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Committee on Herbal Medicinal Products (HMPC)

Opinion of the HMPC on a European Union herbal monograph on *Hypericum perforatum* L., herba

Opinion

The HMPC, in accordance with Article 16h(3) of Directive 2001/83/EC and as set out in the appended assessment report, establishes, by a majority of 19 out of 28 votes a European Union herbal monograph on *Hypericum perforatum* L., herba which is set out in Annex I.

The divergent positions are appended to this opinion.

The Norwegian HMPC member agrees with the above-mentioned recommendation of the HMPC.

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

The European Union herbal monograph and assessment report will be published on the European Medicines Agency website. They replace those adopted on 12 November 2009.

Amsterdam, 23 November 2022

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Annex I: European Union herbal monograph (EMA/HMPC/7695/2021)

Appendix I: Assessment report (EMA/HMPC/244315/2016)

Appendix II: Divergent positions

The members of the HMPC mentioned below did not agree with the HMPC's opinion for the following reason:

Italy has a divergent opinion on the HMPC's position on the European Union herbal monograph on *Hypericum perforatum* L., herb, with regard to the traditional use, due to the high risk of clinically relevant interactions with possible concomitant medications, which is well known.

Further detailed scientific investigations are needed to conclude 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, so that they could be regarded as safe.

The statement in section 4.5 "Patients taking other medicines on prescription are advised to consult a doctor or pharmacist before taking Hypericum." is adequate but is not considered sufficient to eliminate the risk of serious interactions, taking into account the patients often do not read the package leaflet carefully, especially in case of non-prescription drugs.

Therefore, based on the above considerations, the establishment of a monograph on the traditional use of *Hypericum perforatum* L., herba cannot be supported as the requirements related to an acceptable level of safety according to the Directive 2004/24/EC are not fulfilled.

Alessandro Assisi, HMPC Member from Italy

Amsterdam, 21 November 2022

I disagree with the WEU part of the monograph because the evidence does not support that Hypericum perforatum L. has a well¬established medicinal use and a recognised efficacy as required by Article 10a of Directive 2001/83/EC.

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

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 others 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 (MOE).

The efficacy/safety balance in the elderly has not been satisfactorily addressed.

Burt Kroes, HMPC Member from Netherlands

Amsterdam, 21 November 2022

Greece (EL) has a divergent opinion on the HMPC's position on the European Union herbal monograph on *Hypericum perforatum* L., herb, with regard to the traditional use, due to the high risk of clinically relevant interactions with possible concomitant medications, which is well known.

According section 4.5 "Patients taking other medicines on prescription are advised to consult a doctor or pharmacist before taking Hypericum." is adequate but not considered sufficient to eliminate the risk of serious interactions, taking into account the patients often do not read the package leaflet carefully, especially in case of non-prescription drugs.

Therefore, the establishment of a monograph on the traditional use of *Hypericum perforatum* L., herba cannot be supported as the requirements related to an acceptable level of safety according to the Directive 2004/24/EC are not fulfilled.

Ioanna Chinou, HMPC Member from Greece

Amsterdam, 21 November 2022

Hungary (HU) has a divergent opinion on the HMPC's position on the European Union herbal monograph on Hypericum perforatum L., herb, with regard to the traditional use, due to the high risk of clinically relevant herb-drug interactions that are hardly preventable since traditional herbal medicinal products are available without prescription.

The article 71 of Directive 2001/83/EC provides the criteria for classifying a medicinal product as subject to medical prescription.

According to the first criterion, a medicinal product shall be subject to medical prescription when it is likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision. A direct danger, when the product is used according to the patient information, encompasses toxicity, adverse reactions, and interactions with commonly used medicines**.** Hypericum induces cytochrom P450 CYP1A2, CYP2C9, CYP2C19 and CYP3A4 isoenzymes, and P-glikoprotein system as well. Therefore serious, sometimes life-threatening, interactions can be expected with concommitant use of some antiepileptics, antiarrhythmics, immunsuppressants, antiparkinson-agents, lipid-lowering drugs, hormones, cytostatics, antipsychotics, etc. Pharmacodynamic interactions with serotonergic agents have also been described.

Furthermore hypericum should not be used during pregnancy, lactation and should be discontinued at least five days preoperatively in patients undergoing a planned surgical procedure.

As of 19-11-2022, the EudraVigilance database contains 1919 individual case safety reports on hypericum perf, the majority of them originates from European Economic Area.

Julia Pallos, HMPC Member from Hungary

Amsterdam, 21 November 2022

The traditional oral use of hypericum perforatum, herba is not considered justified for the following clinical reasons:

Clinically significant pharmacokinetic interactions with hypericum are well known. As stated in the AR, well-documented and clinically relevant interactions include: (1) reduced blood ciclosporine concentration associated in some cases to rejection episodes; (2) reduced efficacy of the oral contraceptive pill, resulting in unwanted pregnancy; (3) reduced plasma concentration of antiretroviral (e.g. indinavir, nevirapine) and anticancer drugs (e.g. imatinib, irinotecan). Pharmacodynamic interactions with serotonergic agents, leading to serotonin syndrome, have also been described.

There is no clearly established safe dose range where clinically relevant interactions do not occur. While there is some evidence suggesting that interactions might not be massive when the hyperforin content is less than 1mg, the TU monograph also includes preparations with a hyperforin content above 1mg. Hence, clinically meaningful interactions are expected.

The statement in section 4.5 "Patients taking other medicines on prescription are advised to consult a doctor or pharmacist before taking Hypericum." is adequate but is not considered sufficient to eliminate the risk of serious interactions. Patients do not read product informations carefully and especially not for over the counter medicines, as they are perceived as safe. There is also a greater risk of self-medication outside the recommended dose range if the product is used without medical supervision.

Therefore, based on the high risk for clinically relevant interactions and the absence of a clearly defined interaction-free dose, the Finnish Medicines Agency is of the opinion that even low-dose hypericum extracts are not suitable for traditional use.

Maria Paile-Hyvärinen, HMPC member from Finland

Amsterdam, 21 November 2022

We note that the revised TU MO refers to different contraindications and interactions depending on the daily intake of hyperforin (<1mg vs >1mg). It is therefore implied that products with a daily intake of >1mg hyperforin are now acceptable as traditional herbal medicinal products (THMPs). It is our opinion that a daily intake of >1mg hyperforin is not appropriate as a THMP, given the likelihood of interactions. In Ireland, herbal medicines containing St John's Wort must contain a daily dose of <1mg hyperforin to be suitable for registration as a THMP. We consider that the interactions and contraindications should remain, regardless of the daily intake of hyperforin. Although it is unlikely that interactions will occur with St John's Wort products delivering <1mg hyperforin per day when used short term, the safety data is not conclusive. In addition, we do not agree with the wording of indication 1 in relation to the term "temporary mental exhaustion" nor with indication 4 and use of the term "nervous restlessness".

Sarah Kellaghan, HMPC member from Ireland

Amsterdam, 21 November 2022

Due to the amount of interations available in literature and the doubt about the high safety dose, a doctor or a qualified heath care practioner should be consult for the use of Hypericum. For these reasons in my opinion, is not suitable for the traditional use.

Maria Graça Campos, HMPC member from Portugal

Amsterdam, 21 November 2022

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, particularly for the highest daily dose of 1800 mg/day of preparation a). 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 and also by the existence of some concerns about the possible reproductive and developmental toxicity concerns, with some authors being of the opinion that the opinion that teratogenic concentrations may be reached in humans after ingestion of 1800 mg Hypericum extract.

Relating to the traditional use monograph, 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, relating mainly to the possibility of interactions with other medicinal products.

Relating to the indications 1) and 4), the statement to consult a doctor or a qualified health care practitioner if symptom persist 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 or 6 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.

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, considering the existence of other safer therapeutic options.

Ana Paula Martins, HMPC member from Portugal

Amsterdam, 21 November 2022

Cyprus (CY) has a divergent opinion on the HMPC's position on the European Union herbal monograph on Hypericum perforatum L., herba (well-established and traditional use) since the safety level is not considered quite acceptable.

More precisely, as far as the traditional usage is concerned and since it is used as a self-medication, there is a high likelihood of clinically significant interactions with concomitant medicines and further actions are required to ensure patients' safety.

Christina. S. Chrysostomou, HMPC member from Cyprus

Amsterdam, 21 November 2022