



European Medicines Agency
Evaluation of Medicines for Human Use

EMA/HMPC/678923/2009EN
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**OPINION OF THE COMMITTEE ON HERBAL MEDICINAL PRODUCTS ON A
COMMUNITY HERBAL MONOGRAPH ON
HYPERICUM PERFORATUM L., HERBA
(WELL-ESTABLISHED MEDICINAL USE)**

This document was valid from 12 November 2009 until November 2022.

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 20 out of 26 votes, a Community herbal monograph on the well-established medicinal 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 EMA website.

London, 12 November 2009

●n behalf of the HMPC
Prof. I. Chinou, Vice-Chair

ANNEX I: COMMUNITY HERBAL MONOGRAPH (EMEA/HMPC/101304/2008)

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 well-established medicinal use of *Hypericum perforatum* L., herba for the following reason:

The published data could only support a traditional use and the provided scientific data are currently insufficient to recognize St John's Wort preparations as well-established treatment in depressive episodes.

Heterogeneity of methodological approaches, in particular regarding inclusion criteria, sample size, difference in doses tested without satisfactory dose range study make difficult the assessment of results from meta-analysis.

Heterogeneity in results and in effect size is not clearly explained, and some well-conducted studies with sufficient number of patients failed to demonstrate statistically significant difference, when other only showed minimal difference.

Validity of results is questionable in some positive studies due to a minimal or absent placebo response, while the placebo response is generally high in studies in major depressive episodes (MDE). The efficacy/safety balance in the elderly has not been satisfactorily addressed.

All the contra-indications should be mentioned.

Currently, only protease inhibitors, two immunosuppressants, irinotecan and warfarin are listed. Notably, knowing the strong inducing potential of St John's Wort, many drugs with a narrow therapeutic index may become ineffective leading to a negative benefit/risk ratio. This may be highly prejudicial to the patient.

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 well-established medicinal use of *Hypericum perforatum* L., herba for the following reason:

- Concerning indication 1 there is – according to the studies mentioned in the assessment report – no proof of efficacy for the treatment of moderate depressive episodes because placebo-controlled trials in moderate depressive episodes with relapse data and positive results in favour for the mentioned extracts are missing. Thus the demands of the “NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF DEPRESSION” (CPMP/EWP/518/97, Rev.1) are not fulfilled.
- Indication 2 (“Symptoms of mild depressive disorders”) is not a clearly defined disease.
- The monograph is not in line with the German graduated plan procedure on *Hypericum perforatum*.
- Additional contraindications are necessary to address special patient groups.
- The literature published refers partially to extracts which are produced by means of specific procedures. Therefore, a general declaration as given in section 2 does not necessarily guarantee comparable safety and efficacy.

12 November 2009

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

I consider that the evidence does not support the position of *Hypericum perforatum* L. as having well-established medicinal use and recognised efficacy as required by Article 10a of Directive 2001/83/EC.

The published data available on Hypericum extracts are inconsistent and complex. This is further complicated by the fact that the extracts studied have different phytochemical profiles. The constituents of Hypericum responsible for the claimed antidepressant effects have not been elucidated and it is therefore not possible to draw conclusions about equivalence between extracts prepared with the same DER or extraction solvent. The studies fail to meet the criteria of the CHMP '*Note for guidance on clinical investigation of medicinal products in the treatment of depression*'.

Furthermore, 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

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

I consider that the evidence does not support the position of all the proposed preparations of *Hypericum perforatum* L., herba as having well-established medicinal use and recognised efficacy as required by Article 10a of Directive 2001/83/EC.

The published data available on *Hypericum* extracts are inconsistent and complex. This is further complicated by the fact that the extracts studied have different phytochemical profiles. The constituents of *Hypericum* responsible for the claimed antidepressant effects have not been elucidated and it is therefore not possible to draw conclusions about equivalence between extracts prepared with the same DER or extraction solvent. The studies fail to meet the criteria of the CHMP "Note for guidance on clinical investigation of medicinal products in the treatment of depression".

Indication 2 (symptoms of mild depressive disorders) is not a clearly defined disease.

12 November 2009