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Evaluation of Medicines for Human Use

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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

FINAL

COMMUNITY HERBAL MONOGRAPH ON *RHAMNUS FRANGULA* L., CORTEX

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[1] Changes introduced in sections 4.9 and 5.1

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COMMUNITY 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[2, 3]

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC, as amended *Rhamnus frangula* L. (*Frangula alnus* Miller), cortex (frangula bark) • Herbal substance dried, whole or fragmented bark of the stems and branches, standardised • Herbal preparation standardised herbal preparations thereof	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC, as amended

3. PHARMACEUTICAL FORM

Well-established use	Traditional use
Standardised herbal substance or herbal preparation for oral use in solid or liquid dosage forms. 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 cases of occasional constipation.	

[2] The material complies with the Ph. Eur. monographs.
[3] The declaration of the active substance(s) should be in accordance with relevant herbal quality guidance.

4.2. Posology and method of administration

Well-established use	Traditional use
Posology The maximum daily dose of hydroxyanthracene glycosides is 30 mg. This is equivalent to ....(dose of the preparation). The correct individual dose is the smallest required to produce a comfortable soft-formed motion. *Adolescents over 12 years of age, adults, elderly* Herbal substance/preparation equivalent to 10 – 30 mg hydroxyanthracene derivatives, calculated as glucofrangulin A, to be taken once daily at night. Normally it is sufficient to take this medicinal product up to two to three times a week. Not recommended for use in children under 12 years of age (see section 4.3 Contraindications). The pharmaceutical form must allow lower dosages. **Method of administration** As described in the package leaflet corresponding to the pharmaceutical form. **Duration of use** Use for more than 1 - 2 weeks requires medical supervision. 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.	

4.3. Contraindications

Well-established use	Traditional use
Known hypersensitivity to the active substance. 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 state with water and electrolyte depletion. Children under 12 years of age.	

4.4. Special warnings and precautions for use

Well-established use	Traditional use
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 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. If stimulant laxatives are taken for longer than a brief period of treatment, this may lead to impaired function of the intestine and dependence on laxatives. Frangula bark preparation should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents. When frangula bark preparations 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 possible electrolyte imbalance.	

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, with medicinal products, which induce reversion to sinus rhythm (e.g. quinidine) and with medicinal products inducing QT-prolongation. Concomitant use with other medicinal products inducing hypokalaemia (e.g. diuretics, adrenocorticosteroids and liquorice root) may enhance electrolyte imbalance.	

4.6. Pregnancy and lactation

Well-established use	Traditional use
Pregnancy There are no reports of undesirable or damaging effects during pregnancy and on the foetus when used at the recommended dosage. However, as a consequence of experimental data concerning a genotoxic risk of several anthranoids, e.g. emodin, frangulin, chrysophanol and physcion, use is not recommended during pregnancy. **Lactation** Use during breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in breast milk. After administration of other anthranoids, active metabolites, such as rhein, are excreted in breast milk in small amounts. A laxative effect in breast fed babies has not been reported.	

4.7. Effects on ability to drive and use machines

Well-established use	Traditional use
Not relevant.	

4.8. Undesirable effects

Well-established use	Traditional use
Hypersensitivity reactions may occur. 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. Chronic use may lead to disorders in water equilibrium and electrolyte metabolism and may result in albuminuria and haematuria. Furthermore, chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation. Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment. 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, 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, adrenocorticosteroids or liquorice root 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. 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:
Pharmaco-therapeutic group: contact laxatives ATC-code: A 06 AB 1,8-dihydroxyanthracene derivatives possess a laxative effect. Glucofrangulins and frangulins are respectively 0-diglycosides and 0-monoglycosides, which are largely (all β-0-glycosides) not split by human digestive enzymes in the upper gut and therefore not absorbed to a large extent. They are converted by the bacteria of the large intestine into the active metabolites (emodin-9-anthrone). There are two different mechanisms of action: 1. stimulation of the motility of the large intestine resulting in accelerated colonic transit.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

2. influence on secretion processes by two concomitant mechanisms *viz*. 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) resulting in enhanced concentrations of fluid and electrolytes in the lumen of the colon. The motility effects are mediated by direct stimulation of colonic neurons and possibly by prostaglandins. Defaecation takes place after a delay of 8 - 12 hours 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-0-linked glycosides are not split by human digestive enzymes and therefore not absorbed in the upper gut to a 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. After oral administration of frangula bark extract, rhein, emodin and traces of chrysophanol are found in human urine. After administration of other anthranoids, active metabolites, such as rhein, pass in small amounts into breast milk. Animal experiments demonstrated that placental-passage of rhein is low.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

5.3 Preclinical safety data

Well-established use	Traditional use
There are no studies on single dose toxicity, on repeated dose toxicity, on reproductive toxicity or on carcinogenicity. Experimental data, mainly *in vitro* tests showed a genotoxic risk of several anthranoids in the Salmonella microsome assay, emodin, chrysophanol and physcion were weakly mutagenic. 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 string inducer of	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended, unless necessary for the safe use of the product.

UDS in primary hepatocytes. Emodin was also tested with respect to its transforming activity in C3H/M2 mouse fibroblasts *in vitro*. 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. However, *in vivo* studies of other anthranoid-containing herbal substance (senna) in rat hepatocytes (chromosome aberration test, mouse spot test, *in vivo*/*in vitro* UDS (unscheduled DNA synthesis) showed no evidence of any genetic effects. Further 2-year studies on male and female rats and mice with emodin gave no evidence of carcinogenic activity for male rats and female mice, and equivocal evidence for female rats and male mice. Laxative use as a risk factor in colorectal cancer (CRC) was investigated in some clinical trials. Some studies revealed a risk for CRC 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 assess the carcinogenic risk definitely.	

6. PHARMACEUTICAL PARTICULARS

Well-established use	Traditional use
Not applicable.	

7. DATE OF COMPILATION/LAST REVISION

26 October 2006