



London, 5 July 2007
Doc. Ref: EMEA/HMPC/76306/2006

**COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)**

**ASSESSMENT REPORT ON
*RHAMNUS FRANGULA L., CORTEX***

Herbal substance	<i>Rhamnus frangula</i> L. (<i>Frangula alnus</i> Miller), cortex (frangula bark)
Herbal preparation	Dried, whole or fragmented bark of the stems and branches, standardised; standardised herbal preparations thereof
Pharmaceutical forms	Herbal substance for oral preparation
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I. INTRODUCTION

This assessment report reviews the scientific data available on frangula bark (*Rhamnus frangula* L. (*Frangula alnus* Miller)), primarily the clinical data. The core-SPC for Frangulae cortex established in 1994 by the Committee for Proprietary Medicinal Products (CPMP) the German monograph of the Commission E “Frangulae cortex” (1) and the German pharmacovigilance actions for anthranoid-containing laxatives of 21 June 1996 (2) were taken into consideration. Due to the lack of specific clinical data, results of investigations in animals are also referred to. The report also takes into account the literature presented by the European Scientific Cooperative on Phytotherapy (ESCO) to support the monograph “Frangulae cortex (Frangula bark)” (ESCO Monographs, second edition 2003) (3).

Constipation is a common complaint in 1 – 6% of the middle-aged population and 20 – 80 % of the elderly people, and may be treated by laxatives. Constipation also tends to be more prevalent among women. Functional constipation is the most common type without any specific aetiology (4). The most commonly used laxatives are either stimulant preparations (containing anthracenic derivatives), lubricant laxatives (e.g. mineral oils) or bulk forming agents.

Frangula preparations of the dried bark belong to the stimulant laxatives containing hydroxyanthracene derivatives. According to the CPMP core-SPC, they are intended “for short-term use in cases of occasional constipation”. This indication is substantiated by empirical data derived from research into the constituents of frangula bark and their pharmacology and those of other anthranoid-containing herbal substances. There are only limited clinical data available.

Frangula preparations have to be regarded as herbal medicinal products with a “well-established medicinal use” in this indication with respect to the application of Directive 2001/83/EC of the Parliament and of the Council on the Community code relating to medicinal products for human use as amended.

Anthraquinone laxatives such as aloe and senna preparations share a tricyclic anthracene nucleus modified with hydroxyl, methyl, or carboxyl groups to form monoanthrones (54). This report on the assessment of frangula bark therefore refers also to the assessment report on senna leaves and fruits and to the assessment report on aloe.

II. CLINICAL PHARMACOLOGY

II.1 Pharmacokinetics

II.1.1 Phytochemical characterisation

Frangula bark consists of the dried, whole or fragmented bark of the stems and branches of *Rhamnus frangula* L. (*Frangula alnus* Miller). It contains not less than 7.0 per cent of glucofrangulins, expressed as glucofrangulin A ($C_{27}H_{30}O_{14}$; M_r 578.5) and calculated with reference to the dried herbal substance. The material complies with the European Pharmacopoeia monograph “Frangula bark” (ref. 01/2005:0025).

The constituents with known therapeutic activity of frangula bark are emodin-di- and mono-glycosides *viz.* the diglycosides glucofrangulin A (emodin-6-0- α -L-rhamnosyl-8-0- β -D-glucoside) and glucofrangulin B (emodin-6-0- β -D-apiosyl-8-0- β -D-glucoside) and the monoglycosides frangulins A, B, C (emodin-6-0- α -L-rhamnoside, emodin-6-0- β -D-apioside, emodin-6-0- β -D-xyloside) and emodin-8-0- β -D-glucoside.

The herbal substance also contains small quantities of other anthraquinone glycosides, dianthrone and the aglycones emodin and emodin-9-anthrone (3).

Lemli J 1965 (5) confirmed the presence of chrysophanol, emodin and emodin dianthrone in the fresh bark of *Rhamnus frangula*. In addition he identified the heterodianthrone palmidin C. In the fresh bark, the glucofrangulins are available in reduced form, in the stored bark in oxidised form. With this oxidation a saccharolytic process occurs and the stored bark therefore contains a higher amount of frangulin and frangulin-emodin.

The anthrone O-glycosides (reduced form) are supposedly responsible for serious side effects seen in the stomach after oral administration (6). Therefore, the bark should not be used before at least 1 year, so that oxidation of the anthrones can take place.

II.1.2 Absorption, metabolism and excretion

We refer to the assessment report on “*Cassia senna* L. et *Cassa angustifolia* Vahl, folium”.

Glucofrangulin A and B are the main constituents of frangula bark with known therapeutic activity, and they belong to the anthraquinone O-glycosides. For glucofrangulin, **Longo R 1980** (7) has shown that the aglyka moieties are set free in the gut through bacterial β -glycosidases. Mainly anthraquinones aglyka are absorbed.

In comparison to anthrones, anthraquinones are absorbed to a much larger extent (8). This was shown in studies with [^{14}C]rhein anthraquinone and [^{14}C] emodin. Rhein anthraquinone was absorbed to at least 37% of the injected dose after intracecal administration and to 50 – 60 % of an oral dose in rats. [^{14}C] emodin showed the same absorption. The author explains the great difference between rhein anthraquinone and rhein anthrone in terms of chemical stability and reactivity. Rhein anthraquinone does not react with unabsorbable substances present in the intestinal mass and is not degraded to polyphenols. The amount of time which rhein anthrone spends in the intestinal tract is more limited than for rhein anthraquinone. The absorption of rhein anthraquinone is slowly limited by the continuous bacterial reduction. After absorption, the aglyka are distributed over the different organs and tissues of the body. Exact data are missing. The aglyka are excreted in urine (causing the yellow or reddish-brown discoloration of the urine) and bile as glucuronides and sulphates. With three substances (rhein anthrone, rhein and emodin) a fast body clearance was shown.

After oral administration of 600 mg or 400 mg of a powdered frangula extract in 2 volunteers, rhein, emodin and traces of chrysophanol were found in human urine (67).

Frangula bark acts within 8 to 12 hours due to the time taken for transport to the colon and metabolism into the active compounds (3).

II.2 Pharmacodynamics

We also refer to the assessment report on “*Cassia senna* L. and *Cassa angustifolia* Vahl, folium” and to the assessment report on “*Aloe barbadensis* Miller and *Aloe* (various species, mainly *Aloe ferox* Miller and its hybrids)”.

II.2.1 Mode of action

- **Laxative effect**

Constipation is said to be present when passed stools are of hard consistency and when evacuation of faeces is too difficult, too infrequent and irregular. The physiological range for frequency of bowel movements is wide, extending from defaecation three times daily to once every 2 to 3 days. In the pathogenesis of constipation the colon plays a key role because this is where the contents of the gut remain for 24 – 48 hours. During this period the liquid contents from the small intestine are converted into faeces by absorption of water and electrolytes in response to the action of bacteria. These functions are dependent on the interplay of peristaltic processes, which mix the contents and the normal coordination of the anorectal muscles during defaecation. A disturbance involving any of these individual areas may lead to constipation. In this context, functional disturbances are far more common than those of an organic origin. In addition, assessment is problematic because the symptoms

are perceived differently by the individuals affected (9, 10), due to different concepts of what normal bowel habits are.

Frangula bark belongs to the stimulant laxatives. Emodin-9-anthrone is the most important metabolite, which 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 inhibition of absorption of water and electrolytes (Na^+ , Cl^-) into the colonic epithelial cells (antiabsorptive effect) and 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 “*Cassia senna* L. et *Cassia angustifolia* Vahl, folium”).

Results of investigations of **Capasso F et al. 1983** (55) in rat isolated colon suggest that the laxative properties of aloin and 1,8-dihydroxyanthraquinone may depend, at least in part, on increased prostaglandin synthesis by the intestinal tissue.

Frangula bark predominantly contains the anthranoids as anthraquinones. Therefore it is supposed that the influence of frangula bark on fluid absorption and on secretion processes is lower than the influence of other anthranoid-containing herbal substances. Data of a direct clinical comparison of the effects are missing (8).

Cressari A et al. 1966 (11) investigated different constituents of the frangula bark to evaluate the laxative effect in comparison to a standard senna leaves extract (amount of anthranoids not mentioned) in mice. Glucofrangulin and frangulin only showed a laxative effect after oral administration. This effect was nearly 4 to 5 times stronger than the effect of the senna extract. The effect of emodin was comparable with the effect of the senna extract. Physcion and chrysophanol had no noteworthy effect.

The administration of a methanolic extract of frangula bark (17.5 % anthranoid glycosides calculated as 1,8-dihydroxyanthraquinon-glycoside) in mice resulted in a dose dependent decrease of the intestinal transit time. After oral administration of 50 mg/kg body weight defaecation after 4 h took place in 20 % of the mice, after oral administration of 100 mg/kg body weight in 40 %. The ED_{50} was mentioned with 121.5 mg/kg body weight (12, 13).

A methanolic extract of frangula bark (23 % glucofrangulin, 2 % frangulin, 0.5 % aglyka) had a laxative effect in mice with a weight of 20 g after oral administration. The ED_{50} was 3.66 mg/20 g body weight. The ED_{50} of another frangula extract with 25 % glucofrangulin, 1.5 % frangulin and 0.5 % aglyka was 2.45 mg; the ED_{50} of pure glucofrangulin A was 7.97 mg, of pure frangulin A 2.37 mg and of pure emodin 4.67 mg /20 g body weight (7).

The administration of an aqueous suspension of 0.6 g pulverised bark (12 mg anthranoids (glucofrangulin and frangulin) had a laxative effect in humans after 6 to 24 h (12, 14).

- **Other effects**

- Antifungal effect

An alcoholic extract of frangula bark (500 mg dried bark) completely prevented the germination of spores from *Aspergillus fumigatus*, *Penicillium digitatum* and *Fusarium oxysporum* in the agar dilution test (15).

Manojlovic NT et al. 2005 (23) reported the results of a preliminary antifungal screening of the methanol extracts and the major anthraquinone aglyka, alizarin (1,2-dihydroxyanthracene) and emodin (1,8-dihydroxyanthracene), of *Rubia tinctorum* and *Rhamnus frangula* in comparison with the

antifungal activity of the anthraquinone-containing lichen *Caloplaca cerina* and its main secondary metabolite parietin. The methanol extracts were significantly active against the fungi tested: *Trichoderma viride*, *Doratomyces stemonitis*, *Aspergillus niger*, *Penicillium verrucosum*, *Alternaria alternata*, *Aueobasidium pullulans*, *Mucor mucedo*. All three extracts contain anthraquinone derivatives as major secondary metabolites. However, the major isolated anthraquinone aglyca from *Rubia tinctorum* (alizarin), from *Rhamnus frangula* (emodin) and from *Caloplaca cerina* (parietin) were less active against fungi than the corresponding extracts. The *Rhamnus frangula* extract and emodin showed an inhibition as follows: *Trichoderma viride* 63% and 31% respectively; *Doratomyces stemonitis* 45% and 41%; *Aspergillus niger* 41% and 41%; *Penicillium verrucosum* 25% and 18%; *Alternaria alternata* 39% and 56%; *Aueobasidium pullulans* 46% and 41%; *Mucor mucedo* 68% and 48%.

➤ Antiviral effect

Sydiskis RJ et al. 1991 (16) 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 extract inactivated the virus. The active components 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 0.35 µg/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.

➤ Antibacterial effect

Wang HH and Chung JG 1997 (61) reported on studies, which were conducted to examine the dose effects of emodin on inhibition of growth versus DNA damage events in *Helicobacter pylori* from patients who had peptic ulcer disease. Inhibition of growth study from *H. pylori* demonstrated that emodin caused a dose-dependent growth inhibition in *H. pylori* cultures. S1 nuclease sensitivity analysis studies revealed that emodin induced dose-dependent DNA damage in *H. pylori*. The authors concluded that these results suggest that there was a possible relationship between the dose response to emodin and the inhibition of growth and DNA damage in *H. pylori*.

➤ Effect on platelet aggregation

Teng CM et al. 1993 (17) isolated emodin and frangulin B from the plant *Rhamnus formosana*. Emodin inhibited the aggregation of rabbit platelets induced by arachidonic acid and collagen, without affecting that by ADP (adenosine diphosphat) or PAF (platelet-activating factor), while emodin acetate had no antiplatelet effect. Frangulin B inhibited selectively and concentration-dependently collagen-induced aggregation and ATP release in rabbit platelets, without affecting those induced by arachidonic acid, ADP, PAF and thrombin. Frangulin B also inhibited the platelet aggregation induced by trimucyctin which was reported to be a collagen receptor agonist isolated from *Trimeresurus mucrosquamatus* snake venom. The aggregability of platelets inhibited by frangulin B could be recovered after washing the platelets. Frangulin B also selectively suppressed the thromboxane B2 formation caused by collagen, but not those by arachidonic acid and thrombin. Similarly, the formation of inositol phosphate caused by collagen was also suppressed by frangulin B, while that of PAF or thrombin was not affected. In the presence of PGE₁, frangulin B also decreased Mg(2+)-dependent platelet adhesion to collagen. The authors concluded that frangulin B may be an antagonist of collagen receptor in platelet membrane.

➤ Anti-inflammatory effect

Wei BL et al. 2001 (18) assessed *in vitro* the anti-inflammatory activities of the isolated anthraquinone, frangulin B, of *Rhamnus formosana* by determining its inhibitory effects on the chemical mediators released from mast cells, neutrophils, macrophages, and microglial cells. Frangulin B showed potent inhibitory effects on TNF-alpha formation in LPS/IFN-gamma (interferon-gamma)-stimulated murine microglial cell lines N9.

➤ Anticancer effect

Zhang L et al. 1995 (62 and 63) reported on results, obtained with human breast cancer MDA-MB453 cells, which indicated that emodin inhibits *HER-2/neu* tyrosine kinase activity and preferentially suppresses growth and induces differentiation of *HER-2/neu*-overexpressing cancer cells. The *HER-2/neu* proto-oncogene encodes the tyrosine kinase receptor p185neu. Amplification and overexpression of the gene have frequently been observed in human breast cancer and are correlated with poor prognosis. The authors concluded that the results may have chemotherapeutic implications for using emodin to target *HER-2/neu* overexpressing cancer cells.

Zhang L and Hung MC 1996 (64) also investigated the effect of emodin in human non-small cell lung cancer (NSCLC) cells in which overexpression of the *HER-2/neu* proto-oncogene has been also observed. Emodin decreased tyrosine phosphorylation of *HER-2/neu* and preferentially suppressed proliferation of *HER-2/neu*-overexpressing NSCLC cells. Furthermore, the combination of emodin with cisplatin, doxorubicin or etoposide (VP16) synergistically inhibited the proliferation of *HER-2/neu*-overexpressing lung cancer cells, whereas low doses of emodin, cisplatin, doxorubicin or VP16 alone had only minimal antiproliferative effects on these cells.

Zhang L et al. 1999 (65) examined whether emodin can inhibit the growth of *HER-2/neu*-overexpressing tumours in mice and whether emodin can sensitize these tumours to paclitaxel, a commonly used chemotherapeutic agent for breast cancer patients. Special human breast cancer cells were injected s.c. into the flanks of female nu/nu (athymic) mice. Three weeks later, when the solid tumours were palpable, the mice were given either placebo, emodin (40 mg/kg bw), paclitaxel (10 mg/kg bw), or emodin plus paclitaxel by i.p. injection twice a week for 8 weeks. The authors reported that emodin enhanced the effects of paclitaxel on growth and transformation of *HER-2/neu*-overexpressing human breast cancer cells and significantly inhibited tumour growth and prolonged survival of these mice.

Fenig E et al. 2004 (66) conducted a study to determinate if members of the anthraquinone family could be used as adjuncts to increase the growth inhibiting effect of anticancer agents in Merkel cell carcinoma (MCC). An adherent variant of MCC was derived from a previously established MCC cell line suspension. Emodin and aloe-emodin inhibited proliferation of the adherent MCC cells, with a slight advantage of aloe-emodin over emodin. Aloin had no effect on cell proliferation. The chemotherapeutic agents, cis-platinol (abiplastin), doxorubicin (adriablastin), and 5-fluorouracil, and the tyrosine kinase inhibitor STI 571, all independently inhibited the proliferation of adherent MCC cells. The addition of aloe-emodin potentiated their inhibitory effect, especially when low concentrations of the anticancer compounds were used. The addition of emodin was not investigated.

II.2.2 Interactions

Chronic use or abuse of frangula preparations may lead to hypokalaemia like the abuse of all anthranoid-containing laxatives. This hypokalaemia and the increased loss of potassium may increase the activity of cardiac glycosides and interfere with the action of antiarrhythmic agents (interaction with antiarrhythmic medicinal products, which induce reversion to sinus rhythm, e.g. quinidine) and medicinal products inducing QT-prolongation (68). Concomitant use with medicinal products inducing hypokalaemia (e.g. diuretics, adrenocorticosteroids and liquorice root) may aggravate electrolyte imbalance.

The above-mentioned investigations of Teng CM et al. 1993 (17) showed an antagonistic effect of frangulin B to collagen receptor in platelet membrane. This effect resulted in an inhibition of the platelet aggregation. Clinical studies in humans are not available. It is unknown whether these investigations have relevance for the concomitant use with other medicinal products, which inhibit the thrombocyte aggregation. Until now, data are too poor to give special information on such concomitant use in the HMPC monograph.

III. Clinical Efficacy

III.1 Dosage

There are no dose-finding studies available.

The recommended dosage as a laxative for adults, elderly and adolescents over 12 years (20 – 30 mg hydroxyanthracene derivatives only once daily at night) is supported by experts' opinions and by clinical investigations with other anthranoid-containing laxatives like senna preparations. We refer to the assessment report on "*Cassia senna* L. et *Cassa angustifolia* Vahl, folium".

The German Commission E monograph "Frangulae cortex" (1) indicates a daily dose of 20 – 30 mg hydroxyanthracene derivatives calculated as glucofrangulin A, but it recommends that the pharmaceutical form must allow lower dosages than the usual daily dose.

The ESCOP monograph "Frangulae cortex" (3) also recommends 20 – 30 mg hydroxyanthracene derivatives daily.

The recommendation in the pharmacovigilance actions taken in Germany in 1996 for anthranoid-containing laxatives after consideration of the toxicological data (2) only determines a daily maximum limit of 30 mg hydroxyanthracene derivatives.

Through the individual product information (especially the package leaflet), patients should be informed that the correct individual dose is the smallest required to produce a comfortable soft-formed motion. It is therefore preferable to recommend a larger range of 10 – 30 mg hydroxyanthracene derivatives daily.

It is normally sufficient to take an anthranoid-containing laxative up to two to three times a week (69).

III.2 Clinical studies

III.2.1 Constipation

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

Fotiades P et al. 1976 (19) investigated the efficacy of Laxariston® in the treatment of constipation; 3 g of this preparation contain 0.9 g methyl cellulose, 0.3 g frangula bark (13.5 mg hydroxyanthracene derivatives), 0.3 g senna leaves (7.5 mg hydroxyanthracene derivatives), 0.15 g rhubarb root (6.75 mg hydroxyanthracene derivatives) and 0.015 g achillea extract. Laxariston® was given to 61 inpatients with mainly arthritic illness (3 g daily for 26.1 days on average) and to 33 outpatients mainly after abdominal surgery (7.6 g daily for 88.9 days). 31 patients of the whole study population had acute complaints, 20 patients suffered from chronic constipation and 41 patients from "functional" constipation. Special complaints are not mentioned in the publication. The time until disappearance of complaints was evaluated as follows: 0 – 2 days: very good efficacy; 3 – 14 days: good efficacy; 15 – 28 days: satisfactory efficacy; more than 28 days: insufficient efficacy. Laxariston® had a very good efficacy in 71 patients (77.2%), a good efficacy in 19 patients (20.7%) and a satisfactory efficacy in 2 patients (2.1%). In the group with acute complaints, the efficacy was very good in 77.4% and good in 22.6%. In the group with chronic complaints, the efficacy was very good in 35%, good in 55% and satisfactory in 10 %. In the group with functional complaints, the efficacy was very good in 97.6% and good in 2.4%. The tolerance of the preparation was good in all these patients. The efficacy in 2 patients was not evaluated because these patients developed abdominal pain.

Bauer H 1977 (20) administered Laxariston® (specification defined above) to 73 patients with gynaecological diseases and to 95 pregnant women suffering from constipation. Special complaints are not mentioned in the publication.

The first group consisted of 30 patients who underwent a laparotomy in the past, of whom 15 patients additionally took oestrogens, 6 patients with conservative gynaecological diseases and under oestrogenic treatment, 7 patients who took oestrogens and other medicinal products, which influence the intestine motility, 13 patients with pathological-anatomic alteration in the pelvis minor, and 7 patients with constipation not caused by the gynaecological diseases. On average, the women took this medicinal product for 47.2 days and the complaints disappeared in 5.3 days with a daily dose of 5.3 g. The time until disappearance of constipation complaints was assessed as follows: 0-3 days: very good efficacy; 4-5 days: good efficacy; 6-7 days: satisfactory efficacy; >7 days: insufficient efficacy. Efficacy was very good in 41 patients, good in 20 patients and satisfactory in 11 patients. One patient dropped out (reason not given). Six patients (8.2%) complained about adverse reactions (spasms, tenesmus, and nausea) whilst 21 patients (28.8%) reported about positive reactions like weight reduction, decrease of haemorrhoidal complaints, and decrease of flatulence.

In the second group, 14 pregnant women were in the first trimester, 15 in the second one, and 66 women in the third trimester. On average Laxariston® was administered for 61.4 days and the complaints disappeared in 3.9 days with a daily dose of 3.9 g. Efficacy was very good in 55 patients, good in 31 patients, satisfactory in 7 patients and insufficient in 2 patients. This result was not analysed with regard to the different trimesters. Four patients (4.2%) complained about adverse reactions whilst 29 patients (30.5%) reported about positive reactions.

Twelve women in the second group were gynaecologically treated because of a threatening abortion. One of these women only miscarried. There is no information about the state of the new-borns.

It is worth noting that 3 g of Laxariston® contain 27.75 mg hydroxyanthracene derivatives, of which nearly 50% derive from frangula bark. A contribution to the efficacy of Laxariston® by frangula bark is therefore supposable. However, Laxariston® also contains the bulk forming agent methyl cellulose, which also has a laxative effect.

III.2.2 Other studies

Feldman H et al. 1971 (25) conducted a double-blind trial to evaluate Caved-S tablets in 47 patients with active duodenal ulcer. Caved-S tablets contained 380 mg deglycyrrhizinated powdered black liquorice, 100 mg bismuth subnitrate, 100 mg aluminium hydroxide gel, 200 mg magnesium carbonate, 100 mg sodium bicarbonate and 30 mg powdered frangula bark. The content of hydroxyanthracene derivatives is not mentioned. Patients received 2 tablets 3 times daily after meals for 30 days. Tablets were chewed before swallowing. A placebo was administered to 24 patients and 23 patients received Caved-S tablets. Clinical results were similar in both groups. No advantages of Caved-S over placebo were found. No side effects were observed.

Gracza L et al. 1977 (21) described therapeutic results following the use of Bilicura® in 61 outpatients (22 male, 39 female, 21 – 83 years old) with diseases of the hepatocholegastroenteral system, and of Spasmo-Bilicura® in 73 outpatients (18 male, 55 female, 28 – 78 years old).

The composition of one coated tablet Bilicura® was the following: 30mg Extr. Kava-Kava sicc. e rhiz., 40 mg Extr. Cynarae scol. sicc. e fol. recent., 50 mg Extr. Cardui Mariae sicc. e fruct., 20 mg Extr. Aloes, 20 mg Extr. Frangulae sicc. e cort., 30 mg Fel tauri, 5 mg Oleum Menthae pip., and 0.5 mg guajazulene. The content of hydroxyanthracene derivatives was not mentioned. On average the patients took 1 – 2 coated tablets three times daily for 2 weeks. The complaints disappeared in 11 patients, considerably decreased in 20 patients, decreased in 18 patients, and remained unchanged in 4 patients. Two patients discontinued because of diarrhoea, and in 6 cases, there were no data available. A positive efficacy was reported by 80.3 % of the practitioners, and a negative efficacy by 9.9 %. Adverse reactions occurred in 8 patients, with 6 reports of diarrhoea and 2 reports of headache. The tolerance was assessed by 12 patients as 'excellent', by 45 as 'good'.

The composition of one coated tablet Spasmo-Bilicura® was the following: 30mg Extr. Kava-Kava sicc. e rhiz., 40 mg Extr. Cynarae scol. sicc. e fol. recent., 50 mg Extr. Cardui Mariae sicc. e fruct., 10 mg Extr. Aloes, 10 mg Extr. Frangulae sicc. e cort. c. Meth. parat., 30 mg Fel tauri, 5 mg Oleum Menthae pip., 0.5 mg guajazulene, 0.5 mg L-scopolamine-N-methylbromide, and 10 mg Ethaverin-

hydrochloride. The content of hydroxyanthracene derivatives was not mentioned. On average the patients took 1 – 2 coated tablets three times daily for 2 weeks. The complaints disappeared in 23 patients, considerably improved in 30 patients, improved in 9 patients, and remained unchanged in 2 patients. Two patients discontinued because of diarrhoea. Seventeen patients reported immediate analgesia and 45 patients after 3.2 day on average. In 11 cases there were no data available. A positive efficacy was reported by 85 % of the practitioners, and a negative efficacy by 5.4 %. Adverse reactions occurred in 6 patients, with 4 reports of diarrhoea, 1 report of stomach ache and 1 report of xerostomia. The tolerance was assessed by 9 patients as ‘excellent’, by 22 as ‘good’. No data were available for 42 patients.

The contribution of each constituent of the preparation cannot be assessed by this investigation. Data on the amount of hydroxyanthracene derivatives were lacking. The investigated population did not suffer from constipation.

Arndt EM 1982 (22) observed the effectiveness of the product Cefakliman® when taken orally during climacteric deficiency symptoms, over a period of one to four months, in four groups of patients: 1) women in preclimacteric stage; 2) women in the climacterium after prior hormonal therapy; 3) women in the climacterium without prior hormone therapy; and 4) women in the post menopause. In each case, 15 patients from these four groups were treated with Cefakliman® drops, and after the observation period were asked about the subjective improvement of their complaints. Cefakliman® is a combination preparation containing 5 g Ferrum phosphoricum D8, 1 g Lachesis D6, 10 mg Kalium phosphoricum UT, 1 g Aqua silicata, 7.5 g extract of alchemilla and 12.5 g extract of frangula bark. The best results were obtained with women in the post menopause with lighter deficiency symptoms (group 4). Nine women described the treatment success as ‘very good’, 4 women as ‘good’ and 2 women as ‘satisfactory to adequate’. The success with women in the climacterium without prior hormonal therapy (group 3) was almost the same. Here 8 women replied with ‘very good’, 5 women with ‘good’ and 2 women with ‘satisfactory to adequate’. None of the patients from both these groups assessed the therapeutic success as being ‘inadequate’. The results with women in the preclimacteric stage (group 1) were almost as good. Eight women were very satisfied, 4 women described the improvement in their complaints as ‘good’, and 3 women as ‘adequate’. The lowest therapeutic success was obtained with group 2. No improvement was reported by 6 women, ‘adequate to satisfactory’ improvement was reported also by 6 women, and only 3 women assessed the therapeutic success with ‘good’.

III.2.3 Conclusion

There are no recent clinical investigations available, which evaluate frangula bark alone i.e. not in combination with other laxatives, in a representative study population. Two non-controlled investigations of the seventies assessed the efficacy of a combination preparation in patients with constipation; 3 g of this preparation contain 27.75 mg hydroxyanthracene derivatives, of which nearly 50% derive from frangula bark, and 0.9 g of the bulk forming agent methyl cellulose. The daily dose was 3 to 7.6 g on average. A contribution of frangula bark to the efficacy of the investigated product is supposable.

The postulated laxative effect of frangula bark is mainly based on pharmacological data, experts’ opinions (CPMP core-SPC, German Commission E monograph, ESCOP monograph) and clinical experiences. Clinical and pharmacological data obtained on other anthranoid-containing laxatives (please refer to the assessment report on “*Cassia senna* L. and *Cassa angustifolia* Vahl, folium”) and the 2 above-mentioned non-controlled investigations with Laxariston® support the efficacy of this anthranoid-containing herbal substance for short-term use in cases of occasional constipation.

The investigations concerning effects other than the laxative effect are insufficient to support further indications. The other effects mentioned in chapter II.2.1 have indeed only been investigated in experimental studies. Adequate clinical trials are not available.

III.3 Clinical studies in special populations

III.3.1 Use in children

First of all change of nutrition is recommended in constipated children with an increase in daily fibre intake. According to the recommendations from a conference on dietary fibre in childhood, children older than 2 years of age should increase their intake of dietary fibre (increased consumption of a variety of fruits, vegetables, cereal and other grain products) to an amount equal or greater than their age plus 5 g (e.g. 8 g/day at age 3) (24). Change in nutrition should be accompanied with behaviour modification, e.g. increased physical exercise.

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

According to the ESCOP monograph, the use in children under 10 years of age cannot be recommended.

According to the "Note for guidance on clinical investigation of medicinal products in the paediatric population" (CPMP/ICH/2711/99) of 27 July 2000, the age limit between 'children' and 'adolescents' is set to 12 years of age.

III.3.2 Use during pregnancy and lactation

There are no recent investigations available.

As reported above (20), 95 pregnant women suffering from constipation were treated with a combination preparation containing frangula bark. Most of them were in the third trimester. Twelve women were gynaecologically treated because of a threatening abortion. Only one of these women miscarried. No information about the state of the new-borns was given in the publication.

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. This explains why this herbal substance had been misused as an abortifacient agent (12).

Animal experiments demonstrated that placental passage of rhein is small.

Bruggemann IM et al. (26) studied genotoxicity of emodin in the Salmonella/microsome assay, the sisterchromatid exchange (SCE) assay and the hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) forward mutation assay with V79 Chinese hamster cells. In the Salmonella/microsome assay, emodin was found to be positive in TA97, TA100 and TA1537 in the presence of liver homogenate. In TA1537 a weak direct mutagenicity was also observed. In both mammalian test systems, no genotoxicity was found either with or without metabolic activation.

Westendorf et al. 1990 (27) reported on the genotoxicity of several structurally related hydroxyanthraquinones. Frangula bark contains chrysophanol and physcion, albeit in small amounts, and emodin. In the Salmonella microsome assay, emodin, chrysophanol and physcion were weakly mutagenic in strain TA1537 in the presence of S9 mix only. Chrysophanol was also weakly mutagenic in strain T102 without and with exogenous metabolic activation for induction of mutagenicity. No mutagenic effects were observed in the V79-HGPRT mutation assay and in the unscheduled DNA synthesis (UDS) assay for chrysophanol and physcion. Emodin was highly mutagenic in the V79-HGPRT mutation assay. In the UDS assay, emodin was a strong inducer of UDS in primary hepatocytes. Emodin was also tested with respect to its transforming activity in C3H/M2 mouse fibroblasts *in vitro*. Emodin was clearly active in this assay.

Helmholz H et al. 1993 (28) investigated the mutagenic and genotoxic activities of the glycosides emodin and frangulin, of an alcoholic extract of "*Rhamnus frangula*", and of a commercial frangula bark preparation Sanurtin N®, using the *in vitro* salmonella/microsome mutagen test and the deoxyribonucleic acid (DNA) repair test of primary rat hepatocytes. The anthranoid content of 1 g of the alcoholic extract was the following: 50.76 mg glucofrangulin, 86.84 mg frangulin, 30.88 mg emodin, 10.3 mg physcion, and 14.32 mg chrysophanol. One coated tablet of Sanurtin N® contained

8.28 mg glucofrangulin, 0.21 mg frangulin, <0.1 mg emodin, and physcion and chrysophanol only in traces. The tests provided evidence of a dose-dependent increase in the mutation rate or the induction of DNA repair, for the glycosides, the extract of the crude herbal substance and the commercial preparation. The mutagenic potency was larger for emodin than for the alcoholic extract than for frangulin than for Sanurтин N®. The authors concluded that phytotherapeutics based on “*Rhamnus frangula*” can cause genotoxic effects and are potential tumour promoters.

Mengs U et al. 1997 (59) investigated the potential of emodin to induce micronuclei in polychromatic erythrocytes (PCEs). Mice of both genders received a single oral dose of 2,000 mg emodin/kg and were killed 24 and 48 h later. Bone marrow cells were collected from 5 males and 5 females and 2,000 PCEs per animal were scored for the presence of micronuclei. There was no enhancement in the frequency of micronuclei at both preparation intervals when compared to the negative controls. Blood level examinations confirmed the systemic availability of emodin. Plasma levels of up to 190 µg emodin/ml represented concentrations being in the concentration range that induced positive responses in several genotoxicity cell culture assays.

Jahnke GD et al. 2004 (56) evaluated emodin for potential effects on pregnancy outcome. Emodin was administered in feed to timed-mated Sprague-Dawley (CD) rats (0, 425, 850, and 1,700 ppm; gestational day (GD) 6-20), and Swiss Albino (CD-1) mice (0, 600, 2,500 or 6,000 ppm; GD 6-17). Ingested dose was 0, 31, 57, and ~80-144 mg emodin/kg/day (rats) and 0, 94, 391, and 1005 mg emodin/kg/day (mice). Timed-mated animals (23-25/group) were monitored for body weight, feed/water consumption, and clinical signs. At termination (rats: GD 20; mice: GD 17), confirmed pregnant dams (21-25/group) were evaluated for clinical signs: body, liver, kidney, and gravid uterine weights, uterine contents, and number of corpora lutea. Fetuses were weighed, sexed, and examined for external, visceral, and skeletal malformations/variations. There were no maternal deaths. In rats, maternal body weight, weight gain during treatment, and corrected weight exhibited a decreasing trend. Maternal body weight gain during treatment was significantly reduced at the high dose. In mice, maternal body weight and weight gain was decreased at the high dose. Prenatal mortality, live litter size, fetal sex ratio, and morphological development were unaffected in both rats and mice. At the high dose, rat average fetal body weight per litter was unaffected, but was significantly reduced in mice.

The rat maternal lowest observed adverse effect level (LOAEL) was 1,700 ppm; the no observed adverse effect level (NOAEL) was 850 ppm. The rat developmental toxicity NOAEL was ≥ 1,700 ppm. A LOAEL was not established.

In mice, the maternal toxicity LOAEL was 6000 ppm and the NOAEL was 2,500 ppm. The developmental toxicity LOAEL was 6,000 ppm (reduced fetal body weight) and the NOAEL was 2,500 ppm.

No *in vivo* study on reproductive toxicity of frangula bark or frangula bark preparations is available (3).

Conclusion

Experimental data, mainly *in vitro* tests showed a genotoxic risk of several anthranoids (e.g. emodin, chrysophanol, and physcion). However, *in vivo* studies of the crude senna herbal substance (please see the assessment report on “*Cassia senna* L. and *Cassia angustifolia* Vahl, folium”: Chromosome Aberration Test, Mouse Spot Test, *in vivo/in vitro* UDS Test in rat hepatocytes) showed no evidence of any genetic effects (**Heidemann A et al. 1993** (29)). *In vitro* assays overestimate the potential hazard from exposure and must be reevaluated by *in vivo* experiments.

The NOAELs for emodin defined by Jahnke GD are twice the decimal power and above the maximum daily dose of hydroxyanthracene derivatives (30 mg).

However, data on frangula bark and its preparations are insufficient and results of available investigations are not consistent. Use during pregnancy cannot therefore be recommended. Furthermore, other actions like behavioural modification, dietary changes and use of bulk forming agents should be the first actions taken during pregnancy to treat constipation.

Use during lactation is not recommended as there are insufficient data on the excretion of metabolites in breast milk. Investigations with a “standardised senna laxative” (Agiolax®), which also contains *Plantago ovata* seeds/husks as bulk substances, showed that small amounts of active metabolites (rhein) are excreted in breast milk. No laxative effect in breast fed babies has been reported (30).

III.4 Traditional use

Since the 14th century frangula has been used as a medicinal plant. The dried bark has been mostly used as a laxative. Because of its purgative properties, this herbal substance was also used for other diseases like diseases of the liver, gallbladder and spleen, and for dropsy and scabies.

Madaus 1938 (31) describes that in 1556 Hieronymus Bock mentioned frangula bark in his “Kreutterbuch” to cure scurf and affected teeth, but did not mention the laxative properties. He indicates that, in his New-Kreuterbuch in 1626, Matthiolus compared the laxative effect of frangula bark with the effect of rhubarb and that V. Haller in 1755 recommended the use for dropsy. Furthermore Madaus mentions the use for diseases of the liver, gallbladder and spleen, for scabies and as antihelminthic. Frangula bark was also an ingredient in teas used for purification of the blood.

The **British Pharmaceutical Codex 1911** (32), the **Dispensatory of the United States of America 1918** (33) and the **Eclectic Materia Medica, Pharmacology and Therapeutics, 1922** (34) mention frangula bark as a purgative.

In his “Manual of Materia Medica and Pharmacology” **Culbreth 1927** (35) mentions the use as a purgative, tonic and diuretic. The effect resembles that of rhubarb and senna, although milder. Further indications are dropsy, costiveness, constipation during pregnancy and, as an ointment of fresh bark, for parasitic skin affection, itch etc.

Hager 1927 (36) refers to frangula bark as a ‘cheap and effective laxative’. Frangula bark is indicated as also effective for complaints of haemorrhoids and for liver diseases, as a decoction often together with sodium sulphate. Intoxication causes colics, and the fresh bark causes vomiting.

Thoms 1931 (37) also describes the use a mild effective laxative.

Fischer 1966 (38) mentions the use for constipation and all diseases, which can be associated with constipation like liver damage, gallbladder complaints, but even headache and decrease of intellectual power, dizziness, decrease of the ability to see and to concentrate, and heart palpitation.

Dragendorff 1967 (39) describes the emetic effect of fresh bark and the laxative effect of dried bark. Additionally, there is a mention that the bark is externally used for scabies. He does not specify the preparation used.

In **Martindale 1967** (40) frangula bark is described as a mild purgative with properties similar to those of cascara sagrada.

Conclusion

The use of frangula bark as a laxative is mentioned in nearly all above-mentioned references. Due to its laxative properties, the herbal substance was also used as a detoxifier for the blood and other viscera (liver, gallbladder and spleen). In former times such purification was often the first step to treat a lot of diseases. Such a procedure is obsolete now. Furthermore there are no plausible pharmacological data for the purification of the blood and other organs than the bowel.

Rarely the external use of the fresh bark is mentioned. The use in skin affections is surprising because other anthranoid-containing herbal substances, e.g. senna leaves/pods, can cause skin irritations by themselves.

Furthermore the possible risks described in chapter IV have to be taken into account.

None of the above-mentioned uses can therefore be accepted for frangula bark for inclusion in the 'Community list of herbal substances, preparations and combinations thereof for use traditional herbal medicinal products'.

IV. SAFETY

IV.1 Genotoxic and carcinogenic risk

IV.1.1 Preclinical Data

In vivo studies of frangula bark on single dose toxicity, repeated dose toxicity, reproductive toxicity or on carcinogenicity are not available (3).

As mentioned in chapter III.3 Clinical studies in special populations, toxicological data from *in vitro* investigations indicate that several hydroxyanthraquinones might represent a genotoxic risk. However, *in vivo* studies of anthranoid-containing herbal substances (senna) showed no evidence of any genetic effects.

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 (57).

➤ 16-day study in F344/N rats

Groups of 5 male and 5 female rats were fed diets containing 0, 600, 2000, 5,500, 17,000, or 50,000 ppm emodin. This corresponds in males to average daily doses of approximately 50, 170, 480, 1,400, or 3,700 mg emodin/kg bw and in females to 50, 160, 460, 1,250, or 2,000 mg/kg bw. Three female rats died before the end of the study. Mean body weights of males and females exposed to 5,500 ppm or greater were significantly less than those of the controls. Feed consumption by males and females receiving 17,000 or 50,000 ppm was decreased throughout the study. Macroscopic lesions were present in the kidney of rats exposed to 17,000 or 50,000 ppm.

➤ 16-day study in B6C3F₁ mice

The size of the groups and the administered concentrations were the same as described above. The concentrations correspond in males to average daily doses of approximately 120, 400, 1,200 or 3,800 mg/kg bw and in females to 140, 530, 1,600 or 5,000 mg/kg bw. 50,000 ppm equivalents were not calculated due to high mortality. All mice exposed to 50,000 ppm died before the end of the study. Mice in the 17,000 ppm groups lost weight during the study. Feed consumption by 5,500 ppm females was greater than that by the controls throughout the study. Macroscopic lesions were present in the gallbladder and kidney of mice exposed to 17,000 ppm.

➤ 14-week study in rats

Groups of 10 male and 10 female rats were fed diets with 0, 312.5, 625, 1,250, 2,500 or 5,000 ppm emodin. This corresponds to average daily doses of approximately 20, 40, 80, 170, or 300 mg/kg bw in males and females. Among others, relative kidney weights of rats exposed to 1,250 ppm or greater and relative lung weights of rats exposed to 625 ppm or greater were significantly increased compared to the control groups. Relative liver weights were increased in females exposed to 625 ppm or greater. The estrous cycle length was significantly increased in females exposed to 1,250 or 5,000 ppm. All male rats exposed to 1,250 ppm or greater and all exposed female rats had pigment in the renal tubules; and the severity of pigmentation generally increased with increasing exposure concentration. The incidences of hyaline droplets in the cortical epithelial cytoplasm were increased in all groups of exposed males and in females exposed to 312.5, 625, or 1,250 ppm.

➤ 14-week study in mice

The size of the groups and the administered concentrations were the same as described above. This corresponds to average daily doses of approximately 50, 100, 190, 400, or 800 mg/kg in males and 60, 130, 240, 500, or 1,100 mg/kg in females. Relative kidney weights of male mice exposed to 1,250 ppm or greater, relative lung weights of males exposed to 625 ppm or greater, and relative liver weights of female mice exposed to 625 ppm or greater were increased. The incidences and severities of nephropathy were increased in males and females exposed to 1,250 ppm or greater. The incidences of renal tubule pigmentation were significantly increased in males exposed to 1,250 ppm or greater.

➤ 2-year (105 weeks) study in rats

Groups of 65 male and 65 female rats were fed diets containing 0, 280, 830, or 2,500 ppm emodin (equivalent to average daily doses of approximately 110, 320, or 1,000 mg/kg in males and 120, 370, or 1,100 mg/kg in females).

Three Zymbal's gland carcinomas were observed in female rats exposed to 2,500 ppm. This incidence exceeded the range observed for current historical controls and was considered an equivocal finding. At the 6- and 12-month interim evaluations and at 2 years, emodin-related increases in the incidences of renal tubule hyaline droplets occurred in all exposed groups. The incidences of renal tubule pigmentation were significantly increased of all exposed groups of males at 2 years. There were negative trends in the incidences of mononuclear cell leukaemia in male and female rats, and the incidences in the 2,500 ppm groups were significantly decreased. In females exposed to 2,500 ppm, the incidence was below the historical control range; the incidence in males exposed to 2,500 ppm was at the lower end of the historical control range.

➤ 2-year (105 weeks) study in mice

Groups of 60 male mice were fed diets containing 0, 160, 312, or 625 ppm emodin (equivalent to average daily doses of approximately 15, 35, or 70 mg/kg). Groups of 60 female mice were fed diets containing 0, 312, 625, or 1,250 ppm emodin (equivalent to average daily doses of approximately 30, 60, or 120 mg/kg). Low incidences of renal tubule adenoma and carcinoma occurred in exposed male mice; these incidences included one carcinoma each in the 312 and 625 ppm groups. Renal tubule neoplasms are rare in male mice, and their presence in these groups suggested a possible association with emodin exposure. At the 12-month interim evaluation, the severity of nephropathy was slightly increased in males exposed to 625 ppm. Also at 12 months, the severity of nephropathy increased from minimal in the lower exposure groups to mild in females exposed to 1,250 ppm; the incidence in this group was significantly increased compared to the control group. At 2 years, the severities of nephropathy were slightly increased in males exposed to 625 ppm and females exposed to 1,250 ppm. The incidences of nephropathy were significantly increased in all exposed groups of females. At the 12-month interim evaluation, the incidences of renal tubule pigmentation were significantly increased in all exposed groups of males and in females exposed to 625 or 1,250 ppm. The severities increased with increasing exposure concentration. At 2-years, the incidences of renal tubule pigmentation were significantly increased in all exposed groups; severities also raised with increasing exposure concentration.

➤ Genetic toxicology

Emodin was mutagenic in *Salmonella typhimurium* strain TA100 in the presence of S9 activation; no mutagenicity was detected in strain TA98, with or without S9. Chromosomal aberrations were induced in cultured Chinese hamster ovary cells treated with emodin, with and without S9. Three separate *in vivo* micronucleus tests were performed with emodin. A male rat bone marrow micronucleus test, with emodin administered by 3 intraperitoneal injections, gave negative results. Results of acute-exposure (intraperitoneal injection) micronucleus tests in bone marrow and peripheral blood erythrocytes of male and female mice were negative. In a peripheral blood micronucleus test on mice from the 14-week study, negative results were seen in male mice, but a weakly positive response was observed in similarly exposed females.

Conclusion by the “National Toxicology Program’s Board of Scientific Counselors’ Technical Reports Review Subcommittee”:

- The studies give no evidence of carcinogenic activity of emodin in male rats and female mice, and equivocal evidence in female rats and male mice.
- In view of conflicting results on genotoxicity, it was noted the first pass effect and need for metabolic activation suggesting a metabolite as the genotoxic form. The metabolite 2-hydroxyemodin acts as the genotoxin (60).

IV.1.2 Clinical Data

Siegers C-P et al. 1993 (41) reported about a retrospective study of 3,049 patients, who underwent diagnostic colorectal endoscopy. The incidence of pseudomelanosis coli was 3.13% in patients without pathological changes. In those with colorectal adenomas, the incidence increased to 8.64% ($p < 0.01$), and in those with colorectal carcinomas it was 3.29%. This lower rate was probably caused by incomplete documentation of pseudomelanosis coli in those with carcinoma. In a prospective study of 1,095 patients, the incidence of pseudomelanosis coli was 6.9% in patients with no abnormality seen on endoscopy, 9.8% ($p = 0.068$) in patients with adenomas and 18.6% in patients with colorectal carcinomas. From these data a relative risk of 3.04 (1.18, 4.9; 95% confidence interval) can be calculated for colorectal cancer as a result of anthranoid laxative abuse if the pseudomelanosis coli in patients with no abnormality is calculated with 1 %.

Kune GA et al. 1988 (42) and **Kune GA 1993** (43) reported about the “Melbourne Colorectal Cancer Study”. Commercial laxative use as a risk factor in colorectal cancer was investigated as one part of this large population based epidemiological study of colorectal incidence, aetiology and survival. Commercial laxative use was similar in 685 colorectal cancer patients and 723 age/sex matched community based controls. Also, when laxatives were subdivided into various groups containing anthraquinones, phenolphthalein, mineral salts and others, previous laxative intake was similar between cases and controls. Previous use of anthraquinone laxatives and of phenolphthalein containing laxatives was not associated with the risk of colorectal cancer. Furthermore the results of this study suggest that chronic constipation, diarrhoea, and the frequency and consistency of bowel motions are unlikely to be etiologic factors in the development of colorectal cancer. They indicate that it is the diet and not the constipation that is associated with the risk of large-bowel cancer. Additionally, a highly statistically significant association ($p = 0.02$) with the risk of colorectal cancer was found in those who reported constipation and also had a high fat intake.

In a retrospective study a cohort of 2,277 patients was defined by colonoscopy. Among other factors **Nusko G et al. 1993** (44) tested whether in these patients laxative use or the endoscopically diagnosed presence of melanosis coli were risk factors related to colorectal neoplasm. In comparison to patients taking no laxatives, there was no significant increase in colorectal cancer rate either in laxatives users or in patients with melanosis coli. However, there was a statistically significant association between the occurrence of colorectal adenomas and laxative use (relative risk of all patients exposed to laxatives = 1.72; of patients exposed to laxatives without melanosis coli = 1.47). The relative risk of adenoma development in patients with melanosis coli was 2.19. Taking into account that polyps can be diagnosed in the dark mucosa of melanosis coli patients more easily, the authors concluded that even this relative risk of 2.19 seems to be related to a generally enhanced risk of laxative intake rather than to a special group of (anthranoid-containing) laxatives.

Sonnenberg A and Müller AD 1993 (45) performed a meta-analysis, since individual case control studies have failed to resolve the question whether constipation and use of cathartics (purgatives) represent significant risk factors of colorectal cancer. The analysis of 14 previously published (from 1954 to 1988) case control studies revealed statistically significant risks for colorectal cancer associated with both constipation and use of cathartics, the pooled odds ratios (OR) and their 95 percent confidence intervals being 1.48 (1.32-1.66) and 1.46 (1.33-1.61), respectively. The increased risk applied similarly to both sexes, it was higher in cancer of the colon than rectum. Since constipation and cathartics are associated with much lower odds ratios than various dietary

components, such as fat, meat, alcohol, and low-vegetable or low-residue diets, the authors concluded that their risk reflects the confounding influence of underlying dietary habits.

Loew D et al. 1994 (46) conducted a comparative study involving 423 patients with colorectal neoplasms and 522 patients with benign proctologic disorders who were regular users of laxatives for bowel regulation. A pseudomelanosis coli (PMC) test was used as an indicator of exposure to anthranoid-containing laxatives to determine if these preparations were potential colorectal carcinogenics. Results indicated no significant difference of the PMC rates between carcinoma (6.1%) and the control groups (4.2%) ($p \leq 0.197$).

Jacobs EJ et White E 1998 (70) examined the associations of colon cancer with constipation and use of commercial laxatives in a case control study among men and women aged 30 - 62 years (424 incident cases and 414 random-digital-dial controls). Constipation was defined by “feeling constipated to the point of having to take something”. The adjusted relative risk (RR) was 2.0 [95% confidence interval (CI) = 1.2-3.6] for constipation 12-51 times per year, and 4.4 (95% CI = 2.1-8.9) for constipation 52 or more times a year. Cumulative lifetime use of commercial laxatives was also associated with increased risk of colon cancer. When adjusted for constipation, commercial laxative use was no longer associated with increased risk (RR = 0.3, 95% CI = 0.1-0.9 for less than 350 uses; RR = 0.9, 95% CI = 0.4-2.3 for 350 or more uses). The association with constipation remained. In this study, no subject reported use of anthranoid-containing laxatives.

Nusko G et al. 2000 (47) performed a prospective case control study at the University of Erlangen to investigate the risk of anthranoid-containing laxative use for the development of colorectal adenomas or carcinomas. A total of 202 patients with newly diagnosed colorectal carcinomas, 114 patients with adenomatous polyp, and 238 patients (controls) with no colorectal neoplasm who had been referred for total colonoscopy were studied. The use of anthranoid preparations was assessed by standardised interview, and endoscopically visible or microscopic melanosis coli was studied by histopathological examination. There was no statistically significant risk of anthranoid use for the development of colorectal adenomas (unadjusted odds ratio 1.0; 95% CI 0.5-1.9) or carcinomas (unadjusted odds ratio 1.0; 95% CI 0.6-1.8). Even after adjustment for the risk factors age, sex, and blood in the stools by logistic regression analysis the odds ratio for adenomas was 0.84 (95% CI 0.4-1.7) and for carcinomas 0.93 (95% CI 0.5-1.7). Also, there were no differences between the patient and control groups for duration of intake. Macroscopic and high grade microscopic melanosis coli were not significant risk factors for the development of adenomas or carcinomas.

Willems M et al. 2003 (48) described a case of melanosis coli, which occurred in a 39-year old liver transplant 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. From a practical point of view, the authors discouraged the use of anthranoid-containing laxatives, although they stated that “the role of the short-term use of the laxative in the development of this patient’s adenoma is highly speculative” because he “clearly was at risk for developing colonic neoplasm considering his long-standing ulcerative colitis in association with primary sclerosing cholangitis and the use of immunosuppressive medication after liver transplantation”. The authors stated that it remains controversial whether melanosis coli is associated with an increased risk for colorectal cancer because of controversial results of several investigations.

Roberts MC et al. 2003 (71) conducted a population-based, case control study with equal representation by white and black men and women aged 40 – 80 years. Constipation, defined as fewer than three reported bowel movements per week, was associated with a greater than two-fold risk of colon cancer (OR 2.36; 95% CI = 1.41-3.93) adjusted for age, race, sex, and relevant confounders. The OR for constipation was slightly higher for distal than for proximal colon cancers. There was no association with laxative use (OR 0.88; 95% CI = 0.69-1.11). The authors did not explicitly mention anthraquinone-containing laxatives. They mentioned the group “stimulants, fibers, natural remedies,

stool softeners, oils, osmotic agents, enemas, suppositories, and unknown". They mentioned in particular phenolphthalein and magnesium.

Nilsson SE et al. 2004 (49) examined the impact of constipation and laxative treatment on the blood levels of homocysteine, folate and cobalamine in a population-based sample of aged people. Elevated plasma homocysteine secondary to reduced supply of folate and cobalamine, might indicate an increased risk of cancer, and cardiovascular and neurological diseases. The homocysteine level depends on the supply of folate and cobalamine, which constipation and/or laxative treatment might compromise. The study was based on biochemical tests in 341 females and 183 males aged 82 years and older. The concentrations of homocysteine (plasma), folate, cobalamine and urea (serum) were measured in subjects with and without ongoing treatment with laxative products. Values were adjusted for age, gender and frailty, as well as for clinical diagnoses and medicinal therapies known to affect homocysteine levels. Homocysteine levels were increased and those of folate reduced in aged subjects on laxatives. Homocysteine remained elevated after adjusting for frailty and various neurological disorders. There was no significant effect on homocysteine and folate in constipated subjects without laxatives.

Jae Sik Joo et al. 1998 (50) investigated changes occurring on barium enema in patients ingesting stimulant laxatives. The study consisted of two parts. In part 1, a retrospective review of consecutive barium enemas performed on two groups of patients with chronic constipation (group 1, stimulant laxative use (n=29); group 2, no stimulant laxative use (n=26)) was presented to a radiologist, who was blinded to the patient group. A data sheet containing classic descriptions of cathartic colon (historic term for the anatomic alteration of the colon secondary to chronic stimulant laxative use) was completed for each study. Chronic stimulant laxative use was defined as stimulant laxative ingestion more than three times per week for 1 year or longer. To confirm the findings of the retrospective study, 18 consecutive patients, who were chronic stimulant laxative users underwent barium enema examination, and data sheets for cathartic colon were completed by another radiologist (part 2). Colonic redundancy (group 1, 34.5%; group 2, 19.2%) and dilatation (group 1, 44.8%; group 2, 23.1%) were frequent radiographic findings in both patient groups and were not significantly different in the two groups. Loss of haustral folds, however, was a common finding in group 1 (27.6%) but was not seen in group 2 (p<0.005). Loss of haustral markings occurred in 15 (40.5%) of the total stimulant laxative users in the two parts of the study and was seen in the left colon of 6 (40%) patients, in the right colon of 2 (13.3%) patients, in the transverse colon of 5 (33.3%) patients, and in the entire colon of 2 (13.3%) patients. Loss of haustra was seen in patients chronically ingesting bisacodyl, phenolphthalein, senna, and casanthranol. The authors concluded that long-term stimulant laxative use results in anatomic changes in the colon characterised by loss of haustral folds, a finding that suggests neuronal injury or damage to colonic longitudinal musculature caused by these agents.

IV.1.3 Conclusion

Because of the possible genotoxic or tumourigenic risk in experimental investigations and the results of Siegers 1993, pharmacovigilance actions for anthranoid-containing laxatives (2) were initiated in Germany in 1996 : the daily dose and the duration of administration were limited and children, pregnant women and nursing mothers were excluded from the application of frangula bark containing laxatives.

The results of the most recent studies are inconsistent and the question of a possible carcinogenic risk of long-term use of anthranoid-containing laxatives is still open. Some studies revealed a risk for colorectal cancer associated with the use of anthraquinone-containing laxatives, some studies did not. However, a risk was also revealed for constipation itself and underlying dietary habits. Further investigations are needed to determine the carcinogenic risk definitely.

There are also data available suggesting an antitumourigenic effect of emodin, but only to specific cancer cells (see chapter II.2.1 Mode of action).

In his review article **Van Gorkom BA 1999** (51) concluded that although the short-term use of anthranoid laxatives is generally safe, long-term use cannot be recommended.

In “Goodman & Gilman’s The Pharmacological Basis of Therapeutics” (11th edition 2006) (54) the following conclusion is drawn about anthraquinone laxatives: “Regardless of whether a definitive causal relationship can be demonstrated between the use of these agents and colonic pathology, they should not be recommended for chronic or long-term use.”

Taking all available data in consideration, the conditions determined in the above-mentioned pharmacovigilance actions for anthranoid-containing laxatives (2) have to be maintained for the moment.

Long-term administration of anthranoid-containing medicinal products leads to the development over a period of 4 – 13 months of pseudomelanosis coli – pigmentation of the gut wall in the caecum and colon. This condition is produced by the accumulation of macrophages that have stored a brown pigment from the breakdown products of anthranoid (probably lipofuscin) and consequently cause the mucosa to appear brown to blackish-brown in colour. Prevalence among patients with chronic constipation is reported to be 12 – 31%, and 62% following chronic ingestion of anthranoid-containing laxatives. This finding disappears 6 – 12 months after stopping chronic laxative administration. Long-term stimulant laxative use may result in anatomic changes in the colon characterised by loss of haustral folds.

IV.2 Toxicity

Acute toxicity data are available for emodin in mice. The intraperitoneal LD₅₀ (dimethylsulfoxide solvent) is 35 mg/kg; the oral LD₅₀ (dimethylsulfoxide solvent) is greater than 1,000 mg/kg (58).

Repeated dose toxicity studies with emodin was conducted by the National Toxicology Program of the United States of America (see above (57)).

IV.3 Contraindications

Frangula bark preparations should not be used by patients with known hypersensitivity to frangula. The German Health Authority has received one report of an adverse event concerning allergic reactions. After administration of lactulose and frangula extract for constipation, a 74-year old woman developed urticaria the same day and collapsed the next day. She was treated with Hygroton® (hypertension), Rohypnol® (sleep disturbance) and Lexotanil® (nervousness) for a long time. Both medicinal products, lactulose and frangula extract, were regarded as suspect. No further information is available.

Furthermore, like all anthranoid-containing laxatives, frangula bark-containing medicinal products 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.

IV.4 Special warnings and precautions for use

The following warnings and precautions for use are recommended:

Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, have to consult a doctor before taking frangula bark concomitantly (see chapter II.2.2 Interactions).

Like all laxatives, frangula bark 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).

If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of laxatives should be avoided.

Use for more than 1 - 2 weeks requires medical supervision as outlined in the posology section of the Community herbal monograph.

Frangula bark preparations should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.

It cannot be assessed definitely if a longer than a brief period of treatment with stimulant laxatives leads to dependence requiring increasing quantities of the medicinal product, to an atonic colon with impaired function and to aggravation of the constipation.

Müller-Lissner SA 2005 (72) concluded in his review that the arguments in favour of laxative-induced damage to the autonomous nervous system of the colon are based on poorly documented experiments and that, in contrast, the investigations that do not support such damage are well done. The studies in the cited references (Smith B 1968 (73); Riemann JF et al. 1980 (74) and 1982 (75); Berkelhammer C et al. 2002 (76); Meisel JL et al. 1977 (77); Pockros PJ et al. 1985 (78)) showed abnormalities observed in humans (damage to enteric nerves, smooth muscle atrophy; distension or ballooning of axons, reduction of nerve-specific cell structures and increase in lysosomes, and sometimes a total degeneration of whole nerve fibers; short-lived superficial damage to the mucosa). They were uncontrolled observations and the author therefore concluded that the cause of these damages can also be the constipation itself or pre-existing changes of unknown aetiology.

The only study comparing the morphology of the autonomous nervous system of constipated patients taking anthraquinones (aloe) to that of an appropriate control group of constipated patients without laxative intake (**Riecken EO et al. 1990** (79)) did not support the hypothesis that anthraquinone-containing laxatives are able to provoke relevant degenerative changes in the colonic nerve tissue. But this investigation was conducted in 11 matched pairs only.

In the light of existing safety concerns, further warnings and precautions for use are recommended:

If stimulating laxatives are taken for longer than a brief period of treatment, this may lead to impaired function of the intestine and dependence on laxatives.

Patients with kidney disorders should be aware of possible electrolyte imbalance.

When frangula bark preparations are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces (52).

IV.5 Undesirable effects

Like all anthranoid-containing laxatives, frangula bark preparations may produce abdominal pain and colicky gastrointestinal symptoms and passage of liquid stools, in particular in patients with irritable colon. However, these symptoms may also occur generally as a consequence of individual overdosage. In such cases dose reduction is necessary. The correct individual dose is the smallest required to produce a comfortable soft-formed motion (2).

As mentioned above, hypersensitive reactions may occur.

Chronic use may lead to disorders in water equilibrium and electrolyte metabolism.

Dahlmann W et al. 1977 (53) reported the case of a 39-year old woman, who developed hypokalaemia (1.5 mmol/l) with generalised paralysis, reversible organic brain syndrome, and cardiac dysrhythmias after 15 years of laxative use (Tirgon®, a combination preparation of 5 mg bisacodyl, 30 mg Extr. Cort. Frangulae spir. Sicc., 4 mg Extr. Rhei, 1.5 mg Ol. Carvi, 1.5 mg Ol. Ment. pip.). Under continuous and cautious administration of potassium the cardiac rhythm became normal within four days and two days later the paralysis and organic brain syndrome almost disappeared. The cause of the psychiatric symptoms is thought to be cerebral potassium deficiency and an abnormal sodium/potassium equilibrium.

Chronic use may result in albuminuria and haematuria.

Furthermore, use over a long period may lead to pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation (see chapter IV.1.3 Conclusion).

Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment (see chapter II.1.2 Absorption, metabolism and excretion).

IV.6 Interactions

See chapter II.2.2

IV.7 Overdose

Like for all anthranoid-containing laxatives, the 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 supportive 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

Beuers U et al. 1991 (80) reported a case of toxic hepatitis related to abuse of senna glycosides in a 26-year old female, who had taken an extract of senna fruits corresponding to 100 mg of sennoside B daily in addition to the usual dose of 10 g senna leaves twice a week in a laxative tea. When the patient stopped taking senna, aminotransferases fell by 70% within a week and ranged from 20 – 40 U/l subsequently. When the patient took senna alkaloids again, 2 months later, liver function rapidly deteriorated and improved once more when the product was stopped.

Vanderperren B et al. 2005 (81) reported a case of a 52-year old woman, who had ingested, for more than 3 years, one litre of an herbal tea each day made from a bag containing 70 g of dry senna fruits. She developed renal impairment and acute hepatic failure with increase in prothrombin time (international normalised ratio > 7) and development of encephalopathy. The patient recovered with supportive therapy. Surprisingly, large amounts of cadmium were transiently recovered in the urine.

According to the Rucam score (Roussel UCLAF causality assessment method - for detailed information, please see the assessment report on "*Cassia senna* L. and *Cassia angustifolia* Vahl, folium"), these hepatotoxic cases are related to the chronic ingestion of overdoses. *Rhamnus frangula* L., cortex being an anthranoid-containing herbal substance, the possibility of toxic hepatic reactions is referred to in the section 'Overdose' of the Community herbal monograph on frangula bark.

V. OVERALL CONCLUSION

Well-established use: short term use in cases of occasional constipation

There are no recent clinical investigations available, which evaluate frangula bark alone, i.e. not in combination with other laxatives, in a representative study population. Two non-controlled investigations of the seventies assessed the efficacy of a combination preparation in patients with constipation. This preparation contains 27.75 mg hydroxyanthracene derivatives, of which nearly 50% derive from frangula bark, and the bulk forming agent methyl cellulose. A contribution of frangula bark to the efficacy of the investigated preparation is deducible.

The postulated laxative effect of frangula bark is mainly based on pharmacological data, experts' opinions and clinical experiences. Clinical and pharmacological data obtained on other anthranoid-containing laxatives (primarily senna leaf preparations) and the 2 non-controlled investigations with Laxariston® support the efficacy of this anthranoid-containing herbal substance for short-term use in cases of occasional constipation.

The current level of evidence¹ of the available scientific data for “the short-term use of occasional constipation” can be identified as level III to IV because well-designed studies with mono-preparations of frangula bark are missing, but 2 uncontrolled investigations are available.

The conditions determined in the pharmacovigilance actions for anthranoid-containing laxatives have to be maintained for the moment because further investigations are needed to clarify the carcinogenic risk. The results of the most recent studies are inconsistent. However, a risk was also revealed for constipation itself and underlying dietary habits.

The use in children under 12 years of age is contraindicated and use during pregnancy and lactation is not recommended.

Traditional use

Due to its laxative properties, frangula bark was used as a detoxifier for the blood and other viscera. In former times, such a purification was often the first step to treat a lot of diseases. Such a procedure is now obsolete. There are no plausible pharmacological data related to the purification of the blood and other organs than the bowel.

External use of frangula bark was rare and preparations used are not described exactly. The use in skin affections is actually surprising because anthranoid-containing laxatives can cause skin irritations.

In view of existing possible risks, such traditional uses cannot be recommended and referred to in the ‘Community list of herbal substances, preparations and combinations thereof for use traditional herbal medicinal products’. This is in accordance with the German pharmacovigilance actions for anthranoid-containing laxatives.

¹ As referred to in the HMPC ‘Guideline on the assessment of clinical safety and efficacy in the preparation of Community herbal monographs for well-established and of Community herbal monographs/entries to the Community list for traditional herbal products/substances/preparations’ (EMEA/HMPC/104613/2005)