European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS ON DRAFT COMMUNITY HERBAL MONOGRAPH ON *RHEUM PALMATUM* L., AND *RHEUM OFFICINALE* BAILLON, RADIX EMEA/HMPC/189624/2007

Table 1: Organisation(s) providing comments on the draft Community herbal monograph on *Rheum palmatum* L. and *Rheum officinale* Baillon as released for consultation on 5 July 2007 until 15 October 2007.

	Name of organisation or individual
1	The European Scientific Cooperative on Phytotherapy (ESCOP)
2	The Association of the European Self-Medication Industry (AESGP)

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Table 2: Discussion of comments

GENERAL COMMENTS TO DRAFT DOCUMENT
No comments

SPECIFIC COMMENTS ON TEXT		
SECTION TITLE		
Paragraph no.	**Comment and Rationale**	**Outcome**
4.4 Special warnings and precautions for use	The remarks dealing with cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, corticosteroids or liquorice root should only be mentioned under section 4.5 “Interactions with other medicinal products”, since this is a description of interactions. If the remark stays here, then the wording in 4.5 is preferred.	According to the guideline on summary of product characteristics of October 2005 cross-refers are possible and sometimes recommended. The wording in this chapter describes the precaution which should be taken (consult a doctor when taking these medicinal products) and in chapter 4.5 the interaction is described.

4.6 Pregnancy and lactation	The wording of the ESCOP monograph is proposed: "Experimental studies, as well as many years of experience, do not indicate undesirable or damaging effects from anthranoid laxatives during pregnancy or on the foetus when used at the recommended dosage. However, in view of experimental data indicating a genotoxic risk for several anthranoids (e.g. aloe-emodin), avoid during the first trimester or take only under medical supervision."	Use is not recommended during pregnancy because the data for rhubarb are insufficient and experimental data indicating a genotoxic risk for several anthranoids. There are no investigations on reproductive toxicity and in addition there are no clinical data available. Like senna, rhubarb mainly contains dianthron-glycosides, cascara and also frangula and aloe mainly contain 10-glycosyl-anthrones, anthrachinon- and anthron-glycosides. The risk of hydrolysis in aglycones and consequently systemic absorption in the gastrointestinal tract is higher for the anthrachinon- and anthron-glycosides than for the dianthron-glycosides due to the different chemical structures. The amount of aglycones represents the possible genotoxic risk. Even for this reason senna and rhubarb seem to be more appropriate for sensitive patient groups like pregnant women than cascara, frangula and aloe. However only for a specified senna extract the use can be tolerated during the second and third trimester, because special investigations are available.

4.9 Overdose	The sentence "Chronic ingested overdoses of anthranoid containing medicinal products may lead to toxic hepatitis," should be deleted. There are two doubtful reports on senna preparations and maybe one for cascara. This with cascara was believed to be associated with cholestatic hepatitis. The herbal preparation was not investigated and considering the medical history of the patient (paraplegia of the lower body, prior cholecystectomy for gallstones, moderate use of alcohol and co-medication of amitriptyline, cimetidine and baclofen) a causal relationship is questionable. The comment by Breuers et al. may describe the situation best: "The worldwide use and abuse of senna alkaloids (!!) and lack o reports on hepatoxicity prompt us to speculate that the hepatitis in our patient was due to a non-predictable type II reaction in an unusually susceptible person". Furthermore the toxic liver damage has never been observed in routine toxicity studies with senna pods, sennosides or emodin when using high oral dosages. Therefore it has to be asked how the approved SPCs of other active substances (of herbal or chemical defined origin) describe these very rare events of non-prectictable type II reactions which have been described in the literature for a very high number of different active substances.	We agree that concerning the cascara case report a causal relationship is unlikely according to the Roussel UCLAF causality assessment method (RUCAM Score). However, in case of the two reports on senna preparation a relationship must be assumed according to the RUCAM Score. In the case reported by Breuers et al. (1991) liver enzymes decreased rapidly after stopping the senna treatment and increased again after continuing the treatment. In the case reported by Vanderperren et al. (2005) the liver damage returned to normal after stopping the senna ingestion. A positive dechallenge and a positive rechallenge are serious signs for causality according to the WHO assessment of the relationship between an adverse event and the intake of a medicinal product. That the reactions were non-predictable type II reactions is only a speculation as Breuers stated himself. Rhubarb is also an anthranoid containing herbal substance and therefore we also point out the possibility of toxic hepatic reactions in this chapter for rhubarb. We only mentioned "toxic hepatitis" in this chapter and not as undesirable effect when rhubarb was used as recommended. This was discussed and concluded in the MLWP.

5.3 Preclinical safety data	The last but one paragraph should be reworded as follows: "Long-term studies over 2 years on male and female rats with a senna extract or senna pods gave no evidence of carcinogenic activity. In addition, long-term studies with emodin on rats of either gender did not reveal any relevant differences in the tumour ratio between controls and treated animals."	We agree to include the following sentence: "A long-term study over 2 years on male and female rats with a senna pods preparation (anthranoid-containing herbal substance as well) gave no evidence of carcinogenic activity." Concerning the long-term studies with emodin the monograph reports the results of the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services concerning emodin. For female rats and male mice the evidence of carcinogenic activity was equivocal.

5.3 Preclinical safety data	In the last paragraph the sentence "Further investigations are needed…" should be excluded and should be replaced by the sentence: "There is no carcinogenic risk from rheum when used as recommended as an OTC laxative." The first reported positive responses from in vitro experiments on several anthraquinones could not be confirmed by long-term in vivo studies on rodents. Therefore, it can be concluded that a carcinogenic risk does not exist. There is also no evidence of any carcinogenic risk from several human studies and the long-lasting worldwide experience with anthraquinone laxatives, with the exception of one questionable study conducted by Siegers et al. Siegers only concluded that because of a higher relative incidence of Pseudomelanosis coli (PMC) in patients with abnormal changes in the colorectal mucosa laxative abuse is basically responsible for that. The results in the retrospective part of the study from Siegers do not allow drawing the conclusion that laxative abuse generates colorectal cancer. The assumption made that the almost equal amounts of relative incidences of PMC in patients without abnormal mucosal changes and those with carcinoma could be explained by uncomplete documentation is merely speculative. In the prospective part of the study of Siegers the conclusion is made on the basis of the higher relative incidences of PMC in patients with abnormal changes of the mucosa that laxative abuse is the cause of these mucosal changes. At the same time it is said that the incidence of adenomas and carcinomas is age-dependent: In this study the incidence of adenomas and carcinomas in elder patients was higher than in younger patients. It could be argued that there was a higher percentage of younger subjects in the group without abnormal changes of the mucosa (a precise age distribution in the different subgroups is missing in the publication). The increased occurrence of abnormal changes of the colorectal mucosa in the other subgroups could then be a function of age and other factors resulting thereof and not be related to laxative abuse. From a significant correlation between changes of the mucosa and PMC alone a causal correlation could not be deduced even more when a pseudo-correlation could not be excluded. On the basis of the most recent favourable results of the carcinogenicity studies with senna pods which could be transferred to rheum, the FDA come to the assessment that there is no carcinogenic risk from senna when used as recommended as an OTC laxative.	As it is already stated in the assessment report we agree to add in the monograph the sentence: "The short-term use of rheum as recommended can be regarded as safe." Furthermore we agree to reword the first sentence in this paragraph and add "chronic": "Chronic laxative use as a risk factor in colorectal cancer (CRC) was investigated in some clinical trials…" We agree that the study of Siegers of al. has some short-comings. But the interpretation given in the comments also have short-comings. There could be a higher percentage of younger subjects in the group without abnormal changes of mucosa or there could not. As long as there are no further well designed studies available the carcinogenic risk of chronic use cannot assessed definitely.