European Medicines Agency
Evaluation of Medicines for Human Use

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OPINION OF THE COMMITTEE ON HERBAL MEDICINAL PRODUCTS ON A COMMUNITY HERBAL MONOGRAPH ON *HYPERICUM PERFORATUM* L., HERBA (TRADITIONAL USE)

Opinion

1. The HMPC, in accordance with Article 16h(3) of Directive 2001/83/EC, as amended, and as set out in the appended assessment report, establishes, by a majority of 17 out of 28 votes, a Community herbal monograph on the traditional use of *Hypericum perforatum* L., herba which is set out in Annex I.

   The divergent positions are appended to this opinion.

This opinion is forwarded to Member States, to Iceland and Norway, together with its Annex I and appendices.

The Community herbal monograph and assessment report will be published on the EMEA website.

London, 12 November 2009

On behalf of the HMPC
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ANNEX I: COMMUNITY HERBAL MONOGRAPH (EMEA/HMPC/745582/2009)

APPENDIX I: ASSESSMENT REPORT (EMEA/HMPC/101303/2008)

APPENDIX II: DIVERGENT POSITIONS

One of the members of the HMPC did not agree with the HMPC's opinion on the Community herbal monograph on the traditional use of *Hypericum perforatum* L., herba for the following reason:

The traditional use of *Hypericum perforatum* L., herba monograph can not be seen to fulfil the requirements related to acceptable level of safety according to the directive 2004/24/EC.

This is particularly concerning the interactions potential of hypericum with other medicinal products which is not addressed clearly enough in the monograph. The need for a consultation with a doctor or a qualified health care professional is not excluded by the use of this product.

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Two of the members of the HMPC did not agree with the HMPC's opinion on the Community herbal monograph on the traditional use of *Hypericum perforatum* L., herba for the following reason:

The proposed traditional use 'for the relief of temporary mental exhaustion' is not considered to be supported and demonstrated for 30 years. The Assessment Report concludes that *the herbal tea and other mostly liquid extracts orally applied have a long tradition in folk medicine for the treatment of low mood, anxiety, to 'strengthen the nerves'.*

The conclusion that hyperforin is responsible for the interactions and that preparations below 1 mg/day of hyperforin will not have or have negligible interactions with other drug substances which are metabolized by certain CYP450 isoenzymes is considered speculative and requires further detailed scientific investigation.

12 November 2009

Four of the members of the HMPC did not agree with the HMPC's opinion on the Community herbal monograph on the traditional use of *Hypericum perforatum* L., herba for the following reason:

Oral use of preparations of *Hypericum perforatum* L., herba for the proposed indications and under self-medication conditions is not acceptable because of safety concerns.

Both the assessment report and the monograph rely on the assumption that preparations containing hyperforin for a daily intake below 1 mg will have no or negligible interactions. This statement is considered speculative and not based either on clinical data or specific safety studies carried out with the concerned preparations.

Relevant scientific articles and studies, arguing that mechanisms and substances involved in St. John's wort interactions are not yet completely clarified, have not been considered in the assessment report. Four of them are listed below.

1. Kraft K. [New developments in hypericum extracts: data on efficacy and interactions]. Wien Med Wochenschr. 2007; 157:284-7.
2. Gödtel-Armbrust U, Metzger A, Kroll U, Kelber O, Wojnowski L. Variability in PXR-mediated induction of CYP3A4 by commercial preparations and dry extracts of St. John's wort. Naunyn Schmiedebergs Arch Pharmacol. 2007; 375:377-82.
3. Di YM, Li CG, Xue CC, Zhou SF. Clinical drugs that interact with St. John's wort and implication in drug development. Curr Pharm Des. 2008; 14:1723-42.
4. Zhou SF, Lai X. An update on clinical drug interactions with the herbal antidepressant St. John's wort. Curr Drug Metab. 2008; 9:394-409.

Relating to the indication 1, the statement to consult a doctor or a qualified health care practitioner if symptoms persist for more than 2 weeks is conflicting with the knowledge that the onset of the effect on "mental symptoms" of St. John's wort preparations can be expected within 4 weeks of treatment, as stated in the monograph for well-established use. Therefore, patients taking these preparations are exposed to the risk with no possible benefit.

Although long-term safety studies are not available, a limit for duration of use has not been established in the absence of persistence of symptoms.

Finally, the risk of the oral use of self-medication preparations of St. John's wort is not adequately counterbalanced by the possible benefit in the proposed indications, taking into account the existence of other safer therapeutic options.

12 November 2009

One of the members of the HMPC did not agree with the HMPC's opinion on the Community herbal monograph on the traditional use of *Hypericum perforatum* L., herba for the following reason:

The potential of drug interactions associated with Hypericum are by far the best investigated and scientifically proven example of such problems with any herbal medicinal preparation. I regard them manageable with the well-established use of Hypericum for mild and moderate depression (as any other antidepressants), but I do not think that for traditional use such established interactions or their potential should be allowed. Benefit/risk ratio for traditional use is simply too much in the side of risk for interactions.

12 November 2009

One of the members of the HMPC did not agree with the HMPC's opinion on the Community herbal monograph on the traditional use of *Hypericum perforatum* L., herba for the following reason:

- Plausibility of efficacy and positive benefit-risk ratio are not justified for all herbal preparations listed for oral use.
- The monograph is not in line with the german graduated plan procedure on Hypericum perforatum.
- Additional contraindications are necessary to address special patient groups.

12 November 2009

One of the alternate members of the HMPC did not agree with the HMPC's opinion on the Community herbal monograph on the traditional use of *Hypericum perforatum* L., herba for the following reason:

I do not support the first indication for *Hypericum perforatum* L., herba:

"Traditional Herbal Medicinal Product for the relief of temporary mental exhaustion".

I am also of the opinion that all contraindications and interactions should be clearly listed in this Traditional Use Monograph in line with the Well-Established Use Monograph. In my view the omittance of this information poses a safety risk.

12 November 2009

One of the members of the HMPC did not agree with the HMPC's opinion on the Community herbal monograph on the traditional use of *Hypericum perforatum* L., herba for the following reason:

Safety concerns are raised regarding the above monograph. The divergent position is based on the absence or the negligible interactions regarding the oral use of *Hypericum perforatum* L., herba.

12 November 2009