EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

03 March 2021
EMA/HMPC/536348/2018
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Hypericum perforatum* L., herba (traditional use) (EMA/HMPC/45508/2017)

Table 1: Organisations and/or individuals that commented on the 1st draft Revision 1 European Union herbal monograph on *Hypericum perforatum* L., herba (traditional use) as released for public consultation on 8 March 2018until 15 June 2018.

	Organisations and/or individuals
1	Prof. Robert Ancuceanu, Univ. of Medicine and Pharmacy, Bucharest
2	Kooperation Phytopharmaka GbR, Plittersdorfer Str. 218, 53173 Bonn, Germany (Koop Phyto)
3	AESGP

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
Koop Phyto	In general, it is good and necessary that monographs are regularly updated, and this applies especially in case of a drug which is still in the focus of research, as *Hypericum perforatum*. At the same time, it is important, that, while the amount of data has increased since the first version of the monographs on Hypericum were published, constancy of the assessment is kept as far as possible, as this is the precondition for trust of patients, health care professionals and last but not least, manufacturers into the drug and its therapeutic potential. We would like to highlight that this aspect has been taken into account in this revision. Nevertheless there are minor aspects where we would like to contribute comments.	Acknowledged.
AESGP	In general, we appreciate being consulted on the revision of the monographs and assessment reports on Hypericum. Given that there were no major changes of the scientific knowledge on Hypericum since the first release of the monograph and assessment reports, and despite many new published data, it is appreciated that the key information remains unchanged in the revision. This is important as it ensures that the public and companies can rely on the established knowledge on this herbal medicine, which is probably still the herbal medicine with the best evidence worldwide and therefore plays a central role in the field of evidence-based herbal medicines.	Acknowledged.

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
4.2	Robert Ancuceanu	I would like to express my concerns with respect to the herbal preparation h) ("Powdered herbal substance") in the revised draft monograph on *Hypericum perforatum* L., herba (traditional use). I think that the dosage at least, if not the herbal preparation h) as such, are not justified and should either be changed or completely reviewed. In the large majority of clinical trials, various extracts, mostly dry, were used, in doses usually larger than 600 mg/day, most often 900 mg (and even up to 1500 or 1800 mg/day) . For dry extracts, it is to expected, as correctly stated in the draft monograph, that the DER would be around 4-7:1; from my experience with extracting different herbal products (aerial parts), most likely the DER would be 5:1 or 6:1, but for the sake of easy computations and comparison I would use a DER of 5:1. To have an equivalent amount of "powdered herbal substance", for a dose of 900 mg/day, one would have to multiply 900 by 5, i.e. 900x5=4500 mg/day. Moreover, this assumes that the absorption of the active phytochemicals from the "powdered herbal substance" is equivalent to the absorption of the same from the dry extract, but there are reasonable grounds to doubt it to be equivalent (as in the case of the "powdered herbal substance" the hard cell wall will have to be crossed, unlike the active substance, where the phytochemicals reach the physiological environment through mere diffusion. I am well aware that the arguments above make reference to the clinical trials, whereas the monograph is concerned with	Not endorsed. The posology of the herbal preparation h) (powdered herbal substance) has to be in line with the posology which is documented in literature or from medicinal products within the last 30 years. Only in this case the safety of the traditional medicinal use of this herbal preparation can be considered as acceptable. A calculation on a theoretical base is not acceptable for traditional herbal medicinal products.

Section number and heading	Interested party	Comment and Rationale	Outcome
		the traditional use, but it is my view that these monographs still have to have internal consistency and a minimal coherence with the scientific data available. The HMPC itself shows this in practice, because, for instance, in the same draft monograph reference is made to the effects of the extracts and hyperforin on CYP3A4, CYP2C9, CYP2C19 and P-glycoprotein, which are hardly part of the traditional body of knowledge with respect to *Hypericum perforatum* L. Thus, the herbal monograph is not slave only to folk traditions, but also has to pay respect to some extent to the current scientific knowledge (otherwise, we might end up recognizing traditional use for a plant in witchcraft rituals for healing, which may have a long tradition, but is not compatible with the current scientific paradigm). Furthermore, even ignoring the knowledge from the clinical trials, at least the monograph should have internal consistency, and because for the dry extract a DER of 4-7:1 is acknowledged in the monograph, with a daily dosage of 180-360 mg/day, the equivalent for the "powdered herbal substance" a daily dosage of 900-1800 mg/day should be the minimum daily dose, and this assumes that the absorption from the dry extract is similar to that from the powdered herbal substance, which as shown above, is unlikely. Therefore, in my view the best option would be to remove the "powdered herbal substance" from the monograph (at least not to be administered in solid dosage forms, where it would be just a nice placebo); alternatively, at least a higher daily dosage should be recommended for the use of the "powdered herbal substance".	

Section number and heading	Interested party	Comment and Rationale	Outcome
4.3. Contra-indications	Koop Phyto	In products with a dose of hyperforin of ≤ 1 mg, no interactions are anticipated, which is well addressed in the monograph. With regard to products with a daily dose of hyperforin > 1 mg, it is appreciated in general, that more detailed information on interactions is included. Irrespective of that, there are some points which need to be commented in the following. In anticoagulants, a continuous surveillance of coagulability (INR) is mandatory. This surveillance is nowadays well established and effective and includes routinely the adaptation to co-medication. Therefore, it seems adequate to include warfarin (together with phenprocoumon) to the interaction section (4.5), while mentioning it in 4.3 is dispensable.	Not endorsed. As for traditional herbal medicinal products the evidence on the benefit is missing and a certain risk remains the contraindication related to anticoagulants will be kept. In the case of the necessity of anticoagulant therapy other options for the treatment of symptoms mentioned in the indications in the TU part of the monograph should be used.
4.5. Interac-tions with other medicinal products and other forms of interaction	Koop Phyto	As mentioned under 4.3, it seems adequate to include warfarin and phenprocoumon here, while mentioning warfarin in 4.3 is dispensable. It is stated here, that special care should be taken in case of concomitant use of, among other drugs, benzodiazepines, as their metabolism is influenced by CYP3A4, CYP2C9, CYP2C19 or P-glycoprotein and a reduction of plasma concentrations is possible. In this context, it is important to take into account, that the benzodiazepines are a very large group of drug substances, which is characterized by its similar pharmacological mode of	Not endorsed. As for traditional herbal medicinal products the evidence on the benefit is missing and a certain risk remains the contraindication related to anticoagulants will be kept. In the case of the necessity of anticoagulant therapy other options for the treatment of symptoms mentioned in the indications in the TU part of the monograph should be used. Not endorsed because of wording of SmPCs of several benzos (see below):

Section number and heading	Interested party	Comment and Rationale	Outcome
		action. In contrast, the ADME properties of this group of drugs are very diverse. While interactions involving CYP isoenzymes have been described for midazolam, other bezodiazepines as e.g. temazepam, lorazepam and oxacepam are metabolized independently from the CYP pathway, so that interactions based on this mechanism are even not possible. In drug interaction data bases like medIQ, the latter three benzodiazepins are even recommended in case of potential interactions with midazolam. Therefore it seems to be more adequate to mention here midazolam, while omitting the benzodiazepines as a group, especially as any drugs with a potential of CYP mediated interactions are already covered by the general statement "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, because a reduction of plasma concentrations is possible."	Alprazolam SmPC: interactions with CYP3A4 inhibitors. Bromazepam, Diazepam, Midazolam Nitrazepam, Triazolam SmPC: interactions with CYP3A4 inhibitors and inducers. Nitrazepam: Hypericum is mentioned Clobazam: interactions with CYP2C19 and CYP2D6 inhibitors Clonazepam: no such interactions mentioned Therefore the group of benzodiazepines will be kept in the monograph.
4.5. Interac-tions with other medicinal products and other forms of interaction	Koop Phyto	With regard to contraceptives, the following sentences are given at present: 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. These insights are all based on investigations with oral hormonal contraceptives (Hall et al. 2003, Pfrunder et al. 2003, Murphy et al. 2005). No studies have been conducted with hormonal contraceptives administered otherwise. As described e.g. by Wang et al. (2001), a 50 % reduction of the AUC is only	Contraceptives: not endorsed. The reference Wang et al. (2001) refers to the probe drug midazolam and not to hormonal contraceptives. As there are no data regarding the parenteral or local application of hormonal contraceptives the wording should remain in a general way.

Section number and heading	Interested party	Comment and Rationale	Outcome
		seen with oral medication , while no clinical relevant reduction (20%) was seen with parenteral application. Therefore, the above statement can be restricted to oral hormonal contraceptives. Mentioning the triptans under 4.5 needs to be questioned. With two case reports available, in the only one published, i.e. Bonetto et al. 2007/Evans 2008, SSRI (fluoxetin) was used as comedication of a triptan. The combination of a triptan and fluoxetine can lead to the interactions described, without any further comedication, so that FDA has issued a respective warning earlier. In the published case mentioned here, in addition, a meningoencephalitis was not excluded as a cause, and discontinuation of St John´s wort did not lead to an improvement, so that also the triptan and fluoxetine were discontinued. So, sufficient evidence supporting the listing of triptans under 4.5 is lacking. Likewise, mentioning buspirone needs to be questioned, as clinical evidence is based on only two case reports. In the first case (Spinella et al 2002) a concomitant intake of four products, i.e. an American St. John´s wort preparation of unclear composition, buspirone, fluoxetine, melatonin and Gingko biloba led to a mixed hypomania. Already buspirone and fluoxetine together are known to have pro-serotonergic interaction, and the patient had a history of a bipolar disturbance, so that a conclusion on a relevant role of St. John´s wort is not possible. In the second case (Dannawi 2002), serotonergic symptoms	Not endorsed. Triptans may increase the concentration of serotonin when taken together with medicines which reduce the reuptake of serotonin. This mechanism of action may also be relevant for Hypericum. Therefore for safety reasons the concomitant use of triptans and Hypericum should be avoided. Buspirone: not endorsed. Same argumentation as above.

Section number and heading	Interested party	Comment and Rationale	Outcome
		were observed after concomitant use of a combination product corresponding to a daily uptake of 6000 mg Hypericum drug powder of unknown composition, 250 mg tyrosine and 75 mg magnesium together with buspirone. Tyrosine is a standard amino acid that is used by cells to synthetize proteins. In addition, it is a source for the synthesis of monoaminergic transmitters. The symptoms described did not fit to the Sternberg criteria. After discontinuation of the combination product, the buspirone dose was enhanced and later replaced by venlafaxine, which is no conclusive treatment strategy. Overall, it is problematic to draw conclusions on Hypericum preparations in general based on this case report. Accordingly, the evidence to support the inclusion of buspirone to 4.5 is questionable.	

Comments on the Assessment report

Section number and heading	Interested party	Comment and Rationale	Outcome
Introduction	Koop Phyto	As the first version, the revised assessment report on *Hypericum perforatum* is again probably the most comprehensive review on Hypericum available in the scientific literature. The data and their assessment have been to a large extent constant since the issuing of the first version, which is, as mentioned above, appreciable for maintaining trust in the herbal medicinal products as a whole. But the presentation has	Acknowledged.

Section number and heading	Interested party	Comment and Rationale	Outcome
		changed by the introduction of new tables. When checking the study listings, few minor points on some details are obvious:	
3.2.2.	Koop Phyto	In the revised version of the assessment report (page 97), as in its previous version, the field of application mentioned in well-established use is for symptomatic treatment of mild to moderate depressive episodes. It needs to be highlighted here that the diagnosis of depression is solely based on symptoms, so that a symptomatic treatment of depression is indeed a treatment of the depression as such. This fact is taken into account in the present WEU monograph, as the indication is "Herbal medicinal product for the treatment of mild to moderate depressive episodes (according to ICD-10)". We therefore suggest using the latter wording also in the assessment report, i.e. leaving off the term symptomatic from the wording on page 97.	Endorsed. The wording is now identical to the WEU monograph.
3.2.2.	AESGP	In the draft revised version of the assessment report – just as in the previous version – the indication for well-established use reads "for the **symptomatic** treatment of mild to moderate depressive episodes" (p.97). However, in the monograph on *Hypericum perforatum* L. (well-established use part, which is not yet up for consultation), the indication reads "Herbal medicinal product for the treatment of mild to moderate depressive episodes (according to ICD-10). " We therefore assume – and are in favour of this – that the	Endorsed. The wording is now identical to the WEU monograph.

Section number and heading	Interested party	Comment and Rationale	Outcome
		future revision of the EU monograph on *Hypericum perforatum* (well-established use part) will keep the originally adopted indication, i.e. without the term "symptomatic". Rationale: Depression is defined as set of symptoms which is categorized via Hamilton Depression Scale. All antidepressant drugs, no matter whether of herbals or synthetic origin, used this scale in the relevant clinical studies investigating efficacy. Conclusions drawn from the clinical studies result in the indication of treatment of (mild to moderate) depressive episodes without referring to the symptoms. As St. John's wort has proved efficacy versus placebo and equivalent efficacy compared to certain chemical TCA/SSRI in a couple of studies, the wording of the WEU St. John's wort indication shouldn't be different from the wording of the indication of the synthetic drugs. The documented evidence of St. John's wort is further supported by several Reviews such as the Cochrane review. The word "symptomatic" is redundant because depression is defined as a set of symptoms so that the treatment of depression (by both synthetic or herbal medicinal products) is always a symptomatic one. It is even misleading since it suggests a difference between chemical and herbal medicinal products in this regard which is not the case. The outcome of the studies relevant for the assessment report is unchanged, and supports the indication "treatment of depression/mild to moderate depressive episodes". The	

Section number and heading	Interested party	Comment and Rationale	Outcome
		wording of the monograph should be in line with the outcome of the studies; reference is made to the clinical studies mentioned in the List of references of HMPC. Pre-clinical investigations also show anti-depressive activity in different models, also outlined in the pre-clinical studies which are referred to in the List of references.	
3.2. Clinical efficacy p. 83	Koop Phyto	The study Brattström 2009 NEW, which was not included to the Linde metaanalysis, is listed in the section on clinical efficacy, which is unusual, as it is a non-randomized, uncontrolled open label study, so fitting well into the safety section, where it is already listed on p 117.	Endorsed. The reference Brattström 2009 will be deleted in the section clinical efficacy.
3.2. Clinical efficacy p. 117	Koop Phyto	The test product tested in the study Rudolf & Zeller 2004 was STW3, Hypericum extract (DER 5-8:1, ethanol 50% V/V), 1 x 612 mg daily, and not STW3-VI, Hypericum extract (DER 5-8:1, ethanol 50% V/V), 600 mg daily. As correctly presented in the Linde meta-analysis and in section 3.2 on Clinical efficacy, the test product in the study Gastpar et al. 2006 was STW 3-VI, Hypericum extract (DER 3 - 6:1, ethanol 80% V/V), 1 x 900 mg, and not STW 3-VI, 3 x 300 mg. The test product in the study Kresimon et al. 2012 was STW 3-VI, Hypericum extract (DER 3 - 6:1, ethanol 80% V/V), 1 x 900 mg daily, and not STW3-VI, Hypericum extract (DER 5-8:1, ethanol 50% V/V), 600 mg daily.	Rudolf & Zeller: not endorsed. In the publication on page 80 the daily dose of 600 mg is explicitly mentioned. Gastpar et al. 2006: endorsed. Kresimon et al. 2012: endorsed