European Medicines Agency
Evaluation of Medicines for Human Use

London, 7 September 2007
Doc. Ref. EMEA/HMPC/513579/2006 *Corr.*

FINAL

COMMUNITY HERBAL MONOGRAPH ON *RHAMNUS PURSHIANUS* D.C., CORTEX

DISCUSSION IN IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST (MLWP)	January 2007 March 2007
ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	8 March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	15 June 2007
REDISCUSSION IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST (MLWP)	September 2007
ADOPTION BY HMPC	7 September 2007

KEYWORDS	Herbal medicinal products; HMPC; Community herbal monographs; well-established use; *Rhamnus purshianus* D.C.; Rhamni purshianae cortex; cascara

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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 as amended *Rhamnus purshianus* D.C. (*Frangula purshiana* (D.C.) A. Gray ex J.C. Cooper), cortex (cascara) i) Herbal substance dried, whole or fragmented bark, standardised ii) Herbal preparations 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 in solid or liquid 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 cases of occasional constipation.	

[1] The material complies with the Ph. Eur. monographs (Cascara ref. 01/2005:0105; Cascara dry extract, standardised ref. 01/2007:1844).
[2] The declaration of the active substance(s) for an individual finished product 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 cascaroside 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. The pharmaceutical form must allow lower dosages. The use in children under 12 years of age is contraindicated (see section 4.3 Contraindications). **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 section 4.4 Special warnings and precautions for use). **Method of administration** As described in the package leaflet corresponding to the pharmaceutical form.	

4.3. Contraindications

Well-established use	Traditional use
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, corticosteroids or liquorice root, have to consult a doctor before taking cascara concomitantly. Like all laxatives, cascara 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. Cascara preparations should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents. When cascara 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, corticosteroids 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. aloe-emodin, 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. Cascara 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, corticosteroids 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. Cascarosides A and B are mixed anthrone-C- and O-glycosides, Cascarosides C, D, E and F are 8-O-β-D-glucosides, which are largely 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 (mainly 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 *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.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

Defaecation takes place after a delay of 6 - 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 (mainly emodin-9-anthrone). The absorbed anthraquinone aglycones are transformed into their corresponding glucuronides and sulphate derivatives. It is not known to what extent aloe-emodin-9-anthrone is absorbed. However, in the case of senna, animal experiments with radio-labeled rhein-anthrone administered directly into the caecum show that only a very small proportion (less than 10%) of rhein-anthrone is absorbed. 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 recent studies on single dose toxicity, on repeated dose toxicity, or on reproductive toxicity. Experimental data, mainly *in vitro* tests showed a genotoxic risk of several anthranoids in the *Salmonella/* microsome assay, aloe-emodin, 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. Aloe-emodin showed a significant increase in net grains/nucleus. 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 showed a dose-dependent increase in the mutation	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.

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. In *in vivo* studies (micronucleus assay in bone marrow cells of NMRI mice; chromosome aberration assay in bone marrow cells of Wistar rats; mouse spot test [DBA/2J x NMRI]) no indication of a mutagenic activity of aloe emodin was found. 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. Dietary exposure of rats to high doses of the anthraquinone glycosides of cascara for 56 successive days did not cause appearance of aberrant crypti foci (ACF) or increase of incidence of ACF induced by 1,2-dimethyl-hydrazine (DMH). However, in rats treated with both DMH and the highest dose of glycosides, the average number of aberrant crypts per focus, considered a consistent predictor of tumour outcome, was higher than in rats given DMH alone. Rats were treated with azoyxmethane (AOM) and 140 and 420 mg/kg cascara (alone or in combination) for 13 weeks. Cascara did not induce the development of colonic aberrant crypti foci (ACF) and tumours and did not modify the number of AOM-induced ACF and tumours in both doses. 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

7 September 2007