EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 November 2022
EMA/HMPC/72258/2023
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Hypericum perforatum* L., herba (well-established use and traditional use) (EMA/HMPC/7695/2021)

Table 1: Organisations and/or individuals that commented on the 2nd draft Revision 1 European Union herbal monograph on *Hypericum perforatum* L., herba (well-established use and traditional use) as released for public consultation on 15 April 2021 until 15 July 2021.

	Organisations and/or individuals
1	AESGP
2	Kooperation Phytopharmaka GbR (Koop Phyto)

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
AESGP	We appreciate the revision of the European Union monographs on *Hypericum perforatum* L., herba (well-established and traditional use) and the preparation of only one monograph including both uses. This might facilitate comparability of information with respect to both these areas. Especially, the approach to warrant consistency and continuity to the previous versions of the monograph is seen important, given that specific *Hypericum* extracts are used in the treatment even of moderate depressive episodes. Detailed comments, also to the assessment report, and suggestions for changes are presented in the following sections. Texts suggested to be removed are ~~crossed out~~, while additions are underlined, to highlight suggested changes in a transparent way.	
KOOP PHYTO	The revision of the monographs on *Hypericum perforatum* L., herba (well-established and traditional use) and their unification to one monograph, while keeping the general approach of the previous version, is highly appreciated. To keep continuity is very valuable especially in indications reaching up to moderate depressive episodes, which are of vital relevance for patients, pharmacists and physicians. In the following, for readability reasons, phrases to be deleted or replaced are ~~crossed out~~, new wording is underlined.	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
4.1 WEU	AESGP	Proposed wording: Indication 1) Herbal preparations a, b: Herbal medicinal product for the treatment of mild to moderate depressive episodes (according to current ICD classification) Comment/ rationale: As the new version of the diagnostic classification system (ICD-11) is already in preparation and should be implemented by beginning of 2022 we consider the explicit mentioning of the then outdated ICD 10 could be misleading in the near future. We hence suggest referring to the current ICD classification not to entail a change of the monograph as soon as the ICD classification number changes.	Deletion endorsed. Mentioning of ICD classification no longer relevant.
4.1 WEU	Koop Phyto	Proposed wording: Indication 1) Herbal preparations a, b: Herbal medicinal product for the treatment of mild to moderate depressive episodes ~~(according to ICD-10)~~.	Deletion endorsed. Mentioning of ICD classification no longer relevant.

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		Comment/ rationale: Given that *Hypericum* products are very important in an OTC setting, i.e. recommended by pharmacists, who do not refer to the ICD classification. The reference to the ICD classification in the indication does not contribute to clarification, but rather leads to questions. Therefore the reference to ICD should be omitted from the indication in the monograph or, if keeping it in at all, to leave it to the applicant to refer to it, but not to make it mandatory. In addition, given the frequent revisions of the ICD system, reference to a specific version will be outdated soon and should therefore be avoided	
4.2 WEU	AESGP	Proposed wording: **Posology** *Adults and elderly* Herbal preparation a): Single dose: 300-600 mg Dosage frequency: 1-3 times daily Daily dose: 600-1800 mg Herbal preparation b): ~~900 mg, once daily~~	Endorsed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Single dose: 900 mg Dosage frequency: 1 single daily dose Daily dose: 900 mg Herbal preparation c): 600 or 612 mg, ~~once daily~~ Single dose: 600 or 612 mg Dosage frequency: 1 single daily dose Daily dose: 600 or 612 mg or Single dose: 250-600 mg Dosage frequency: 2-3 times daily Daily dose: 500-1200 m Comment/ rationale: The posology of all preparations should be described consistently and therefore preferably stay as in the current effective version of the HMPC monograph, as of course not only the dosage, but also the dosage form is important from the perspective of evidence-based medicine. The same argumentation applies to the herbal preparation c	Endorsed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		(600 or 612 mg) and the description of the posology should be revised accordingly.	
4.2 WEU	Koop Phyto	Proposed wording: **Posology** *Adults and elderly* Herbal preparation a): Single dose: 300-600 mg Dosage frequency: 1-3 times daily Daily dose: 600-1800 mg Herbal preparation b): ~~900 mg, once daily~~ Single dose: 900 mg Dosage frequency: 1 single daily dose Daily dose: 900 mg Herbal preparation c): 600 or 612 mg, ~~once daily~~	Endorsed. Endorsed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Single dose: 600 or 612 mg Dosage frequency: 1 single daily dose Daily dose: 600 or 612 mg or Single dose: 250-600 mg Dosage frequency: 2-3 times daily Daily dose: 500-1200 m Comment/ rationale: It seems to be important to have a uniform approach to all preparations, and to keep the existing description of the dosing schemes, also as reducing changes to a minimum will also help HCPs and patients used to the present description.	
4.2 WEU	AESGP	It is proposed to add under Herbal preparation c) for oral use *500 mg, once daily* Rationale: Since October 2003, a *Hypericum perforatum*, L., herba preparation under the name Remotiv extra has been approved on the Hungarian market as a once daily formulation (500 mg, once daily, DER 4–7:1, extraction solvent ethanol 57.9% V/V) *Therefore, this product fulfils the requirements of well-established use criteria and should be added to the monograph.*	Not endorsed. The controlled clinical trials with this particular herbal preparation were performed with a posology of 2 times 250 mg.

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		References: Max Zeller Söhne AG, Registration status of Z-99052 St. John's wort film coated tablets 500 mg, 2021. PACKAGE LEAFLET: INFORMATION FOR THE USER: Remotiv extra 500 mg film coated tablet (En/ HUN).	
4.2 WEU	Koop Phyto	Proposed addition under c) for oral use Single dose: 500 mg Dosage frequency: 1 single daily dose Daily dose: 500 mg Rationale: *Hypericum perforatum*, L., herba preparation (name: Remotiv extra) is approved in Hungary since 2003 (500 mg, once daily, DER 4–7:1, extraction solvent ethanol 57.9% V/V), thereby meeting well established use.	
4.3 WEU	AESGP	Referring to the comments on interactions, we wish to mention that in section 4.3 on contraindications, again different texts are applicable depending on the same amounts of hyperforin as in section 4.5. This time, no reference is made regarding duration of use. If maximum duration of use is to be considered a factor for contraindications as well, this should be clarified in the monograph. In this case, guidance should also be provided on what texts are to be used if hyperforin content remains below the relevant threshold but extended durations of	As the onset of clinically relevant interactions might occur even during a short period of use the same contraindications and warnings related to interactions apply to TU when the daily hyperforin intake is above 1 mg. Only for short term use interactions are very unlikely provided the daily intake of hyperforin is below 1 mg. The monograph does not foresee an extended duration of use. Therefore the decision on adequate

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		use are possible.	warnings have to be clarified in a procedure for marketing registration.
4.3 WEU	Koop Phyto	Proposed wording: Hypersensitivity to the active substance. Concomitant use with cyclosporine, tacrolimus for systemic use, amprenavir, indinavir and other protease inhibitors in the treatment of HIV infection (in case these substances are substrates of CYP3A4, CYP2C9, CYP2C19 and P-glycoprotein), irinotecan, imatinib and other cytostatic agents (in case these substances are substrates of CYP3A4, CYP2C9, CYP2C19 and P-glycoprotein) ~~and warfarin~~ (see section 4.5 'Interactions with other medicinal products and other forms of interaction'). Comment and rationale: Only substances, which are metabolized by the isoenzymes mentioned above are at least possible subjects to interactions, not other members of the resp. substance classes. Given that a contraindication for whole groups of medicinal products can lead to an exclusion of relevant treatment options, it seems not to be justified for products lacking an interaction potential. Efficacy of warfarin needs to be anyway well monitored and controlled, so the dose can be easily adapted in case an interaction would occur. Therefore, excluding patients from the treatment with St. John´s wort seems not to be justified.	Partly endorsed. The wording except for warfarin has been modified. Contraindication of anticoagulants of the coumarin type: Change not endorsed. The SmPCs of coumarin type anticoagulants in several EU member states indicate a contraindication of the concomitant use of *Hypericum* products.

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		It therefore seems to be justified to remove warfarin as a contraindication and to add it instead under 4.5, and to include the following sentence in 4.4: <u>In case of comedication with anticoagulants of the coumarin type the coagulation values (as INR respectively) should be closely monitored.</u>	
4.5 WEU	AESGP	The PRAC concluded that: "*The induction of CYP3A4, CYP2C9, CYP2C19 and P-glycoprotein by hypericum is well documented; the magnitude is directly correlated to the content of hyperforin in the herbal preparation. Pharmacokinetic interactions are documented for several drug substances metabolised via the mentioned enzymes having with a narrow therapeutic range. Hypericum extracts should not be used concomitantly with these substances. Adequate studies with extracts with low hyperforin content are available which could justify exemptions in the wording of contraindications, special warnings and in the interactions section of the SmPC.* *All MAHs having marketing authorisation for orally used products exceeding 1 mg daily dose of hyperforin content are requested to closely monitor safety information from all available sources in association with Hypericum perforatum L, herba on the following specific issues and to discuss them in the next PSUR, as applicable.* *New findings suggest drug interactions via CYP1A2, CYP2D6, and CYP2E1, however robust evidence are lacking. These safety issues will be kept under close monitoring for gathering further data. These preliminary data do not affect the positive*	Partly endorsed. AR and monograph are adapted to the conclusions of the PRAC. Induction of CYP2D6 is deleted in the

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		benefit-risk balance." (EMA/PRAC/582574/2018) **Therefore, it is proposed that the HMPC adds a foot note that assessors take into account this PRAC conclusion when assessing a specific medicinal product.** Rationale: *This reflects the conclusion of the PRAC Assessment Report EMA/PRAC/582574/2018 (excerpt copied above).* *A comprehensive drug interaction study was published (Zahner et al., 2019 Clin Pharmacol Ther.). Adequate studies are summarized in a review article (Nicolussi et al., 2019 Br J Pharmacol).*	monograph but kept in the AR. Footnote to the monograph not endorsed. Assessors should know PRAC conclusions.
4.5 WEU	Koop Phyto	The PRAC conclusion on the induction of CYP3A4, CYP2C9, CYP2C19 and P-glycoprotein and its correlation to the content of hyperforin in the herbal preparation (EMA/PRAC/582574/2018) is proposed to be taken into account when assessing the application for marketing authorization for a specific product.	This aspect is clearly stated in the AR.
4.5 TU	AESGP	In this chapter, it is correctly stated that low-hyperforin extracts (≤ 1 mg hyperforin) do not lead to an induction of cytochrome P 450 enzymes. This is in line with a comprehensive drug-drug interaction study by Zahner *et al*. (2019). However, according to current data, it can be assumed that a CYP induction is not to be expected even after more than two-weeks of intake of a low-hyperforin extract. This also applies	According to the guidance on pharmacokinetic interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) an interaction study should aim to investigate the interaction effect at the time-point where the induction or inhibition effect is at or near its maximum. For the interaction with CYP3A4 there is the advice given that a duration of the interaction study of 10-14

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		even if the drug-drug interaction studies only observed a period of 10 to 14 days of extract administration. In a study by Adiwidjaja *et al.,* 2019, it is described that already 5 to 9 days are sufficient to observe a maximum induction by hyperforin of CYP3A4 as well as CYP2C9 and CYP2C19 (Adiwidjaja *et al.* 2019). The PBPK model of hyperforin was simulated in this study for daily administration for 14 days and compared with PK data from healthy volunteers administered a St. John's wort extract (WS 5572) containing 45 mg hyperforin (hyperforin content 5%, daily dose = 900 mg = 45 mg administered dose of hyperforin) for 8 days (Biber *et al.,* 1998). Based on the PBPK model, it appears that due to the hepatic hyperforin half-life of 23.1 h, a maximum induction is reached within 4.8 days. In enterocytes, maximum (steady state) induction is reached within 7.5 days (t1/2 hyperforin enterocytes 35.9 h). This is consistent with the general pharmacokinetics rule that steady-state levels/effects are reached after about 5 half-lives. In addition, Adiwidjaja *et al*. 2019, show that hyperforin-induced CYP3A4 induction is hepatic linear, but intestinal non-linear. It also becomes clear that at a daily dose of ≤1 mg hyperforin, neither hepatic nor intestinal induction of clinical concern is to be expected. The authors also show that an accumulation of hyperforin in plasma after repeated administration can be excluded, since steady state effects are reached after 5 half-lives.	days is recommended which is considered in the study by Zahner *et al*. (2019). However, it remains unclear whether this study duration can be considered also appropriate for the other enzymes included in the study. This fact is not discussed in the publication. The limitation of the duration of use for TU is additionally considered necessary from a medical point of view. As the traditional medicinal products are to be used without medical supervision a limitation of the duration of self-medication is required.

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		Clinically significant DDI risks occur with products containing more than 1% hyperforin or an intake of more than 1 mg hyperforin daily (EMA/PRAC 2018). As PBPK modelling showed, 90% of maximal enzyme induction in the gut and liver occurs within about 5 to 9 days after daily administration with the active ingredient rifampicin or with high-dose hyperforin (hyperforin content 5%, daily dose 900 mg = daily hyperforin dose thus 45 mg) (Adiwidjaja *et al*., 2019, Kapetas *et al*., 2019). Clinically relevant CYP3A4 inductions are not expected with a daily dose of ≤ 1 mg hyperforin. Based on the design and duration (10 days) of the cocktail study described above, it can therefore be concluded that clinically significant pharmacokinetic interactions between Ze 117 and drugs metabolised by CYP3A4 are negligible. A clinically relevant induction due to hyperforin would have occurred after 5-9 days of treatment. Moreover, there are medicinal products in the market, particularly herbal teas that contain less than 1 mg of hyperforin in the daily dose but require extended durations of use, especially if the symptoms of indication no. 4 are treated. **Conclusion: With regard to drug interactions, there is no reason to limit the intake of a low-hyperforin herbal preparation (for example extract, herbal tea, powdered herbal substance) in the monograph to a period of two weeks. As stated above, we suggest that the HMPC adds a foot note that assessors take into account this PRAC**	

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		conclusion when assessing a specific MP. For further references see (reference list below): Adiwidjaja (2019) Biber (1998) Kapetas (2019) Derendorf 2020	
4.5 WEU and TU	AESGP	daily dose of hyperforin >1mg **A) benzodiazepines** Suggested wording: 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 (e.g., ami-triptyline, fexofenadine, ~~benzodiazepines~~, alprazolam, diazepam, triazolam, midazolam, methadone, simvastatin, digoxin, finasteride, warfarin), because a reduction of plasma concentrations is possible. Comment and rationale: The denomination of the group "benzodiazepines" should be replaced by the substance "midazolam" for which a pharmacokinetic interaction had been described in the literature. The whole group of "benzodiazepines" on the	**Benzodiazepines:** Partly endorsed. The wording is revised. **Contraception:** Not endorsed. The possible interaction with hypericum is contained in the product information of hormonal intrauterine devices. **Triptans:** Endorsed. Triptans are deleted from pharmacodynamics interactions. **Serotonin syndrome:** Not endorsed. The proposed sentence is worded following the recommendation of the PRAC in the PSUSA on

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		contrary also includes substances being neither substrate of the isoenzymes known to be relevant for a pharmacokinetic interaction with *Hypericum* preparations nor of the P-gp transporter (e.g. Temazepam, Oxazepam, Lorazepam) therefore we propose to not to mention the group as such. If the comedication in question is neither metabolized via the respective isoenzymes nor substrate of the respective transporter, a pharmacokinetic interaction shall be not only unlikely, but impossible. As already outlined under 4.3: In contrast to the pharmacodynamic interactions, pharmacokinetic interactions are not predictable by the mode of action of a substance. Transferring pharmacokinetic interactions from one or even some substances to the whole group of medicinal products is therefore not substantiated by scientific facts. **B) Contraception** Proposed wording: The reduction of plasma concentrations of oral hormonal contraceptives may lead to increased intermenstrual bleeding and reduced safety in birth control. Women using oral hormonal contraceptives should take additional contraceptive measures. Comment and rationale: The available data regarding this possible interaction are -to our knowledge – all derived from studies or published case	Hypericum. **Drug interactions, footnote** Deletion not endorsed. Regulatory practice demonstrates that the majority of medicinal products contain listings of drugs which might be interacted by *Hypericum*. Therefore the footnote explains where to find such a listing valid at least at the time of drafting the assessment report. This list may be used as guidance for the individual product information. Such a footnote is not considered to be understood to be included in an SmPC. Modified wording proposed: For a list of drugs of which the metabolism is evidently and significantly interacted by herbal preparations of Hyperici herba see the assessment report chapter 5.5.4. This list may be used as guidance for the product information of individual products.

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		reports with **oral** hormonal contraceptives – mostly also low-dosed micro-pills (please see assessment report where the studies of Hall *et al*., 2003, Pfrunder *et al*., 2003, Will-Shahab *et al.*, 2009, Fogle *et al*., 2006, Murphy *et al*., 2005 are cited in this context). Even this evidence is inconsistent in outcomes- depending on preparations or parameters used- together with high intraindividual differences within the subjects. As the way of application has furthermore a high influence on the bioavailability and the possibility for pharmacokinetic interactions, a simple extrapolation of data obtained from studies with **oral** hormonal contraceptives to all other hormonal contraceptives is- in our opinion- scientifically not justified. To give an example: This wording would also include hormonal intrauterine devices with merely local mode of action (such as the "hormone spiral"/ e.g. "Mirena" in Germany). It is hardly understandable how a (systemic) pharmacokinetic interaction shall take place and influence the efficacy of such a device where the applicated hormone is acting directly on the endometrium. **C) Serotonine syndrome - triptans** Proposed wording: Pharmacodynamic interactions: Hypericum dry extract may contribute to serotonergic effects when combined with antidepressants such as serotonin	

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		reuptake inhibitors (e.g. sertraline, paroxetine, nefazodone), buspirone ~~or with triptans.~~ ~~Very rarely undesired effects (serotonine syndrome) with autonomic dysfunctions (such as perspiration, tachycardia, diarrhoea, fever), mental alterations (such as agitation, disorientation), and motor alterations (such as tremor or myoclonias) can occur in combination with serotonin-uptake inhibitors or other serotonergic active substances.~~ Comment and rationale for deletion of triptans: There is still no scientifically convincing evidence for interactions between Hypericum and triptans. The only source of original data seems to be a case report where a serotonine syndrome was diagnosed after concomitant administration of Hypericum together with fluoxetine and eletriptan (Bonetto *et al.*, 2007). After withdrawal of the Hypericum product the symptoms did not vanish, but after withdrawal of the triptan and the fluoxetine they did. Therefore a causality between Hypericum application and the described interactions is by no means demonstrated by this case report. In addition, Evans (2008) questioned whether the symptoms described were indeed conform with the Hunter serotonin toxicity criteria and whether other aetiologies were completely ruled out. Triptans therefore should not be	

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		mentioned. Comments and Rationale for deleting the paragraph (Very rarely undesired effects…..): We suggest to delete this paragraph as the possibility of pharmacodynamic interactions with other serotonergic agents most probably resulting in enhancement of serotonergic side effects is sufficiently described by the first sentence. Evidence on both is scarce and has not increased since 2009 to our knowledge- which is reflected also in the current assessment report. The causality between use of St. John's wort as comedication of serotonergic agents and the development of a serotonine syndrome had never been established as clear clinical evidence is lacking. The single case reports (Lantz *et al*., 1999, Waksman *et al*., 2000), show partly deficiencies in diagnostics. The diagnosis of a true "serotonine syndrome" for the case reports described, i.e. a really severe and life threatening state of the patient have been thoroughly evaluated and doubted e.g. by Schulz *et al.* (2006). Moreover even a close chronological relation to the use of Hypericum is not always guaranteed (Waksman *et al.,* 2000), as the Hypericum product had been already withdrawn three days before starting the administration of the SSRI (paroxetine). Some antidepressants of the SSRI type are able to cause serotonergic effects even without further comedication if the	

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		dosages are high enough (SPCs, Fischer 1995). **D) Drug interactions** Proposed wording: ~~Footnote 7 For a list of drugs interacting with herbal preparations of Hyperici herba see the assessment report chapter 5.5.4~~ Comment and rationale: The Footnote 7 might be misinterpreted as implying that the wording verbetum should be included in the SmPC. If the wording is kept as proposed it might contradict the declared intention of the Rapporteur (refer to page 218 of the Assessment report on *Hypericum perforatum* L., herba 2nd Draft – Revision 1): "The HMPC agreed that the content of the monograph concerning drug interactions should be kept in a more general style as each new detected interaction would require a revision of the monograph. Moreover a more general style including examples would encourage a prescriber / pharmacist to search for current status of knowledge on interactions at the time of use of a Hypericum product." The Footnote on the contrary would implicate exactly a final and terminating validity of this list- which was obviously not	

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		intended.	
4.5 WEU and TU	Koop Phyto	daily dose of hyperforin >1mg Proposed wording: 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 (e.g., amitriptyline, fexofenadine, ~~benzodiazepines~~, midazolam, methadone, simvastatin, digoxin, finasteride, warfarin), because a reduction of plasma concentrations is possible. Comment and rationale: Among the benzodiazepines, there are substances, which are not metabolized by any enzymes with any potential for interactions by *Hypericum* preparations, as e.g. Temazepam, Oxazepam and Lorazepam. So, the benzodiazepines are no good example here and would be better replaced by midazolam, for which an interaction potential is backed by clinical evidence . Proposed wording: The reduction of plasma concentrations of oral hormonal contraceptives may lead to increased intermenstrual bleeding and reduced safety in birth control. Women using oral hormonal contraceptives should take additional contraceptive measures.	See above.

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		Comment and rationale: Only in combination with **oral** contraceptives, especially the micro-pills interactions had been detected in at least some of the published studies. This is as well reflected by the published studies and case reports which are cited in the assessment report. For contraceptives not taken orally, as e.g. hormonal intrauterine devices acting locally and not systemically, there are neither case reports nor studies available showing an interaction, so that they should not be included here. Proposed wording: Pharmacodynamic interactions: *Hypericum* dry extract may contribute to serotonergic effects when combined with antidepressants such as serotonin reuptake inhibitors (e.g. sertraline, paroxetine, nefazodone), buspirone ~~or with triptans.~~ ~~Very rarely undesired effects (serotonine syndrome) with autonomic dysfunctions (such as perspiration, tachycardia, diarrhoea, fever), mental alterations (such as agitation, disorientation), and motor alterations (such as tremor or myoclonias) can occur in combination with serotonin-uptake inhibitors or other serotonergic active substances.~~ Comment and rationale for deletion of triptans:	

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		While serotonin reuptake inhibitors (SSRIs) can lead to a serotonin syndrome even when taken alone, this is not the case for *Hypericum* products (see also below). A case report where a serotonine syndrome was diagnosed after concomitant administration of *Hypericum* together with fluoxetine and eletriptan (Bonetto *et al.,* 2007) is not a proof even for a side effect of triptans, but of fluoxetine, and even less for an interaction with *Hypericum*. Evans (2008) had even strong doubts, whether the symptoms described were indeed indicating a serotonin syndrome i.e. in accordance to the Hunter serotonin toxicity criteria, and whether other aetiologies were sufficiently excluded. So, an interaction with triptans would be a based on theoretical considerations, weakened by the fact that there is also no clinical proof for strong serotonergic effects of *Hypericum*, and would not be backed by the available evidence. Comments and rationale for deleting the paragraph on very rarely undesired effects: Also today, the available evidence for interactions of *Hypericum* with serotonergic agents is unclear, as in all cases, the symptoms described can be explained by the co-medication alone, and, moreover, it is even unclear whether they are compatible with the criteria for a serotonine syndrome at all. As there seems to be no new evidence available since 2009, as also the assessment report indicates, and the first sentence already describes a possibility of pharmacodynamic interactions	

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		resulting in enhancement of serotonergic side effects, this new paragraph is not necessary. The single case reports (Lantz *et al*., 1999, Waksman *et al*., 2000), show partly deficiencies in diagnostics. The diagnosis of a true "serotonine syndrome" for the case reports described, i.e. a severe and life threatening state of the patient have been assessed and questioned already by Schulz *et al*. (2006). In the case report of Waksman *et al.,* 2000, even the temporal relationship to Hypericum is raising doubts, given that paroxetine treatment which is supposed to interact, started three days after the end of the *Hypericum* treatment. Antidepressants of the SSRI type have been described to cause serotonergic effects without any comedication, especially when given in high doses (Fischer 1995). Proposed wording: ~~Footnote 7 For a list of drugs interacting with herbal preparations of Hyperici herba see the assessment report chapter 5.5.4~~ Comment and rationale: The Footnote 7 can be seen as a suggestion to refer to or even include the list from the assessment report in SPCs of products. But this very long list is not intended and also not suitable to be used in that way. In the Assessment report (2nd Draft, revision 1, p 218) the	

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		rapporteur states: "The HMPC agreed that the content of the monograph concerning drug interactions should be kept in a more general style as each new detected interaction would require a revision of the monograph. Moreover a more general style including examples would encourage a prescriber / pharmacist to search for current status of knowledge on interactions at the time of use of a *Hypericum* product." The footnote could be misunderstood in a way, that this list is complete and conclusive, which would not be helpful for prescribers / pharmacists. Therefore this sentence should be deleted from the monograph.	
4.6 WEU and TU	AESGP	Safety during pregnancy and breast-feeding has not been established. Studies in animals have shown signs of reproductive toxicity (see section 5.3 'Preclinical safety data'). The use is not recommended during pregnancy and lactation. No fertility data available. Proposed wording for second sentence: <u>Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity and lactation.</u> Comments and rationale: Also as of today, studies on fertility and reproduction, which have been conducted in state of the art and guideline conform	Not endorsed. As there is evidence of potential signs of reproductive toxicity the statement is considered correct. Data from dossiers cannot be considered for assessment by the HMPC.

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		models, do not indicate reproductive toxicity or detrimental effects on fertility. Studies showing negative effects have been conducted in non suitable models (mostly *in vitro* or with parenteral application) or with insufficiently defined non-standardized extracts and with non-guideline conform models (Gregoretti *et al.,* 2004). These data therefore do not reliably contradict the sentence above, that animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Reproduction and developmental toxicity has been examined in state of the art models, to our knowledge for at least three different preparations. No toxic effect was detected. Pivotal studies according to current guidelines have been conducted with the extract STW 3, an extract well defined and referred to in this monograph. Fertility in rats, embryo-fetal development in rats and rabbits, and prenatal and postnatal development including maternal functions, in rats were conducted. No signs of reproduction or developmental toxicity were found with the applied doses of up to 1000 mg STW 3 per kg b.w., so showing, that there is no reproduction toxicological effect. The studies are part of the pharmacological-toxicological documentations of the corresponding products registered in several European countries, e.g. Austria and Germany, and accessible through the respective documentations.	

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		For the assessment of the general tolerability of treated dams during gestation and for the evaluation of the intrauterine development during the different stages of embryonic/foetal development, the extract Ze 117 was investigated in a Segment II study in rats. The study of Klaus (1998) was performed in compliance with the ICH recommendations for "Detection of Toxicity to Reproduction for Medicinal Products". 24 inseminated female Wistar rats per group were treated daily from day 6 to 17 p.c. with the test article applied orally by gavage with doses of 0, 100, 300 and 1000 mg/kg body weight and day, respectively. There were no treatment-related effects on appearance and behaviour as well as on other clinical observations in the dams at all dose-levels tested up to and including the dose level of 1000 mg/kg b.w. per day. Body weight and feed consumption were unaffected. No treatment-related gross pathological findings or mortality occurred. The pregnancy and resorption rates as well as the number of fetuses were unaffected by the treatment. Placental and fetal weights did not reveal any indication of treatment-related effects at all dose levels tested. External and visceral examinations of the fetuses revealed no treatment-related findings. The skeletal evaluation of the fetuses neither revealed any indications for treatment-related malformations nor on effects on the stage of ossification. Chan *et al.* (2001) examined the potential teratogenic effects of isolated hypericin, using the explanted rat's embryo model. Embryos were explanted at gestational day 9.5 and cultured *in*	

Section number and heading	Interested party	Comment and Rationale	Outcome
		vitro for 48 hours in a culture medium containing hypericin in a final concentration of 0 to 142 ng/ml. At gestational day 11.5, embryos were examined by a blinded rater. Morphological changes were found with the highest hypericin concentrations (71.0 and 142.0 ng/ml). The authors point to serum levels of up to 78 ng/ml after application of 1800 mg per day of *Hypericum* extract by Schempp *et al.* (1999) and thus to potentially teratogenic effects (Chan *et al.*, 2001). With the recommended dose schemes of SJW products this level of hypericin is not reached. In addition, the test system applied by Chan *et al*. (2001) allows direct contact between embryo and hypericin containing medium, a situation not known in humans due to the blood-placenta barrier. So, this study is no basis to derive a relevant risk for the therapeutic uses of SJW extracts in humans. Rayburn *et al.* (2000) tested the development of mice offspring in a randomized, placebo-controlled manner after antenatal exposition to SJW. A daily dose of SJW (0.75 mg/g of food consumed), equivalent to that in human beings according to body surface, was chosen. CD-1 mice were randomly assigned to consume either SJW (n = 45) or placebo (n = 45) for 2 weeks before conception and throughout gestation. Behavioural testing consisted of early developmental tasks of geotaxis, separation vocalization, and homing, followed by motor, anxiety, and depression assessments into adulthood. Birth weights of male offspring were less in the SJW group than in the placebo group (1.68 vs. 1.75 g; $p < 0.05$). Post learning	

Section number and heading	Interested party	Comment and Rationale	Outcome
		sessions did not show any significant differences. In conclusion, prenatal exposure to a therapeutic dose of SJW did not have a major impact on certain cognitive tasks in mice offspring (Rayburn *et al.,* 2001a). Rayburn *et al.* (2001b) determined whether prenatal exposure to SJW affects long-term growth and physical maturation of mouse offspring. Forty CD-1 mice were randomly assigned to receive daily doses of either 180 mg/kg per day of SJW (n = 20) or placebo (n = 20) for 2 weeks before conception and throughout gestation. Perinatal outcomes, growth, and physical milestones of the offspring were compared in a blinded manner. The gestational ages at delivery and litter sizes did not differ between the SJW-exposed and the placebo exposed offspring. The body weight, body length, and head circumference measurements from postnatal day 3 through adulthood increased in a manner that was indistinguishable between the two groups of offspring, regardless of gender. No differences in reaching physical milestones (teeth eruptions, eye opening, and external genitalia) were noted between the 2 groups. The reproductive capability, perinatal outcomes, and growth and development of the second-generation offspring were unaffected by SJW exposure. Maternal administration of *Hypericum* before and throughout gestation did not affect long-term growth and physical maturation of exposed mouse offspring (Rayburn *et al.,* 2001b). In a review on safety of SJW during pregnancy and lactation, Dugoua *et al.* (2006) report no impact on maternal weight gain or duration of gestation on	

Section number and heading	Interested party	Comment and Rationale	Outcome
		Sprague-Dawley rats exposed to dietary doses of SJW 1 to 25 times the recommended human dose. SJW had no impact on maternal weight gain or duration of gestation. Offspring body weights were similar to controls, although there was a tendency towards lower weight on treatment with SJW. There were no SJW related behavioural alterations on any measure (Dugoua *et al*., 2006). Adequate tests on reproduction toxicity have been performed, using SJW extracts defined according to regulatory requirements. We ask that the phrase related to reproduction toxicity be changed to a wording in the sense of: Tests on reproduction toxicity did not point to a specific risk during pregnancy and lactation.	
4.6 WEU and TU	Koop Phyto	Safety during pregnancy and breast-feeding has not been established. ~~Studies in animals have shown signs of reproductive toxicity (see section 5.3 'Preclinical safety data').~~ The use is not recommended during pregnancy and lactation. No fertility data available. Proposed wording for second sentence: <u>Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity and lactation.</u>	See above

Section number and heading	Interested party	Comment and Rationale	Outcome
		Comments and rationale: On a first view, evidence on safety during fertility and reproduction seems to be contradictory and unclear. But a closer view shows, that the studies, which have been conducted in state of the art and guideline conform models, do not indicate reproductive toxicity or detrimental effects on fertility. Studies showing negative effects have been conducted in non suitable models (mostly *in vitro* or with parenteral application) or even with insufficiently defined and non-standardized extracts and in questionable models which do not comply with current guidelines (Gregoretti *et al.*, 2004). There results can therefore not be seen as valid and reliable. Given these studies are not interpretable or not valid, they also would not contradict the sentence above, that animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Reproduction and developmental toxicity has been examined in state of the art models for at least three different preparations, and no toxic effect were detected. As mentioned earlier, pivotal studies according to current guidelines have been conducted with the extract STW 3, an extract well defined and referred to in this monograph. Fertility in rats, embryo-foetal development in rats and rabbits, and	

Section number and heading	Interested party	Comment and Rationale	Outcome
		prenatal and postnatal development including maternal functions, in rats were conducted. No signs of reproduction or developmental toxicity were found with the applied doses of up to 1000 mg STW 3 per kg b.w., so showing, that there is no reproduction toxicological effect. The studies are part of the pharmacological-toxicological documentations of the corresponding products registered in several European countries, e.g. Austria and Germany, and accessible through the respective documentations. As stated earlier, the extract Ze 117 was investigated in a Segment II study in rats. The study of Klaus (1998) was performed in compliance with the ICH recommendations for "Detection of Toxicity to Reproduction for Medicinal Products". 24 inseminated female Wistar rats per group were treated daily from day 6 to 17 p.c. with the test article applied orally by gavage with doses of 0, 100, 300 and 1000 mg/kg body weight and day, respectively. There were no treatment-related effects on appearance and behaviour as well as on other clinical observations in the dams at all dose-levels tested up to and including the dose level of 1000 mg/kg b.w. per day. Body weight and feed consumption were unaffected. No treatment-related gross pathological findings or mortality occurred. The pregnancy and resorption rates as well as the number of foetuses were unaffected by the treatment. Placental and foetal weights did not reveal any indication of treatment-related effects at all dose levels tested. External and visceral examinations of the foetuses revealed no treatment-related	

Section number and heading	Interested party	Comment and Rationale	Outcome
		findings. The skeletal evaluation of the foetuses neither revealed any indications for treatment-related malformations nor on effects on the stage of ossification. Chan *et al*. (2001) examined the potential teratogenic effects of isolated hypericin, using the explanted rat's embryo model. Embryos were explanted at gestational day 9.5 and cultured *in vitro* for 48 hours in a culture medium containing hypericin in a final concentration of 0 to 142 ng/ml. At gestational day 11.5, embryos were examined by a blinded rater. Morphological changes were found with the highest hypericin concentrations (71.0 and 142.0 ng/ml). The authors point to serum levels of up to 78 ng/ml after application of 1800 mg per day of *Hypericum* extract by Schempp *et al.* (1999) and thus to potentially teratogenic effects (Chan *et al*., 2001). With the recommended dose schemes of SJW products this level of hypericin is not reached. In addition, the test system applied by Chan *et al*. (2001) allows direct contact between embryo and hypericin containing medium, a situation not known in humans due to the blood-placental barrier. So, this study is no basis to derive a relevant risk for the therapeutic uses of SJW extracts in humans. Rayburn *et al*. (2000) tested the development of mice offspring in a randomized, placebo-controlled manner after antenatal exposition to SJW. A daily dose of SJW (0.75 mg/g of food consumed), equivalent to that in human beings according to body surface, was chosen. CD-1 mice were randomly assigned	

Section number and heading	Interested party	Comment and Rationale	Outcome
		to consume either SJW (n = 45) or placebo (n = 45) for 2 weeks before conception and throughout gestation. Behavioural testing consisted of early developmental tasks of geotaxis, separation vocalization, and homing, followed by motor, anxiety, and depression assessments into adulthood. Birth weights of male offspring were less in the SJW group than in the placebo group (1.68 vs. 1.75 g; $p < 0.05$). Post learning sessions did not show any significant differences. In conclusion, prenatal exposure to a therapeutic dose of SJW did not have a major impact on certain cognitive tasks in mice offspring (Rayburn *et al.*, 2001a). Rayburn *et al*. (2001b) determined whether prenatal exposure to SJW affects long-term growth and physical maturation of mouse offspring. Forty CD-1 mice were randomly assigned to receive daily doses of either 180 mg/kg per day of SJW (n = 20) or placebo (n = 20) for 2 weeks before conception and throughout gestation. Perinatal outcomes, growth, and physical milestones of the offspring were compared in a blinded manner. The gestational ages at delivery and litter sizes did not differ between the SJW-exposed and the placebo exposed offspring. The body weight, body length, and head circumference measurements from postnatal day 3 through adulthood increased in a manner that was indistinguishable between the two groups of offspring, regardless of gender. No differences in reaching physical milestones (teeth eruptions, eye opening, and external genitalia) were noted between the 2 groups. The reproductive capability, perinatal outcomes, and	

Section number and heading	Interested party	Comment and Rationale	Outcome
		growth and development of the second-generation offspring were unaffected by SJW exposure. Maternal administration of *Hypericum* before and throughout gestation did not affect long-term growth and physical maturation of exposed mouse offspring (Rayburn *et al*., 2001b). In a review on safety of SJW during pregnancy and lactation, Dugoua *et al*. (2006) report no impact on maternal weight gain or duration of gestation on Sprague-Dawley rats exposed to dietary doses of SJW 1 to 25 times the recommended human dose. SJW had no impact on maternal weight gain or duration of gestation. Offspring body weights were similar to controls, although there was a tendency towards lower weight on treatment with SJW. There were no SJW related behavioural alterations on any measure (Dugoua *et al*., 2006). I.e., adequate tests on reproduction toxicity have been performed, using SJW extracts defined according to regulatory requirements, without results which could raise safety concerns. Therefore, it seems adequate to use a wording in the sense of: Tests on reproduction toxicity did not point to a specific risk during pregnancy and lactation.	
4.9 TU	AESGP	The draft provides texts on overdoses with defined amounts of dry extract to be included into the SMPC. Unlike in other sections of the monograph, this text is not dependent on the composition of the medicinal product, so it is basically applicable to any traditional use preparation of *hypericum,*	Endorsed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		even if it is a liquid extract or a herbal tea. We consider it confusing for the patient if precautions are included in the package leaflet that do refer to other preparations than the one the patient is actually using. Therefore we propose to modify section 4.9 of the monograph so that all texts referring to dry extracts are only applicable if the medicinal product actually contains a dry extract ("a" from section 2 of the monograph)."	
4.9 TU	Koop Phyto	Texts on overdoses to be included into the SMPC are related to defined amounts of dry extract. It is not sufficiently clear, that, as in other sections of the monograph, these texts are applicable only to the respective medicinal products, and not to e.g. a liquid extract or a herbal tea. Therefore we propose to modify section 4.9 of the monograph so that texts referring to dry extracts are only applicable to medicinal product containing dry extracts (point a in section 2 of the monograph)."	Endorsed.
5.1 WEU	AESGP	Proposed wording: *Hypericum* dry extract inhibits the synaptosomal uptake of the neurotransmitters noradrenaline, serotonine and dopamine. Subchronic treatment causes a down-regulation of β-adrenergic receptors; it changes the behaviour of animals in several antidepressant models (e.g., forced swimming test) similarly to synthetic antidepressants. Napthodianthrones (e.g. hypericin, pseudohypericin), phloroglucin derivatives (e.g. hyperforin) and flavonoids contribute to the activity.	Partly endorsed. The down-regulation of receptors is indirectly included in the first sentence. Agreement to add the statement regarding change of behaviour in animal models.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Comment and rationale: We suggest to keep the former wording as on the one hand the scientific basis of the described mechanisms is still valid and on the other hand the mechanism of normalization of the disturbed neurotransmission would be incomplete, if only the effect of the reuptake inhibition is described. It is a long-known fact that the reuptake inhibition and the assumed prolonged availability of the respective neurotransmitters in the synaptic cleft alone can e.g. not explain the lagged onset of clinical effect. Only the combination of pre- and postsynaptic effects (as the mentioned down-regulation of β-adrenergic receptors) leads to a plausible mechanism also in the clinical sense. The information on change of behaviour in several animal models is as well valuable for the HCPs as these models have been widely used for synthetic antidepressants as well and therefore give the possibility to compare. As for mental or mood disorders biomarkers for quick evaluation of mechanistic effects are rarely existing, these results give nevertheless information on mode of action in a systemic model which is at least always more relevant than *in vitro* data alone. Taken together with the existing clinical evidence on efficacy of the herein considered preparations, he given information should be a helpful guidance for HCPs.	
5.1 WEU	Koop Phyto	Proposed wording: *Hypericum* dry extract inhibits the synaptosomal uptake of the neurotransmitters noradrenaline, serotonine and dopamine.	See above.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Subchronic treatment causes a down-regulation of β-adrenergic receptors; it effects in several antidepressant models are similar to those of synthetic antidepressants. Napthodianthrones (e.g. hypericin, pseudohypericin), phloroglucin derivatives (e.g. hyperforin) and flavonoids contribute to the activity. Comment and rationale: We suggest to keep a more detailed description of the evidence as it is important for the understanding of the mechanism of normalization of the disturbed neurotransmission, that not only the reuptake inhibition is described, but that the reuptake inhibition and the assumed prolonged availability of the respective neurotransmitters in the synaptic cleft alone can e.g. not explain the lagged onset of the clinical effect. It is only a combination of pre- and postsynaptic effects (as the mentioned down-regulation of β-adrenergic receptors) which can plausibly explain the clinical effects. Mentioning also these pharmacological models widely used also for synthetic antidepressants is important for the credibility of the effectivity of the treatment in HCPs.	
5.3 WEU and TU	AESGP	~~Several studies on extracts of and isolated compounds from *Hypericum perforatum* report in- vitro and in-vivo effects that could affect the development of foetuses from treated mothers.~~ Proposed wording:	Not endorsed, see above.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Study results are inconsistent concerning reproductive toxicity. While several studies on insufficiently defined extracts and isolated compounds from *Hypericum perforatum* report in- vitro and in-vivo effects questioning reproductive safety, state of the art studies with well-defined extracts do not show effects that could affect the development of foetuses from treated mothers, but support reproductive safety. Comment and rationale: As the numerous studies presented in the comments to section 4.6. show, all studies on fertility and reproduction, which have been conducted in state of the art and guideline conform models, do not indicate reproductive toxicity or detrimental effects on fertility. Studies showing negative effects have been conducted in non-suitable models (mostly *in vitro* or with parenteral application) or with insufficiently defined non-standardized extracts and non-standard study design (Gregoretti *et al.*, 2004). These data therefore seem not valid and therefore do not to rule out the sentence above, that animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.	
5.3 WEU and TU	Koop Phyto	~~Several studies on extracts of and isolated compounds from *Hypericum perforatum* report in- vitro and in-vivo effects that could affect the development of foetuses from treated mothers.~~ Proposed wording:	See above.

Section number and heading	Interested party	Comment and Rationale	Outcome
		While several studies on insufficiently defined extracts and isolated compounds from *Hypericum perforatum* report in-vitro and in-vivo effects questioning reproductive safety, state of the art studies with well-defined extracts prepared according to regulatory requirements support reproductive safety. Comment and rationale: As an assessment of the numerous studies already referred to in the comments to section 4.6. shows, the studies on fertility and reproduction, which have been conducted in state of the art and guideline conform models, do not indicate reproductive toxicity or detrimental effects on fertility. As mentioned, studies showing negative effects have been conducted in non-suitable models (mostly *in vitro* or with parenteral application) or with insufficiently defined non-standardized extracts and non-standard study design (Gregoretti *et al.,* 2004). These data therefore seem not valid and therefore do not to rule out the sentence above, that animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.	
References			
References	AESGP	*In the following, references cited above are listed, with the exception of references, which have been cited in this or in earlier versions of the HMPC documents on* Hypericum:	The references Biber *et* al. (1998) and Zahner *et al.* (2019) are already contained in the LoR. The reference Adiwidjaja *et al.* (2019) is added to the LoR.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Adiwidjaja, J., Boddy, A.V., and Mclachlan, A.J. (2019). Physiologically Based Pharmacokinetic Modelling of Hyperforin to Predict Drug Interactions with St John's Wort. Clin Pharmacokinet 58, 911-926. Biber, A., Fischer, H., Romer, A., and Chatterjee, S.S. (1998). Oral bioavailability of hyperforin from *hypericum* extracts in rats and human volunteers. Pharmacopsychiatry 31 Suppl 1, 36-43. Derendorf, H., Expert Statement, Study Design and Duration Assessment of Clinical Evaluation of Ze 117 for Potential Pharmacokinetic Drug Interactions, 2020 Kapetas, A.J., Sorich, M.J., Rodrigues, A.D., and Rowland, A. (2019). Guidance for Rifampin and Midazolam Dosing Protocols To Study Intestinal and Hepatic Cytochrome P450 (CYP) 3A4 Induction and De-induction. AAPS J 21, 78. Max Zeller Söhne AG, Registration status of Z-99052 St. John's wort film coated tablets 500 mg, 2021 Nicolussi *et al.* (2019) Clinical relevance of St. John's wort drug interactions revisited. *Br J Pharmacol*. doi/10.1111/bph.14936 PACKAGE LEAFLET: INFORMATION FOR THE USER: Remotiv extra 500 mg film coated tablet (En/ HUN) SmPC of Ze 117 (SmPC-Remotiv-2019-CH). Zahner *et al*. (2019) No Clinically Relevant Interactions of St.	The other cited references are acknowledged but considered not relevant for the AR.

Section number and heading	Interested party	Comment and Rationale	Outcome
		John's Wort Extract Ze 117 Low in Hyperforin With Cytochrome P450 Enzymes and P-glycoprotein. Clin Pharmacol Ther. 106:432-440.	
References	Koop Phyto	*All references cited above have been cited in this or in earlier versions of the HMPC documents on* Hypericum*, so that they do not need to be listed here.*	
Comments on AR	AESGP		
5.5.4. Drug interactions and other forms of interaction		*The PRAC correctly concluded that: "Adequate studies with extracts with low hyperforin content are available which could justify exemptions in the wording of contraindications, special warnings and in the interactions section of the SmPC." (EMA/PRAC/582574/2018)* Therefore, we ask that the HMPC adopts the conclusion and adds it to the paragraph on page 189. Rationale: A comprehensive drug interaction study was published (Zahner *et al*., 2019 *Clin Pharmacol Ther*.). Adequate studies are summarized in a review article (Nicolussi *et al*., 2019 *Br J Pharmacol*.) In addition, the first SmPC of a low hyperforin St. John's wort extract (Ze 117) without pharmacokinetic interactions, special warnings and contraindications was approved (SmPC-Remotiv-	Endorsed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		2019-CH).	
		In chapter 5.5.4 on page 220, the following sentence refers to the interaction study by Zahner *et al*. *"There is evidence that* Hypericum *preparations containing low amounts of hyperforin do not induce enzyme activity under certain circumstances (oral dose 1 times daily 500 mg, less than 1 mg hyperforin per day, duration of intake 1 week)".* *However, the following sentence in the same paragraph implies that the study duration of 10 days is not sufficient to exclude pharmacokinetic interactions over a longer period. "As the duration of use required for achievement of an antidepressant activity is significantly longer the possible omission of contraindications and warnings in the product information should be assessed within procedures for marketing authorisation for a concrete product case by case".* *Comment: In a study by Adiwidjaja et al., 2019, it is described that already 5 to 9 days are sufficient to observe a maximum induction by hyperforin of CYP3A4 as well as CYP2C9 and CYP2C19 (Adiwidjaja et al., 2019). The PBPK model of hyperforin was simulated in this study for daily administration for 14 days and compared with PK data from healthy volunteers administered a St. John's wort extract (WS 5572) containing 45 mg hyperforin (hyperforin content 5%, daily dose = 900 mg = 45 mg administered dose of hyperforin) for 8 days (Biber et al., 1998). Based on the PBPK model, it appears that due to the hepatic hyperforin half-life of 23.1 h, a maximum*	See above

Section number and heading	Interested party	Comment and Rationale	Outcome
		induction is reached within 4.8 days. In enterocytes, maximum (steady state) induction is reached within 7.5 days (t1/2 hyperforin enterocytes 35.9 h). This is consistent with the general pharmacokinetics rule that steady-state levels/effects are reached after about 5 half-lives. *In addition, Adiwidjaja et al. show that hyperforin-induced CYP3A4 induction is hepatic linear, but intestinal non-linear. It also becomes clear that at a daily dose of ≤1 mg hyperforin, neither hepatic nor intestinal induction of clinical concern is to be expected. The authors also show that an accumulation of hyperforin in plasma after repeated administration can be excluded, since steady state effects are reached after 5 half-lives.* *Clinically significant DDI risks occur with products containing more than 1% hyperforin or an intake of more than 1 mg hyperforin daily (EMA/PRAC 2018). As PBPK modelling showed, 90% of maximal enzyme induction in the gut and liver occurs within about 5 to 9 days after daily administration with the active ingredient rifampicin or with high-dose hyperforin (hyperforin content 5%, daily dose 900 mg = daily hyperforin dose thus 45 mg) (Adiwidjaja et al., 2019, Kapetas et al., 2019). Clinically relevant CYP3A4 inductions are not expected with a daily dose of ≤ 1 mg hyperforin. Based on the design and duration (10 days) of the Zahner et al. study described above, it can therefore be concluded that clinically significant pharmacokinetic interactions between Ze 117 and drugs*	

Section number and heading	Interested party	Comment and Rationale	Outcome
		metabolised by CYP3A4 are negligible. A clinically relevant induction due to hyperforin would have occurred after 5-9 days of treatment. We suggest to re-evaluate the sentence: "As the duration of use required for achievement of an antidepressant activity is significantly longer the possible omission of contraindications and warnings in the product information should be assessed within procedures for marketing authorisation for a concrete product case by case" to take into account the data provided above and the PRAC conclusion. For further references see (reference list below): Adiwidjaja 2019 Biber 1998 Kapetas 2019 Derendorf 2020	