The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

RHEI RADIX

SUMMARY REPORT

1. According to the European Pharmacopoeia and also the German Pharmacopoeia (DAB 10) *Rhei radix* (rhubarb) is the peeled and dried root of *Rheum palmatum* L., *Rheum officinale* Baillon or hybrids of these two species. Other monographs also permit the un-peeled root.

   The root contains a complex mixture of anthraquinone derivatives (anthranoids), of which the majorities are present as glycosides. The main anthraquinone-aglycones are chrysophanol, aloe-emodin, physcion and rhein. Sixty to 80% of the anthranoids consist of monoglycosides of these aglycones, while 10 to 25% are glycosides of dianthrones of the aglucones. Among the latter are the sennosides A and B which are also the main active compounds in the two anthraquinone-containing crude drugs *Sennae folium* and *Sennae fructus*. The total content in *Rhei radix* of anthraquinone derivatives is 3 to 12%. The root also contains 5 to 10% of a complex mixture of tannins of the gallotannin- and catechintype.

2. In veterinary medicine a preparation containing 20% of *Rhei radix* (incombination with methionine (15%), boldo (10%), choline dihydrogen citrate (5%), niacin (5%) and lactose (45%) is used orally in cattle at a daily dose of 40 to 80 mg/kg bw, divided into at least two administrations per day. It is used as a powder to be mixed with the feed or drinking water and is administered until remission of the symptoms (usually a few days). The product is indicated for treatment of hepatic dysfunction, hepatic congestion and hepatitis of alimentary origin.

   A second preparation is a liquid preparation, containing a fluidextract of *Rhei radix* in combination with fluid extracts of *3* other crude drugs. The concentration of *Rhei radix* corresponds to 2 mg/ml of anthranoids, calculated as rhein. The indications are various forms of gastric complaints in cattle, swine, sheep and horses. The maximum dose of the preparation is for calves, sheep and swine 0.50 ml/kg b.w. (1 mg of anthranoids) and for foals 120 ml/animal (240 mg of anthranoids). The treatment can be repeated after 24 hours.

   A third preparation is a powder containing also, *Cinchonae cortex*, *Anisi stellati fructus*, *Torula* yeast, calcium hydroxide, calcium carbonate, magnesium oxide, cobalt sulphate heptahydrate and, as excipients, sodium lauryl sulphate and sucrose. The concentration of *Rhei radix* in the preparation is 1.44%. The indications for use are various gastric complaints including forestomach atony, acute indigestion with rumenal atony and gastric catarrh. The preparation is intended to be used for cattle, sheep and goats in doses corresponding to 10 g of *Rhei radix* to cattle weighing more than 200 kg and 2.5g to sheep and goats (up to 50 kg bw).

   A fourth preparation contains *Rhei radix* at a concentration of 49% in a mixture of 5 powdered crude drugs, which is used for treatment of various gastric disorders in cattle, horses, swine, sheep and goats. The dose to cattle and horses corresponds to 9 g of *Rhei radix* 3 times a day for treatment of gastric disorders and to 27 g twice a day for treatment of constipation. The doses for the smaller animals correspond to 4.5 g of *Rhei radix* three times a day and 13.5 g twice a day, respectively.

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3. In human medicine, extracts of *Rhei radix* are used to treat constipation at a single oral dose corresponding to 20 to 30 mg of total anthraquinones, calculated as rhein. The content of tannins in the root counteract the laxative effect of the anthraquinones and *Rhei radix* is therefore considered to be a milder laxative than other anthraquinone-containing crude drugs. However, the use in humans of anthraquinone containing herbal preparations has been restricted in some Member States to short-term treatment of constipation only, as frequent or long-term use has been associated with increased risk of intestinal tumours.

4. Bacteria in the colon hydrolyse the anthraquinone glycosides and reduce the liberated aglycones to anthranols which increase colonic motility by stimulation of Auerbach's plexus. Evacuation of the bowl generally occurs 6 hours or more after administration. Glycosides of anthranoids are poorly absorbed after oral administration. The anthranols can be absorbed from the colon to a moderate degree and the absorbed material may be excreted in the bile (with possible effects on the small intestine), and in saliva, milk and urine.

5. Haemostatic effect on experimental gastric bleeding and in clinical gastro-intestinal bleeding has been reported in Chinese journals. Chinese investigators have reported antineoplastic activity of emodin in Ehrlich ascites carcinoma cells and in leukaemia L1210 cells. These workers also reported an *in vivo* inhibitory effect against P388 leukaemia in mice for rhein and aloe emodin. Other Chinese pharmacological studies include suppressive action on rat ultramotility, blood urea nitrogen reducing action, antiinflammatory and antipyretic action. The latter effects are described to the tannin fraction.

6. No information was provided on pharmacokinetics of *Rhei radix.* Of a dose (5 g) taken as a standardised Senna laxative, 0.007% was excreted (as rhein) into breast milk of humans. The main constituents of senna are sennosides, which are also present in *Rhei radix.*

7. No information was provided on acute toxicity or on repeated dose toxicity of *Rhei radix.* An intraperitoneal LD_{50} of 35 mg/kg bw has been reported for emodin (species not given).

8. No information was provided on reproductive toxicity, teratogenicity or immunotoxicity.

9. Genotoxic effects of free anthranoids such as aloeemodin, chrysophanol, emodin and physcion, are reported from *in vitro* tests (*Salmonella*-microsomal assay in *Salmonella typhimurium,* DNS-repair in primary hepatocytes of rats). In a dose of 5 mg/plate, an aqueous extract (1:6) of *Rhei radix* had mutagenic effect on *Salmonella typhimurium* TA 98 following metabolic activation with S-9 mixture. However, this effect was not obtained with *Salmonella typhimurium* TA 100. In a rec-assay with *Bacillus subtilis* for DNA-damage he same extract (6 mg/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 indicating them to be weakly genotoxic

10. In a very recent publication, which is yet only available as draft reports results of 2-year feed studies there was no evidence of carcinogenic activity of emodin in male rats exposed to 280, 830 or 2500 mg/kg feed. There was equivocal evidence of carcinogenic activity of emodin in female rats based on a marginal increase in the incidence of Zymbal´s gland carcinoma. There was equivocal evidence of carcinogenic activity of emodin in male mice based on a low incidence of uncommon renal tubule neoplasms. There was no evidence of carcinogenic activity of emodin in female mice exposed to 312, 625 or 1250 mg/kg feed.

11. A recently (April 1999) published review article states that anthranoid laxatives has a potential role in both the initiation and promotion of tumorigenesis but that the short-term use of these substances is generally safe whereas long-term use cannot be recommended.

12. In humans occasional cases of abdominal discomfort such as colic or cramps are reported. Prolonged use or overdosage can result in diarrhoea with excessive loss of water and electrolytes, particularly potassium.

13. Aloe emodin, emodin and rhein inhibit *in vitro* growth of *Bacillus subtilis* and *Staphylococcus aureus*. Rhein is most effective. Antimicrobial activity was also noted against several other microorganisms.

14. No information on residues was provided.

Conclusions and recommendation

Having considered that:

- *Rhei radix* is used in a small number of animals and only for infrequent or non-regular treatments,
- the animals treated with *Rhei radix* are unlikely to be sent for slaughter during or immediately after treatment,
- the anthraquinone glycosides are poorly absorbed from the intestine and there is only a moderate absorption of the aglycones and their reduction products;

The Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for *Rhei radix* and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active Substance(s)	Animal species	Other provisions
Rhei radix, standardised extracts and preparations thereof	All food producing species	