6 May 2020
EMA/HMPC/909434/2019
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Rhamnus purshiana* DC., cortex

Final – Revision 1

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 purshiana* DC., cortex
Herbal preparation(s)		Comminuted herbal substance or preparations thereof, standardised
Pharmaceutical form(s)		Standardised herbal substance as herbal tea for oral use. Standardised herbal preparations in liquid or solid dosage forms for oral use.
First assessment	Rapporteur(s)	W. Knöss
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Table of contents

List of abbreviations

ACF	aberrant crypt foci
ADP	adenosine diphosphate
AOM	azoxymethane
ATP	adenosine triphosphate
DMH	1,2-dimethyl-hydrazine
ED_{50}	half-maximal effective concentration
ESCOP	European Scientific Cooperative on Phytotherapy
HAD	hydroxyanthracene derivatives
LPS	lipopolysaccharide
NO	nitric oxide
NTP	National Toxicology Program
PAF	platelet-activating factor
PGE1	prostaglandin E1
RIA	radioimmunoassay
TNF-alpha	tumor necrosis factor alpha

1. Introduction

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

- Herbal substance

***Rhamnus purshiana* DC. cortex or Cascara bark**

Cascara consists of the dried, whole or fragmented bark of *Rhamnus purshiana* DC. (*Frangula purshian* Benichou *a* (DC.) A. Gray. It contains not less than 8.0% of hydroxyanthracene glycosides of which not less than 60% consists of cascarosides, both expressed as cascarosides A ($C_{27}H_{32}O_{14}$; Mr 580.5) and calculated with reference to the dried herbal substance. This complies with the European Pharmacopeia monograph "Cascara Bark" (Ph. Eur. 9:0105).

Active constituents

The constituents with known therapeutic activity of cascara are cascarosides A, B, C, D, E and F (Wagner and Demuth 1976, Griffini *et al.,* 1992, Hänsel *et al.,* 1994, Manitto *et al.,* 1995).

Cascarosides A and B are mixed anthrone-C- and O-glycosides, being the 8-O-β-D-glucosides of 10-(S)-desoxyglucosyl aloe-emodin anthrone and 10-(R)-desoxyglucosyl aloe-emodin anthrone (aloins A and B) respectively, they are diastereo-isomers.

Cascarosides C and D are the 8-O-β-D-glucosides of 10-(R)(S)-desoxyglucosyl chrysophanol anthrone (chrysaloins A and B).

Cascarosides E and F are the 8-O-β-D-glucosides of 10-(R)(S)-desoxyglucosyl emodin anthrone. The total hydroxyanthracene complex of the dried bark consists of 60-70% cascarosides, 10-30% aloins A and B together with chrysaloins A and B and 10-20% of a mixture of hydroxyanthracene O-glycosides including the monoglucosides of aloe-emodin, chrysophanol, emodin and physicion together with the corresponding aglyka (HagerRom 2003).

The fresh bark contains mono-anthrone-O-glycosides, dianthrones, C-glycosides, aloe-emodin-O-glycosides and free anthrones. Eighty (80)-90% of the free anthrones are bound as C-glycosides and 10-20% are bound as O-monoanthrone glycosides. During the drying procedure the mono-anthrones and their O-glycosides, which cause undesirable emetic effects, are oxidized to dianthrone- and anthraquinone-O-glycosides. These forms are free of these unwanted effects (Van Os 1976).

- Herbal preparation(s)

Cascara bark is used as comminuted herbal substance. Additionally, some extracts are also standardised to a defined content of hydroxyanthracene glycosides.

A standardised dry extract of cascara bark is described in the European Pharmacopoeia (Ph. Eur. 9:1844). Standardised cascara bark dry extract is produced from cascara bark (Ph. Eur. 9:0105). The extract is produced from the herbal substance by a suitable procedure using either boiling water or a hydroalcoholic solvent, at least equivalent in strength to ethanol (60% V/V). It contains not less than 8.0% and not more than 25.0% of hydroxyanthracene glycosides, of which not less than 60% consists of cascarosides, both expressed as cascarosides A ($C_{27}H_{32}O_{14}$; Mr 580.5). The measured content does not deviate from the value stated on the label by more than +/- 10%.

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

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 cascara bark preparations compared to the more commonly used stimulant laxatives 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**
Rhamnus purshiana DC. cortex (Cascara	For short-term use in cases of occasional	Herbal tea for oral use; Adults and children	WEU, DE, authorised 1990, Standard

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
cortex)	constipation.	from 10 years: 0.45 g/150 ml boiling water 1 cup of tea daily	Marketing Authorisation according to section 36 of the German Medicinal Products Act
Dry extract of *Rhamnus purshiana* DC. cortex (4.2-5.6:1) 57-108 mg, equivalent to 20 mg hydroxyanthracene derivatives, calculated as cascaroside A, extraction solvent: ethanol 52% (m/m)	For short-term use in cases of occasional constipation.	Film-coated tablet >12 years: 1-1.5 tablet; once daily	since 1976, DE, WEU
Liquid extract of *Rhamnus purshiana* DC. cortex (1:1.0-1.2) 500 mg, equivalent to 20 mg hydroxyanthracene derivatives, calculated as cascaroside A, extraction solvent: ethanol 30% (m/m)	For short-term use in cases of occasional constipation.	Oral liquid 1 g =1 ml= 30 drops >12 years: 30-50 drops in a half cup of hot water; once daily	since 1976, DE, WEU
Powdered Herbal Substance (*Rhamnus purshiana* DC. cortex)	For short-term use in cases of occasional constipation	Tablets containing 320 mg corresponding to 26.88 mg/tablet hydroxyanthracene glycosides calculated as cascaroside A. Posology for adults and adolescents: The maximum daily dose of hydroxyanthracene glycosides is 30 mg. This is equivalent to 1 tablet per day.	Authorised as WEU in June 2010, ES. It was previously registered by the former registration scheme for herbal products (Registration date: July 2005).
Powdered Herbal Substance (*Rhamnus purshiana* DC. cortex)	For short-term use in cases of occasional constipation	Capsules containing 250 mg corresponding to 20 mg/capsule hydroxyanthracene glycosides calculated as	Authorised as WEU in May 2011, ES. It was previously registered by the

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		cascaroside A. Posology for adults and adolescents: One capsule per day.	former registration scheme for herbal products (Registration date: January 1996).

This overview is not exhaustive. It is provided for information only and it 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

Historically the dried, aged bark of *Rhamnus purshiana* is called "cascara sagrada" ('sacred bark' in Spanish) (Madaus 1938/1976), a name that is still today used in some publications. The trees are native to the Pacific coast of North America from British Columbia to California (Trease and Evans 1972). In Evans (2009) it is pointed out that a cascara, probably *Rhamnus californica*, was known to early Mexican and Spanish priests of California, while *Rhamnus purshiana* was not described until 1805 and its bark was not introduced into medicine until 1877 by Dr. J. H. Bundy (Evans 2009; Parke Davis & Company 1885; Trease and Evans 1972).

The medicinal use of cascara cortex as a purgative or laxative is known in Europe since 1880 (Madaus 1938/1976). British Pharmaceutical Codex (1911), "Hagers Handbuch der Pharmazeutischen Praxis" (Frerichs *et al.*, 1927), and Martindale, 25th edition (Todd 1967) all indicate such a use.

The Eclectic Materia Medica, Pharmacology and Therapeutics (Felter 1922) refers to the use in cases of sick headache due to atonic sluggishness of the bowels. Cascara was also used in gastric and duodenal catarrh, with jaundice, and in chronic diarrhoea when accompanied by hepatic torpor.

Madaus (1938/1976) reports that Clarke (1853-1931) also indicated its use for rheumatic complaints in his material medica, published 1900-1902.

Martindale (Todd 1967) describes the action of cascara as a bitter stomachic given in small dose before meals.

Dragendorff (1967) compares the use of cascara with the use of frangula bark. Fresh bark has an emetic effect and dried bark a laxative effect. Additionally, the bark is used externally for scabies. The preparation or the underlying pharmacological action was not specified.

The dispensatory of the United States of America (Remington and Wood 1918) describes the use of cascara as vegetable cathartic.

The accepted historical use of cascara bark led to the establishment of the German Kommission E Monograph (Kommission E 1993), the European Scientific Cooperative on Phytotherapy (ESCOP) monograph on Cascara Bark (ESCOP 1999) and the WHO monograph (WHO 2002). German pharmacovigilance actions for anthranoid-containing laxatives including cascara 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**
Rhamnus purshiana DC. cortex	Cases of 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 cascaroside A. The correct individual dose is the lowest achieve a soft formed tool.	Kommission E monograph 1993
Rhamnus purshiana DC. cortex	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 cascaroside A, to be taken once daily at night.	ESCOP monograph 1999
Rhamnus purshiana DC. cortex	Short-term use in cases of 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 cascaroside 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 cascara bark as a laxative for use in constipation is recognised and well documented in authoritative texts. Based on the products authorised in the European Union and with regard to demonstrating an acceptable level of safety (see later sections), the 10 years of well-established use can be accepted for cascara bark (see Table 3).

In view of the standardisation and the known mode of action of hydroxyanthracene glycosides, the HMPC agreed to define the herbal preparations 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 based on the well-established use is mentioned.

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 10-30 mg 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 (*Rhamnus purshiana* DC. cortex) Powdered herbal substance Containing 20-30 mg hydroxyanthracene derivatives, calculated as cascaroside A	Short-term use in cases of occasional constipation	Herbal tea preparation corresponding to 20-26.88 mg/dosage form hydroxyanthracene derivatives Daily dose: 10-30 mg hydroxyanthracene derivatives, calculated as cascaroside A	Standard Marketing Authorisation in DE (1990); Kommission E (1993) since 1996 and 2005, ES; WEU
Dry extract of *Rhamnus purshiana* DC. cortex (4.2-5.6:1) 57-108 mg, equivalent to 20 mg hydroxyanthracene derivatives, calculated as cascaroside A, extraction solvent: ethanol 52% (m/m)	Short-term use in cases of occasional constipation	Film-coated tablet >12 years: 1-1.5 tablet; once daily	since 1976, DE, WEU
Liquid extract of *Rhamnus purshiana* DC. cortex (1:1.0-1.2) 500 mg, equivalent to 20 mg hydroxyanthracene derivatives, calculated as cascaroside A, extraction solvent: ethanol 30% (m/m)	Short-term use in cases of occasional constipation	Oral liquid 1 g =1 ml= 30 drops >12 years: 30-50 drops in a half cup of hot water; once daily	since 1976, DE, WEU

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

Cascara bark belongs to the stimulant laxatives.

Data on herbal preparations

Investigations of D'Angelo (1993) suggest that the laxative effect is to be attributed to qualitative rather than quantitative changes in colonic motility. He developed a computerised method for quantitative analysis of colonic motility in the conscious dog and applied it to the study of the motor effects of cascarosides and their metabolites administered directly into the colonic lumen.

Dose-response studies were carried out with a standardised cascara extract (containing 40% of cascarosides A, B, C and D), aloin, aloe-emodin and aloin-emodin anthrone. With the exception of the extract, which was active only at 60 mg/kg, all the compounds in the 30-60 mg/kg dose-range induced defaecation. The defaecation was usually accompanied by the occurrence of propagating spike bursts. However, overall colonic spike activity was not affected by any of the compounds tested in the 10-60 mg/kg dose-range. The latency of the extract and aloin-induced defaecation was significantly longer than the latency of the other compounds. The difference in the latency for induction of defaecation is probably due to pharmacokinetic factors; the extract and aloin are pro-drugs and require hydrolysis by bacterial glycosidases in order to be active on the colon, while aloe-emodin and aloe-emodin anthrone are the active metabolites.

Cohen (1982) dosed rats (gastric gavage) with the cathartics cascara, phenolphthalein, senna or ricinoleic acid with or without a 3-day pre-treatment with indomethacin. Limited details are available on the cascara and senna preparations administered (cascara: 100 µl/kg fluid extract; senna: 2 tablets/kg). Jejunum, proximal and distal ileum and colon were assayed for prostaglandin E (PGE) content by RIA. Without pre-treatment, the mean concentration of PGE-like material was higher than control in the proximal ileum (with phenolphthalein), in the jejunum, proximal and distal ileum (with ricinoleic acid), and in the colon (with senna), although only in the latter case was this statistically significant. Cascara did not show any noteworthy increase. Indomethacin significantly reduced the PGE content of all tissue in all treatment groups, but did not completely prevent the increase in PGE content induced by phenolphthalein, senna and ricinoleic acid. In addition, cascara also showed in this case a significant increase in the colon. The author concluded that the contact cathartics increase PGE-synthesis by the gastro-intestinal tract and this could in part explain their action.

Investigations of Izzo *et al.*, (1996, 1997) suggest that nitric oxide (NO) is a possible mediator for the laxatives effect of anthranoid-containing products. Senna (fruit extract containing 45% sennoside B; 60 mg/kg p.o.) and cascara (bark extract containing 20% cascaroside A; 800 mg/kg p.o.) *ex vivo* significantly increased Ca^{2+} dependent constitutive NO synthase activity in the rat colon. Induction of NO synthase (12% of the total NO synthase) was associated with cascara, but not senna, administration. Dexamethasone, which inhibits the expression of the inducible NO synthase, significantly and dose-dependently reduced cascara- (but not senna-) induced diarrhoea and colonic fluid secretion. The authors concluded that senna probably exerts its laxative effect through stimulation of the constitutive isoform of NO synthase, while the inducible isoform of NO synthase also seems to be involved in the laxative effect of cascara.

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

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Herbal preparations				
Cascara extract (standardised 40% cascarosides A, B, C, D) Aloin Aloe-emodin Aloe-emodin anthrone	Administration to colonic lumen 30-60 mg/kg	*in vivo* in dogs	D'Angelo, 1993	All compounds in 30-60 mg/kg dose-range induced defaecation with the exception of the extract, which was active only at 60 mg/kg.
Cascara (fluid extract 100 µl/kg; no further details) phenolphthalein (16 mg/kg) senna (2 tablets; no further details) ricinoleic acid (4 ml/kg)	with or without a 3-day pre-treatment with indomethacin	*in vivo* in rats: gastric gavage jejunum, proximal and distal ileum and colon were assayed for PGE content by RIA	Cohen, 1982	Contact cathartics increase PGE-synthesis by the gastro-intestinal tract and this could in part explain their action.
Senna fruit extract (45% sennoside B) Cascara bark extract (20% cascaroside A)	60 mg/kg p.o. 800 mg/kg p.o.	*ex vivo* rat colon	Izzo *et al.*, 1996; 1997	Both extracts significantly increased Ca^{2+} -dependent constitutive NO synthase activity. Induction of NO synthase (12% of the total NO synthase) was associated with cascara, but not senna, administration.

3.1.2. Secondary pharmacodynamics

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.

3.1.3. Safety pharmacology

There are no data for cascara preparations.

3.1.4. Pharmacodynamic interactions

For interactions, see section 5.5.4.

Conclusions

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

Emodin-9-anthrone is the most important metabolite that 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 (anti-absorptive 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 derive also from other anthranoid-containing herbal substances, however 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 cascara 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 herbal preparations (De Witte and Lemli 1990). Most studies involve senna preparations and constituents thereof (see the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016)).

The role of intestinal bacteria in formation of active metabolites of the cascarosides and their derivatives has been investigated *in vitro* by Dreessen and Lemli (1988). When incubated with caecal extract from germ free rats cascarosides A and B or C and D were not metabolised. For animals, having conventional gut microflora there was a distinction between rats and guinea pigs. The incubates from guinea pigs produced the C-glycosides barbaloin and desoxy-aloin, while these from rats were able to further metabolise the C-glycosides into aloe-emodin anthrone or chrysophanol anthrone and small amounts of aloe-emodin or chrysophanol. After 48 hours incubation unchanged cascarosides

were not recovered. When incubated with the Streptococcus species, the cascarosides were hydrolysed to barbaloin or desoxy-aloin, respectively, but no further chemical reduction took place (no metabolic components have been detected).

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 cascara bark on single dose toxicity are limited.

Schmidt (1955) reported no mortality in rats after a single oral administration of cascara sagrada (no further details provided) at 6 g/kg and of aloin at 7.5 g/kg body weight (b.w.). The amount of hydroxyanthracene derivatives is not reported.

3.3.2. Repeat dose toxicity

Data on herbal preparations

In vivo studies of cascara bark on repeated dose toxicity are limited.

Schmidt (1955) investigated chronic toxicity *in vivo* in rats by administration of 600 mg/kg b.w./day cascara (no further details provided) daily for 3 months. Eosinophilic precipitations were found in the renal tubules, and the rats developed a fatty liver. Laboratory tests showed negative results. The amount of hydroxyanthracene derivatives is not reported.

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 cascara bark preparations are 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).

3.3.4. Carcinogenicity

Data on herbal preparations

Borelli *et al*., (2001) investigated the effects of bisacodyl, a synthetic organic compound used as laxative drug (4.3 and 43 mg/kg) together with cascara (140 and 420 mg/kg: no further details provided) on azoxymethane (AOM)-induced aberrant crypt foci (ACF) and tumours. Rats were divided

in 10 groups and treated with AOM and laxatives (alone or in combination) for 13 weeks. At the end of treatment, animals were killed and the colon removed and examined. Cascara did not induce the development of colonic ACF and tumours nor did it not modify the number of AOM-induced ACF and tumours in both doses.

Bisacodyl given alone did not induce the development of colonic ACF and tumours in both doses, too. However, bisacodyl (4.3 mg/kg) coupled with AOM increased the number of crypt per focus, but not the number of tumours. Bisacodyl (43 mg/kg) significantly increased the number of crypt per focus and tumours. The authors concluded that the results of this study indicate the absence of any promoting or initiating activity of a laxative and diarrhoeal dose of cascara. However, the information on the cascara preparation tested is limited and the results conflict with the findings of Mereto *et al.* (1996), see below, who reported weak promoting effects of cascara and senna HADs. Taking account of the absence of confirmatory studies on defined preparations this potential safety concern is considered unresolved.

Data on hydroxyanthracene derivatives

Mereto *et al.* (1996) investigated anthraquinone glycosides of senna (standardised sennosides A and B; 0.1% or 0.2% of diet) and cascara (mixture of standardised cascarosides A, B, C and D: 0.05% or 0.1% of diet) for their ability to induce ACF in the rat colon mucosa, which are considered putative pre-neoplastic lesions. Dietary exposure (0.1% of the diet) of these glycosides for 56 successive days did not cause appearance of 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. These findings suggest that senna and cascara glycoside might behave as weak promoters in rat carcinogenesis.

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 cascara 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 cascara preparations.

3.3.8. Conclusions

There are limited data for cascara preparations.

3.4. Overall conclusions on non-clinical data

There are limited data for cascara 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

For anthranoid-containing laxatives in general it is referred to 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

Laxative effect

There are no data for cascara preparations.

Other effects

Foert *et al*., (1994) conducted a study to evaluate if a fluid extract of cascara leads to a reduction of gallbladder volume in healthy human subjects. Sufficient gallbladder-motor function was documented by a more than 50% reduction of gallbladder-volume after a test-meal. Gallbladder-emptying was compared to placebo by ultrasonography using the ellipsoid method. Gallbladder-volume was measured in intervals of 10 min for a period of 120 min. On day 1, all subjects had the test meal. On day 2 and 3 cascara extract or placebo were given in random order. Twenty volunteers received 2 ml, 20 received 3 ml containing 36 mg or 54 mg Cascaroside A, respectively. Cascaroside A (54 mg) caused a significant gallbladder contraction. This effect was more rapid but less intense than after the test meal.

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

There are limited data for cascara preparations.

Vyth and Kamp (1979) isolated aloe-emodin, emodin and chrysophanol from a powdered cascara extract after oxidative hydrolysis. After oral administration of 60 mg or 100 mg of a powdered cascara extract in 2 volunteers, rhein and traces of chrysophanol were found in human urine. Because rhein was not present in the administered extract, the authors suggested a process in the body in which for example chrysophanol is oxidised to rhein.

4.2. Clinical efficacy

There are limited clinical studies with cascara 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 assessment reports for 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 cascara preparations.

4.2.2. Clinical studies (case studies and clinical trials)

Constipation
The only available clinical investigations of cascara bark as a laxative evaluate its efficacy in combination preparations. There are no controlled clinical studies available.

Bowel cleansing effect

Investigations to assess the bowel cleansing effect of cascara have been conducted with a combination of a cascara preparation and a saline cathartic (magnesium sulphate). Therefore, the effectiveness of cascara alone cannot be assessed. In any event, the combination preparation with cascara was inferior to an oral solution of polyethylene glycol 3350 and electrolytes regimen.

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 cascara bark as a laxative in children.

Elderly

When cascara preparations are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces because of the experiences in children wearing sanitary napkins.

Conclusion on clinical studies in special populations
The data available are not sufficient to show the efficacy and safety of cascara 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 a vast amount of data regarding the use of osmotic laxatives whereas data on cascara preparations are lacking.

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no clinical studies available that evaluate cascara bark alone or 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 cascara bark preparations.

Children
There are no data on use of cascara bark preparations in children.

It is referred to 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 cascara 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 adreno-corticosteroids 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
For anthranoid-containing laxatives in general it is referred to the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016); cases of hepatotoxicity are reported related to the chronic ingestion of overdoses.

The following report is associated specifically with the use of a cascara bark preparation.

Nadir *et al*., (2000) reported a case of a severe cholestatic hepatitis in a 48-year-old Mexican male, who developed right upper quadrant pain, nausea, anorexia, abdominal bloating, and yellowing of his skin with increase of the liver enzymes 3 days after using cascara, one capsule three times a day for 3 days. Each of these capsules contained 425 mg of aged cascara bark, having a reported 5% cascaroside potency (21.25 mg). He concomitantly used amitriptyline 25 mg at bedtime, cimetidine 400 mg, and baclofen 10 mg twice a day. With the exception of cascara, these medications were continued. The patient was known to use alcohol in moderate amounts for up to 3 years prior to this event. One week later, he was known to have ascites. Over the next 3 months, the patient experienced resolution of both his ascites and jaundice.

The Roussel UCLAF causality assessment method has been developed to assess cases of liver impairment. In 1993, an international group of experts published the so-called RUCAM Score to evaluate cases of hepatotoxicity (Danan and Benichou 1993). The score was validated and the results published (Benichou *et al*., 1993).

Assessment
Rucam Score +2 unlikely: The liver injury in this case is classified as a mixed liver injury. ALT increased to 999 U/L (normal range 7-56 U/L) and alkaline phosphatase to 309 U/L (normal range 43-122 U/L). No information is given of the course of these parameters. The time to onset was less than 5 days. Moderate use of alcohol is known. Baclofen and amitriptyline are known to cause increase of liver enzymes. No re-challenge took place. The ingested dose of cascara was twice the recommended.

Nephritis
For anthranoid-containing laxatives in general it is referred to the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).
There are no specific reports associated with the use of cascara bark preparations.

Adesunloye (2003) described a case of a 52-year-old woman with haemoglobin SC disease, who developed acute tubule-interstitial nephritis after 5-day administration of a herbal remedy called CKLS. Following haemodialysis, the renal function improved. CKLS comprises a mixture of ingredients, among

which are *Aloe vera*, chamomile, cascara, chaparral (creosote bush), mullein (*Verbascum thapsus*), uva ursi, fenugreek, cayenne, dandelion, and eucalyptus. It is supposed to be a colon, kidney, liver, and spleen purifier. The authors concluded that the nephrotoxicity observed was most likely caused by *Aloe vera* and cascara. However, uva ursi has been associated with albuminuria, haematuria, and urine cast, and chaparral with cystic renal disease and cystic renal cell carcinoma. There is no detailed information available concerning the exact preparation and amount of anthranoids. The causality cannot be assessed.

Melanosis coli
For anthranoid-containing laxatives in general it is referred to the assessment report on "*Senna alexandrina* Mill." (EMA/HMPC/228759/2016).

For cascara bark specifically, the German Health Authority has received 2 reports of adverse events.

Melanosis coli was detected in a 42 year old woman after administration of a mono-preparation of cascara for 4 years.

Urticaria
A patient developed urticaria taking a combination of cascara and a saline agent. The patient concomitantly used mebeverine, but cascara was considered to be the suspect medication.

Giavina-Bianchi *et al*., (1997) reported a case of a 30 year old man, who had been working for 2 years in a pharmacy where he weighed and prepared chemical products without using a mask, gloves, or other protective measures. The man started to experience episodes of sneezing, coryza, and nasal pruritus and congestion after 6 months of work. Later he developed a dry cough, chest pain, sensations of chest tightening, dyspnoea, and wheezing. The symptoms worsened when he entered the pharmacy, and when he manipulated capsules containing cascara and passion flower preparations. Laboratory tests showed 14% eosinophilia with 8,000 leukocytes / µl and total IgE levels of 1130 IU/ml. The prick test was positive for cascara and passion flower at all dilutions tested.

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

Cascara bark preparations should not be used by patients with known hypersensitivity to cascara.

Furthermore, as with all anthranoid-containing laxatives, cascara 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).

Cascara 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 cascara 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

Cascara 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 the 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 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.
- Cascara 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, QT-prolongation inducing medicinal products, diuretics, adrenocorticosteroids or liquorice root, should consult a doctor before taking cascara bark concomitantly.
- Like all laxatives, cascara 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 cascara 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 cascara 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 and 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.

5.5.5. Fertility, pregnancy and lactation

There are no data for cascara bark preparations.

As with other HAD preparations, it is possible in theory, 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 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 cascara preparations and possible excretion of metabolites into breast milk. However, animal experiments demonstrated that placental passage of rhein from other HADs is low (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 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 (senna leaf and aloe 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)

Cascara 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 cascara 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 cascara bark available that 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 (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 and therefore those these data are taken to substantiate the well-established use of preparations containing cascara bark.

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 the potential genotoxicity and carcinogenicity of anthraquinones and derivatives.

In the indication described in the European Union herbal 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