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

Evidence-based classification review for Hypericum perforatum L., herba

(ATC code N06AX25)

2025

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Introduction

The availability of medicines with or without a medical prescription has implications for 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 different interpretation and implementation of the provisions and since important additional classification criteria are not harmonised.

The Committee of Experts on the Classification of Medicines as Regards their Supply (CD-P-PH/PHO) is co-ordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM, Council of Europe) and its work programme is based on Committee of Ministers Resolution CMRes(2018)1 on the classification of medicines as regards their supply. The CD-P-PH/PHO reviews the national legal supply status of medicinal products for human use, performs assessment according to Guidelines on key considerations in issuing recommendations on the classification of active substances as regards their supply (prescription and non-prescription status) and issues recommendations on the classification of medicines and their supply conditions to health authorities of the Council of Europe Member States parties to the European Pharmacopoeia Convention. It is important to note that the CD-P-PH/PHO does not issue recommendations on the classification of particular medicinal products, but on active substances with their respective Anatomical Therapeutic Chemical (ATC) codes.

The approach to the classification of herbal medicines described below was endorsed by the CD-P-PH/PHO in November 2025, and has no legal status.

Classification of herbal medicines

This section outlines the rationale behind the CD-P-PH/PHO's recommendations related to herbal medicines with a complete ATC code (consideration of a herbal medicine with an incomplete ATC code may be justified only in very rare cases).

The term "Herbal medicines" can be understood in different ways. In the context of the CD-P-PH/PHO recommendations, herbal medicines are medicines with a complete ATC code containing an active substance based on "herbals" – plants or parts of plants with a marketing authorisation based on well-established use application. "Non-herbal" medicines and food supplements are out of the scope of this document. The approach to traditional use herbal medicines is outlined in the document; however, these medicines are not assessed by the CD-P-PH/PHO.

The CD-P-PH/PHO assessment can contribute to the harmonisation of the classification and conditions of supply of herbal medicines across the Member States.

The European Union (EU) legislation sets out various regulatory pathways to obtain a marketing authorisation of a herbal medicine; however, information on the authorisation type is not included in the labelling of medicines. Consequently, the regulatory pathway behind these medicines, which partly determines their classification and supply conditions, is not clear to patients and sometimes even to healthcare professionals.

The regulatory pathway for herbal medicines in the EU is illustrated below (European Medicines Agency (EMA) website; "Member State" refers here to EU Member States:

Regulatory pathway	Main requirements on safety and efficacy	Where to apply
Traditional use registration (Article 16a(1) of Directive 2001/83/EC)	• No clinical tests and trials on safety and efficacy are required as long as sufficient safety data and plausible efficacy are demonstrated • Involves assessment of mostly bibliographic safety and efficacy data • Must have been used for at least 30 years, including at least 15 years within the EU • Are intended to be used without the supervision of a medical practitioner and are not administered by injection	• National competent authority of a Member State for national, mutual recognition and decentralised procedures
Well-established use marketing authorisation (Article 10a of Directive 2001/83/EC)	• Scientific literature establishing that the active substances of the medicinal products have been in well-established medicinal use within the EU for at least ten years, with recognised efficacy and an acceptable level of safety • Involves assessment of mostly bibliographic safety and efficacy data	• National competent authority of a Member State for national, mutual recognition and decentralised procedures • EMA if centralised procedure applies
Stand-alone or mixed application (Article 8(3) of Directive 2001/83/EC)	• Safety and efficacy data from the company's own development or a combination of own studies and bibliographic data	• National competent authority of a Member State for national, mutual recognition and decentralised procedures • EMA if centralised procedure applies

Medicines authorised via a traditional use authorisation are intended to be used without the supervision of a medical practitioner, i.e. have a non-prescription status. The CD-P-PH/PHO will identify herbal medicines with a complete ATC code authorised as traditional herbal medicines only, and for which a monograph has been issued by the Committee on Herbal Medicinal Products (HMPC) of the EMA. As traditional herbal medicines are out of scope of the evaluation by the CD-P-PH/PHO, the conditions of the monograph are followed and non-prescription status is recommended without any evaluation. These medicines are shown in Table 1.

Table 1 - Herbal medicines with a complete ATC code with traditional use authorisation only and an HMPC monograph

INN (ATC code)	Monograph available on
Crataegi folium cum flore (C01EB04)	https://www.ema.europa.eu/en/medicines/herbal/crataegi-folium-cum-flore
Centellae asiatica herba, incl. combinations (D03AX14)	https://www.ema.europa.eu/en/medicines/herbal/centellae-asiaticae-herba
Lavandulae aetheroleum (N05BX05)	https://www.ema.europa.eu/en/medicines/herbal/lavandulae-aetheroleum
Althaeae radix (R05CA05)	https://www.ema.europa.eu/en/medicines/herbal/althaeae-radix
Pruni africanae cortex (G04CX01)	https://www.ema.europa.eu/en/medicines/herbal/pruni-africanae-cortex

These medicines have monographs available, based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC, as amended (traditional use). Therefore, these medicines should be non-prescription according to the conditions of the monographs. The EMA list of HMPC monographs with traditional use authorisation only is very long; however, most of the medicines do not have an ATC code or have an incomplete ATC code, and therefore they are not included in Table 1.

For the other regulatory pathways, the classification outcome can be different, and it is important to establish conditions of supply and a recommendation on the classification.

For well-established use herbal medicines with a complete ATC code, regardless of whether there is a monograph issued by the HMPC (see Table 2), the CD-P-PH/PHO will assess the conditions of supply and issue a recommendation on the classification.

Table 2 - Herbal medicines with a complete ATC code with well-established use authorisation, with or without an HPMC monograph, on the EMA herbal medicines list

Agni casti fructus (G02CX03)	Menthae piperitae aetheroleum (A03AX15)
Capsici fructus (M02AB01)	Planataginis ovatae semen or Plantaginis ovatae seminis tegumentum or Psylli semen (A06AC01)
Cimifugae rhizoma (G02CX04)	Rhamni purshianae cortex (A06AB07)
Gingko folium (N06DX02)	Ricini oleum (A06AB05)
Hederae helicis folium (R05CA12)	Sabalis serrulatae fructus (G04CX02)
Hippocastani semen (C05CX03)	Sennae folium and/or Sennae fructus (A06AB06)
Hyperici herba (N06AX25)	Valerianae radix (N05CM09)
Lini semen (A06AC05)	

The Evidence-based classification review (EBR) for Hypericum perforatum L., herba (St. John's wort, Hyperici herba), one of these medicines, is provided below.

Well-established use herbal medicines with an incomplete ATC code are listed in Table 3 for information only.

Table 3 - Herbal medicines with an incomplete ATC code with well-established use authorisation, with or without an HPMC monograph, on the EMA herbal medicines list

Aloes folii succus siccatus (A06AB)	Rhei radix (A06AB)
Echinaceae purpurae herba (R05X)	Salicis cortex (N02BG)
Frangulae cortex (A06AB)	Valerianae radix/Lupuli flos (N05CM)
Menthae piperitae folium (A03AX)	Vitis viniferae folium (C05CX)
Plantaginis ovatae seminis tegumentum (C10AX)	Zingiberis rhizome (A04AD)

Regulatory pathways are not applicable to non-EU countries; however, the rationale related to the classification of herbal medicines provided by the CD-P-PH/PHO could be considered in any setting.

Evidence-based classification review

Note: The document Guidelines on key considerations in issuing recommendations on the classification of active substances as regards their supply (prescription and non-prescription status) should be consulted.

1. Active substance

Hypericum perforatum L., herba (St. John's wort, Hyperici herba)

2. ATC code

N06AX25

3. First level assessment

3.1 Characteristics of the active substance

Hyperici herba is widely used in herbal medicinal products, traditional herbal medicinal products, food supplements and food (herbal tea).

Herbal medicinal products have been registered in several Member States.

Herbal medicinal products contain dry extract of Hyperici herba. The amount of active constituents depends on the preparation.

The European Union herbal monograph on Hypericum perforatum L., herba [1] provides three options for herbal preparation in the form of dry extract for well-established use depending on drug extract ratio (DER) and extraction solvent: DER 3-7:1, extraction solvent methanol 80% V/V; DER 3-6:1, extraction solvent ethanol 80% V/V; DER 2.5-8:1, extraction solvent ethanol 50-68% V/V.

Hyperici herba has been marketed for more than 5 years in a Member State with available post-authorisation safety data.

Mechanism of action: Hypericum dry extract inhibits the synaptosomal uptake of the neurotransmitters noradrenaline, serotonin and dopamine. Naphthodianthrones (e.g. hypericin, pseudohypericin), phloroglucin derivatives (e.g. hyperforin) and flavonoids contribute to the activity [1,2].

3.2 Pharmaceutical form/Route of administration

Dry extract of Hyperici herba is available in solid dosage forms (film-coated tablets, coated tablets, hard capsules), for oral use [1,2].

3.3 Intended therapeutic indication

1) Herbal medicinal product for the treatment of mild to moderate depressive episodes in adults [1].

Suitable for prescription status: psychiatric condition, medical diagnosis needed, medical supervision of treatment efficacy needed.

2) Herbal medicinal product for the short-term treatment of symptoms in mild depressive disorders in adults [1].

Possibly suitable for non-prescription status

Conclusion of First level assessment

It is not definitely concluded that the active substance should have prescription status applied. Depending on the therapeutic indication, Hyperici herba may be considered for prescription status or exemption from prescription status. Second level assessment is required to further evaluate the appropriate supply status.

Hyperici herba (N06AX25) with the indication “for the treatment of mild to moderate depressive episodes” should have prescription status, sub-categorised in List II (the patient may continue the treatment without renewed medical advice and the supply can be repeated unless otherwise directed by the prescriber).

4. Second level assessment

4.1 Assessment of use

Indication for the short-term treatment of symptoms in mild depressive disorders in adults may be considered for exemption from prescription status.

Sign and symptoms of “mild depressive disorders” like lowered mood, reduction of energy, decrease in activity can be readily recognised without medical intervention. The condition is considered minor. The symptoms of “mild depressive disorders” are similar to symptoms of clinical depression, so there is a risk of misdiagnosis.

Identified risk(s): the risk of misdiagnosis (depressive disorders vs. depressive episodes/clinical depression).

4.2 Safety profile

4.2.1 Direct risks

Toxicity

Studies on acute toxicity and repeated dose toxicity did not show signs of toxic effects.

Contraindications, special warnings and precautions for use

Contraindications include:
- hypersensitivity to the active substance;
- concomitant use with coumarin-type anticoagulants, cyclosporine, everolimus, sirolimus, tacrolimus for systemic use, fosamprenavir, indinavir and other protease inhibitors, nucleoside reverse transcriptase inhibitors, irinotecan, imatinib and other cytostatic agents metabolised by CYP3A4, CYP2B6, CYP2C9, CYP2C19 or transported by P-glycoprotein.

Interactions

Pharmacokinetic interactions:
- coumarin-type anticoagulants, cyclosporine, everolimus, sirolimus, tacrolimus for systemic use, fosamprenavir, indinavir and other protease inhibitors, nucleoside reverse transcriptase inhibitors, irinotecan, imatinib and other cytostatic agents metabolised by CYP3A4, CYP2B6, CYP2C9, CYP2C19 or transported by P-glycoprotein (contraindicated);
- drug substances the metabolism of which is influenced by CYP3A4, CYP2B6, CYP2C9, CYP2C19 or P-glycoprotein (e.g. amitriptyline, fexofenadine, alprazolam, diazepam, midazolam, methadone, simvastatin, digoxin, finasteride), because a reduction of plasma concentrations is possible;
- reduction of plasma concentrations of hormonal contraceptives;
- possible interactions with products used during general and regional anaesthesia.

Pharmacodynamic interactions:
- serotonergic effects may occur when combined with antidepressants such as serotonin reuptake inhibitors (e.g. sertraline, paroxetine) or buspirone;
- very rarely serotonin syndrome may occur in combination with serotonin-uptake inhibitors or other serotonergic active substances.

Adverse reactions

Gastrointestinal disorders (such as nausea, abdominal pain, diarrhoea).

Allergic skin reactions, photosensitivity reaction.

Fatigue, restlessness [1].

4.2.2 Indirect risks

Delayed diagnosis

Risk of delayed diagnosis of other conditions and introduction of other forms of treatment.

4.3 Strength, posology and treatment duration

Strength and posology depend on the preparation.

Treatment duration: 6 weeks; the onset of the effect can be expected within 4 weeks of treatment [1].

4.4 Special populations (paediatric, elderly, hepatic and renal impairment, pregnancy and breast-feeding, others)

Use in children and adolescents under 18 years of age is not recommended, as insufficient data are available.

Use during pregnancy and lactation is not recommended, as safety has not been established [1].

4.5 Risk mitigation measures

Table 4 – Identified risk and mitigation measures

Identified risk(s)	Mitigation measures
Photosensitivity	Special warning in product information (SmPC, PIL): During the treatment intense UV-exposure should be avoided.
Interaction	Contraindications and special warnings in product information.
Misdiagnosis/delayed diagnosis	Treatment duration of up to 6 weeks. Product information states that the onset of the effect can be expected within 4 weeks of treatment. If the symptoms persist during the use of the medicinal product, a doctor should be consulted. Pack size limited to 6-week treatment.

4.6 Post-marketing data

Dry extract of Hypericum perforatum has been in well-established medicinal use within the EU for at least 10 years, with recognised efficacy and an acceptable level of safety.

4.7 Public health/Socioeconomic impact

There are no specific risks regarding Hyperici herba use that cannot be minimised by mitigation measures. It is beneficial for patients to have access to self-treatment for mild disorders. No other medicinal product for the treatment of mild depressive disorders with non-prescription status has been identified.

Conclusion of Second level assessment

The assessment of this level allows the decision that the active substance, under described conditions, could have **prescription status (List II*) with exemptions** (to allow for non-prescription supply).

** List II: the supply of a medicine containing a List II active substance can be renewed. This classification applies 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. On contrary, the supply of a medicine containing a List I substance should not be renewed without the prescriber having so specified. 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. See Resolution CM/Res (2018)1 for further details.*

RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Depending on the conditions, the active substance could have prescription status or non-prescription status.

Conditions for non-prescription status:

Pharmaceutical form/route of administration: oral use, solid dosage form (tablets, capsules).

Therapeutic indications: short-term treatment of symptoms in mild depressive disorders.

Age group: adults (over 18 years old)

Special groups (hepatic and renal impairment, pregnancy and breast-feeding, others): use during pregnancy and lactation is not recommended.

Maximum pack size: for up to 6-week treatment

Single dose: 600 mg or 612 mg once a day, or 250-600 mg two to three times daily with a daily dose of 600-1200 mg.

Risk mitigation measures (if applicable): treatment duration of up to 6 weeks; pack size for 6-week treatment, contraindications, special warnings and interactions in product information.

REFERENCES

[1] European Medicines Agency, Committee on Herbal Medicinal Products: EMA/HMPC/7695/2021 - European Union herbal monograph on Hypericum perforatum L., herba, Revision 1, 2022 (accessed in May 2025 from https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-hypericum-perforatum-l-herba-revision-1_en.pdf).

[2] Martindale: The Complete Drug Reference 40th Edition, 2020.

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Introduction and Classification of herbal medicines sections (sections common to all EBRs for herbals) - drafted within the Herbals Working Group by Sandra Monteiro (Infarmed – National Authority of Medicines and Health Products, Portugal) in collaboration with (in alphabetical order): Elona Cilku (MALMED - Agency for Medicines and Medical Devices, North Macedonia), Denisse Mazilu (National Medicines Agency, Romania), Guoda Radavičiūtė (State Medicines Control Agency of Lithuania), Katarzyna Żywiec (Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Poland), and the EDQM Secretariat (Daniela Mayerová).