EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Rhamnus frangula* L. cortex

Draft - Revision

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Rhamnus frangula* L. (*Frangula alnus* Miller), cortex
Herbal preparation(s)	Comminuted herbal substance or preparations thereof, standardised
Pharmaceutical form(s)	*Standardised herbal substance as herbal tea for oral use*
Rapporteur(s)	L. Anderson (revision); C. Werner (first version)
Assessor(s)	L. Anderson (revision); C. Werner (first version)
Peer-reviewer	J. Wiesner

Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Rhamnus frangula* L., cortex. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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List of abbreviations

ADP	adenosine diphosphate
ATP	adenosine triphosphate
ED_{50}	half maximal effective concentration
ESCOP	European Scientific Cooperative on Phytotherapy
HAD	hydroxyanthracene derivatives
IFN-gamma	Interferon gamma
LPS	lipopolysaccharide
NTP	National Toxicology Program
PAF	platelet-activating factor
PGE1	prostaglandin E1
Ph. Eur.	European Pharmacopoeia
TNF-alpha	tumor necrosis factor alpha

1. Introduction

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

- Herbal substance

Frangula bark
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. Ph. Eur. 9:0025).

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, dianthrones and the aglycones emodin and emodin-9-anthrone (Wagner and Horhammer 1969, Labadie 1970, Hörhammer and Wagner 1972, Wagner and Demuth 1974, Lemli and Cuveele 1978.

Lemli (1965) 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 oxidisation 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 (Van Os 1976). Therefore, the bark should not be used before at least 1 year, so that oxidation of the anthrones can take place.

- Herbal preparations

Frangula bark is used as comminuted herbal substance. There is also a standardised dry extract of frangula bark described in the European Pharmacopoeia. Standardised Frangula bark dry extract (Ph. Eur. 9:1214) is produced from frangula bark (Ph. Eur. 9:0025). The extract is produced from the herbal drug by a suitable procedure using ethanol (50-90 per cent V/V). It contains not less than 15.0 per cent and not more than 30.0 per cent of glucofrangulins, expressed as glucofrangulin A ($C_{27}H_{30}O_{14}$; Mr 578.5) (dried extract). The measured content does not deviate from that stated on the label by more than ± 10 per cent.

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

Not applicable.

1.2. Search and assessment methodology

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

Search engines used: Google

Scientific databases: PubMed, DIMDI, SciFinder

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

Toxicological databases: ToxLine

Pharmacovigilance resources: Vigilance central

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

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

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

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

2. Data on medicinal use

2.1. Information about products on the market

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

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Frangulae cortex	Herbal medicinal product for short-term use in cases of occasional constipation.	Herbal tea for oral use; Adults and children from 10 years: 0.5 g/150 ml boiling water 1 cup of tea daily	WEU, DE, authorised 1990, Standard Marketing Authorisation according to section 36 of the German Medicinal Products Act

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

Information on relevant combination medicinal products marketed in the EU/EEA
Not applicable

Information on other products marketed in the EU/EEA (where relevant)
Not applicable

2.1.2. Information on products on the market outside the EU/EEA
Not applicable

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

Since the 16th century frangula has been used as a medicinal plant (Madaus 1938). The dried bark has been mostly used as a laxative. Due to its purgative properties, this herbal substance was also used for other diseases such as diseases of the liver, gallbladder and spleen, and for dropsy and scabies.

Madaus (1938) 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 mentioned 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), the Dispensatory of the United States of America (Remington and Wood 1918) and the Eclectic Materia Medica, Pharmacology and Therapeutics (Felter 1922) mention frangula bark as a purgative.

In his “Manual of Materia Medica and Pharmacology” Culbreth (1927) mentions the use as a purgative, tonic and diuretic. The effect is reported to resemble 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 affections, itch etc.

Frerichs *et al*. (1927) 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) also describes the use as a mild effective laxative.

Fischer (1966) 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) describes the emetic effect of fresh bark and the laxative effect of dried bark. Additionally, there is a mention that the bark is used externally for scabies. He does not specify the preparation used.

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

The accepted historical use of frangula bark led to the establishment of the German Kommission E Monograph (Kommission E 1993), the European Scientific Cooperative on Phytotherapy (ESCOP) monograph on Frangula Bark (2017) and the WHO monograph (2002). German pharmacovigilance actions for anthranoid-containing laxatives including frangula bark were instigated in June 1996 which

were intended as a framework for the safe use of hydroxyanthracene derivatives (HAD) containing herbal medicinal products (Bundesinstitut für Arzneimittel und Medizinprodukte 1996).

Table 2: Overview of historical data

Herbal preparation	**Documented Use / Traditional Use**	**Pharmaceutical form,** **Strength, Posology** **Duration of use**	**Reference**
Frangulae cortex	Constipation	Cut bark, powder or dried extracts for teas, decoction, cold maceration or elixir. Liquid or solid forms of medication exclusively for oral use. 20 - 30 mg HAD daily, calculated as glycofrangulin A. The correct individual dose is the lowest achieve a soft formed stool.	Frangulae cortex (Kommission E monograph 1993)
Frangulae cortex	For short-term use in cases of occasional constipation	The correct individual dose is the smallest required to produce a comfortable soft formed motion. Adults and children from 10 years on: Preparations equivalent to 20-30 mg HAD, calculated as glycofrangulin A, to be taken once daily at night.	Frangulae cortex ESCOP Monograph 2017
Frangulae cortex	Short-term use in occasional constipation	The correct dosage is the smallest necessary to produce a soft stool. Daily dosage: 0.5-2.5g taken directly or in a decoction; 0.5-2.5 ml 25% ethanol extract. Adults and children over 12 years: standardized daily dose equivalent to 20–30mg hydroxyanthracene derivatives (calculated as glucofrangulin A) taken at bedtime, or in two divided doses, one in the morning and one at bedtime.	WHO monographs on selected medicinal plants. Volume 2, 2002

2.3. Overall conclusions on medicinal use

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

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

The recommended dosage as a laxative for adults, elderly and adolescents over 12 years (20 – 30 mg hydroxyanthracene derivatives once daily at night) is supported by experts' opinions and by clinical investigations with other hydroxyanthracene-containing laxatives, notably preparations of senna and aloes (see assessment reports on *Senna alexandrina* Mill. (EMA/HMPC/228759/2016) and *Aloe barbadensis* Mill. (EMA/HMPC/759585/2015). Following the approach in these monographs to minimise the amount used, the range recommended is 10 - 30mg hydroxyanthracene derivatives daily.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Comminuted herbal substance	Short-term use in cases of occasional constipation	Herbal tea preparation Daily dose: 10-30 mg hydroxyanthracene derivatives, calculated as glucofrangulin A	Standard Marketing Authorisation in DE (1990); Kommission E monograph (1993)

3. Non-Clinical Data

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

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

3.1.1. Primary pharmacodynamics

Laxative effect
Frangula bark belongs to the stimulant laxatives.

Data on herbal preparations
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 took place after 4 h in 20% of the mice; after oral administration of 100 mg/kg body weight in 40% of the mice (no information concerning negative control). The ED_{50} was mentioned with 121.5 mg/kg body weight (Vogel 1975 cited also in Blaschek *et al*. 2003).

A methanolic extract (Soxhlet) of frangula bark (containing 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 183mg/kg body weight (bw). The ED_{50} of another frangula extract with 25% glucofrangulin, 1.5% frangulin and 0.5% aglyka was 122.5 mg/kg bw (Longo 1980).

Data on hydroxyanthracene derivatives
Cresseri *et al*. (1966) investigated different HAD constituents of frangula bark to evaluate the laxative effect in comparison to a standard senna leaf extract (amount of anthranoids not stated) 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 used, although for glucofrangulin there were signs of a reduction concerning the relative effectiveness. The effect of emodin was comparable to the effect of the senna extract. Physcion and chrysophanol had no noteworthy effect.

In mice with a weight of 20 g the ED_{50} of pure glucofrangulin A was 398.5 mg/kg bw, of pure frangulin A 118.5 mg/kg bw and of pure emodin 233.5 mg/kg bw after oral administration (Longo 1980).

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 (De Witte 1993).

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

Herbal preparation tested	**Posology**	**Experimen-tal model**	**Reference**	**Main non-clinical conclusions**
Herbal preparations				
methanolic extract of frangula bark (17.5% anthranoid glycosides calculated as 1,8-dihydroxyanthraquinon-glycoside)	oral administration of 50 mg/kg bw oral administration of 100 mg/kg bw	*in vivo* mice	Vogel, 1975 cited also in Blaschek *et al*. 2003	defaecation after 4 h in 20% mice defaecation after 4 h in 40% mice (no information concerning negative control)
methanolic extract of frangula bark (23% glucofrangulin, 2% frangulin, 0.5% aglyka) frangula extract with 25% glucofrangulin, 1.5% frangulin and 0.5% aglyka	oral gavage 25 ml/kg bw (0.5 ml/mouse): 3 doses of standard solution (frangulin A) and 3 doses of sample in 12 animals Initial doses: 75-180 mg/kg bw in aqueous solution with 1% tragacanth gum (average doses with fair activity).	*in vivo* mice	Longo, 1980	ED_{50}: 183 mg/kg bw ED_{50}: 122.5 mg/kg bw
Hydroxyanthracene derivatives				
Glucofrangulin Frangulin		in vivo mice	Cresseri *et al*. 1966	laxative effect of glucofrangulin and frangulin nearly 4 to 5 times stronger than an undefined senna extract. for glucofrangulin

Herbal preparation tested	Posology	Experimen-tal model	Reference	Main non-clinical conclusions
				signs of a reduction concerning the relative effectiveness
glucofrangulin A frangulin A emodin	oral gavage 25 ml/kg bw (0.5 ml/mouse): 3 doses of standard solution (frangulin A) and 3 doses of sample in 12 animals Initial doses: 75-180 mg/kg bw in aqueous solution with 1% tragacanth gum (average doses with fair activity).	*in vivo* mice	Longo, 1980	ED_{50}:398.5 mg/kg bw ED_{50}:118.5mg /kg bw ED_{50}: 233.5 mg/kg bw

3.1.2. Secondary pharmacodynamics

Antifungal effect

Data on herbal preparations

An alcoholic extract (details not provided) 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 (Guerin and Reveilliere 1984).

Manojlovic *et al*. (2005) reported the results of a preliminary antifungal screening of the methanol extracts of *Rhamnus frangula* and *Rubia tinctorum* and the major anthraquinone aglyka, alizarin (1,2-dihydroxyanthracene) and emodin (1,8-dihydroxyanthracene), 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 aglyka 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% and18%; *Alternaria alternata* 39% and 56%; *Aueobasidium pullulans* 46% and 41%; *Mucor mucedo* 68% and 48%.

Antiviral effect

Data on herbal preparations

Sydiskis *et al*. (1991) tested the virucidal effects of hot glycerine extracts from *Rheum officinale, Aloe barbadensis, Rhamnus frangula, Rhamnus purshianus*, and *Cassia angustifolia* against herpes simplex

virus type 1. All the plant extracts inactivated the virus. The active constituents in these plants were separated by thin-layer chromatography and identified as anthraquinones.
Anthraquinone glycosides should be ineffective. The extract of *Rhamnus frangula* was completely virucidal after 15 min incubation with herpes simplex virus type 1. The ID_{50} was 0.35 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.

Effect on platelet aggregation

Data on hydroxyanthracene derivatives

Teng *et al*. (1993) 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 trimucytin which was reported to be a collagen receptor agonist isolated from *Trimeresurus muscrosquamatus* 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

Data on hydroxyanthracene derivatives

Wei *et al*. (2001) 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-stimulated murine microglial cell lines N9.

3.1.3. Safety pharmacology

There are no data for frangula preparations.

3.1.4 Pharmacodynamic interactions

For interactions see section 5.5.4.

Conclusions

There are limited data for frangula bark preparations. The pharmacodynamic data available show a laxative effect in mice which supports the use of frangula bark preparations in cases of constipation. It is generally assumed, by analogy with other HAD-containing laxatives, such as senna, that the mode of action is similar.

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 "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016)).

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

Data on herbal preparations

There are no data for frangula preparations.

Data on hydroxyanthracene derivatives

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

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

3.3.1. Single dose toxicity

Data on herbal preparations

In vivo studies of frangula bark on single dose toxicity are not available.

3.3.2. Repeat dose toxicity

Data on herbal preparations

In vivo studies of frangula bark on repeated dose toxicity are not available.

Data on hydroxyanthracene derivatives

Emodin

In 2001 the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services published a technical report on toxicology and carcinogenesis studies of emodin (NTP 2001).
For discussion and conclusions - see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

3.3.3. Genotoxicity

Data on herbal preparations

Limited genotoxicity studies for frangula bark preparations are available.

Helmholz *et al*. (1993) investigated the mutagenic and genotoxic activities of an alcoholic extract of "Rhamnus frangula" (100 g powder extracted with 500 ml ethanol 70%; no further information given), and of the glycosides emodin and frangulin, using the in vitro salmonella/microsome mutagen test (TA 1537, only) 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. The tests provided evidence of a dose-dependent increase in the mutation rate or the induction of DNA repair, for the glycosides and the extract of the crude herbal substance. The mutagenic potency was larger for emodin than for the alcoholic extract than for frangulin. The authors concluded that phytotherapeuticals based on "Rhamnus frangula" can cause genotoxic effects and are potential tumour promoters.

Data on hydroxyanthracene derivatives

Emodin

In 2001 the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services published a technical report on toxicology and carcinogenesis studies of emodin (NTP 2001).
For discussion and conclusions - see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

See Helmholz *et al*. (1993) above.

Frangulin

See Helmholz *et al*. (1993) above.

3.3.4. Carcinogenicity

Data on herbal preparations

There are no data for frangula preparations.

Data on hydroxyanthracene derivatives

Emodin

In 2001 the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services published a technical report on toxicology and carcinogenesis studies of emodin (NTP 2001).
For discussion and conclusions - see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

3.3.5. Reproductive and developmental toxicity

In vivo studies of frangula bark on reproductive toxicity are not available.

3.3.6. Local tolerance

There are no studies available regarding local tolerance.

3.3.7. Other special studies

There are no data for frangula preparations.

3.3.8. Conclusions

There are limited data for frangula preparations.

3.4 . Overall conclusions on non-clinical data

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

The use during pregnancy is contraindicated in the monograph because experimental data raise concerns about a potential genotoxic risk for several anthranoids, e.g. emodin and aloe-emodin.

4. Clinical Data

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

4.1. Clinical pharmacology

See the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

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

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 (Schultz 1950).

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

There are no data for frangula preparations.

4.2. Clinical efficacy

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

4.2.1. Dose response studies

There are no dose-finding studies available for frangula preparations.

4.2.2. Clinical studies (case studies and clinical trials)

Constipation

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

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

Children

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

Conclusion on clinical studies in special populations

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

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no recent clinical studies available which evaluate frangula bark alone and not in combination with other laxatives in a representative population in the indication, constipation.
The postulated laxative effect is mainly based on the pharmacological data, experts' opinions and clinical experiences.

5. Clinical Safety/Pharmacovigilance

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

There are no clinical safety studies on frangula bark preparations.

Children

There are no data on use of frangula bark preparations in children.
See the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016) for discussion on senna use in children.

5.2 Patient exposure

There are no data for frangula bark preparations.

5.3 Adverse events, serious adverse events and deaths

As for all anthranoid-containing laxative, 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

See the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016); cases of hepatotoxicity are reported related to the chronic ingestion of overdoses. There are no reports associated with the use of frangula bark preparations.

Nephritis

See the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).
There are no reports associated with the use of frangula bark preparations.

Melanosis coli

See the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016), folium and fructus).

Willems *et al.* (2003) 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. Since there had been preliminary reports suggesting a possible role of anthranoid-containing laxatives in the development of colorectal adenomas and cancer, the authors discouraged their use.

5.4 Laboratory findings

No data available.

5.5 Safety in special populations and situations

Elderly

No data available.

5.5.1 Use in children and adolescents

The use in children is contraindicated (see section 5.5.2)

5.5.2 Contraindications

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

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

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

5.5.3 Special Warnings and precautions for use

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 (Kommission E 1993).

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

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

The following warnings and precautions for use are recommended:

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

5.5. 4 Drug interactions and other forms of interaction

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

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

The above-mentioned investigations of Teng *et al*. (1993) showed an antagonistic effect of frangulin B to collagen receptors in platelet membranes. 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 thrombocyte

aggregation. Data are insufficient to date and it is not possible to advise on such concomitant use in the European Union monograph.

5.5.5 Fertility, pregnancy and lactation

There are no data for frangula bark preparations.

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

Lactation

There are no data on use of frangula preparations and possible excretion of metabolites into breast milk. However, animal experiments demonstrated that placental passage of rhein from other HADs is small (see assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016)).

Conclusion on fertility, pregnancy and lactation.

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

No fertility data are available.

5.5.6 Overdose

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

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

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

5.5.8 Safety in other special situations

No data available.

5.6 Overall conclusions on clinical safety

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

6. Overall conclusions (benefit-risk assessment)

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

Well-established use:

short-term use in cases of occasional constipation

WHO ATC: A06AB07

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.
There are no well-designed non-experimental descriptive studies with mono-preparations of frangula bark available which investigate the short-term use in occasional constipation. Evidence is obtained from pharmacological data, experts' reports and opinions and extensive clinical experiences as well as reference to related HAD-containing herbal preparations viz. senna leaf and aloe preparations.

Clinical and pharmacological data obtained on other anthranoid-containing laxatives (primarily senna leaf preparations) support the efficacy of this anthranoid-containing herbal substance for short-term use in cases of occasional constipation.

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

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

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

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

Annex

List of references