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Committee on Herbal Medicinal Products (HMPC)

European Union herbal monograph on *Hypericum perforatum* L, herba and *Cimicifuga racemosa* (L.) Nutt., rhizoma

Draft

Initial assessment	
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BG (bulgarski): Жълт кантарион, стрък / Черен кохош, Клопогон, Цимифуга (корен) CS (čeština): třezalková nať / ploštičníkový kořen DA (dansk): Perikon/sølvlys jordstængel DE (Deutsch): Johanniskraut / Cimicifugawurzelstock EL (elliniká): υπερικού πόα/ακταίας βοτρυοειδούς ρίζωμα EN (English): St. John's wort / black cohosh ES (español): hipérico, sumidad de / cimicífuga, rizoma de ET (eesti keel): FI (suomi): mäkikuisma, verso / tähkäkimikki, juurakko FR (français): Millepertuis (sommité fleurie de) / Actée à grappes (rhizome d') HR (hrvatski): zelen gospine trave / cimicifugin podanak HU (magyar): közönséges orbáncfű virágos hajtás / rövidágú poloskavész gyökértörzs IT (italiano): Iperico sommità fiorite / Cimicifuga rizoma	LT (lietuvių kalba): Jonažolių žolė / Kekinių blakėžudžių šakniastiebiai LV (latviešu valoda): Asinszāles laksti / Ķekarainās sudrabsveces saknenis MT (Malti): Fexfiex / Riżoma tal-Koħox NL (Nederlands): Sint-janskruid / zwarte amerikaanse slangenwortel PL (polski): zestawienia preparatów ziela dziurawca i kłącza pluskwicy groniastej PT (português): hipericão / cimicifuga, rizoma RO (română): iarbă de sunătoare / rizom de cimicifuga SK (slovenčina): vňať ľubovníka / podzemok ploštičníka SL (slovenščina): zel šentjanževke / korenika grozdnate svetilke (cimicifuge) SV (svenska): johannesört, ört / läkesilverax, jordstam IS (íslenska): NO (norsk): Prikkperikum / klaseormdruejordstengel

European Union herbal monograph on *Hypericum perforatum* L., herba and *Cimicifuga racemosa* (L.) Nutt., rhizoma

1. Name of the medicinal product

To be specified for the individual finished product.

2. Qualitative and quantitative composition[1, 2]

Well-established use	Traditional use
	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC Fixed combination of *Hypericum perforatum* L., herba and *Cimicifuga racemosa* (L.) Nutt., rhizoma i) Herbal substance Not applicable ii) Herbal preparations Dry extract from Hyperici herba (DER 3.5-6:1), extraction solvent ethanol 60% (V/V) and Dry extract from Cimicifugae rhizoma (DER 6-11:1), extraction solvent propanol 40% (V/V)

3. Pharmaceutical form

Well-established use	Traditional use
	Herbal preparations in solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.

[1] The declaration of the active substance(s) for an individual finished product should be in accordance with relevant herbal quality guidance.

[2] The material complies with the Ph. Eur. monographs (ref. 2069 and 1874)

4. Clinical particulars

4.1. Therapeutic indications

Well-established use	Traditional use
	Traditional herbal medicinal product used for the relief of mild climacteric complaints like hot flushes and sweating when associated with temporary mental exhaustion. The product is a traditional herbal medicinal product for use in the specified indications exclusively based upon long-standing use.

4.2. Posology and method of administration

Well-established use	Traditional use
	Posology *Female adults* Single dose: First 8 weeks: 140 mg / 7.5 mg, twice daily From week 9: 70 mg / 3.75 mg, twice daily Daily dose: First 8 weeks: 280 mg/ 15 mg From week 9: 140 mg/ 7.5 mg There is no relevant indication for men, children and adolescents. **Duration of use** If symptoms do not improve or worsen after 6 weeks a qualified health care practitioner should be consulted. Treatment should not be taken for more than 6 months without medical advice. **Method of administration** Oral use. To be taken at the same time of day, if possible (morning and evening).

4.3. Contraindications

Well-established use	Traditional use
	Hypersensitivity to the active substances.

Well-established use	Traditional use
	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 (see section 4.5 'Interactions with other medicinal products and other forms of interaction')

4.4. Special warnings and precautions for use

Well-established use	Traditional use
	Patients with an existing or previous liver disorder should use this combination with caution. Patients should stop the use and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (icterus, dark urine, severe upper stomach pain, nausea, loss of appetite, tiredness). Patients who have been treated or who are undergoing treatment for breast cancer or other hormone-dependent tumours should not use this combination without medical advice. If vaginal bleeding occurs or other symptoms occur, a doctor should be consulted. Not to used together with oestrogens unless advised by a doctor. During the treatment intense UV-exposure should be avoided. If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

4.5. Interactions with other medicinal products and other forms of interaction

Well-established use	Traditional use
	Patients taking other medicines on prescription should are advised to consult a doctor or pharmacist before taking Hypericum. Pharmacokinetic interactions: Daily dose of hyperforin ≤ 1 mg: As the daily intake of hyperforin is less than 1 mg, no clinically relevant interactions are reported for concomitantly administered drugs which are metabolised via CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4 or transported by P-glycoprotein. Pharmacokinetic interactions with drugs which are metabolised via other CYP-enzymes have not been investigated. Daily dose of hyperforin > 1 mg: Hyperici herba preparations induce the activity of CYP3A4, CYP2B6, CYP2C9, CYP2C19 and P-glycoprotein. 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 is contraindicated. Special care should be taken in case of concomitant use of all 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. The reduction of plasma concentrations of hormonal contraceptives may lead to increased intermenstrual bleeding and reduced safety in birth control. Women using hormonal contraceptives should take additional contraceptive measures. Prior to elective surgery possible interactions with products used during general and regional

Well-established use	Traditional use
	anaesthesia should be identified. If necessary, the herbal medicinal product should be discontinued. The elevated enzyme activity returns within 1 week after cessation to normal level. Pharmacodynamic interactions: Hyperici herba preparations may contribute to serotonergic effects when combined with antidepressants such as serotonin reuptake inhibitors (e.g., sertraline, paroxetine) or buspirone. Very rarely undesired effects (serotonin syndrome) with autonomic dysfunctions (such as perspiration, tachycardia, diarrhoea, fever), mental alterations (such as agitation, disorientation), and motor alterations (such as tremor or myoclonias) can occur in combination with serotonin-uptake inhibitors or other serotonergic active substances.

4.6. Fertility, pregnancy and lactation

Well-established use	Traditional use
	Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. Women of childbearing potential should consider using effective contraception during treatment (see section 4.4 and 4.5). No fertility data available.

4.7. Effects on ability to drive and use machines

Well-established use	Traditional use
	No studies on the effect on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Well-established use	Traditional use
	Psychiatric disorders: Restlessness, anxiety, mania. The frequency is not known.

Well-established use	Traditional use
	Nervous system disorders: Headache, neuropathy, dizziness. The frequency is not known. Gastrointestinal disorders: Nausea, abdominal pain, diarrhoea, dyspepsia. The frequency is not known. Hepatobiliary disorders: Liver toxicity (including hepatitis, jaundice, disturbances in the liver function tests). The frequency is not known. Skin and subcutaneous tissue disorders: Allergic skin reactions (urticaria, itching skin, exanthema). Fair-skinned individuals may react with dysesthesia (e.g., tingling, sensitivity cold or pain, burning sensation) and intensified sunburn-like symptoms under intense sunlight. The frequency is not known. General disorders: Fatigue, facial oedema and peripheral oedema. The frequency is not known. Investigations: Weight gain. The frequency is not known If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted

4.9. Overdose

Well-established use	Traditional use
	No case of overdose has been reported.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Well-established use	Traditional use
	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC.

5.2. Pharmacokinetic properties

Well-established use	Traditional use
	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC.

5.3. Preclinical safety data

Well-established use	Traditional use
	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC, unless necessary for the safe use of the product. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed on the combination. Evidence from *in-vitro* and *in-vivo* pharmacological studies suggests that Cimicifugae rhizoma extracts do not influence the latency or development of breast cancer. However, contradictory results have been obtained in other in-vitro experiments. In Cimicifugae rhizoma-treated (isopropanolic black cohosh extract equivalent to 40 mg of root and rhizome), tumour-bearing, female transgenic mice, the percentage of mice with detectable metastatic lung tumours at necropsy was increased compared to those on the control diet. However, in the same experimental model, no increase in primary breast tumour was seen. Influence on breast cancer or other hormone-depending tumours cannot be excluded. Several studies on extracts of and isolated compounds from *Hypericum perforatum* report *in vitro* and *in vivo* effects that could affect the development of foetuses from treated mothers. Phototoxicity: After oral application of dosages of 1800 mg of an *Hypericum perforatum* extract per day for 15 days the skin sensitivity against UVA was increased, and the minimum dose for pigmentation was significantly reduced. In the recommended dosage, no signs of phototoxicity are reported.

6. Pharmaceutical particulars

Well-established use	Traditional use
	Not applicable.

7. Date of compilation/last revision

22 January 2025