global Allergy and Asthma European Network Task Force Recommendation 2010 - available at: https://goo.gl/7AhWL4

EAACI/GA^{2}LEN/EDF/WAO guideline: management of urticaria, 2009 - available at: https://goo.gl/HLDeto

Jensen LL, Rømsing J, Dalhoff K. A Danish survey of antihistamine use and poisoning patterns. Basic Clin Pharmacol Toxicol 2017; 120(1): 64-70. Available at: https://goo.gl/F8un4Q

Springer International Publishing. Promethazine status changes to prescription-only in Denmark. Reactions Weekly 2015 - 1535. Available at: https://goo.gl/wauc8J
HPRA 2011 - New advice regarding non-prescription cough and cold remedies for young

children - available at: https://goo.gl/JLW8qd

LIST OF AUTHORS

Dr Elaine BRESLIN
Health Products Regulatory Authority (HPRA)
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
DUBLIN 2 (Ireland)

Dr Irena MEISSNER-WANTUCH
Ministry of Health
UL. Akacjowa 9
05-540 ZALESIE GORNE (Poland)

Ms Sandra MONTEIRO
National Authority of Medicines and Health Products (INFARMED)
Parque da Saude de Lisboa
Av. do Brasil 53
1749-004 LISBON (Portugal)

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