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Committee on Herbal Medicinal Products (HMPC)

European Union herbal monograph on *Hypericum perforatum* L., herba (traditional use)

Draft

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BG (bălgarski): Жълт кантарион, стрък	LT (lietuvių kalba): Jonažolių žolė
CS (čeština): třezalková nať	LV (latviešu valoda): Asinszāles laksti
DA (dansk): Perikon	MT (malti): fexfiex
DE (Deutsch): Johanniskraut	NL (nederlands): Sint Janskruid
EL (elliniká): πόα υπερικού- υπερικόν	PL (polski): Ziele dziurawca
EN (English): st. john's wort	PT (português): hipericão
ES (espanol): hipérico, sumidad de	RO (română): iarbă de sunătoare
ET (eesti keel): naistepunaürt	SK (slovenčina): Vňať ľubovníka
FI (suomi): mäkikuisma	SL (slovenščina): zel šentjanževke
FR (français): millepertuis (sommité fleurie de)	SV (svenska): johannesört,ört
HR (hrvatski): zelen gospine trave	IS (íslenska):
HU (magyar): orbáncfű	NO (norsk): prikkperikum, johannesurt
IT (italiano): Iperico sommità fiorite	

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European Union herbal monograph on *Hypericum perforatum* L., herba (traditional use)

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 *Hypericum perforatum* L., herba (St. John's wort) i) Herbal substance Not applicable ii) Herbal preparations a) Dry extract (DER 4-7:1), extraction solvent ethanol 38% (m/m) = 45% V/V b) Liquid extract (DER 1:4-20), extraction solvent vegetable oil c) Liquid extract (DER 1:13), extraction solvent maize oil or other suitable vegetable oil d) Tincture (ratio herbal substance : extraction solvent 1:10), extraction solvent ethanol 45-50% (V/V) e) Liquid extract (DER 1:2-7), extraction solvent ethanol 50% (V/V)[3] f) Expressed juice from the fresh herb (DER 1:0.5-0.9) g) Comminuted herbal substance h) Powdered herbal substance

3. Pharmaceutical form

Well-established use	Traditional use
	Comminuted herbal substance as herbal tea for oral use.

[1] The declaration of the active substance for an individual finished product should be in accordance with relevant herbal quality guidance.
[2] The material complies with the Ph. Eur. monograph (ref.01/2017:1438).
[3] A narrow DER to be specified for an individual medicinal product.

Well-established use	Traditional use
	Herbal preparations a, h in solid dosage forms for oral use. Herbal preparations b, c, d, e, f in liquid dosage forms for oral use. Herbal preparations b, d, e in liquid or semi-solid dosage forms for cutaneous use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.

4. Clinical particulars

4.1. Therapeutic indications

Well-established use	Traditional use
	Indication 1) Herbal substance, herbal preparations a, c, d, e, f, g, h: Traditional herbal medicinal product for the relief of temporary mental exhaustion. Indication 2) Herbal preparations b, d, e: Traditional herbal medicinal product for the symptomatic treatment of minor inflammations of the skin (such as sunburn) and as an aid in healing of minor wounds. Indication 3) Herbal preparation g: Traditional herbal medicinal product for the symptomatic relief of mild gastrointestinal discomfort. Indication 4) Herbal preparation g: Traditional herbal medicinal product for the supportive treatment of nervous restlessness and sleep disorders. The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

4.2. Posology and method of administration[4]

Well-established use	Traditional use
	Posology Indication 1) *Adults and Elderly* Herbal preparation a) Single dose: 60-180 mg Daily dose: 180 - 360 mg Herbal preparation c) Single dose: 200 mg Daily dose: 600 mg Herbal preparation d) Single dose: 2-4 ml Daily dose: 6-12 ml Herbal preparation e) Single dose: 0.8-1.5 ml Daily dose: 2.4-4.5 ml Herbal preparation f) Single dose: 10 – 20 ml Daily dose: 10-30 ml Herbal preparation g) Herbal tea: 1.5 - 2 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion, 3 times daily Herbal preparation h) Single dose: 300 – 500 mg Daily dose: 900 – 1000 mg Children, adolescents The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use'). Indication 2) *Adolescents, adults, elderly* Herbal preparation b: Cutaneous administration of the undiluted

[4] For guidance on herbal substance/herbal preparation administered as herbal tea or as infusion/decoction/macerate preparation, please refer to the HMPC 'Glossary on herbal teas' (EMA/HMPC/5829/2010 Rev.1).

Well-established use	Traditional use
	herbal preparation Herbal preparations d, e: Cutaneous administration of the undiluted or diluted herbal preparation *Children* The use in children under 12 years of age is not recommended (see section 4.4 ‘Special warnings and precautions for use’). Indication 3) *Adults, elderly* Herbal preparation g: Herbal tea: 2 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion, 2 times daily *Children, adolescents* The use in children and adolescents under 18 years of age is not recommended (see section 4.4 ‘Special warnings and precautions for use’). Indication 4) *Adults, elderly* Herbal preparation g: Herbal tea: 2-3 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion, 2 times daily *Children, adolescents* The use in children and adolescents under 18 years of age is not recommended (see section 4.4 ‘Special warnings and precautions for use’). **Duration of use** Indications 1) and 4) If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. Indications 2) and 3) If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Well-established use	Traditional use
	Method of administration Indications 1), 3) and 4) Oral use Indication 2) Cutaneous use

4.3. Contraindications

Well-established use	Traditional use
	Daily dose of hyperforin ≤ 1 mg: Hypersensitivity to the active substance. *Daily dose of hyperforin > 1 mg:* Hypersensitivity to the active substance. Concomitant use with cyclosporine, tacrolimus for systemic use, amprenavir, indinavir and other protease inhibitors, irinotecan and warfarin (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
	Indications 1), 3) and 4) During the treatment intense UV-exposure should be avoided. Since no sufficient data are available the use in children and adolescents under 18 years of age is not recommended. For herbal preparations containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included. Indication 2) During the treatment intense UV-exposure of the respective skin areas should be avoided. Since no data on the safe use in children are available, the use in children under 12 years of age is

Well-established use	Traditional use
	not recommended. If signs of skin infections are observed, a doctor or a qualified healthcare practitioner should be consulted.

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

Well-established use	Traditional use
	Indications 1), 3) and 4) *Daily dose of hyperforin ≤ 1 mg:* In the case of a daily intake of hyperforin less than 1 mg and of a duration of use not longer than 2 weeks (see section 4.2. 'Posology and method of administration'), no clinically relevant interactions are to be expected. Patients taking other medicines on prescription should consult a doctor or pharmacist before taking Hypericum. *Daily dose of hyperforin > 1 mg:* Hypericum dry extract induces the activity of CYP3A4, CYP2C9, CYP2C19 and P-glycoprotein. The concomitant use of cyclosporine, tacrolimus for systemic use, amprenavir, indinavir and other protease inhibitors, irinotecan and warfarin is contraindicated (see section 4.3. 'Contraindications'). Special care should be taken in case of concomitant use of all drug substances the metabolism of which is influenced by CYP3A4, CYP2C9, CYP2C19 or P-glycoprotein (e.g., amitriptyline, fexofenadine, benzodiazepines, 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 anaesthesia should be identified. If necessary the herbal medicinal product should be discontinued. The elevated enzyme activity returns within 1 week

Well-established use	Traditional use
	after cessation to normal level. Hypericum dry extract may contribute to serotonergic effects when combined with antidepressants such as serotonin reuptake inhibitors (e.g. sertraline, paroxetine, nefazodone), buspirone or with triptans. Patients taking other medicines on prescription should consult a doctor or pharmacist before taking Hypericum. Indication 2) None reported

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. No fertility data available.

4.7. Effects on ability to drive and use machines

Well-established use	Traditional use
	Indications 1), 3) and 4) No adequate studies on the effect on the ability to drive and use machines have been performed. Indication 2) Not relevant

4.8. Undesirable effects

Well-established use	Traditional use
	Indications 1), 3) and 4) Gastrointestinal disorders, skin reactions, fatigue and restlessness may occur. The frequency is not known. Fair-skinned individuals may react with intensified sunburn-like symptoms under intense sunlight. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner

Well-established use	Traditional use
	should be consulted. Indication 2) Skin reactions may occur. 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
	Indications 1), 3) and 4) After the intake of up to 4.5 g dry extract per day for 2 weeks and additionally 15 g dry extract just before hospitalisation seizures and confusion have been reported. After ingestion of massive overdoses, the patient should be protected from sunlight and other UV-light sources for 1-2 weeks. Indication 2) 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 as amended.

5.2. Pharmacokinetic properties

Well-established use	Traditional use
	Daily dose of hyperforin ≤ 1 mg: Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended. *Daily dose of hyperforin > 1 mg:* The absorption of hypericin is delayed and starts about 2 hours after administration. The elimination half-life of hypericin is about 20 hours, the mean

Well-established use	Traditional use
	residence time about 30 hours. Maximum hyperforin levels are reached about 3-4 hours after administration; no accumulation could be detected. Hyperforin and the flavonoid miquelianin can cross the blood-brain-barrier. Hyperforin induces the activity of the metabolic enzymes CYP3A4, CYP2C9, CYP2C19 and PGP dose-dependently via activation of the PXR system. Therefore the elimination of other drug substances may be accelerated, resulting in decreased plasma concentrations.

5.3. Preclinical safety data

Well-established use	Traditional use
	Studies on acute toxicity and repeated dose toxicity did not show signs of toxic effects. The weak positive results of an ethanolic extract in the AMES-test (Salmonella typhimurium TA 98 and TA 100, with and without metabolic activation) could be assigned to quercetin and are irrelevant to human safety. No signs of mutagenicity could be detected in further in-vitro and in-vivo test systems. Tests on reproductive toxicity revealed equivocal results. Tests on the carcinogenic potential have not been performed. Phototoxicity: After oral application of dosages of 1800 mg of an 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
	The amounts of hyperforin should be specified in the dossier (see 4.3, 4.5 and 5.2).

7. Date of compilation / last revision

30 January 2018