EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 September 2019
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Committee on Herbal Medicinal Products (HMPC)

European Union herbal monograph on *Rhamnus frangula* L., cortex

Final – Revision 1

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Discussion in Working Party on European Union monographs and European Union list (MLWP)	January 2006 March 2006
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End of consultation (deadline for comments).	30 June 2006
Re-discussion in MLWP	September 2006
Adoption by HMPC Monograph (EMEA/HMPC/76307/2006) AR (EMEA/HMPC/76306/2006) List of references (EMEA/HMPC/76304/2006) Overview of comments received during the public consultation (EMEA/HMPC/342513/2006) HMPC Opinion (EMEA/HMPC/429405/2006)	07 September 2006
First systematic review	
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BG (bulgarski): Зърнастец, кора CS (čeština): krušinová kůra DA (dansk): Frangulabark DE (Deutsch): Faulbaumrinde EL (elliniká): φλοιός φραγκούλης EN (English): frangula bark ES (español): frángula, corteza de ET (eesti keel): paakspuukoor FI (suomi): paatsaman, kuori FR (français): bourdaine (écorce de) HR (hrvatski): krkavinina kora HU (magyar): kutyabengekéreg IT (italiano): Frangola corteccia	LT (lietuvių kalba): Šaltekšnių žievė LV (latviešu valoda): Krūkļa miza MT (Malti): qoxra tal-alaternu NL (Nederlands): Vuilboombast PL (polski): Kora kruszyny PT (português): amieiro negro, casca RO (română): scoarţă de cruşîn SK (slovenčina): kôra krušiny SL (slovenščina): skorja navadne krhlike SV (svenska): brakved, bark IS (íslenska): NO (norsk): frangulabark

European Union herbal monograph on *Rhamnus frangula* L., cortex

1. Name of the medicinal product

To be specified for the individual finished product.

2. Qualitative and quantitative composition[1, 2]

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC. *Rhamnus frangula* L. (*Frangula alnus* Miller), cortex (frangula bark) i) Herbal substance Not applicable ii) Herbal preparations Comminuted herbal substance or herbal preparations thereof, standardised	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC.

3. Pharmaceutical form

Well-established use	Traditional use
Standardised comminuted herbal substance as herbal tea for oral use. Standardised herbal preparations in liquid or solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.	

4. Clinical particulars

4.1. Therapeutic indications

Well-established use	Traditional use
Herbal medicinal product for short-term use in	

[1] The declaration of the active substance(s) for an individual finished product should be in accordance with relevant herbal quality guidance.

[2] The material complies with the Ph. Eur. monographs (ref.: 0025; 1214)

Well-established use	Traditional use
cases of occasional constipation.	

4.2. Posology and method of administration[3]

Well-established use	Traditional use
Posology *Adolescents, adults, elderly* *Single dose:* Herbal preparation equivalent to 10–30 mg hydroxyanthracene derivatives, calculated as glucofrangulin A, to be taken once daily at night. The correct individual dose is the smallest required to produce a comfortable soft-formed motion. Herbal tea: amount of comminuted herbal substance equivalent to not more than 30 mg hydroxyanthracene derivatives in 150 ml of boiling water as herbal infusion The use in children under 12 years of age is contraindicated (see section 4.3 Contraindications). The pharmaceutical form must allow lower dosages. **Duration of use** Not to be used for more than 1 week. Usually it is sufficient to take this medicinal product up to two to three times during that week. If the symptoms persist during the use of the medicinal product, a doctor or a pharmacist should be consulted. See also section 4.4 Special warnings and precautions for use. **Method of administration** Oral use	

[3] For guidance on herbal substance/herbal preparation administered as herbal tea or as infusion/decoction/macerate preparation, please refer to the HMPC 'Glossary on herbal teas' (EMA/HMPC/5829/2010 Rev.1).

4.3. Contraindications

Well-established use	Traditional use
Hypersensitivity to the active substance. Cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis), abdominal pain of unknown origin, severe dehydration state with water and electrolyte depletion. Pregnancy and lactation (see section 4.6 and 5.3). Children under 12 years of age.	

4.4. Special warnings and precautions for use

Well-established use	Traditional use
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, have to 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). When preparations containing frangula bark are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces. Patients with kidney disorders should be aware of	

Well-established use	Traditional use
possible electrolyte imbalance. If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted. For liquid dosage forms containing ethanol the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.	

4.5. Interactions with other medicinal products and other forms of interaction

Well-established use	Traditional use
Hypokalaemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides and interacts with antiarrhythmic medicinal products. Concomitant use with diuretics, adrenocorticosteroids and liquorice root may enhance loss of potassium.	

4.6. Fertility, pregnancy and lactation

Well-established use	Traditional use
Pregnancy The use during pregnancy is contraindicated because of experimental data concerning a genotoxic risk of several anthranoids, e.g. emodin and frangulin. **Lactation** The use during lactation is contraindicated because after administration of anthranoids, active metabolites, such as rhein, were excreted in breast milk in small amounts. **Fertility** No fertility data are available (see section 5.3 preclinical safety data).	

4.7. Effects on ability to drive and use machines

Well-established use	Traditional use
No studies on the effect on the ability to drive and use machines have been performed.	

4.8. Undesirable effects

Well-established use	Traditional use
Hypersensitivity: Hypersensitivity reactions (pruritus, urticaria, local or generalised exanthema) may occur. Gastrointestinal disorders: Frangula bark may produce abdominal pain and spasm 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. Furthermore, chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation. Kidney and urinary tract symptoms: Long term use may lead to water and electrolyte imbalance and may result in albuminuria and haematuria. Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment. The frequencies are not known. If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.	

4.9. Overdose

Well-established use	Traditional use
The major symptoms of overdose/abuse are griping pain and severe diarrhoea with consequent losses of fluid and electrolytes. Treatment should	

Well-established use	Traditional use
be supportive with generous amounts of fluid. Electrolytes, specifically potassium, should be monitored. This is particularly important in the elderly. Chronic ingested overdoses of anthranoid containing medicinal products may lead to toxic hepatitis.	

5. Pharmacological properties

5.1. Pharmacodynamic properties

Well-established use	Traditional use
Pharmacotherapeutic group: contact laxatives Proposed ATC-code: A06AB 1.8-dihydroxyanthracene derivatives possess a laxative effect. Glucofrangulins and frangulins are respectively *O*-diglycosides and *O*-monoglycosides, which are largely (all *β*-*O*-glycosides) not split by human digestive enzymes in the upper gut and therefore not absorbed to large extent. They are converted by the bacteria of the large intestine into the active metabolite (emodin-9-anthrone). There are two different mechanisms of action: 1. Stimulation of the motility of the large intestine resulting in accelerated colonic transit. 2. Influence on secretion processes by two concomitant mechanisms: (i) inhibition of absorption of water and electrolytes (Na^+, Cl^-) into the colonic epithelial cells (anti-absorptive effect) and (ii) increase of the leakiness of the tight junctions and stimulation of secretion of water and electrolytes into the lumen of the colon (secretagogue effect) resulting in enhanced concentrations of fluid and electrolytes in the lumen of the colon. Defaecation occurs after a delay of 8-12 hours following laxative intake due to the time taken for transport to the colon and metabolisation into the active compound.	

5.2. Pharmacokinetic properties

Well-established use	Traditional use
The β-*O*-linked glycosides are not split by human digestive enzymes and therefore not absorbed in the upper gut to large extent. They are converted by the bacteria of the large intestine into the active metabolite (emodin-9-anthrone). Mainly anthraquinone aglycones are absorbed and transformed into their corresponding glucuronides and sulphate derivatives. Rhein, emodin and traces of chrysophanol are found in human urine after oral administration of frangula bark extract. Active metabolites, such as rhein, pass in small amounts into breast milk. Animal experiments demonstrated that placental-passage of rhein is low.	

5.3. Preclinical safety data

Well-established use	Traditional use
There are no preclinical tests available on frangula bark preparations. In the *in vitro* salmonella/microsome mutagen test and the deoxyribonucleic acid (DNA) repair test of primary rat hepatocytes emodin and frangulin, an alcoholic extract of “Rhamnus frangula”, and a commercial frangula bark preparation showed a dose-dependent increase in the mutation rate or the induction of DNA repair. Studies with emodin (a constituent of frangula bark preparations) revealed effects on oestrus cycle length and nephropathy in mice. Furthermore, several hydroxyl anthracene derivatives were mutagenic and genotoxic in several *in vitro* test systems, however this was not proven in *in vivo* systems. In long term carcinogenicity studies effects on kidneys and colon/caecum were reported. The reproductive toxicity observed was linked to maternal toxicity due to diarrhoeal effects.	

6. Pharmaceutical particulars

Well-established use	Traditional use
Not applicable	

7. Date of compilation / last revision

25 September 2019