20 March 2024
EMA/HMPC/509547/2023
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Rhodiola rosea* L., rhizoma et radix

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Rhodiola rosea* L., rhizoma et radix as released for public consultation on 19 July 2023 until 19 October 2023.

	Organisations and/or individuals
1	AESGP
2	KOOP Phyto Kooperation Phytopharmaka, Plittersdorfer Str. 218, 53173 Bonn
3	Schwabe Dr. Willmar Schwabe GmbH & Co. KG, Willmar-Schwabe-Str. 4, D-76227 Karlsruhe, Germany

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
Koop	The Kooperation Phytopharmaka is a German scientific society that works to strengthen herbal medicines in the healthcare system. Kooperation Phytopharmaka highly appreciates the revision of the 'European Union herbal monograph on *Rhodiola rosea* L., rhizoma et radix' and the publication of the respective draft (EMA/HMPC/24177/2023) together with the draft assessment report and the draft list of references. Herewith we provide comments of the Kooperation Phytopharmaka and kindly ask for their consideration.	

Specific comments on text

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German Translation of the herbal drug	AESGP	Comment: We propose to retain the common German name "Rosenwurzwurzelstock". Rational: The translation on p. 2 has been changed in German (DE) from Rosenwurzwurzelstock to Rosenwurz-Wurzelstock mit	Endorsed. However, this translation into the German language must be considered as a provisional one. The draft Ph. Eur. Monograph has been published in Pharmeuropa 34.3 with the title 'Rhodiola root and rhizome'. The final title as well as the title in the official translation of

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		Wurzeln, which leads to reduced readability/comprehensibility by the patient, as they tend not to be able to distinguish between rootstock and root. In addition, this deviates from the short form in the English (EN) translation: Arctic root. Furthermore, the correct Latin name and the long form are also given in full in the appropriate places, e.g. 2. qualitative and quantitative composition.	Ph. Eur. into the German language have to be considered as official translation then.
4.5. Interactions with other medicinal products and other forms of interaction	AESGP	Comment: The current wording in the draft monograph is: "Rhodiola rosea may decrease the activity of CYP2C9. With simultaneous treatment, there is a risk of an increase in the plasma concentration of medicinal substances that are metabolized by CYP2C9 (e.g. warfarin and phenytoin). In case a drug is converted to its active metabolite via CYP2C9 (e.g losartan) the effect may be decreased during simultaneous treatment with Rhodiola rosea." Clinically relevant interactions of Rhodiola rosea extracts have not been reported. A PK interaction study with losartan and its active metabolite EXP3174 as probe substrates indicated a modest (21%) decrease in the ratio of EXP3174/ losartan plasma levels upon pre-treatment with Rhodiola rosea extract. The data from this study are not sufficient to conclude on an interaction potential with other substances. The statement in the monograph is not in line with the discussion in the drafted assessment report: the findings are partly conflicting; the clinical relevance is unclear. Moreover,	Endorsed. Modified wording for the monograph: • "No clinically relevant interactions have been observed."

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		the proposed information is difficult to understand even for healthcare professionals. Therefore, we propose to clearly state that clinically relevant interactions of Rhodiola rosea extracts have not been reported. Rationale: Due to some limitations of the study of Thu et al. (2016) the findings obtained with losartan are not sufficient to draw conclusions on the interaction potential of Rhodiola rosea extracts with substrates of CYP2C9 such as warfarin and phenytoin. Therefore, we propose to delete the information in parentheses regarding warfarin and phenytoin as potentially interacting substances. Losartan is not an optimal phenotyping substance for CYP2C9 since the PK of losartan and its metabolite EXP-3174 involves not only CYP2C9 but also CYP3A4 and efflux transporters [Lo et al., 1995; Soldner et al., 2000]. Approximately 14% of the dose of losartan is converted to the active metabolite EXP-3174 [Lo et al., 1995]. Despite this observation, the plasma-levels of EXP-3174 are 4-fold higher than those of losartan which is due to a ten-fold lower clearance of EXP-3174 in comparison to losartan. Thus, the plasma level of the metabolite EXP3174 is rather determined by its elimination rate than by its formation rate by CYP2C9 [Lo et al., 1995]. Therefore, the interaction of Rhodiola rosea extract with losartan observed by Thu et al. (2016) can probably only partly be explained by the claimed inhibition of CYP2C9 and an explanation of the results to other substrates of CYP2C9 is not warranted.	

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		Non-clinical data on the influence of Rhodiola rosea extract on CYP2C9 are contradictory as well. One animal study found an influence of Rhodiola extract on the PK of losartan [Spanakis et al., 2013] whereas another study with warfarin as substrate did neither show a pharmacokinetic interaction nor changes in the pharmacodynamic effect of warfarin [Panossian et al., 2009]. As correctly stated in the draft assessment report, in the published case reports of suspected drug interactions none of the reported concomitantly applied drug substances is mainly metabolised by CYP2C9. Only amitriptyline is partially metabolised via CYP2C9. Therefore, in the reported cases, a potential inhibition of CYP2C9 does not serve as explanation for the observed interactions. Due to its complex PK, the use of losartan in cocktail interaction studies requires the cumulative determination of the AUCs0-8h losartan and EXP-3174 in urine as described in the validated procedure for the "Inje cocktail" [Ryu et al., 2007]. This procedure was not applied by Thu et al. (2016). The ratio of the plasma concentrations EXP-3174/ losartan was only determined at one single time point (t= 4h) which limits the relevance of the findings. With this method a modest 21% reduction of the ratio EXP-3174/ losartan was found upon pre-treatment with Rhodiola rosea extract. This result narrowly missed the lower limit for bioequivalence of 80% (i.e. 20 % reduction of plasma concentration) in comparison to the control period without Rhodiola pre-treatment.	

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		Thus, in case of losartan, a clinically relevant decrease of the pharmacodynamic effect is not expected by the modest interaction described by Thu et al. (2016), taking also into account that both losartan and its metabolite EXP3174 are pharmacologically active [Lo et al., 1995]. Therefore, a warning regarding the concomitant use of Rhodiola rosea extract with Losartan is not considered necessary. Proposed change (if any): "No clinically relevant interactions observed."	
4.5.	KOOP Phyto	Comment and rational: The revision includes additional information regarding a possible inhibition of the CYP2C9 enzyme and an associated interaction with drugs metabolized via this enzyme. Following statement was added to the monograph: "Rhodiola rosea may decrease the activity of CYP2C9. With simultaneous treatment, there is a risk of an increase in the plasma concentration of medicinal substances that are metabolized by CYP2C9 (e.g. warfarin and phenytoin). In case a drug is converted to its active metabolite via CYP2C9 (e.g losartan) the effect may be decreased during simultaneous treatment with Rhodiola rosea". As described in the draft assessment report on Rhodiola rosea L., rhizoma et radix this statement is mainly based on the study of Thu et al. (2016a), which "indicates an inhibiting influence of a Rhodiola extract on CYP2C9. The findings on pharmacokinetic interactions due to stimulation or inhibition of	See above

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		other CYP enzymes are partly contradictory. From the published case reports none of the reported concomitantly applied drug substances is mainly metabolised by CYP2C9, only amitriptyline is partially metabolised via CYP2C9. Considering the limitation of the duration of use in the monograph to 2 weeks (without consultation of a doctor) the clinical relevance of this finding is considered of less relevance." Additionally, the EMA Guideline on the investigation of drug interactions [1] provides guidance for the evaluation of enzyme inhibitors and their clinical relevance. It states: "Enzyme inhibitors may be classified based on their potency, i.e. magnitude of the mean effect on mean oral clearance of a probe drug for the enzyme when the inhibitor is administered at its highest therapeutic dose. A strong inhibitor causes a > 5 fold increase in the plasma AUC values or ≥ 80% decrease in oral clearance, a moderate inhibitor causes a > 2-fold increase in the plasma AUC or 50 - ≤ 80% inhibition of oral clearance, a mild inhibitor causes 1.25 to 2 fold increase in the plasma AUC or ≤ 50% inhibition of oral clearance." (Appendix VIII, p. 51). Thu et al. 2016a shows, that "a statistically significant 21% decrease in the EXP-3174/losartan ratio was found after pretreatment with R. rosea (p = 0.023), indicating a reduced CYP2C9 metabolic activity", which means that there is clearly a less than 1.25fold increase in the plasma AUC resp. > 50% inhibition of oral clearance, given that even the quotient of both is just only 21 %. Accordingly, this is even below a mild influence, but rather no relevant influence. This is also given	

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		by the heterogeneity of measurements mentioned in the article which just points to scatter, especially as the study seems to be short-term. Additionally, further non-clinical data from Noeldner et al. 2010 [2] presented information on the potential interaction of WS® 1375, a 60% ethanol extract of roots and rhizomes of Rhodiola rosea L. with CYP enzymes. The assay was performed using microsomes, prepared from freshly isolated human hepatocytes. The IC50 values of CYP 2C9 given by Noeldner et al. 2010 is 77 µg/ml, which highly differs from the IC50 value of 19,2 µg/ml presented by Thu et al. 2017, indicating that the IC50 value is strongly depending on the respective Rhodiola rosea extract and the assay used. Thus, a general statement to the potential interactions of Rhodiola rosea preparations with other medicinal products cannot be deduced from one study only. Therefore, we recommend adjusting the statement as follows. Proposed change (if any): As the non-clinical data are inconsistent and the "clinical relevance of this finding is considered of less relevance" we propose to change the information in the monograph section 4.5 to: "No clinically relevant interactions known."	
4.5.	Schwabe	***Current wording and proposal for revision:*** ~~*Rhodiola rosea may decrease the activity of CYP2C9. With simultaneous treatment, there is a risk of an increase in the plasma concentration of medicinal substances that are metabolized by CYP2C9 (e.g. warfarin and phenytoin). In case a drug is converted to its active metabolite via CYP2C9 (e.g losartan) the effect may be decreased during simultaneous treatment with Rhodiola rosea.*~~	See above

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		Clinically relevant interactions of Rhodiola rosea extracts have not been reported. **Rationale** The statement in the monograph is not in line with the discussion in the drafted assessment report: the findings are partly conflicting, the clinical relevance is unclear. Moreover, the proposed information is difficult to understand even for healthcare professionals. Therefore, we propose to clearly state that clinically relevant interactions of Rhodiola rosea extracts have not been reported. Due to some limitations of the study of Thu et al. (2016) (see below) the findings obtained with losartan are not sufficient to draw conclusions on the interaction potential of Rhodiola rosea extracts with substrates of CYP2C9 such as warfarin and phenytoin. Therefore, we propose to delete the information in parentheses regarding warfarin and phenytoin as potentially interacting substances. Losartan is not an optimal phenotyping substance for CYP2C9 since the PK of losartan and its metabolite EXP-3174 involves not only CYP2C9 but also CYP3A4 and efflux transporters [*Lo et al., 1995; Soldner et al., 2000*]. Approximately 14% of the dose of losartan is converted to the active metabolite EXP-3174 [Lo et al., 1995]. Despite this observation, the plasma-levels of EXP-3174 are 4-fold higher than those of losartan which is due to a ten-fold lower clearance of EXP-3174 in comparison to losartan. Thus, the plasma level of the metabolite EXP3174 is rather determined by its elimination rate than by its formation rate by CYP2C9 [Lo et al., 1995]. Therefore, the interaction of Rhodiola rosea extract with losartan observed by Thu et al. (2016) can probably only partly be explained by the claimed inhibition of CYP2C9 and an	

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		extrapolation of the results to other substrates of CYP2C9 is not warranted. Non-clinical data on the influence of Rhodiola rosea extract on CYP2C9 are contradictory as well. One animal study found an influence of Rhodiola extract on the PK of losartan [*Spanakis et al., 2013*] whereas another study with warfarin as substrate did neither show a pharmacokinetic interaction nor changes in the pharmacodynamic effect of warfarin [*Panossian et al., 2009*]. As correctly stated in the draft assessment report, in the published case reports of suspected drug interactions none of the reported concomitantly applied drug substances is mainly metabolised by CYP2C9. Only amitriptyline is partially metabolised via CYP2C9. Therefore, in the reported cases, a potential inhibition of CYP2C9 does not serve as explanation for the observed interactions. Due to its complex PK, the use of losartan in cocktail interaction studies requires the cumulative determination of the $AUCs_{0\text{-}8h}$ losartan and EXP-3174 in urine as described in the validated procedure for the "Inje cocktail" [*Ryu et al., 2007*]. This procedure was not applied by Thu et al. (2016). The ratio of the plasma concentrations EXP-3174/ losartan was only determined at one single time point (t= 4h) which limits the relevance of the findings. With this method a modest 21% reduction of the ratio EXP-3174/ losartan was found upon pre-treatment with Rhodiola rosea extract. This result narrowly missed the lower limit for bioequivalence of 80% (i.e. 20 % reduction of plasma concentration) in comparison to the control period without Rhodiola pre-treatment. Thus, in case of losartan, a clinically relevant decrease of the pharmacodynamic effect is not expected by the modest interaction described by Thu et al. (2016), taking also into	

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		account that both losartan and its metabolite EXP3174 are pharmacologically active [Lo et al., 1995]. Therefore, a warning regarding the concomitant use of Rhodiola rosea extract with Losartan is not considered necessary. Please also refer to comments on Draft assessment report.	
4.8. Undesirable effects	Schwabe	**Current wording and proposal for revision:** Nervous system disorders: mild headache~~, nervousness, insomnia, dizziness~~ Gastrointestinal disorders: mild gastrointestinal complaints, e.g nausea~~, vomiting~~ Skin and subcutaneous tissue disorders/ immune system disorders: mild hypersensitivity reactions The frequency is not known. Please refer to comments on section 4.8 of the HMPC assessment report. In summary, no consistent new evidence about adverse drug reactions (i.e., adverse events with suspected causal relationship) of *Rhodiola rosea* extracts became available since the compilation of the HMPC monograph from publicly available sources. Regarding the reports from Eudravigilance, it remains unclear how the conclusion was drawn that nervousness, dizziness and insomnia are considered to be adverse reactions of Rhodiola rosea with reasonable suspicion of causality. A thorough causality assessment based on well documented cases is crucial here, since the reported symptoms may be manifestations of the indication for which the Rhodiola preparations were used. Since no information was provided about the signal detection and validation process, it seems that it seems that merely adverse event terms from cases without other co-medication were adopted into section 4.8 of the monograph. It may be questioned whether the overall reporting quality of the ICSRs in Eudravigilance was sufficient	Partly endorsed. The information on the signal management activities carried out by Dr. Willmar Schwabe is acknowledged. However, the listed undesirable effects in monograph section 4.8 were not based mainly on EudraVigilance data. To make this more clear, the assessment report have been updated in sections 5.1 and 5.3. The listed undesirable effects are based on overall data from published clinical studies, supported by EudraVigilance data. In addition, regulatory practice has to be considered. Although monographs are not expected to substitute for SmPCs in MA/TUR applications, HMPC acknowledged the issues raised in an external query received by EMA (see HMPC Minutes for the meeting on 28-30 March 2023), in particular the choice of terms included in section 4.8 Undesirable effects of monographs vis-à-vis standards for adverse events terminology (use of MedDRA terminology and classification system). Therefore, it is the current view of HMPC that listed adverse reactions in monograph

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		to draw valid conclusions on possibly related adverse reactions of Rhodiola rosea extracts. From publicly available sources headache and nausea have been reported in the literature not only adverse events (AE, see table 6 of draft assessment report) but also as adverse drug reactions (ADRs) with a certain consistency [*Kasper and Dienel, 2017; Svedlund et al., 2017*]. Moreover, ADR terms indicative of allergic skin reactions have been mentioned [*Kasper and Dienel, 2017; Svedlund et al., 2017; Koop et al., 2020*]. As summarized by the HMPC in section 5.6 of the HMPC draft assessment report, the reported adverse events were mild, therefore we suggest adding this information to section 4.8 of the HMPC monograph. Regarding the gastrointestinal ADRs we suggest using the more comprehensive term "mild gastrointestinal complaints" and stating nausea as an example. Moreover we propose to add "mild hypersensitivity reactions" to section 4.8 of the monograph. This is in accordance with recent signal management activities carried out by Dr. Willmar Schwabe, resulting in the description of headache, gastrointestinal complaints and hypersensitivity reactions (all non-serious, mild) as undesirable effects with sufficient indication of causality in the Company Core Safety Information.	section 4.8 should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term (PT) level and as a general rule, the adverse reactions should be assigned to the most relevant system organ class (SOC) related to the target organ. The references in total do not allow to conclude on the severity of the adverse events. Therefore this will not be taken up into the monograph. Therefore section 4.8 of the revised monograph will mention: Nervous system disorders: Headache. The frequency is not known. Gastrointestinal disorders: Nausea, abdominal pain, diarrhoea. The frequency is not known. Skin and subcutaneous tissue disorders: Skin rash, itching. The frequency is not known.
4.8. Undesirable effects	AESGP	Comment: Compared to the first version from 2012, this revision includes additional information regarding possible undesirable effects of Rhodiola rosea preparations, which we consider to be symptoms of the underlying disease. Following undesirable effects are added:	See above.

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		a) Nervous system disorders: Headache, nervousness, insomnia, dizziness b) Gastrointestinal disorders: Nausea, vomiting Rational: As described in the draft assessment report of the Rhodiola rosea monograph, the undesirable effects are mainly based on an evaluation of the adverse events listed in the Eudravigilance data base. In the following we present an exemplarily performed analysis of the EudraVigilance data analysis system (EVDAS) and the accessible and cited literature regarding the undesirable effect "headache" caused by Rhodiola rosea preparations. Analysis of the EudraVigilance data analysis system (EVDAS) From the EVDAS and the line listings, no causal relationship between the intake of a Rhodiola rosea product and headache can be derived. Compared to the sales figures, which are limited to Germany and Austria only, the number of four reports from the query line listings is very low. The same applies to the EVDAS, in which thirteen reports can be found, which however refer to various Rhodiola rosea preparations and were also reported, amongst others, from the UK and Sweden. The associated CIOMS reports also do not provide any relevant additional information. Out of the thirteen reports, additional comedications can be found in seven. This comedication could also be responsible for the occurrence of	

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		headache. According to the assessment report, only those cases were evaluated from the EVDAS in which only the Rhodiola preparation was taken, so that only four cases can be used for the evaluation. Analysis of the cited literature Two publications (Kasper & Dienel 2017; Lekomtseva et al. 2017) are cited in the assessment report, from which the following statement is derived: "Adverse events with possible causal relationship should be included in the monograph". When reviewing the full texts of the publications, there is mentioned in the introduction that headache can also occur as a symptom in the underlying disease (burn-out or chronic fatigue). In contrast, in both publications "nervous disorders" are stated as adverse reactions, but a further specification of the adverse reactions "nervous disorders" is missing. Therefore, the proportion of headaches in this population is unknown, and if headaches occurred, they may have been a symptom of the underlying disease. Kasper and Dienel are more specific when they say: "A causal relationship with the study drug was rated "possible" in 5/46 (10.9%) subjects who reported head pressure, light-headedness, nausea, feeling irritated, and eye swelling. ..." However, an exact description of the adverse reactions is missing. In addition, "head pressure" and "light headedness" are not identical to "headache." Additionally, the cited study of De Bock et al. 2004 with twelve patients describes headache (with unclear wording) in	

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		one or two patients. In our opinion, the number of patients is too low to be representative. Based on this analysis, the recommendation to include "headache" in the product information under side effects cannot be substantiated either based on the EVDAS data or on the literature cited in the assessment report. There are indeed references in the literature to the occurrence of neurological and/or gastrointestinal side effects when taking Rhodiola preparations. However, a causal relationship with the intake is unclear. Therefore, there is no clear evidence for "headache" as an undesirable effect of Rhodiola rosea preparations. Furthermore, referring to the comments on section 4.8 of the HMPC assessment report no new evidence about adverse drug reactions (i.e., adverse events with suspected causal relationship) of Rhodiola rosea extracts became available since the compilation of the HMPC monograph from publicly available sources. Regarding the reports from Eudravigilance, it remains unclear how the conclusion was drawn that headache, nervousness, dizziness and insomnia are considered to be adverse reactions of Rhodiola rosea with reasonable suspicion of causality. A thorough causality assessment based on well documented cases is crucial here, since the reported symptoms may be manifestations of the indication for which the Rhodiola preparations were used. Since no information was provided about the signal detection and validation process, it seems that merely adverse event terms from cases without other co-medication were adopted	

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		into section 4.8 of the monograph. It may be questioned whether the overall reporting quality of the ICSRs in Eudravigilance was sufficient to draw valid conclusions on possibly related adverse reactions of Rhodiola rosea extracts. As summarized in section 5.6 of the HMPC draft assessment report, the reported adverse events were mild, therefore we suggest at least to add "mild" to section 4.8 of the HMPC monograph. It is essential to examine if the named undesirable effects are rather symptoms of the underlying disease, in this case "stress". As Rhodiola rosea preparations are indicated "for the relief of symptoms of stress, such as fatigue and exhaustion" and headache, nervousness, insomnia, dizziness, nausea and vomiting are well known symptoms of stress [Anghelescu et al. 2018, Lohmann-Haislah 2012] we would like to note that the listed undesirable effects may rather be symptoms of the underlying disease than undesirable effects. Proposed change (if any): As by definition symptoms of the disease are not undesirable effects, we recommend retaining the existing wording. "None known. If adverse reactions occur, a doctor or a qualified health care practitioner should be consulted." Or at least we propose the following wording:	

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		"Mild nervous system disorders and mild gastrointestinal disorders may occur. The frequency cannot be estimated from the available data. If adverse reactions occur, a doctor or a qualified health care practitioner should be consulted."	
4.8.	KOOP Phyto	Comment: Following undesirable effects were added to the draft monograph: • Nervous system disorders: Headache, nervousness, insomnia, dizziness • Gastrointestinal disorders: Nausea, vomiting We assume that the named undesirable effects are symptoms of the underlying disease "stress", which is the therapeutic indication of Rhodiola rosea preparations. Rational: The Undesirable effects newly added to 4.8. in the new draft monograph are well known and typical symptoms of the disorder treated with the medicine, as is demonstrated by respective explanations on the web pages of two renowned institutions in the field, the Mayo Clinic and the UK NHS. Furthermore, these symptoms of stress are also well described in the publication of Anghelescu et al. 2018 [3]. Per definition „Undesirable effects" are effects of the treatment, i.e. reactions on the treatment. The lack of a	See above.

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		reaction on the treatment, i.e. of an effect, can therefore, by definition not be an undesirable effect. Accordingly, symptoms of the disorder treated with the medicine, which occur during treatment, are indicating a lack of efficacy of the treatment. This lack of efficacy is not an effect of the treatment and therefore also not an undesirable effect of the treatment. Proposed change (if any): We therefore call for the retention of the current wording: "None known. If adverse reactions occur, a doctor or a qualified health care practitioner should be consulted."	
5.3. Preclinical safety data	KOOP Phyto	Comment: "Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended, unless necessary for the safe use of the product. Data on adequate tests on reproductive toxicity, genotoxicity and carcinogenicity are not publicly available." Contrary to the wording, public results of reproductive toxicity, genotoxicity and carcinogenicity are published. The SmPC of the authorized herbal medicine Vitango® [4] in Germany describes under 5.3 Preclinical safety data: "The AMES test showed no evidence of a relevant mutagenic potential of the medicinally active ingredient.	Monograph: Not endorsed. The data regarding the medicinal product Vitango are confidential data and not publicly available. Therefore they cannot be presented and assessed in the assessment report and consequently not be included in the monograph. Assessment report: Not endorsed. The LD50 is considered not relevant for the safe medicinal use of Rhodiola.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Studies with dry extracts of Rhodiola rosea rootstock with roots in rats and rabbits showed no evidence of maternal toxicity and/or teratogenic potential up to oral doses of 2700 mg/kg/d. Studies on postnatal development after pre- and postnatal exposure are not available. Studies in animals are inadequate with respect to carcinogenicity." [4] (translated from German to English). Furthermore, toxicity is described in a review article of Brown et al. 2002 [5]: "R. rosea has a very low level of toxicity. In rat toxicity studies, the LD50 (lethal dose at which 50 percent of animals die) was calculated to be 28.6 ml/kg, approximately 3,360 mg/kg. The equivalent rhodiola dosage in a 70 kg man would be about 235 gm or 235,000 mg. Since the usual clinical doses are 200-600 mg/day, there is a huge margin of safety." [5] Proposed change (if any): "Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended, unless necessary for the safe use of the product. In vitro and in vivo data do not indicate any reproductive toxicity, genotoxicity or carcinogenicity." Proposed change in the Assessment Report: We propose to add the preclinical data described in [4] into the assessment report under Chapter 3.3.3 as follows: "A	

Section number and heading	Interested party	Comment and Rationale	Outcome
		publicly available SmPC describes that an AMES test showed no evidence of a relevant mutagenic potential of the medicinally active ingredient." We further propose to add the preclinical data described in [4] and [5] into the assessment report under Chapter 3.3.1 single-dose toxicity as follows: "Studies with dry extracts of Rhodiola rosea rootstock with roots in rats and rabbits showed no evidence of maternal toxicity and/or teratogenic potential up to oral doses of 2700 mg/kg/d". [4] "In rat toxicity studies, the LD50 (lethal dose at which 50 percent of animals die) was calculated to be 28.6 ml/kg, approximately 3,360 mg/kg." [5]	

AESGP references:
References (references not mentioned in the HMPC reference list are printed in bold)

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[4] SmPC Vitango®

[5] Brown R, Gerbarg P, Ramazanov Z. Rhodiola rosea - A Phytomedicinal Overview. HerbalGram 2002;56:40-52

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