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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

COMMUNITY HERBAL MONOGRAPH ON *HYPERICUM PERFORATUM* L., HERBA

DISCUSSION IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST (MLWP)	March 2008 May 2008 July 2008 September 2008 November 2008
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ADOPTION BY HMPC	

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

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COMMUNITY 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 as amended	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)	*Hypericum perforatum* L., herba (St. John's Wort)
i) Herbal substance Not applicable	i) Herbal substance Whole or broken, dried flowering tops, harvested during flowering time.
ii) Herbal preparations A) Dry extract (DER 3-6:1), extraction solvent methanol (80% v/v), hypericin 0.10-0.30%, hyperforin > 2%, flavonoids > 6.0% B) Dry extract (DER 4-7:1), extraction solvent methanol (80% v/v), hypericin 0.10-0.30%, hyperforin > 2%, flavonoids > 6.0% C) Dry extract (DER 3-6:1), extraction solvent ethanol (80% v/v), hypericin 0.10-0.30%, hyperforin > 2%, flavonoids > 6.0% D) Dry extract (DER 5-7:1), extraction solvent ethanol (60% v/v), hypericin 0.10-0.30%, hyperforin > 2%, flavonoids > 6.0% E) Dry extract (DER 5-7:1), extraction solvent ethanol (60% v/v), hypericin 0.10-0.30%, hyperforin > 2%, flavonoids > 6.0% F) Dry extract (DER 2.5-5:1), extraction solvent ethanol (60% v/v), hypericin 0.10-0.30%, hyperforin > 2%, flavonoids > 6.0% G) Dry extract (DER 5-8:1), extraction solvent ethanol (50% v/v), hypericin 0.10-0.30%, hyperforin > 2%, flavonoids > 6.0%	ii) Herbal preparations[3] A) Dry extract (DER 4-7:1), extraction solvent ethanol 38% (v/v) B) Dry extract (DER 3.5-6:1), extraction solvent ethanol 60% (m/m) C) Dry extract (DER 5-7:1), extraction solvent ethanol 70% (m/m) D) Liquid extract (DER 1:4-20), extraction solvent vegetable oil[4] E) Liquid extract (DER 1: 13), extraction solvent maize oil F) Tincture (DER 1:10), extraction solvent ethanol 45-50% (v/v) G) Tincture (DER 1:5), extraction solvent ethanol 50% (v/v) H) Liquid extract (DER 1:2), extraction solvent ethanol 50% I) Liquid extract (DER 1: 5-7), extraction solvent ethanol 50%. J) Expressed juice from the fresh herb (DER 1.25-2.5:1) [5] K) Comminuted herbal substance

[1] The material complies with the Ph. Eur. monograph (ref. 01/2008:1438)
[2] The declaraction of the active substance(s) for an individual finished product should be in accordance with the relevant herbal quality guidance.
[3] For safety reasons, the amount of hyperforin and hypericin should be specified.
[4] Preparation: maceration of the fresh or dried herbal substance with vegetable oil over a period of 2 days to several weeks under sun light exposure.
[5] Fresh material complies with the Ph. Eur. monograph (ref. 01/2008:1438) when dried.

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 for tea preparation. Herbal preparations A, B, C, E, F, G, H, I, J, K in liquid or solid dosage forms for oral use. Herbal preparations D, F, G, K 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
Herbal medicinal product for the symptomatic treatment of mild depressive episodes.	Indication 1: Herbal substance, herbal preparations A, B, C, E, F, G, H, I, J, K: Traditional herbal medicinal product for the relief of temporary mental exhaustion (neurasthenia). Indication 2: Herbal preparations D, F, G, K: 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. 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

Well-established use	Traditional use
Posology *Adults and elderly*: Herbal preparation A: Single dose: 300 mg Dosage frequency: 3 times daily Daily dose: 900 mg Herbal preparation B: Single dose: 300-600 mg Dosage frequency: 1-3 times daily Daily dose: 600-1800 mg	**Posology** Indication 1: *Adults and elderly*: Herbal preparation A: Single dose: 60-180 mg Daily dose: 180-360 mg Herbal preparation B: Single dose: 85-300 mg Daily dose: 510-600 mg

Herbal preparation C: Single dose: 900 mg Dosage frequency: 1 single daily dose Daily dose: 900 mg Herbal preparation D: Single dose: 350 mg Dosage frequency: 3 times daily Daily dose: 1050 mg Herbal preparation E: Single dose: 400 mg Dosage frequency: 2 times daily Daily dose: 800 mg Herbal preparation F: Single dose: 300-600 mg Dosage frequency: 2-3 times daily Daily dose: 900-1200 mg Herbal preparation G: Single dose: 612 mg Dosage frequency: 1 single daily dose Daily dose: 612 mg *Children and 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** 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	Herbal preparation C: Single dose: 270 mg Daily dose: 540 mg Herbal preparation E: Single dose: 200 mg Daily dose: 600 mg Herbal preparation F: Single dose: 2-4 ml Daily dose: 6-12 ml Herbal preparation G: Single dose: 1-1.5 ml Daily dose: 3-4.5 ml Herbal preparation H: Single dose: 0.8-1.2 ml Daily dose: 2.4-3.6 ml Herbal preparation I: Single dose: 1.3 ml Daily dose: 4.0 ml Herbal preparation J: Single dose: 10-20 ml Daily dose: 10-20 ml Herbal preparation K: For tea preparation: Single dose: 2 g Daily dose: 4 g In solid dosage forms: 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 preparations D, K: Cutaneous administration of the undiluted herbal preparation Herbal preparations F, G: 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'). **Duration of use** Indication 1: 2 weeks 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. Indication 2: 1 week 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** Indication 1: Oral use Indication 2: Cutaneous use

4.3. Contraindications

Well-established use	Traditional use
Hypersensitivity to the active substance. Hypericum dry extract must not be used concomitantly with cyclosporine, tacrolimus, digoxin, amprenavir, indinavir and other protease-inhibitors, irinotecan and other cytostatic agents.	Indication 1: Hypersensitivity to the active substance. Hypericum extracts must not be used concomitantly with cyclosporine, tacrolimus, digoxin, amprenavir, indinavir and other protease-inhibitors, irinotecan and other cytostatic agents. Indication 2: Hypersensitivity to the active substance.

4.4. Special warnings and precautions for use

Well-established use	Traditional use
When coadministered with anticoagulants from the coumarin-type the serum concentration of these substances should be controlled regularly. During the treatment intense UV-exposure should be avoided. The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia. Since no sufficient data on the safe use in children are available the use in children and adolescents under 18 years of age is not recommended.	Indication 1: When coadministered with anticoagulants from the coumarin-type the serum concentration of these substances should be controlled regularly. During the treatment intense UV-exposure should be avoided. The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia. Since no data on the safe use in children and adolescents are available, the use in children and adolescents under 18 years of age is not recommended. For tinctures 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 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
Contraindicated is the concomitant use of cyclosporine, tacrolimus, digoxin, amprenavir, indinavir and other protease-inhibitors, irinotecan and other cytostatic agents. Special care should be taken with alprazolam, amitriptyline, fexofenadine, benzodiazepines, methadone, simvastatin, theophyline, midazolam, triptans and warfarin, because a reduction of plasma concentrations is possible.	Indication 1: Contraindicated is the concomitant use of cyclosporine, tacrolimus, digoxin, amprenavir, indinavir and other protease-inhibitors, irinotecan and other cytostatic agents. Special care should be taken with alprazolam, amitriptyline, fexofenadine, benzodiazepines, methadone, simvastatin, theophyline, midazolam, triptans and warfarin, because a reduction of plasma concentrations is possible.

The reduction of plasma concentrations of oral contraceptives may lead to bleeding and unwanted pregnancies. Hypericum dry extract may cause a serotonergic syndrome when combined with antidepressants such as serotonin reuptake inhibitors (e.g. sertraline, paroxetine, nefazodone) or with buspirone.	The reduction of plasma concentrations of oral contraceptives may lead to bleeding and unwanted pregnancies. Hypericum dry extract may cause a serotonergic syndrome when combined with antidepressants such as serotonin reuptake inhibitors (e.g. sertraline, paroxetine, nefazodone) or with buspirone. Patients taking other medicines on prescription should consult a doctor or pharmacist before taking Hypericum. Indication 2: None reported.

4.6. Pregnancy and lactation

Well-established use	Traditional use
In the absence of sufficient data, the use during pregnancy and lactation is not recommended.	In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

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.	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
Gastrointestinal disorders, allergic reactions of the skin, 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 pharmacist should be consulted.	Indication 1: Gastrointestinal disorders, allergic reactions of the skin, 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 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 ingestion of overdoses the patient should be protected from sunlight and other UV-sources for 1-2 weeks.	Indications 1, 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 and serotonine. Subchronic treatment causes a down-regulation of beta-adrenoreceptors; it changes the behaviour of animals in several antidepressant models (e.g., forced swimming test) similar to other 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 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 half-life of hypericin is about 37 hours. Maximum hyperforin levels are reached about 3 hours after administration; no accumulation could be detected. Hyperforin and the flavonoid miquelianin can cross the blood-brain-barrier. Hyperforine induces the activity of the iso enzyme CYP3A4. The elimination of other drug substances may be therefore accelerated, resulting in decreased plasma concentrations.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended. Hyperforin is a strong enzyme inducer and may interact with many medicinal products.

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	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. No signs of mutagenicity could be detected in further in vitro and in vivo test systems. No adequate tests on reproduction toxicity have been performed. 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 sensitivy against UVA was increased, and the minimum dose for pigmentation was significantly reduced. In the recommended dosage no signs of phototoxicity are reported.	in the AMES-test (Salmonella typhimurium TA 98 and TA 100, with and without metabolic activation) could be assigned to quercetin. No signs of mutagenicity could be detected in further in vitro and in vivo test systems. No adequate tests on reproduction toxicity have been performed. 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 sensitivy 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, hyperforin and flavonoids[6].	Not applicable.

7. DATE OF COMPILATION/LAST REVISION

6 November 2008

[6] Ph. Eur. monograph (ref. 01/2008:0765) Extracts.