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Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Rheum palmatum* L. and *Rheum officinale* Baillon, radix - Draft Revision 1 (EMA/HMPC/113700/2019)

Table 1: Organisations and/or individuals that commented on the draft revised European Union herbal monograph on *Rheum palmatum* L. and *Rheum officinale* Baillon, radix (EMA/HMPC/113700/2019) as released for public consultation on 15 October 2019 until 15 January 2020.

	Organisations and/or individuals
1	Wroclawskie Zaklady Zielarskie "Herbapol" S.A.; Poland
2	The Association of the European Self-Care Industry - AESGP

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	Antiviral activity of rhubarb and traditional topic use should be mentioned.	Endorsed, see below.

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
2.1.1	AESGP	Traditional topical use in case of inflammation in oral cavity and pharyngitis (see table 1 below) (Pyralvex pur. Fachinformation Österreich 2018). Rhubarb root according to Ph. Eur. is used. Active substance: Rheum palmatum L. or Rheum officinale Baillon or their hybrids or a mixture of these two species and/or their hybrids, radix Indication: Topical use in case of inflammation – 1. Inflammation of the oral and pharyngeal mucosa and gums 2. For mucosal defects in poor-fitting dentures 3. As an adjuvant in the treatment of pharyngitis only on doctor's orders Pharmaceutical form / Posology / Duration of use:	Partially endorsed. The product is mentioned in the assessment report. It is displayed in section "Information on relevant combination medicinal products marketed in the EU/EEA" as from the information available it is a combination product (*Rheum palmatum* L. / *Rheum officinale* (according to Ph. Eur.) plus *Rheum emodi*) However, it does not fall into the scope of the assessment report and monograph which is Rhei radix as described in the Ph. Eur. monograph as single active substance. No changes are justified for the monograph. .

Section number and heading	Interested party	Comment and Rationale	Outcome
		Adults and adolescents over the age of 12 year: Apply solution (after removal of dentures) to the inflamed areas 3 or 4 times a day with a brush. Regulatory status: Traditional use in Austria	
2.1.1	AESGP	Information on relevant combination medicinal products marketed in the EU/EEA: Pyralvex, a combination medicinal product with salicylic acid and rhubarb extract is approved in Austria 29.04.1950. Rhubarb root according to Ph. Eur. is used. Phytovir a combination medicinal product with rhubarb and sage extracts is approved in Austria 13.08.2009. Rhubarb root according to Ph. Eur. is used.	Endorsed.
2.1.2	AESGP	Information on products on the market outside the EU/EEA: Pyralvex, a combination medicinal product with salicylic acid and rhubarb extract is approved in Switzerland since 23.04.1941. Rhubarb root according to Ph. Eur. is used. Phytovir a combination medicinal product with rhubarb and sage extracts is approved in Switzerland since 26.04.2001. Rhubarb root according to Ph. Eur. is used.	Endorsed.
3.1.2	AESGP	In a direct pre-infection incubation assay different anthraquinones (i.e. emodin, emodin anthrone, emodin bianthrone and hypericin) were active against HSV-1 and HSV-2. The following general pattern of activity was found:	Endorsed.

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		hypericin greater than emodin bianthrone greater than emodin anthrone greater than emodin. Chrysophanic acid, aloe-emodin, and sennosides A and B did not possess any activity against any of the viruses tested (Andersen *et al*., 1991) at all.	
3.1.2	AESGP	Emodin, one of the active ingredients of rhubarb root Ph. Eur. and an active ingredient of Rheum tanguticum, was tested against HSV in tissue culture cells. Emodin was found to inhibit the replication of HSV-1 and HSV-2 at the concentration of 50 µg/ml with antiviral index of 2.07 and 3.53, respectively (Xiong, 2011).	Endorsed.
3.1.2	AESGP	Injection of an ethanolic extract of Chinese rhubarb in mice infected with HSV was as effective as acyclovir (Wang, 2003).	Not endorsed. The publication is only available in Chinese.
3.1.2	AESGP	Emodin, one of the active ingredients of rhubarb root Ph. Eur. and an active ingredient of Rheum tanguticum, was tested against HSV. Emodin was orally administered to infected mice were beginning at 24 h post-HSV exposures with dosages of 3.3 g/kg/day, 6.7 g/kg/day, and 11.3 g/kg/day, respectively, for 7 days. The emodin treatment increased the survival rate of HSV-infected mice, prolonged survival time and showed higher efficacy of HSV elimination from brain, heart, liver and ganglion, compared to the viral controls. The antiviral activity of emodin was found to be equivalent to that of acyclovir (Xiong, 2011).	Endorsed.
4.2. Posology and method of administration	*W.Z.Z. "Herbapol" S.A.*	The following information was introduced in section 'Duration of use' of the draft revised monograph: 'Not to be used for more than 1 week.'	Not endorsed. The assessment report explains that "the duration of use is limited to a maximum of one week […] to

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		Currently this section of the monograph states: 'Use for more than 1 - 2 weeks requires medical supervision.' The change in the maximum duration of use is not justified by the emergence of new scientific data. The safety of stimulant laxatives has not been disputed since the first publication of monograph in 2007. On the contrary, groups of European and American experts in recent publications have suggested the possibility of utilizing stimulant laxatives as a treatment for chronic constipation also with possible longer treatment course. Concept of intestinal neurologic damage due to anthranoid-containing medicinal products use has been questioned in stance of American Gastroenterological Association (AGA) published in 2013. It is important to note AGA underlined the evidence for efficacy in chronic constipation is strongest for osmotic and stimulant laxatives. French National Society of Coloproctology (FNSC) in 2018 supported position of AGA concerning safety of stimulant laxatives in the context of treatment chronic constipation. In the their guideline FNSC critically reviewed also other concerns regarding risks of this treatment modality including potential risk of carcinogenic effect. FNSC summarized available data with the recommendation that stimulant laxatives are now considered safe drugs and can be more easily prescribed as a second-line treatment of chronic constipation. We believe that the introduction of the proposed change in the monograph will argue with the current guidelines on therapy. It can also raise unreasonable concerns in patients if they receive a recommendation of longer therapy than 1 week from their	consider adverse effects of long-term misuse and also the potential genotoxicity". New pre-clinical data have been published for hydroxyanthracene derivatives. The HMPC has decided to consider the totality of data. The results are taken into account for all respective monographs on herbal substances containing hydroxyanthracene derivatives. Therefore and based on this new pre-clinical data the duration of administration is restricted to one week.

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		doctor. In our opinion, duration of use should be limited only in the context of self-treatment, but the monograph should leave the possibility of deciding on the length of therapy to the doctor, hence we believe that the wording in this section of the monograph should not be changed. We suggest the wording in section 'Duration of use' should be left unchanged as follows: 'Use for more than 1 - 2 weeks requires medical supervision.' References: 1. Bharucha A.E., Pemberton J.H., Locke G.R. Ill: AGA technical review on constipation. Gastroenterology 2013, 144:218-238. 2. Vittona V., Damonc H., Benezecha A. *et al*., for the SNFCP CONSTI Study Group: Clinical practice guidelines from the French National Society of Coloproctology in treating chronic constipation. Eur J Gastroenterol Hepatol 2018, 30:357-363.	
4.2.2	AESGP	A prospective, randomised, controlled, double-blind pilot study was performed to investigate the efficacy and tolerability of a cream with rhubarb extract. A total of 66 patients participated in the study, of whom 45 received rhubarb cream and 21 Zovirax cream (active ingredient aciclovir). The results of the study showed no statistically significant difference between the two study products. A clear trend to a better action of Zovirax cream was however seen for the first primary target criterion, the healing time in all cured patients. The mean healing time was 6.5±2.5 days (mean ± SD) in the Zovirax group (n=21) and 7.4±3.2 days in the rhubarb group (n=39). Due to the rather unsatisfactory results of this study, the study with rhubarb cream was interrupted after the first interim	Partially endorsed. The mono preparation study referred to in the introduction of Saller *et al.*, 2001 is mentioned in the assessment report but the combination study as such was not considered of relevance.

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		evaluation, and a combined preparation with rhubarb and sage extracts was developed for study (Saller, 2001) instead. The efficacy of a combined topical preparation with rhubarb and sage extracts, a single-agent preparation with sage extract and a reference treatment was investigated in a double-blind, comparative, randomised trial. A total of 149 patients participated, and 145 patients (111 female, 34 male) of whom 64 received the rhubarb-sage cream, 40 the sage cream and 41 Zovirax cream could be evaluated by intention-to-treat analysis. The dried rhubarb extract (23 mg/g) is a standardised aqueous- ethanolic extract according to the German Pharmacopoeia (DAB) with 4.0-6.0% hydroxyanthracene derivatives. The dried sage extract (23 mg/g) is an aqueous extract. The reference product was Zovirax cream (Zovirax(R) Creme) with the active ingredient aciclovir (50 mg/g). The mean time to healing in all cured patients was 7.6 days with the sage cream, 6.7 days with the rhubarb-sage cream and 6.5 days with Zovirax cream. There were statistically significant differences in the course of the symptoms; at the 1st follow-up visit, there was a significant advantage for Zovirax cream compared to sage cream for both parameters 'swelling' and 'pain', while at the 2nd follow-up visit, there was a significant difference in favour of the rhubarb-sage cream compared to the sage cream. The combined topical sage-rhubarb preparation proved to be as effective as topical aciclovir cream and tended to be more active than the sage cream (Saller, 2001). References:	

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		Andersen DO, Weber ND, Wood SG, Hughes BG, Murray BK, North JA. In vitro Virucidal Activity of Selected Anthraquinones and Anthraquinone Derivates. Antiviral Research 1991, 16:185-96. Pyralvex pur. Fachinformation Österreich 2018. Saller R, Büechi S, Meyrat R, Schmidhauser C. Combined herbal preparation for topical treatment of Herpes labialis. Forsch Komplementarmed Klass Naturheilkd. 2001, 8(6):373-82. Wang ZY, Xu B, Song YY, Wang GT, Xu HZ, Wang XF, Xue YL, Wang ZY, Yu XP. Inhibition effects of rhubarb ethanol extract on herpes simplex virus infection in vivo [in Chinese]. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 2003, 17:169–173. Xiong HR, Luo J, Hou W, Xiao H, Yang ZQ. The effect of emodin, an anthraquinone derivative extracted from the roots of Rheum tanguticum, against herpes simplex virus in vitro and in vivo. J Ethnopharmacol. 2011. 133(2):718-23.	