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Committee on Herbal Medicinal Products (HMPC)

European Union herbal monograph on *Hypericum perforatum* L., herba

Final – Revision 1

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Keywords	Herbal medicinal products; HMPC; European Union herbal monographs; well-established use; traditional use; *Hypericum perforatum* L., herba; Hyperici herba; St. John's wort

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

European Union herbal monograph on *Hypericum perforatum* L., herba

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 marketing authorisation application of Article 10(a) of Directive 2001/83/EC *Hypericum perforatum* L., herba (St. John's wort) i) Herbal substance Not applicable. ii) Herbal preparations[3] a) Dry extract (DER 3-7:1), extraction solvent methanol 80% V/V b) Dry extract (DER 3-6:1), extraction solvent ethanol 80% V/V c) Dry extract (DER 2.5-8:1), extraction solvent ethanol 50-68% V/V[4]	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 1:5), extraction solvent ethanol 50-70% V/V e) Tincture (ratio herbal substance: extraction solvent 1:10), extraction solvent ethanol 45-50% V/V f) Liquid extract (DER 1:2-7), extraction solvent ethanol 50% V/V[4] g) Liquid extract from fresh herb (DER 1:1), extraction solvent ethanol 96% V/V h) Expressed juice from the fresh herb (DER 1:0.5-0.9) i) Stabilised expressed juice from fresh herb: The fresh herb is first stabilised over a boiling ethanol, then pressed and adjusted with water to a DER of

[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] The herbal preparations comply with the Ph. Eur. monograph (ref. 01/2017: 1874)
[4] A narrow range of the DER to be specified for each individual medicinal product.

Well-established use	Traditional use
	1:1. j) Comminuted herbal substance k) Powdered herbal substance

3. Pharmaceutical form

Well-established use	Traditional use
Herbal preparation in solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.	Comminuted herbal substance as herbal tea for oral use. Comminuted herbal substance for infusion preparation for cutaneous use. Herbal preparations a), k) in solid dosage forms for oral use. Herbal preparations b), c), d), e), f), g), h), i) in liquid dosage forms for oral use. Herbal preparations b), e), f) 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 preparations a), b): Herbal medicinal product for the treatment of mild to moderate depressive episodes. Indication 2) Herbal preparation c): Herbal medicinal product for the short-term treatment of symptoms in mild depressive disorders.	Indication 1) Herbal preparations a), c), d), e), f), g), h), j), k): Traditional herbal medicinal product for the relief of temporary mental exhaustion. Indication 2) Herbal preparations b), d), e), j): 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 i), j): Traditional herbal medicinal product for the

Well-established use	Traditional use
	symptomatic relief of mild gastrointestinal discomfort. Indication 4) Herbal preparation j): Traditional herbal medicinal product for the supportive treatment of nervous restlessness and associated with difficulties in falling asleep. 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[5]

Well-established use	Traditional use
Posology *Adults and elderly* Herbal preparation a): Single dose: 300-600 mg Dosage frequency: 1-3 times daily Daily dose: 600-1800 mg Herbal preparation b): Single dose: 900 mg Dosage frequency: 1 single daily dose Daily dose: 900 mg Herbal preparation c): Single dose: 600 mg or 612 mg Dosage frequency: 1 single daily dose Daily dose: 600 mg or 612 mg or Single dose: 250-600 mg Dosage frequency: 2-3 times daily Daily dose: 500-1200 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').	**Posology** Indication 1) *Adults and Elderly* Herbal preparation a) Single dose: 60-180 mg Dosage frequency: 2-3 times daily Daily dose: 180 - 360 mg Herbal preparation c) Single dose: 200 mg Dosage frequency: 3 times daily Daily dose: 600 mg Herbal preparation d) Single dose: 1-1.5 ml Dosage frequency: 3 times daily Daily dose: 3-4.5 ml Herbal preparation e) Single dose: 2-4 ml Dosage frequency: 3 times daily Daily dose: 6-12 ml Herbal preparation f) Single dose: 0.8-1.5 ml Dosage frequency: 3 times daily

[5] 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
Duration of use Indication 1) 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. Indication 2) Six weeks. 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. **Method of administration** Oral use.	Daily dose: 2.4-4.5 ml Herbal preparation g) Single dose: 5ml Dosage frequency: 4 times daily Daily dose: 20 ml Herbal preparation h) Single dose: 10 – 20 ml Dosage frequency: 1-3 times daily Daily dose: 10-30 ml Herbal preparation j) Herbal tea: 1.5 - 2 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion, 2-3 times daily Daily dose: 3-6 g Herbal preparation k) Single dose: 300 – 500 mg Dosage frequency: 2-3 times daily 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), e), f): Cutaneous administration of the undiluted herbal preparation Herbal preparation j): Comminuted herbal preparation for infusion preparation for cutaneous use: 2 g of the comminuted herbal substance in 150 ml of water, several times daily as washing or impregnated dressing *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)

Well-established use	Traditional use
	Adults, elderly Herbal preparation i) Single dose: 2.5 ml Dosage frequency: 3 times daily Daily dose: 7.5 ml Herbal preparation j): 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 j): 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. **Method of administration** Indications 1), 3) and 4)

Well-established use	Traditional use
	Oral use. Indication 2) Cutaneous use.

4.3. Contraindications

Well-established use	Traditional use
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 (see section 4.5 'Interactions with other medicinal products and other forms of interaction').	*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 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
Indications 1) and 2) 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.	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. 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 not recommended.

Well-established use	Traditional use
	If signs of skin infections are observed, a doctor or a qualified healthcare practitioner should be consulted. Indications 1) and 2) 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.

4.5. Interactions with other medicinal products and other forms of interaction[6]

Well-established use	Traditional use
Patients taking other medicines on prescription are advised to consult a doctor or pharmacist before taking *Hypericum*. Pharmacokinetic interactions: 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 (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, 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	Patients taking other medicines on prescription are advised to consult a doctor or pharmacist before taking *Hypericum*. Pharmacokinetic interactions: Indications 1), 3) and 4) *Daily dose of hyperforin ≤ 1 mg:* As the daily intake of hyperforin is less than 1 mg and of a duration of use not longer than 2 weeks 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

[6] For a list of drugs of which the metabolism is evidently and significantly interacted by herbal preparations of Hyperici herba see the Assessment report EMA/HMPC/244315/2016 chapter 5.5.4. This list may be used as guidance for the product information of individual products.

Well-established use	Traditional use
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 after cessation to normal level. Pharmacodynamic interactions: Hypericum dry extract 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.	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, 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 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. Indication 2) None reported

4.6. Fertility, pregnancy and lactation

Well-established use	Traditional use
Safety during pregnancy and breast-feeding has not been established. Studies in animals have	Safety during pregnancy and breast-feeding has not been established. Studies in animals have

Well-established use	Traditional use
shown signs of reproductive toxicity (see section 5.3 'Preclinical safety data'). The use is not recommended during pregnancy and lactation. No fertility data available.	shown signs of reproductive toxicity (see section 5.3 'Preclinical safety data'). The use is not recommended during pregnancy and lactation. No fertility data available.

4.7. Effects on ability to drive and use machines

Well-established use	Traditional use
No adequate studies on the effect on the ability to drive and use machines have been performed.	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
Gastrointestinal disorders (such as nausea, abdominal pain and diarrhoea), allergic skin reactions, fatigue and restlessness may occur. The frequency is not known. Fair-skinned individuals may react with dysesthesia (e.g. tingling, sensitivity cold or pain, burning sensation) and intensified sunburn-like symptoms under intense sunlight. If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.	Indications 1), 3) and 4) Gastrointestinal disorders (such as nausea, abdominal pain and diarrhoea), allergic skin reactions, fatigue and restlessness may occur. The frequency is not known. Fair-skinned individuals may react with dysesthesia (e.g. tingling, sensitivity cold or pain, burning sensation) and intensified sunburn-like symptoms under intense sunlight. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner 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
After the intake of up to 4.5 g dry extract per day for 2 weeks and additionally 15 g dry extract just	Indication 1)

Well-established use	Traditional use
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.	Herbal preparation a): 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. Indications 1) (herbal preparations b-k), 2), 3) and 4) No case of overdose has been reported.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Well-established use	Traditional use
Pharmacotherapeutic group: Other antidepressants ATC code: N06AX *Hypericum* dry extract inhibits the synaptosomal uptake of the neurotransmitters noradrenaline, serotonin and dopamine. It changes the behaviour of animals in several antidepressant models (e.g., forced swimming test) similarly to synthetic antidepressants. Napthodianthrones (e.g. hypericin, pseudohypericin), phloroglucin derivatives (e.g. hyperforin) and flavonoids contribute to the activity.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC.

5.2. Pharmacokinetic properties

Well-established use	Traditional use
The time to maximum plasma concentration (T_{max}) of hypericin is 4-12 hours and the elimination half-life ($T_{½}$) is about 19-36 hours. Maximum hyperforin levels are reached (T_{max}) about 3-4 hours after administration and the elimination half-life ($T_{½}$) is about 15-63 hours. Hyperforin can cross the blood-brain-barrier. Hyperforin induces the activity of the metabolic enzymes CYP3A4, CYP2B6, CYP2C9, CYP2C19 and	*Daily dose of hyperforin ≤ 1 mg:* The time to maximum plasma concentration (T_{max}) of hypericin is 4-12 hours and the elimination half-life ($T_{½}$) is about 19-36 hours. *Daily dose of hyperforin > 1 mg:* The time to maximum plasma concentration (T_{max}) of hypericin is 4-12 hours and the elimination half-life ($T_{½}$) is about 19-36 hours.

Well-established use	Traditional use
P-glycoprotein dose-dependently via activation of the PXR system. Therefore, the elimination of other drug substances may be accelerated, resulting in decreased plasma concentrations.	Maximum hyperforin levels are reached (T_{max}) about 3-4 hours after administration and the elimination half-life ($T_{½}$) is about 15-63 hours. Hyperforin can cross the blood-brain-barrier. Hyperforin induces the activity of the metabolic enzymes CYP3A4, CYP2B6, CYP2C9, CYP2C19 and P-glycoprotein 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. Several studies on extracts of and isolated compounds from *Hypericum perforatum* report in vitro and in vivo effects that could affect the development of fetuses from treated mothers. Tests on the carcinogenic potential have not been published. 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.	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. Several studies on extracts of and isolated compounds from *Hypericum perforatum* report in vitro and in vivo effects that could affect the development of fetuses from treated mothers. 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
Extracts should be quantified with respect to hypericin[7]. The amounts of hyperforin and of	The amounts of hyperforin should be specified in

[7] Ph. Eur. monograph (ref. 07/2015:0765) Herbal Drug Extracts

Well-established use	Traditional use
flavonoids should be declared.	the dossier (see 4.3, 4.5 and 5.2).

7. Date of compilation/last revision

23 November 2022