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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

FRANGULAE CORTEX

SUMMARY REPORT

1. *Frangulae cortex* is the dried bark of *Rhamnus frangula*. The bark contains a mixture of anthraquinone derivatives (anthranoids) of which the majority is present as glycosides. The total content of anthranoids is 2 to 6%. The main derivatives are glycosides of emodin such as glucofrangulin A and B and frangulin A and B. The free aglycones emodin, chrysophanol and physcion are also present in varying concentrations. The fresh bark contains reduced derivatives of anthranoids (anthrones and anthranols). These have a very strong purgent activity and before the bark is used for medicinal purposes it must be stored for at least one year. Tannins and small quantities of peptide alkaloids have also been found.

2. In veterinary medicine *Frangula cortex* is used as a fluid extract in a liquid preparation, also containing fluid extracts of three other crude drugs, in a concentration corresponding to 6 mg/ml of anthranoids, calculated as frangulaemodin. Indications are: various forms of gastric complaints in cattle, swine, sheep and horses. The maximum dose of the preparation for calves, sheep and swine is 50 ml/100 kg bw (= 300 mg of anthranoids) and for foals is 120 ml/animal (= 720 mg of anthranoids). The treatment can be repeated after 24 hours.

   In human medicine *Frangulae cortex* is used to treat constipation at a daily oral dose corresponding to 20 to 180 mg of total anthranoids. 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.

3. Bacteria in the colon hydrolyse the anthraquinone glycosides and reduce the liberated aglycones to anthrones (and anthranols) which increase colonic motility by stimulation of Auerbach's plexus. Evacuation of the bowl generally occurs 6 hours or more after 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.

4. Following oral administration anthraquinone glycosides are poorly absorbed from the small intestine. Studies on humans of the anthranoid *aloe-emodin*, which is structurally related to the aglycone of the glycofrangulins, show that metabolites are present in kidney and muscles up to 48 hours after administration. For liver, residues were found 96 hours after administration (see summary report on *Aloes*).

   Information on the excretion into milk is not available for *Frangulae cortex*. However limited excretion of rhein (an anthranoid structurally related to the aglycone of the glycofrangulins) into breast milk of humans has been reported (median value: 0.007% of the dose resulting from daily intake of 5 g of a standardised senna-based laxative).

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5. No information was provided on acute toxicity or on repeated dose toxicity of *Frangulae cortex*. Vomiting and spasmodic gastrointestinal complaints can occur as side effects to the purgative effect or with overdosages (no figures). Long-term use leads to losses of electrolytes, in particular K^+-ions, and as a result of this to hyperaldosteronism, inhibition of intestinal motility and enhancement of the effect of cardioactive steroids, in rare cases also to heart arrhythmia, nephropathies and accelerated bone deterioration.

   An intraperitoneal LD_{50} of 35 mg/kg bw has been reported for emodin (animal species not given). Repeated dose toxicity studies with emodin (the aglycone of the glucofrangulins) in rats and mice have been conducted under the National Toxicology Program of the United States of America. Emodin was given in the feed for 16 days or 14 weeks. Observed effects included reduced feed consumption, body weight gain and increase of the final body weight changed haematological parameters in the 14-week study at the high doses and macroscopic kidney and/or gallbladder lesions in the 16-day study. In rats no effects were observed at dietary doses up to 2000 mg/kg feed (390 and 540 mg/kg bw in males and females respectively), while in the 14-week study no effects were reported at the lowest dose of 312.5 mg/kg feed (equivalent to 50 and 60 mg/kg bw, respectively).

6. No information was provided on reproductive toxicity or on teratogenicity.

7. Carcinomas in the colon can occur after long-term administration of anthranoids. Emodin is genotoxic in mouse lymphoma L5178Y cells, binds non-covalently to DNA and inhibits topoisomerase activity. Emodin is mutagenic in V79 cells and is active in the DNA-repair assay and in the C3H/M2 transformation assay. Emodin is also mutagenic in *Salmonella typhimurium* strain TA 1537 after metabolic activation. Chromosomal aberrations were observed in Chinese hamster ovary (CHO) cells *in vitro* with and without metabolic activation. *In vivo* micronucleus tests in rat and mouse bone marrow and in mouse peripheral blood after intraperitoneal injection and in male mice in peripheral blood after oral administration were negative, while weakly positive results were seen in female mice after oral administration of the substance. Ethanol extracts of the bark are genotoxic in *Salmonella typhimurium* strain TA 1537 in the presence of microsomes from rat-liver (S9 mixture) and are also active in the DNA-repair assay.

   For emodin, a result of 2-year feed studies has recently been reported (only available as a draft). 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 neoplasm. There was no evidence of carcinogenic activity of emodin in female mice exposed to 312, 625 or 1250 mg/kg feed.

   No genotoxicity of emodin was found either with or without metabolic activation in two mammalian testsystems: the sister-chromatid exchange (SCE) assay and the hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) forward mutation assay with V79 Chinese hamster cells.

   A review article published in April 1999 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.

8. No information on immunotoxicity was provided.

9. Emodin inhibits *in vitro* growth of *Bacillus subtilis* and *Staphylococcus aureus*. Antimicrobial activity is also noted against several other micro-organisms.

10. No information on residues was provided.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for Veterinary Medicinal Products for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- *Frangulae cortex* is expected to be used in a small number of individual animals only, for infrequent or non-regular treatments,
- the animals treated with *Frangulae cortex* are unlikely to be sent for slaughter during or immediately after treatment,
- glucosidic anthranoids - which are the main anthranoid components - are poorly absorbed from the intestine,
- although there is a concern for a potential role of anthranoid laxatives in initiation and promotion of tumorigenesis a short-term exposure of humans to these compounds is considered to be generally safe;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for *Frangulae cortex* 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
Frangulae cortex, standardised extracts and preparations thereof	All food producing species	