EUROPEAN MEDICINES AGENCY
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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Rheum palmatum* L. and *Rheum officinale* Baillon, radix

Final – Revision 1

Based on Article 10a of Directive 2001/83/EC (well-established use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)		*Rheum palmatum* L. and *Rheum officinale* Baillon
Herbal preparation(s)		Comminuted herbal substance or preparations thereof, standardised
Pharmaceutical form(s)		Standardised herbal substance as herbal tea for oral use.
First assessment	Rapporteur(s)	W Knöss
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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance

Rhubarb root consists of the whole or cut, dried underground parts of *Rheum palmatum* L. or *Rheum officinale* Baillon or of hybrids these two species or a mixture. The underground parts are often divided; the stem and most of the bark with the rootlets are removed. It contains not less than 2.2% of hydroxyanthracene derivatives, expressed as rhein ($C_{15}H_8O_6$, Mr 284.2), calculated with reference to the dried herbal substance according to European Pharmacopoeia (European Pharmacopoeia 9:0291).

Herbal preparations thereof have to be standardised to their amount of hydroxyanthracene derivatives, calculated as rhein.

Active constituents

Rhubarb contains a complex mixture of different hydroxanthracene derivatives. The amount is 3 to 12% depending on the method of determination. These hydroxanthracene derivatives mainly (60–80%) consist of mono- and diglycosides of 1,8-dihydroxyanthraquinones aloe-emodin, chrysophanol, emodin, physcion and rhein (Zhang *et al*. 1988), and only small amounts of the respective aglycones. Dianthrone glycosides (sennosides) are also present (10-25%). Oshio *et al*. (1974) isolated sennosides E and F besides the sennosides A, B and C from the rhizome of *Rheum palmatum* L. Also small amounts of anthrone glycosides depending on the time of harvesting and the conditions of drying are found. The level of the oxidised forms is maximal in the summer and almost nil in the winter (Blaschek *et al*. 2004, Hänsel *et al*. 1994, Van Os 1976, Chirikdjian *et al*. 1983, Engelshowe 1985).

Rhubarb also contains tannin constituents, such as gallotannins (ca. 5%), chromones, phenylbutanones and traces of volatile oil (Blaschek *et al*. 2004, Weiss 1990, Hänsel *et al*. 1999, Miyazawa *et al*. 1996).

Chemotaxonomical investigations have shown that the underground parts of *Rheum palmatum* L. or of *Rheum officinale* Baillon do not contain stilbenes such as rhaponticin (Engelshowe 1985). Other analytical investigations discovered several different stilbenes. Kubo and Murai (1991) isolated two stilbene glycosides, 4'-O-methylpiceid and rhaponticin, from a methanolic extract of the root of *Rheum palmatum*, which was purchased at a marketplace in Indonesia. Further investigations are necessary to clarify the analytic and the kind of herbal substances investigated whether these were not any falsifications (Blaschek *et al*. 2004) mostly with *Rheum rhapontium*. According to the European Pharmacopoeia it has to be shown that, the herbal substance does not contain rhaponticin (European Pharmacopoeia 9:0291).

- Herbal preparations

Rhubarb root is used as comminuted herbal substance.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

1.2. Search and assessment methodology

Literature search was done in medical and scientific databases as MEDLINE, National Centre for Biotechnology Information (NCBI), Cochrane Database of Systematic Reviews TOXLINE (date of search: August 2018) via PubMed, DIMDI and SciFinder.

Search engines used: Google

Scientific databases: PubMed, DIMDI, SciFinder

Medical databases: MEDLine, Cochrane Database of Systematic Reviews, EMBASE, BioMed Central

Toxicological databases: ToxLine

Pharmacovigilance resources: Vigilance central

Data from EU and non-EU regulatory authorities: World Health Organization; NTP Technical Report on emodin. Other resources: Historical literature according to list of references.

Assessor's comment

There are limited data for rhubarb root preparations compared to the more commonly used stimulant laxatives preparations of Aloe and Senna species. This report should therefore be read in conjunction with the assessment reports for Aloe barbadensis Mill. and Aloe (various species, mainly Aloe ferox Mill. and its hybrids) folii succus siccatus (EMA/HMPC/759585/2015) and Senna alexandrina Mill. (Cassia senna L.; Cassia angustifolia Vahl), folium and fructus (EMA/HMPC/228759/2016).

Note: For ease of reference, these are hereafter referred to as *Aloe barbadensis* Mill. (EMA/HMPC/759585/2015) and *Senna alexandrina* Mill. (EMA/HMPC/228759/2016).

Studies on relevant isolated hydroxyanthracene derivatives, in particular, relating to emodin, which are already discussed in the assessment reports on *Aloe barbadensis Mill.* (EMA/HMPC/759585/2015) and *Senna alexandrina Mill.* (EMA/HMPC/228759/2016) are not repeated in this assessment report; instead a reference to EMA/HMPC/759585/2015 or EMA/HMPC/228759/2016 is made, as appropriate.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Rheum palmatum L. or *Rheum officinale* Baillon or their hybrids or a mixture of these two species and/or their hybrids, radix	Herbal medicinal product for short-term use in cases of occasional constipation.	Herbal tea for oral use; Adults and children from 10 years: 1.65 g/150 ml boiling water	WEU, DE, authorised 1990, Standard Marketing Authorisation according to section 36 of the German Medicinal Products Act

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		1 cup of tea daily	

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was completed.

Information on relevant combination medicinal products marketed in the EU/EEA

A combination medicinal product with salicylic acid and rhubarb extract is approved in Austria and Germany for topical use (inflammation of the oral mucosa and the gums - stomatitis/gingivitis). Rhubarb root according to Ph. Eur. is used.

A combination medicinal product with rhubarb and sage extracts is approved in Austria for topical use (*Herpes labialis*). Rhubarb root according to Ph. Eur. is used.

A combination medicinal product with rhubarb (according to Ph. Eur.) and *Rheum emodi* is approved in Austria for topical use (inflammation of the oral/pharyngeal mucosa and gums; mucosal defects in poor-fitting dentures; adjuvant in the treatment of pharyngitis).

These specific combinations are not subject of this assessment on the use of Rhei radix as single active substance.

Information on other products marketed in the EU/EEA (where relevant)

Not applicable

2.1.2. Information on products on the market outside the EU/EEA

Combination medicinal products with salicylic acid and rhubarb extract as well as rhubarb and sage extracts (see above) are also approved in Switzerland for topical use.

2.2. Information on documented medicinal use and historical data from literature

Rhubarb has been medicinally used in China for many centuries and rhubarb root is mentioned in an early herbal book of the 27thcentury BC (Madaus 1938/1976). The Chinese Materia Medica (Zhu 1998) described the traditional use as follows: "Purging heat and loosening the bowels, used for retention of the feces and abdominal pain, fever with constipation and dysentery with inadequate discharge of the bowels; reducing heat in the blood and counteracting toxicity, used for hematemesis and epistaxis, inflammation of the eyes and swelling of the throat and gum due to heat in the blood; jaundice caused by damp-heat. Externally used for scalds and burns; eliminating blood stasis, traumatic injuries, haemorrhage from the upper gastrointestinal tract, appendicitis with abdominal pain, boils, sores and abscess".

From Madaus (1938/1976) it can be seen that Paracelsus (1494–1541) used rhubarb as a laxative and as a purgative for the gall, Lonicerus also indicated the use as a purgative of the liver and for fever in his herbal book from 1564 and the purgative effects were also described by Bock (1565) and Matthiolus (1626). Matthiolus also used rhubarb for dysentery with bloody diarrhoea, haematemesis and hypermenorrhoea. The use as a laxative and purgative, but also as an antidiarrhoeal agent was confirmed by von Haller (1755) and Weinmann (1745); Weinmann also used rhubarb as a tonic.

Hecker (1814) favoured the use for diarrhoea more than for constipation. He also used rhubarb as a tonic and styptic. The anti-diarrhoeal and styptic effects are only achieved by small doses (0.1-0.3 g), which shall inhibit fermentation process, gastric acid and mucus secretion and improve appetite (Madaus 1938/1976). This is confirmed by Weiss (1974) and Martindale (Todd 1967, Wade 1977), but the recommended dose in Martindale is 0.2–1 g: "Rhubarb is a mild anthraquinone purgative. It differs from other anthraquinone purgatives in that it exerts an astringent action after purgation; with small doses the astringent action predominates and rhubarb is therefore used as an astringent bitter and occasionally in the treatment of diarrhoea" (Todd 1967; Wade 1977).

Clarus (1860) (as cited in Madaus 1938/1976) and Weiss (1974) ascribed choleric properties to rhubarb.

Frerichs *et al.* (1927) indicated that rhubarb has a laxative effect when administered in repeated or in higher doses. Rhubarb is also used as a stomachic and to improve appetite, for gastrointestinal catarrh and liver and spleen diseases.

According to Madaus (1938/1976) rhubarb was used as a laxative, a stomachic and for liver and spleen diseases in Denmark. The bark of the root was used for cough and cold in Lithuania. In Austria rhubarb was used as a laxative and purgative, and in Hungary also a laxative.

The accepted historical use of rhubarb root led to the establishment of the German Kommission E Monograph (Kommission E 1993), the European Scientific Cooperative on Phytotherapy (ESCOP) monograph on rhubarb root (ESCOP 2003) and the WHO monograph (WHO 1999). German pharmacovigilance actions for anthranoid-containing laxatives including rhubarb root, which were intended as a framework for the safe use of hydroxyanthracene derivatives (HAD) containing herbal medicinal products (Bundesinstitut für Arzneimittel und Medizinprodukte 1996) were instigated in June 1996.

Table 2: Overview of historical data

Herbal preparation	**Documented use/Traditional use**	**Pharmaceutical form,** **Strength, Posology** **Duration of use**	**Reference**
Rheum palmatum L. or *Rheum officinale* Baillon or their hybrids or a mixture of these two species and/or their hybrids, radix	Constipation	Cut roots, powdered or dried extracts for teas, decoction, cold maceration or elixir. Liquid or solid forms of medication exclusively for oral use. 20-30 mg hydroxyanthracene derivatives daily, calculated as rhein. The correct individual dose is the lowest to achieve a soft formed stool.	Kommission E (1993)
Rheum palmatum L. or *Rheum officinale* Baillon or	For short-term use in cases of occasional	The correct individual dose is the smallest required to produce a comfortable soft	ESCOP (2003)

Herbal preparation	Documented use/Traditional use	Pharmaceutical form, Strength, Posology Duration of use	Reference
their hybrids or a mixture of these two species and/or their hybrids, radix	constipation.	formed motion. Adults and children from 10 years on: Preparations equivalent to 20-30 mg hydroxyanthracene derivatives, calculated as rhein, to be taken once daily at night.	
Rheum palmatum L. or *Rheum officinale* Baillon or their hybrids or a mixture of these two species and/or their hybrids, radix	Short-term use in occasional constipation.	The proper dosage is the smallest necessary to produce a soft stool. Daily dosage: 0.5-2.5 g taken directly or in a decoction; 0.5-2.5 ml 25% ethanol extract. Adults and children over 12 years: standardised daily dose equivalent to 20–30 mg hydroxyanthracene derivatives (calculated as rhein) taken at bedtime, or in two divided doses, one in the morning and one at bedtime.	WHO (1999)

2.3. Overall conclusions on medicinal use

The use of rhubarb root as a laxative for use in constipation is recognised and well documented in authoritative texts. On the basis of the products authorised in the European Union and with regard to an acceptable level of safety having been being demonstrated (see later sections), the 10 years of well-established use has been accepted for rhubarb root since the initial establishment of the Monograph in 2006 (see Table 3).

In view of the standardisation and the known mode of action of anthraquinone glycosides, the HMPC agreed to define the herbal preparation in the monograph by reference to the standardisation on these constituents known to be responsible for the therapeutic activity. In the posology, reference to a range for standardisation, which is based on the well-established use is mentioned.

The recommended dosage as a laxative for adults, elderly and adolescents over 12 years (20–30 mg hydroxyanthracene derivatives once daily at night) is supported by expert opinions and clinical investigations with other hydroxyanthracene-containing laxatives, notably preparations of senna and aloe (see assessment reports on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016) and "*Aloe*

barbadensis Mill." (EMA/HMPC/759585/2015)). Following the approach in these monographs to minimise the amount used, the range recommended is 20 – 30 mg hydroxyanthracene derivatives daily.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Comminuted herbal substance of *Rheum palmatum* L. or *Rheum officinale* Baillon or their hybrids or a mixture of these two species and/or their hybrids, radix	Short-term use in cases of occasional constipation.	Herbal tea preparation Daily dose: 20-30 mg hydroxyanthracene derivatives, calculated as rhein	Marketing authorisation in DE (1990)

3. Non-Clinical Data

This section should be read in conjunction with the assessment report for "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

Rhubarb root belongs to the stimulant laxatives.

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

3.1.1. Primary pharmacodynamics

Data on herbal preparations

Harima *et al*. (1994) measured sennoside A content in hot-water extracts from 17 varieties of rhubarb (details of the botanical nomenclature not provided) obtained from the Japanese market. The contents were between 0.4 and 18.8 mg/g extract. The authors also examined the respective cathartic effects (no information about the method available) of the different extracts in male mice. A weak correlation was recognised between the sennoside A content and the cathartic effects.

Data on hydroxyanthracene derivatives

Chirikdjian *et al*. (1983) isolated physcion diglycoside from rhubarb roots and showed that this compound had a laxative activity similar to physcion monoglycoside in mice when administered orally. With physcion diglycoside the onset of the purgative effect was observed 2 hours later than with physcion monoglycoside. Physcion itself showed no remarkable effect. Only higher doses (300 and 450 mg/kg b.w.) slightly increased the number of defaecations; stool consistency did not change.

Yagi *et al*. (1997) explored the mechanism involved in the synergistic purgative action of aloe-emodin anthrone and rhein anthrone, the active metabolite of sennoside C, a purgative constituent of rhubarb and senna. Aloe-emodin anthrone and rhein anthrone and their equimolar mixture, induced excretion of an approximately equal amount of faeces by intracaecal administration of 23.2 µmol/kg dose in mice (standard dose). The amount of wet faeces induced by aloe-emodin anthrone was less than those of rhein anthrone and the mixture. At the same dose, rhein anthrone and the mixture significantly stimulated large intestinal propulsion, though aloe-emodin anthrone had little stimulatory effect. At ½

dose, aloe-emodin anthrone and rhein anthrone decreased net water absorption, but could not reverse it to achieve net secretion. At this dose, the mixture significantly decreased net water absorption and reversed it into net secretion. These anthrones did not stimulate mucus secretion in the colon at less than ½ dose. The authors conclude that the synergistic purgative effect of aloe-emodin anthrone and rhein anthrone in mice results from synergistic stimulation of large intestinal transit and large intestinal water secretion.

Yagi and Yamauchi (1999) investigated the purgative effects of intracaecally administered rhein anthrone and anthraquinones such as aloe-emodin and chrysophanol isolated from rhubarb, emodin and rhein, and the possible synergistic effects of the anthraquinones with rhein anthrone in mice. The anthraquinones were less potent purgatives than rhein anthrone, but the equimolar mixture of aloe-emodin and rhein anthrone had synergistic potentiating effects. An equimolar mixture of other anthraquinones and rhein anthrone tended to potentiate the purgative activity.

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	**Posology**	**Experimental model**	**Reference**	**Main non-clinical conclusions**
Hydroxyanthracene derivatives				
physcion diglycoside physcion monoglycoside physcion	Oral administration 100, 200, 300 and 450 mg/kg b.w.	*In vivo* In mice	Chirikdjian *et al*. (1983)	Physcion diglucoside and monoglucoside shown to have similar laxative effect Onset of the purgative effect of diglucoside observed 2 hours later than with monoglycoside Physcion had limited effect; higher doses (300 and 450 mg/kg b.w.) slightly increased number of defaecations
rhein anthrone aloe-emodin anthrone	Intracaecal application 23.2 µmol/kg (standard dose)	*In vivo* in mice (22–32 g)	Yagi *et al*. (1997)	Synergistic purgative effect of aloe-emodin anthrone and rhein anthrone in mice resulting from synergistic stimulation of large intestinal transit and large intestinal water secretion
rhein anthrone aloe-emodin chrysophanol emodin rhein	Intracaecal application Chemicals suspended (5 ml kg^{-1}) in 1% aqueous Tween 80	*In vivo* In mice (22–32 g)	Yagi and Yamauchi (1999)	Anthraquinones were less potent purgatives than rhein anthrone, but the equimolar mixture of aloe-emodin and rhein anthrone had synergistic potentiating effects

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
				an equimolar mixture of other anthraquinones and rhein anthrone tended to potentiate the purgative action

3.1.2. Secondary pharmacodynamics

Antibacterial and antimycotic effects

Data on herbal preparations

Due to the content of tannin constituents, rhubarb preparations were used for diarrhoea, gastritis and enteritis and as a styptic (Blaschek *et al*. 2004, ESCOP 2003).

Blaszczyk *et al*. (2000) screened 56 dried Chinese plants for their antimycotic properties *in vitro*; 10% aqueous extracts were used. The extract of *Rheum palmatum* L. (radix and rhizoma) showed antimycotic activity against *Aspergillus fumigatus* and *Candida albicans* comparable to that of nystatin. The growth of *Geotrichum candidum* and *Rhodotorula rubra* was also inhibited, but to a lesser extent.

Cyong *et al*. (1987) screened *in vitro* extracts of 178 Chinese herbs for their antibacterial activity against Bacteroides fragilis, a major anaerobic microorganism in the intestinal flora in humans. Only rhubarb root extract (*Rheum officinale;* 70%THF extract) was found to have significant activity and the purified active substance was identified as rhein. Rhein also has potent activity against Candida albicans and weak activity against *Escherichia coli* and *Bacillus subtilis*. Negligible or no activity was shown against e.g. *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, and *Staphylococcus aureus*.

Bae *et al*. (1998) tested different herbal substances for their inhibitory effect on *Helicobacter pylori* (HP) and on the HP urease in vitro. HP was isolated from the gastric antrum of chronic gastric patients. HP also produces a vacuolating toxin and its toxicity may be potentiated by urease-mediated ammonia production. HP urease is considered to play critical roles in the pathogenesis of gastric and peptic ulcer. Therefore, eradication of this bacteria and inhibition of the HP urease seems to be important for the treatment. The water extract of *Rheum palmatum* rhizome very strongly inhibited the growth of HP at 1 mg/ml, but it has no inhibitory effect on the urease activity.

Antiviral effect

Data on herbal preparations

Sydiskis *et al*. (1991) tested the virucidal effects of hot glycerine extracts from *Rheum officinale, Aloe barbadensis, Rhamnus frangula, Rhamnus purshianus*, and *Cassia angustifolia* against herpes simplex virus type 1. All the plant extracts inactivated the virus. The active constituents in these plants were separated by thin-layer chromatography and identified as anthraquinones. Anthraquinone glycosides should be ineffective. The extract of *Rhamnus frangula* was completely virucidal after 15 min incubation with herpes simplex virus type 1. The ID_{50} was 0.35µg/ml whilst 0.75 µg/ml inhibited the replication to an amount of 90%. A 90% higher concentration was not cytotoxic against WI-38-cells and renal cells of monkeys. A purified sample of aloe emodin was prepared from aloin, and its effects on the infectivity of herpes simplex virus type 1 and type 2, varicella-zoster virus, pseudorabies virus, influenza virus, adenovirus, and rhinovirus were tested by mixing virus with dilutions of aloe emodin

for 15 min at 37°C, immediately diluting the sample, and assaying the amount of infectious virus remaining in the sample. The results showed that aloe emodin inactivated all of the viruses tested except adenovirus and rhinovirus. Electron microscopic examination of anthraquinone-treated herpes simplex virus demonstrated that the envelopes were partially disrupted. These results showed that anthraquinones extracted from a variety of plants are directly virucidal to enveloped viruses.

Hsiang *et al*. (2001) screened 31 herbs in five different preparations (cold aqueous, hot aqueous, ethanolic, acidic ethanolic, and methanolic extracts) for their antiviral activities. Seven extracts, which showed significant antiviral activities, were further investigated for their antiviral mechanisms *in vitro*. Ethanolic extract of *Rheum officinale* prevented the process of Herpes simplex attachment and penetration.

Data on hydroxyanthracene derivatives

Andersen *et al*. (1991) tested different anthraquinones (i.e. emodin, emodin anthrone, emodin bianthrone and hypericin) in a direct pre-infection incubation assay. These substances were mildly active against Vesicular stomatitis virus, vaccinia virus, Parainfluenza virus type 3, HSV-1 and HSV-2. The following general pattern of activity was found: emodin bianthrone>emodin anthrone>emodin. Chrysophanic acid, aloe-emodin, and sennosides A and B did not possess activity against any of the viruses tested.

Xiong *et al*. (2011) studied the effect of emodin, one of the active ingredients of rhubarb root Ph. Eur., against HSV in tissue culture cells. Emodin was found to inhibit the replication of HSV-1 and HSV-2 at concentration of 50 µg/ml with antiviral index of 2.07 and 3.53, respectively. It was orally administered to infected mice beginning at 24 hours post-HSV exposures with dosages of 3.3, 6.7 and 11.3 g/kg per day, respectively, for 7 days. The emodin treatment increased the survival rate of HSV-1 and HSV-2 infected mice, prolonged survival time and showed higher efficacy of HSV elimination from brain, heart, liver and ganglion, compared to the viral controls. The best results were obtained with the medium dosage groups. Toxicity was observed in the highest dosage group. The antiviral activity of emodin in the medium dosage group was found to be similar to that of acyclovir.

Studies in renal failure

Data on herbal preparations

Yokozawa *et al*. (1984, 1985, 1986 and 1987) examined the effect of orally administered aqueous extract of roots of *Rheum officinale* Baillon in rats with chronic renal failure induced by an adenine diet. The herbal preparation caused a marked decrease of blood urea nitrogen and creatinine, and a decrease of methyl-guanidine and guanidine-succinic acid levels. Hypocalcaemia, hyper-phosphataemia, and free amino acid patterns were also improved.

Zhang and Nahas (1996) studied the effect of orally administered aqueous extract of dry roots of *Rheum palmatum* (150 mg per day from day 30 to day 120, in drinking water) on the course of chronic renal failure in rats submitted to subtotal nephrectomy. Rhubarb treatment had no effect on the systemic hypertension. Rhubarb-treated rats had significantly less proteinuria when compared to the untreated group. Renal function was comparable in both groups, but the severity of glomerulosclerosis was significantly reduced in the treated group.

Yokozawa *et al*. (1997) administered an aqueous dry extract of rhubarb (*Rheum officinale* Baillon) 125 mg/kg b.w. per day orally to rats with diabetic nephropathy induced by subtotal nephrectomy and injection of streptozotocin for 80 consecutive days. High blood and urinary glucose levels were ameliorated. Furthermore, improvement of hyperlipidaemia, and accelerated excretion of urinary urea nitrogen and creatinine were observed. The changes were significant compared to untreated controls.

Because the herbal substance is used as an anticoagulant and haemostatic agent in Chinese medicine, Kosuge and Ishida (1985) tried to identify the anticoagulative principle of *Rheum palmatum* L. by a combination of partition, fractional precipitation and column chromatography on silica gel and plasma recalcification time determination in mice. D-catechin was identified as the anticoagulative principle. D-catechin has been also isolated from *Sanguisorba* and *Hypericum* species, although these herbal substances are commonly used as haemostatics in Chinese medicine. The clinical relevance concerning efficacy and safety has to be proven. Up to now, no adverse event dealing with a bleeding event has been reported during short-term use in cases of occasional constipation.

Other studies with herbal preparations

An extract of *Rheum palmatum* L. increased the sensitivity to paclitaxel at a concentration of 10 µg/ml and 50 µg/ml significantly whilst not to 5-fluorouracil in HeLa cells (human cervical carcinoma cell line). Paclitaxel is a MDR1 substrate whereas 5-fluorouracil is not such a substrate. Rhodamine123 was used to evaluate the MDR1-mediated transport. Rhodamine123 uptake by HeLa cells was significantly increased by the presence of rhubarb at 100 µg/ml. The authors concluded that the effect is mediated by an inhibition of MDR1 function in tumour cells and that the combination of anticancer drugs with some herbal extracts contributes to the enhancement of clinical outcomes in cancer chemotherapy (Takara *et al.* 2005; see also pharmacokinetic interactions).

Several Chinese plant extracts were tested to screen for pharmacological activities that could be relevant to the treatment of cognitive disorders. A simple and rapid enzyme essay on thin layer chromatography (TLC) plates has been developed for the screening of acetylcholinesterase and butyryl-cholinesterase inhibition in plant extracts. The hexane extract of *Rheum officinale* Baillon showed a clear activity whereas the methanolic and the chloroform extract showed no activity (Primschitz 2005).

Other studies with hydroxyanthracene derivatives

A cytotoxic anthraquinone glycoside, pulmatin, 1,8-dihydroxy-3-methyl-anthraquinone-1-O-ß-d-glycoside, and its congeners, chrysophanein and physcionin, have been isolated as minor components from a methanolic extract of the root of *Rheum palmatum*. These anthraquinone glycosides exhibited moderate cytotoxic activity against several types of carcinoma cells (HeLa epithelioid carcinoma cells, BT-20 human breast carcinoma cells). The authors also isolated two stilbene glycosides, 4'-O-methylpiceid and rhapontin. Therefore, falsifications of the herbal substance cannot be ruled out (Kubo *et al*. 1992).

Kazuhiro *et al*. (2000) reported on phytoestrogen properties of emodin isolated from an aqueous extract of the rhizome of *Rheum palmatum*. Emodin binds to the oestrogen receptor and activates transcription through oestrogen responsive elements (ERE). However, the exact mechanism is still unclear. The inhibition of casein kinase II (CKII) by emodin may play a role because this kinase phosphorylates serine-167 on the human oestrogen receptor, which results in increased oestrogen response element binding and transcriptional activation.

3.1.3. Safety pharmacology

There are no data for rhubarb root preparations.

3.1.4. Pharmacodynamic interactions

For interactions see section 5.5.4.

3.1.5. Conclusions

There are limited data for rhubarb root preparations.

The pharmacodynamic data available show a mild laxative effect in mice with rhubarb root preparations that supports the use in cases of constipation. It is generally assumed, by analogy with other HAD-containing laxatives, such as senna, that the mode of action is similar.

The postulated laxative effect is also supported by the pharmacological data, even though most of the data derive from investigations with isolated constituents of rhubarb and not with the preparation or the herbal substance itself. Pharmacological data obtained from other anthranoid-containing laxatives complete these scientific findings.

Emodin-9-anthrone is the most important metabolite that is produced by the bacteria of the large intestine. The mode of action is based on two mechanisms. Firstly, colonic motility is increased leading to a reduced transit time. Secondly, an influence on secretion processes by two concomitant mechanisms, namely the inhibition of absorption of water and electrolytes (Na^+, Cl^-) into the colonic epithelial cells (antiabsorptive effect) and the increase of the leakiness of the tight junctions and stimulation of secretion of water and electrolytes into the lumen of the colon (secretagogue effect), results in enhanced concentrations of fluid and electrolytes in the lumen of the colon.

These findings are based on investigations with different anthrones deriving also from other anthranoid-containing herbal substances, but the results of these investigations are not always consistent (see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

The phytoestrogen properties of emodin need to be confirmed and elucidated by further investigations.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Data on herbal preparations

There are no data for rhubarb root preparations.

Data on hydroxyanthracene derivatives

Detailed information concerning the metabolism and pharmacokinetic characteristics of anthranoid derivatives are available only in a few cases; there are no data for rhubarb root preparations (de Witte 1993). Most studies involve senna preparations and constituents thereof (see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016)".

Pharmacokinetic interactions

Takara et al. (2005) concluded an inhibition of MDR1 function in tumour cells by a rhubarb extract from *in vitro* investigations. However, rhodamine123, the substrate used is also transported by transporters for organic cations, and therefore it is not a selective substrate. It is not known whether the HeLa cell line expressed MDR1-gene in a constant way.

This might infer that rhubarb influences this transport system in some way but to date this observation is too weak to draw any conclusion concerning possible interactions.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

3.3.1. Single dose toxicity

Data on herbal preparations

In vivo studies of rhubarb root on single dose toxicity are not available.

3.3.2. Repeat dose toxicity

Data on herbal preparations

In vivo studies of rhubarb root on repeated dose toxicity are limited.

Yan *et al*. (2006) investigated the toxicity of total rhubarb (rhizomes of *Rheum palmatum* L.) anthraquinones (TRAs) on Sprague Dawley rats. TRAs were orally administered for 13 weeks. Twenty animals were randomly allocated into four groups. TRAs were dissolved in 0.5% sodium carboxymethylcellulose solution and each group was administered *per os* once daily for 13 weeks a dose of 0, 140, 794, 4500 mg/kg b.w.. That corresponds to a maximum human equivalent dose (HED) of 726 mg/kg. After that, rats were sacrificed under halothane anaesthesia and all main organs and glands were taken for histopathology studies. In the highest dose group, nephrotoxicity was discernible at 13 weeks. There was no clear morphologic change in the kidney of the control group, while in the TRAs tested group, swollen and denatured renal tubule epithelial cells were observed. The results of gene differential expression study indicated the TRAs affect mostly on the oxidative stress pathway, cell cycles, nutrients metabolism, thus caused renal tubule epithelial cells to be swelled and denatured in histopathology study. CYP1A1, which is regarded as a carcinogen-metabolising enzyme, was dramatically up-regulated and may account for the genotoxicity. Mitogen-activated protein kinase (MAPK) kinase 6 was identified to be the target gene which causes cell cycle arrest and proliferation inhibition and contributes to the nephrotoxicity in rats. However, the discernible nephrotoxicity was only observed at the high dose group. According to the authors, therapeutic dosage of TRAs is 420 mg per day, 7 mg/kg b.w. respectively, if one person weighs 60 kg. Therefore, the maximum dosage used in the experiment is 104 times the clinical dose (based on HED).

Data on hydroxyanthracene derivatives

Emodin

In 2001, the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services published a technical report on toxicology and carcinogenesis studies of emodin (NTP 2001).

For discussion and conclusions-see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

3.3.3. Genotoxicity

Data on herbal preparations

Limited genotoxicity studies for rhubarb root preparations are available.

Paneitz and Westendorf (1999) compared ethanolic extracts of different Rheum species with respect to their mutagenicity in the Salmonella/microsome assay with strains TA 98, TA 100 and TA 1537. The root extract of *Rheum officinale* Baillon was weakly mutagenic in strain TA 1537 even without metabolic activation at a dosage of 300 µg per plate and the effect was enhanced by addition of S9-mix, at dosage of 30 µg per plate. The authors concluded that the positive effect without metabolic

activation might be due to the content of aloe-emodin, which is the only direct-acting mutagenic anthraquinone present in Rheum species, whereas the enhancement of the mutagenic potency after addition of S9-mix is probably related to emodin.

In a dose of 5 mg per plate, an aqueous extract (1:6) of Rhei radix (no further specification is given) had a mutagenic effect on Salmonella typhimurium TA 98 following metabolic activation with S9-mixture. However, this effect was not obtained with *Salmonella typhimurium* TA 100. In a rec-assay with *Bacillus subtilis* for DNA-damage the same extract (6 mg per plate) gave a positive result. A methanolic (1:6) extract gave no response in the same tests. Sennoside B and rhein did not induce significant numbers of chromosomal aberrations or aberrant cells in bone marrow cells of Swiss mice (Committee for Veterinary Medicinal Products 1999).

Data on hydroxyanthracene derivatives

Emodin

In 2001, the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services published a technical report on toxicology and carcinogenesis studies of emodin (NTP 2001).

For discussion and conclusions-see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

3.3.4. Carcinogenicity

Data on herbal preparations

There are no data for rhubarb root preparations.

Data on hydroxyanthracene derivatives

Emodin

In 2001, the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services published a technical report on toxicology and carcinogenesis studies of emodin (NTP 2001).

For discussion and conclusions, see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

3.3.5. Reproductive and developmental toxicity

In vivo studies of rhubarb root preparations on reproductive toxicity are not available.

3.3.6. Local tolerance

There are no studies available regarding local tolerance.

3.3.7. Other special studies

There are no data for rhubarb root preparations.

3.3.8. Conclusions

There are limited data for rhubarb root preparations.

3.4. Overall conclusions on non-clinical data

There are limited data for rhubarb root preparations.

The findings are therefore based on investigations with different anthrones deriving from other anthranoid-containing herbal substances, but the results of these investigations are not always consistent (see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016)).

The use during pregnancy is contraindicated in the monograph because experimental data concerning a genotoxic risk of several anthranoids, e.g. emodin and aloe-emodin.

4. Clinical Data

This section should be read in conjunction with the assessment report for "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

4.1. Clinical pharmacology

For anthranoid-containing laxatives in general it is referred to the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Several investigations with different Chinese and Japanese herbal preparations have been reported, however, limited details are available for the preparations studied. The investigations with *Rheum palmatum* L. and *Rheum officinale* Baillon are summarised below.

Mitsuma *et al*. (1998) investigated the differences in cathartic actions of three different types of rhubarb: rhubarb A (produced in the Province of Sichuan, China), rhubarb B (*Rheum coreanum*, cultivated and processed in Japan), rhubarb C (tablets manufactured with the processed rhizome of *Rheum palmatum* from the Province of Qing-Hai, China). The three types were administered to 12 healthy volunteers for 3 days. Pharmacological effects were evaluated in terms of the number of bowel movements, bowel sounds, urinary volume and various blood chemical parameters. From the results, the authors concluded that the processed rhubarb (C), with a weaker cathartic action, was suitable for therapeutic use in patients with chronic renal failure.

4.1.2 Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Vyth and Kamp (1979) isolated rhein, aloe-emodin, emodin, physcion and chrysophanol from powdered root of rhubarb (no further specification is given) after oxidative hydrolysis. After oral administration of 65 mg or 200 mg of powdered root of rhubarb in 2 volunteers, rhein was found in human urine. The sample collected in the morning contained more anthraquinones than those collected at noon.

Zhu *et al*. (2005) compared the pharmacokinetic parameters of rhein administered by retention enemas with those of conventional oral dosing of rhubarb extract (aqueous extract of *Rheum officinalis* Baillon). The amounts of rhein, emodin, aloe-emodin, chrysophanol, physcion on the extract were 12.308, 1.337, 1.594, 1.204, 1.615 mg/g, respectively. Eight healthy male volunteers were enrolled in a prospective crossover study. All subjects received a single dose of rhubarb extract (50 mg/kg corresponding to about 54 mg hydroxyanthracene derivatives, body weight 60 kg) on two separate occasions, once orally, once by a retention enema. Rhein plasma concentration was measured by

HPLC. The plasma rhein levels rapidly rose after oral administration and then slowly declined. The curve fitted a two-compartment model well. Concerning the retention enema administration, the distribution of rhein reached its C_{max} at 53.46±33.10 minutes after a rapid ascent, characteristic of fast absorption. The distribution and elimination of the plasma rhein followed a one-compartment model. The C_{max}, $AUC_{0-\infty}$, AUMC (area under the first moment of plasma concentration-time curve) were significantly higher in oral administration, while Vd (volume of distribution) of rhein after oral administration was significantly lower. However, no statistically significant differences between the two treatments for any other pharmacokinetic parameters such as T_{max}, $t_{1/2}$, $MRT_{0-\infty}$ (mean residue time), CL (body clearance) were observed. Two subjects reported mild to moderate diarrhoea, which resolved without treatment. No clinically meaningful changes in examinations findings or vital signs were observed.

4.2. Clinical efficacy

Laxative effect

There is a limited number of clinical studies with rhubarb root as a single active ingredient–see below. However, the clinical efficacy is generally assumed from the well-established and documented medicinal use in authoritative texts and monographs as reflected in the Assessment reports supporting the European Union herbal monographs for "*Aloe barbadensis* Mill." (EMA/HMPC/759585/2015) and "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

Rhubarb acts within 8 to 12 hours due to the time taken for transport to the colon and metabolisation into the active compounds (ESCOP 2003). The content of tannin agents may possibly counteract the laxative effect of the anthraquinones and rhubarb is therefore considered a milder laxative than other anthraquinones.

Other effects

In a publication on testing a combination of rhubarb extract/ sage extract against sage extract alone and acyclovir for topical treatment of *Herpes labialis* Saller *et al*. (2001) make reference to an unpublished prospective, randomised, controlled, double-blind screening study (Meyrat & Büechi 1999; not available as reference) which was performed to investigate the efficacy and tolerability of a cream with rhubarb extract (not further specified). A total of 66 patients participated in the study, of whom 45 received rhubarb cream and 21 acyclovir cream. The authors report that results of the study showed no statistically significant difference between the two study products. The mean healing time was 6.5±2.5 days (mean±SD) in the acyclovir group (n=21) and 7.4±3.2 days in the rhubarb group (n=39).

The original study is not publicly available to allow assessment and to draw any conclusions.

4.2.1. Dose response studies

There are no dose-finding studies available for rhubarb root preparations.

4.2.2. Clinical studies (case studies and clinical trials)

Constipation

The available clinical investigations of rhubarb root evaluate its efficacy in combination preparations only. There are no controlled clinical studies available.

4.3. Clinical studies in special populations (e.g. elderly and children)

Children

There are no available systematic clinical data, which evaluate the use of rhubarb root as a laxative in children.

In China, herbal treatment of neonatal jaundice (NNL) has been practiced for a long time. Even to-date, a variety of herbal ingredients, including *Rheum officinale* (Da-huang), is prescribed to jaundiced infants, often in combination with modern treatment such as phototherapy and exchange transfusion. Their efficacy and safety have not, however, been systematically tested. No data are available on the exact preparations, the doses administered and the positive and negative outcomes (Fok 2001).

Conclusion on clinical studies in special populations

The data available are not sufficient to show the efficacy and safety of rhubarb root to treat constipated children, if change of nutrition and increase of daily fibre intake is not effective. The Cochrane (Gordon *et al*. 2013) review showed a vast amount of data regarding the use of osmotic laxatives whereas data on rhubarb root preparations are lacking.

Other effects

From 1989 to 1992, 151 chronic renal failure (CRF) patients with initial serum creatinine level of 328±92 mmol/l (3.7 mg/dL) were enrolled to compare the clinical effectiveness of rhubarb (*Rheum palmatum* L.), an ACE inhibitor as well as a combined regimen of rhubarb and ACE inhibitor, captopril, in a prospective open-label trial. All patients were also kept on a low-protein (0.6 g/kg per day) and low-phosphorus (10 mg/kg per day) diet. After follow-up of an average of 32.5 months (range, 15 to 62), uraemic symptoms of nausea and anorexia in most of the treated patients improved. The frequency of reaching a serum creatinine greater than or equal to 8 mg/dL was 54.3% for the captopril group, 25.9% for the rhubarb-treated group, and 13.1% for those receiving the combined regimen. The slope of the reciprocal serum creatinine versus time in months suggests that the progression rate of renal failure in the groups of patients treated with rhubarb was slowed down. Rhubarb also lowered the cholesterol and triglyceride levels of CRF patients. The authors concluded that this effect might be helpful in preventing the development of glomerulosclerosis (Peng *et al*. 2005, Li and Wang 2005, Li 1996).

Four hundred and sixty-five (465) patients with upper gastrointestinal bleeding took *Rheum palmatum* L. (Da-huang) up-to a maximum of 15.4 g herbal substance. Blood was not found any more in the faeces after 1.5 days in 97% of the patients. The data are limited because the original Chinese publication is not available (Blaschek *et al*. 2004).

Zhou and Jiao (1990) have studied alcohol extracts of tablets of rhubarb for 10 years. Three hundred and twelve (312) patients with gastric and duodenal ulcer bleeding were divided into three groups, namely, *Rheum officinale* Baillon, *Rheum palmatum* L. and *Rheum tanguticum* Maxim ex Balf. By using double-blind measurement of effect, the efficiencies of the groups appeared to be 90.7%, 93.7%, and 92.8% respectively. The time taken for the stool occult blood changing from positive to negative was 57.1, 53.4 and 56 hours, respectively. The differences were not significant ($p>0.05$). The data are also limited to the details in the English abstract because the original publication is available in Chinese only.

4.4 Overall conclusions on clinical pharmacology and efficacy

There are no recent clinical studies that evaluate rhubarb root alone and not in combination with other laxatives in a representative population in the indication, constipation, available.

The postulated laxative effect is mainly based on the pharmacological data, experts' opinions and clinical experience.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

There are no clinical safety studies on rhubarb root preparations.

Children

There are no studies on the use of rhubarb root preparations in children.

It is referred to the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016) for discussion on senna use in children.

5.2. Patient exposure

There are no data for rhubarb root preparations.

5.3. Adverse events, serious adverse events and deaths

As for all anthranoid-containing laxatives, major symptoms of overdose/abuse are griping pain and severe diarrhoea with consequent losses of fluid and electrolyte, which should be replaced. Diarrhoea may cause potassium depletion, in particular. Potassium depletion may lead to cardiac disorders and muscular asthenia, particularly where cardiac glycosides, diuretics or adrenocorticosteroids are being taken at the same time.

Treatment should be supported with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly.

Furthermore, chronic ingestion of overdoses of anthranoid-containing medicinal products may lead to toxic hepatitis (see below).

Hepatitis

For anthranoid-containing laxatives in general it is referred to the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016); cases of hepatotoxicity are reported, related to the chronic overdose ingestion.

There are no specific reports associated with the use of mono-preparations of rhubarb root.

Yuen *et al*. (2006) studied the clinical outcome of traditional Chinese medicine (TCM)-induced hepatotoxicity in chronic hepatitis B patients. Forty-five chronic hepatitis B patients in 2004 with liver dysfunction requiring hospitalisation in the Queen Mary Hospital, The University of Hong Kong in Hong Kong, were prospectively screened for traditional Chinese medicine intake. The inclusion criteria were HBsAg positivity, intake of TCM within 6 months prior to admission, elevated bilirubin levels of more than two times upper limit of normal or elevated level of at least one of the liver enzymes. Patients with other possible cause for hepatotoxicity, e.g. any other virus hepatitis, alcohol intake, hepatotoxic medication were excluded. Seven patients had liver derangement attributable to the intake of TCM. Possibly hepatotoxic components were identified by extensive literature research. *Rheum palmatum* L. and *Cassia obtusifolia* L. were identified to be potential hepatotoxic components, though these components were taken together with more than ten other Chinese herbal substances. In view of this, it is not possible to definitively establish causality.

Nephritis

For anthranoid-containing laxatives in general it is referred to the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

There are no specific reports associated with the use of rhubarb root preparations.

Melanosis coli

For anthranoid-containing laxatives in general it is referred to the assessment report on "Senna alexandrina Mill." (EMA/HMPC/228759/2016).

Willems *et al*. (2003) described a case of melanosis coli, which occurred in a 39-year old liver transplanted patient, who took an over-the-counter product containing aloe, rheum and frangula. The typical brownish pigmentation of the colonic mucosa developed in a period of ten months. The anthranoid medication was stopped and follow-up colonoscopy one year later showed normal looking mucosa once more. However, in contrast to previous examinations, a sessile polypoid lesion was found in the transverse colon. Histology showed tubulovillous adenoma with extensive low-grade dysplasia. Since there had been preliminary reports suggesting a possible role of anthranoid-containing laxatives in the development of colorectal adenomas and cancer, the authors discouraged their use.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Elderly

No data available.

5.5.1. Use in children and adolescents

The use in children is contraindicated (see section 5.5.2).

5.5.2. Contraindications

Rhubarb root preparations should not be used by patients with known hypersensitivity to rhubarb.

Furthermore, as with all anthranoid-containing laxatives, rhubarb root preparations should not be used in cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis), abdominal pain of unknown origin, severe dehydration states with water and electrolyte depletion (Kommission E 1993, Bundesinstitut für Arzneimittel und Medizinprodukte 1996).

Rhubarb root preparations are contraindicated in children under 12 years of age, because of lack of data regarding constipation in children and general safety concerns.

The use of preparations containing rhubarb root is contraindicated in pregnant and lactating women, because the potential for carcinogenicity has not been fully excluded and because after administration of anthranoids, active metabolites, such as rhein, were excreted in breast milk in small amounts.

5.5.3. Special Warnings and precautions for use

Rhubarb root preparations should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents (Kommission E 1993).

See the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016) for discussion on long-term effects of the use of stimulant laxatives.

It is not clear from available evidence if the use of stimulant laxatives for longer than a brief period of treatment leads to dependence requiring increasing quantities of the medicinal product, an atonic colon with impaired function and aggravation of the constipation. However, as a precaution, the long-term use of stimulant laxatives should be avoided.

The following warnings and precautions for use are recommended:

- Long-term use of stimulant laxatives should be avoided, as use for more than a brief period of treatment may lead to impaired function of the intestine and dependence on laxatives.
- If laxatives are needed every day the cause of the constipation should be investigated.
- Rhubarb root preparations should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.
- Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, should consult a doctor before taking rhubarb root concomitantly.
- Like all laxatives, rhubarb root preparations should not be taken by patients suffering from faecal impaction and undiagnosed, acute or persistent gastro-intestinal complaints, e.g. abdominal pain, nausea and vomiting, unless advised by a doctor, because these symptoms can be signs of potential or existing intestinal blockage (ileus).
- In line with the guidance for the related HAD preparations, when preparations containing rhubarb root are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces (see assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016)).
- Patients with kidney disorders should be aware of possible electrolyte imbalance.

5.5.4. Drug interactions and other forms of interaction

Chronic use or abuse of rhubarb root preparations may lead to hypokalaemia like the abuse of all anthranoid-containing laxatives (see assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016). This hypokalaemia and the increased loss of potassium may increase the activity of cardiac glycosides and interfere with the action of antiarrythmic agents (interaction with antiarrhythmic medicinal products, which induce reversion to sinus rhythm, e.g. quinidine) and medicinal products inducing QT-prolongation. Concomitant use with medicinal products inducing hypokalaemia (e.g. diuretics, adrenocorticosteroids and liquorice root) may aggravate electrolyte imbalance.

The hypokalaemia can be aggravated by thiazide diuretics and by loop diuretics in particular, but not by potassium-sparing diuretics such as amiloride. However, the patient cannot always differentiate between the different kinds of diuretics. All kind of diuretics should therefore be mentioned. Because the mechanism, which this interaction is based on, is described in the SmPC, the doctor can decide whether the concomitant use of a given diuretic is a concern or not.

5.5.5. Fertility, pregnancy and lactation

There are no data for mono-preparations of rhubarb root used in pregnancy.

As with other HAD preparations, in theory, it is possible that reflex stimulation might occur, involving not only the colon but also uterine muscles and then might lead to the development of hyperaemia in the pelvic region and to miscarriage as a result of neuromuscular stimulation of uterine muscles (See assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016)).

Lactation

There are limited data on the use of rhubarb root preparations and possible excretion of metabolites into breast milk.

Faber and Strenge-Hesse (1988) investigated the excretion of rhein, active metabolite of sennosides, in 100 breast milk samples of 20 post-partum women after intake of a standardised senna laxative commercial final product, which also contained seeds of *Plantago ovata* as bulk substances. After daily dosing of 5 g of the senna laxative containing 15 mg sennosides for 3 days, the rhein concentration in milk samples from every lactation during 24 hours post-dose varied between 0 and 27 ng/ml with values below 10 ng/ml in 94%. Based on median values, 0.007% of the sennoside intake (calculated as rhein) was excreted in breast milk. None of the breast-fed infants had an abnormal stool consistency. Assuming a (theoretical) complete metabolism of sennosides to rhein in the mother, the amount of rhein delivered to the infant (ng/kg b.w.) is by the factor 10^{-3} below the rhein intake of the mother.

Bright and Takyi (1970) reported when rhubarb was taken by lactating mothers, the amount excreted in the milk was too small to affect the baby. There is no detailed information available.

However, animal experiments demonstrated that placental passage of rhein from other HADs is low (see assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016)).

Conclusion on fertility, pregnancy and lactation

Use during pregnancy and lactation is contraindicated due to preclinical data regarding potential genotoxicity of anthranoids; in addition, there are insufficient data on the excretion of metabolites in breast milk and small amounts of active metabolites (rhein) from other HADs are excreted in breast milk. A laxative effect in breast-fed babies has not been reported.

No fertility data are available.

5.5.6. Overdose

The section on overdose of the monograph refers to major symptoms of chronic use and abuse such as griping pain and severe diarrhoea with consequent losses of fluid and electrolytes and the potential risk of toxic hepatitis (see section 5.3 and section 5.5.4).

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed.

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

In line with the evaluation of other HAD-containing stimulant laxatives (senna leaf and aloe preparations), concerns have been raised regarding possible genotoxicity and potential carcinogenicity leading to limiting the daily dose and the duration of administration. For discussion on the current position, see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

6. Overall conclusions (benefit-risk assessment)

Rhubarb root preparations fulfil the requirements for well-established medicinal use according to Article 10a of Directive 2001/83/EC in the following indication:

Well-established use:

Short-term use in cases of occasional constipation

WHO ATC: A06AB

There are no recent clinical investigations available, which evaluate rhubarb root alone, i.e. not in combination with other laxatives, in a representative study population.

There are no well-designed non-experimental descriptive studies with mono-preparations rhubarb root that investigate the short-term use in occasional constipation available. Evidence is obtained from pharmacological data, experts' reports and opinions and extensive clinical experience as well as reference to related HAD-containing herbal preparations (senna leaf and aloe preparations).

Clinical and pharmacological data obtained on other anthranoid-containing laxatives (primarily senna leaf preparations) support the efficacy of this anthranoid-containing herbal substance for short-term use in cases of occasional constipation and therefore these data are taken to substantiate the well-established use of preparations containing rhubarb root.

The use in children under 12 years of age, pregnant and lactating women is contraindicated.

The duration of use is limited to a maximum of one week (for short-term use in cases of occasional constipation) to address potential adverse effects of long-term misuse and the potential genotoxicity and carcinogenicity of anthraquinones and derivatives.

In the indication described in the European Union monograph the benefit/risk ratio is considered positive.

Hydroxyanthracene derivatives are considered by the HMPC as constituents with known therapeutic activity.

Annex

List of references