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COMMITTEE FOR HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

COMMUNITY HERBAL MONOGRAPH ON FRANGULA BARK (FRANGULAE CORTEX)

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COMMUNITY HERBAL MONOGRAPH ON FRANGULA BARK (FRANGULAE CORTEX)

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished products.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC, as amended **Active ingredients** Frangula bark in the crude or processed state in appropriate dosage units **Definition** 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.[1] **Constituents** 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. There are also small quantities of other anthraquinone glycosides, dianthrones and the aglycones emodin and emodin-9-anthrone.	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 crude or processed herbal substance	

[1] The herbal substance complies with the European Pharmacopoiea.

for oral preparation in solid or liquid dosage forms (to be specified for the individual finished product). The pharmaceutical form should be described according to the standard terms by the European Pharmacopoeia.	

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Well-established use	Traditional use
For short term use in cases of occasional constipation.	None

4.2. Posology and method of administration

Well-established use	Traditional use
Dosage 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 at night. The dosage refers to one administration. The pharmaceutical form must allow lower dosages. **Method of administration** For oral administration	

4.3. Contraindications

Well-established use	Traditional use
Patients with known hypersensitivity to frangula should not use frangula bark preparations. Not to 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. Children under 12 years.	

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 a 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. If stimulating laxatives are taken for longer than a brief period of treatment, this may lead to dependence requiring increasing quantities of the medicinal product, an atonic colon with impaired function and aggravation of the constipation. 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.	

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

Well-established use	Traditional use
The absorption of orally administered medicinal products may be reduced. 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** Breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in breast milk. Small amounts of active metabolites (rhein) are excreted in breast milk after ingestion of a senna preparation. 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 known	

4.8. Undesirable effects

Well-established use	Traditional use
Hypersensitive reactions may occur very rarely. Very rarely 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/abuse may lead to disorders in water equilibrium and electrolyte metabolism. 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. Chronic use 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.	

4.9. Overdose

Well-established use	Traditional use
The major symptoms are griping pain and severe diarrhoea with consequent losses of fluid and electrolyte, which should be replaced. Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly and the young.	

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 mechanisms of action: 1. an influence on the motility of the large intestine (inhibition of the Na^+/K^+pump and of the Cl^- channels at the colonic membrane) resulting in accelerated colonic transit. 2. an influence on secretion processes (stimulation of mucus and chloride secretion) resulting in enhanced fluid secretion. 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.	Not required as per Article 16 c(1)(a) iii) of Directive 2001/83/EC, as amended

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. Active metabolites, e.g. rhein, pass in small amounts into breast milk. Animal experiments demonstrated that placental-passage of rhein is small.	Not required as per Article 16 c(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 UDS in primary hepatocytes. Emodin was has 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. Commercial laxative use as a risk factor in colorectal cancer was investigated in some clinical trials. The results of the more recent studies are	Not required as per Article 16 c(1)(a) iii) of Directive 2001/83/EC, as amended

inconsistent and the possibility of a carcinogenic risk of long-term use of anthranoid-containing laxatives cannot be assessed definitely.	

6. DATE OF COMPILATION

9 March 2006