EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

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

2nd Draft – Revision 1

Initial assessment	
Discussion in Working Party on European Union monographs and list (MLWP)	March 2008 May 2008 July 2008 September 2008 November 2008
Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation	6 November 2008
End of consultation (deadline for comments).	15 February 2009
Re-discussion in MLWP	July 2009 September 2009 November 2009
Adoption by Committee on Herbal Medicinal Products (HMPC) Monograph (**WEU**) (EMA/HMPC/101304/2008) Monograph (**TU**) (EMEA/HMPC/745582/2009) Assessment report (EMA/HMPC/101303/2008) List of references (EMA/HMPC/101620/2008) Overview of comments received during public consultation (EMA/HMPC/258853/2009) HMPC Opinion (**WEU**) (EMEA/HMPC/M/H/0063) HMPC Opinion (**TU**) (EMEA/HMPC/M/H/0066)	12 November 2009

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First systematic review	
Discussion in Working Party on Community monographs and list (MLWP)	Apr 2016 Jan 2017 May 2017 Sep 2017 Nov 2017
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Adoption 2nd Draft revision 1 (**WEU** +**TU**) by Committee on Herbal Medicinal Products (HMPC) for release for consultation	3 March 2021 Second consultation
Start of public consultation	31 March 2021 Second consultation
End of consultation (deadline for comments). Comments should be provided using this template to hmpc.secretariat@ema.europa.eu	30 June 2021

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- υπερικόν 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): orbáncfű 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 (well-established and 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 marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended *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 as amended *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)[5] f) Expressed juice from the fresh herb (DER 1:0.5-0.9) g) Comminuted herbal substance h) Powdered herbal substance

[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 product
[5] A narrow DER to be specified for an individual medicinal product.

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. 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 preparations a, b: Herbal medicinal product for the treatment of mild to moderate depressive episodes (according to ICD-10). 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: 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 associated with difficulties in falling asleep. The product is a traditional herbal medicinal product for use in specified indications exclusively

Well-established use	Traditional use
	based upon long-standing use.

4.2. Posology and method of administration[6]

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): 900 mg, once daily Herbal preparation c): 600 or 612 mg, once daily 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'). **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) 6 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.	**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: 2-4 ml Dosage frequency: 3 times daily Daily dose: 6-12 ml Herbal preparation e) Single dose: 0.8-1.5 ml Dosage frequency: 3 times daily Daily dose: 2.4-4.5 ml Herbal preparation f) Single dose: 10 – 20 ml Dosage frequency: 1-3 times daily 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, 2-3 times daily Daily dose: 3-6 g Herbal preparation h) Single dose: 300 – 500 mg Dosage frequency: 2-3 times daily

[6] 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
Method of administration Oral use.	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 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

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

4.3. Contraindications

Well-established use	Traditional use
Hypersensitivity to the active substance.	*Daily dose of hyperforin ≤ 1 mg:*
Concomitant use with cyclosporine, tacrolimus for systemic use, amprenavir, indinavir and other protease inhibitors in the treatment of HIV infection, irinotecan, imatinib and other cytostatic agents and warfarin (see section 4.5 'Interactions with other medicinal products and other forms of interaction').	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 in the treatment of HIV infection, irinotecan, imatinib and other cytostatic agents 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) and 2)	Indications 1), 3) and 4)
During the treatment intense UV-exposure should be avoided.	During the treatment intense UV-exposure should be avoided.
Since no sufficient data are available, the use	Since no sufficient data are available the use in

Well-established use	Traditional use
in children and adolescents under 18 years of age is not recommended.	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. 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[7]

Well-established use	Traditional use
Pharmacokinetic interactions: *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	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:* Pharmacokinetic interactions: *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. 'Contraindica-

[7] For a list of drugs interacting with herbal preparations of Hyperici herba see the assessment report chapter 5.5.4

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, nefazodone), buspirone or with triptans. Very rarely undesired effects (serotonine 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. Patients taking other medicines on prescription should consult a doctor or pharmacist before taking *Hypericum*.	tions'). 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 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, nefazodone), buspirone or with triptans. Very rarely undesired effects (serotonine 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. 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 breast-feeding has not been established. Studies in animals	Safety during pregnancy and breast-feeding has not been established. Studies in animals have

Well-established use	Traditional use
have 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

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 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), 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
Pharmacotherapeutic group: Other antidepressants ATC code: N06AX *Hypericum* dry extract inhibits the synaptosomal uptake of the neurotransmitters noradrenaline, serotonine and dopamine. 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 as amended.

5.2. Pharmacokinetic properties

Well-established use	Traditional use
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 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	*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 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 mi-

Well-established use	Traditional use
system. Therefore, the elimination of other drug substances may be accelerated, resulting in decreased plasma concentrations.	quelianin 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. 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[8]. The amounts of hyperforin and of flavonoids should be declared.	The amounts of hyperforin should be specified in the dossier (see 4.3, 4.5 and 5.2).

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

7. Date of compilation/last revision

03 March 2021