EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Senna alexandrina* Mill. (*Cassia senna* L.; *Cassia angustifolia* Vahl)[1], folium and fructus

Draft revision

Based on Article 10a of Directive 2001/83/EC (well-established use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Senna alexandrina* Mill. (*Cassia senna* L.; *Cassia angustifolia* Vahl), folium and fructus
Herbal preparation(s)	Comminuted herbal substance or herbal preaparations 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.
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Senna alexandrina* Mill. (*Cassia senna* L.; *Cassia angustifolia* Vahl), folium and fructus. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

1 The botanical name of the herbal substance has been changed, see section 1 of the assessment report for further details.

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1. Introduction

Senna alexandrina Mill. has recently been identified as the correct name of a plant species (www.theplantlist.org; Wichtl, 2016), which had been classified before as two different species, *Cassia senna* L. and *Cassia angustifolia* Vahl. These two species had already been known as very closely related. It is also intended to use *Senna alexandrina* Mill. in the respective monographs of the European Pharmacopeia and therefore the European monographs will be/have been renamed accordingly. Leaves and fruits of both species contain a similar spectrum of hydroxyanthracene derivatives, which are accepted as the active constituents.

This assessment reports is including data relevant for the European Union herbal monographs on senna leaves and senna pods. Whenever reference is made to literature, this assessment report displays the species name which had been originally used in the reference document.

In addition, in this assessment report the English common names "senna fruits" and "senna pods" are used for the herbal substance "Sennae frucuts". Citations based on references may use the term from the original publication.

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

- Herbal substance(s)

Senna leaves

The herbal substance senna leaves consist of the dried leaflets of *Cassia senna* L. (*Cassia acutifolia* Del.), known as Alexandrian or Khartoum senna, or *Cassia angustifolia* Vahl, known as Tinnevelly senna, or a mixture of the two species, now collectively subsumed under the item *Senna alexandrina* Mill. The herbal substance contains not less than 2.5 percent of hydroxyanthracene glycosides, calculated as sennoside B ($C_{42}H_{38}O_{20}$; M_r 863). The material complies with the European Pharmacopoiea monograph "Senna leaf" (Ph.Eur.: 0206). The active constituents are the anthranoids that are present in the leaf of the herbal substance as dianthrones (75 – 80 %) and as anthrones (20 – 25 %).

The herbal substance also contains small quantities of other dianthrone diglycosides, monoanthraquinone glycosides and aglycones. The amount of aglycones increases during storage. The naphthalene glycosides are without pharmacological significance but have been used to differentiate the two species of senna, when this was reflecting the taxonomic status: tinnevellin glycoside was found only in *Cassia angustifolia* Vahl, and 6-hydroxymusizin glycoside only in the mature plants of *Cassia senna* L. (Lemli *et al.,* 1981, Lemli *et al.,* 1983).

Senna pods

Alexandrian senna pods (Sennae fructus acutifoliae) consist of the dried fruit of *Cassia senna* L. (*Cassia acutifolia* Delile). They contain not less than 3.4 % of hydroxyanthracene glycosides, calculated as sennoside B ($C_{42}H_{38}O_{20}$; M_r 863) with reference to the dried herbal substance. The material complies with the European Pharmacopoiea monograph "Senna pods, Alexandrian" (Ph.Eur.: 0207).

The main active constituents are sennosides A and B (ca. 4%), which are rhein-dianthrone diglycosides. Smaller amounts of other dianthrone diglycosides, monoanthraquinone glycosides and aglycones are also present.

Historically, Tinnevelley senna pods (Sennae fructus angustifoliae) consist of the dried fruit of *Cassia angustifolia* Vahl. They contain not less than 2.2 % of hydroxyanthracene glycosides calculated as sennoside B ($C_{42}H_{38}O_{20}$; M_r 863) with reference to the dried herbal substance. The material complies with the European Pharmacopoiea monograph "Senna pods, Tinnevelly" (Ph.Eur.: 0208).

The main active constituents are sennosides A and B (ca. 2.5 %), which are rhein-dianthrone diglycosides. The herbal substance also contains small quantities of other dianthrone diglycosides, monoanthraquinone glycosides and aglycones.

The constituents of senna leaves and fruits are comparable, only the percentage distribution seems to be different. 85 to 90 % dianthrone glycosides and 10 to 15 % anthrone glycosides were found in the fruits. Nearly 95 % of the sennosides are sennosides A, A1 and B, and 5 % are sennosides C and D. The fraction of the naphthalene glycoside tinnevellin glycoside is only found at 0.3 %. The senna leaves contain 75 to 80 % dianthrone and 20 to 25 % anthrone, which are predominantly present as glycosides. Nearly 80 % of the sennosides are sennosides A, A1 and B, and 20 % are sennosides C and D. In the leaves tinnevellin glycoside is present at 0.4 % (Westendorf 1993).

The amount of anthranoids of the emodin and aloe-emodin type is generally higher in the leaves than in the fruits (Kommission E, 1993).

- Herbal preparation(s)

  Senna leaves and fruits are commonly used as comminuted herbal substance. Additionally, there are some extracts which are also standardised on a defined content of hydroxyl anthracene glycosides. There is also a standardised dry extract of senna leaves described in the European Pharmacopeia. Standardised senna leaf dry extract is produced from Senna leaf (Ph.Eur.: 0206). The extract is produced from the herbal substance by a suitable procedure using ethanol (50-80 per cent V/V). It contains not less than 5.5 % and not more than 8.0 % of hydroxyanthracene glycosides, calculated as sennoside B ($C_{42}H_{38}O_{20}$; M_r 863) with reference to the dried extract. The measured content does not deviate from the value stated on the label by more than +/- 10 %. (Ph.Eur.: 1261)

- 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.

  There are manifold combinations of senna leaves or fruits with other herbal substances or herbal preparations with a laxative effect. With respect to the diverse nature of these products they are not described in detail in the AR. There are combinations of senna leaves and senna fruits because the combination is facilitating adjustment to a defined content of hydroxy anthraquinone derivatives. Such combinations can be evaluated in analogy to the monographs on senna leaves and senna pods as the therapeutic principle is identical and overall composition of natural compounds of these herbal substances is similar.

1.2. Search and assessment methodology

This assessment report reviews the scientific data available for senna leaves and senna pods (*Senna alexandrina* Mill., folium and *Senna alexandrina* Mill., fructus (= *Cassia senna* L. and *Cassia angustifolia* Vahl, folium and *Cassia senna* L. and *Cassia angustifolia* Vahl, fructus)). References presented by the

European Scientific Cooperative on Phytotherapy (ESCOP) to support the monographs "Sennae folium (Senna Leaf)" (ESCOP Monographs 2nd edition 2003), "Sennae fructus acutifoliae (Alexandrian Senna Pods)" (ESCOP Monographs 2nd edition 2003) and "Sennae fructus angustifoliae (Tinnevelley Senna Pods)" (ESCOP Monographs, second edition 2003) and literature presented by the World Health Organization (WHO; 1999) for the monographs "Folium Sennae" and "Fructus Sennae" were taken into account.

Literature search was done via PubMed, DIMDI and SciFinder in medical and scientific databases as MEDLINE, National Center for Biotechnology Information (NCBI), Cochrane Database of Systematic Reviews TOXLINE (date of search: September 2015). For the unqualified terms (Cassia, Senn*, Aloe, Cassia clinical trials; senn* and cassia and *in vitro*; *anthroquinones and *in vitro*, rhein and *in vitro*, aloe-emodin and *in vitro*, senn* and cassia and *in vivo*; anthroquinones and *in vivo*, rhein and *in vivo* aloe-emodin and *in vivo*, senn* and cassia and preclin*; senn* and cassia, rhein, aloe-emodin hydroxyanthracen* and safety; senn* and cassia, rhein, aloe-emodin hydroxyanthracen* and the different indications) as text words in the title, abstract, and full journal article. The search strategy included the terms for senn* and cassia, rhein, aloe, and terms for the specific diseases or conditions derived from its traditional use and current indications, supplemented with those expected from non-clinical studies with aloe. In addition to the PubMed and SciFinder literature search, bibliographies of review articles and eligible articles were examined in an effort to identify all available literature that may not have been identified by the database research. Randomised studies that used combination products with senn* and cassia as one of its ingredients are not included.

Since the spectrum of constituents of senna leaf is comparable to that of senna fruit, this report also considers scientific data available for senna fruits (pods).

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: WHO Monograph; NTP Technical Reports on Aloe vera whole leaf extract and Emodin; IARC Monograph Aloe vera; NTP Technical Reports on *Cassia Senna* whole leaf extract and Rhein; IARC Monograph *Cassia senna*;

Other resources: Historical literature according to list of references

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

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Senna leaf			
Dry extract (DER 84.4:1) from Sennae folium, extraction solvent methanol 75% V/V, standardised to 47.5-52.5% hydroxyanthracene derivatives corresp. to 12 mg per coated tablet	Constipation	Coated tablet Adults and adolescents: 1-2 coated tablets/day	WEU since 2013; AT
Dry extract (DER 84.4:1) from Sennae folium, extraction solvent methanol 75% V/V, standardised to 47.5-52.5% hydroxyanthracene derivatives corresp. to 48 mg per 'Täfelchen' (= chocolate like bar)	Constipation	Chocolate like bar Adults and adolescents: ¼ - ½ bar per day	WEU since 1985; AT
Cassiae Sennae L. Folii (*C. acutifolia* Delile) extractum siccum hydro-alcoholicum (ethanolum 60 per centum) 66.6 mg (eq. 10 mg Sennoside B)	Symptomatic treatment of constipation, after exclusion of serious disorders	Coated tablets 2-3 tablets/day Maximal 2 weeks Contra-indicated for children younger than 12 years	28/10/2002 Bibliographical BE
Sennae folium (Sennablad) 60 g.	Symptomatic treatment of constipation, except from mechanical origin, with a contactlaxativum. Only	Powder for oral use The maximal daily dose corresponds to 30 mg hydroxyanthraceen glycosides (1	01/11/1977 Complete registration BE

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	for occasional use.	measuring spoon) ¼-1 measuring spoon 2 -3 times/week Maximal 2 weeks Contra-indicated for children younger than 12 years.	
Sennae folium	Herbal medicinal product for short-term use in cases of occasional constipation. Cleaning of bowel before diagnostic endoscopic and radiological examination.	Herbal tea for oral use 1 tea bag (1 g of the herbal substance) equivalent to 15 – 30 mg of hydroxyanthracene derivatives, calculated as sennoside B, to be taken once daily at night. Normally it is sufficient to take this medicinal product up to two to three times a week. Use for more than 1 - 2 weeks requires medical supervision.	WEU, authorised 1995; CZ
Sennae folium	Herbal medicinal product for short-term use in cases of occasional constipation	1 tea bag (1 g of the herbal substance) equivalent to 25 – 30 mg of hydroxyanthracene derivatives, calculated as sennoside B, to be taken once daily at night. Normally it is sufficient to take this medicinal product up to two to three times a week. Use for more than 1 - 2 weeks requires medical supervision.	WEU, authorised 1996 CZ

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Sennae folium	Herbal medicinal product for short-term use in cases of occasional constipation	1 g of the herbal substance equivalent to 25 – 30 mg of hydroxyanthracene derivatives, calculated as sennoside B, to be taken once daily at night. Normally it is sufficient to take this medicinal product up to two to three times a week. Use for more than 1 - 2 weeks requires medical supervision.	WEU, authorised 1996; CZ
Herbal tea 1.7 g Sennae folium standardized to 30 mg sennoside B	Herbal medicinal product for short-term use in cases of occasional constipation	Herbal tea; adults and adolecents take ½ to 1 cup of tea daily 1-2 weeks	WEU 1978 DE
Herbal tea 0.8 g Sennae folium standardized to 22 mg sennoside B	Herbal medicinal product for short-term use in cases of occasional constipation	Herbal tea; adults and adolecents take ½ to 1 cup of tea daily 1-2 weeks	WEU 1978 DE
Herbal tea 1.5 g Sennae folium standardized to 15 mg sennoside B	Herbal medicinal product for short-term use in cases of occasional constipation	Herbal tea; adults and adolescents take 1 to 2 cup of tea daily 1-2 weeks	WEU 2002 DE
Sennae folium	Herbal medicinal product for short-term use in cases of occasional constipation	Tea bags Adults and children from 10 years on drink one cup of 150 ml containing 0.5 g sennae fructus; 10-15 min preparation time. Use for more than 1 - 2 weeks requires medical supervision.	WEU 2002 Standardzulassung DE
Calcium sennosides equivalent to 7.5 mg	As a laxative for the relief of occasional or	Syrup 7.5 mg/5 ml Syrup is	Full MA IE

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
per 5 ml total sennosides (calculated as sennoside B)	non-persistent constipation.	for oral administration. Adults, including the elderly and children over 12: Two 5 ml spoonfuls. Not to be given to children under 12 years except on medical advice. Where administration to children is necessary, the recommended dose is as follows. Children over 6 years: One 5 ml spoonful. Children aged 2 to 6 years: Half to one 5 ml spoonful in 24 hours. Should be taken as a single dose at bedtime by adults and in the morning by children. New users should start with the lowest dose and increase it, if necessary, by one half of the initial dose each day. Once regularity has been regained the dosage should be gradually reduced and stopped.	Not relevant with respect to products in the market, because the products is not a herbal medicinal product. Information in the assessment report is kept, because due to standardisation data are supportive.
Sennae folium herbal substance dried leaflets	Herbal medicinal product for short-term use in cases of occasional constipation	Herbal tea The maximum daily dose of hydroxyanthracene	WEU Since May 1998; SK

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		glycosides is 30 mg. Duration of use: 1-2 weeks	
Sennae folium, herbal tea in teabags	For short-term use in cases of occasional constipation.	One sachet contains 0.9 g of Sennae folium, corresponding to 16.2 mg - 30 mg hydroanthracene glycosides expressed as sennoside B. Adolescents over 12 years of age, adults, elderly: to be taken once daily at night. Normally it is sufficient to take this medicinal product up to two to three times a week. Contraindicated for use in children under 12 years of age. Use for more than 1 - 2 weeks requires medical supervision.	WEU, since 1999; LV
Sennae folium, herbal tea in teabags	For short-term use in cases of occasional constipation.	One sachet contains 1.2 g of Sennae folium, corresponding up to 30 mg hydroanthracene glycosides. Adolescents over 12 years of age, adults, elderly: to be taken once daily at night. Normally it is sufficient to take this medicinal product up to two to three times a week. Contraindicated for use in children under 12	WEU, since 1999; LV

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		years of age. Use for more than 1 - 2 weeks requires medical supervision.	
Sennae folii extractum	For short-term use in cases of occasional constipation	Each tablet contains extract corresponding to 13.5 mg of sennosides calcium. Adolescents over 12 years of age, adults, elderly: 1 tablet once daily at night. If necessary, dose can be increased to 2 tab. Normally it is sufficient to take this medicinal product up to two to three times a week. Contraindicated for use in children under 12 years of age. Use for more than 1 - 2 weeks requires medical supervision.	WEU, since 1999 and 2003 LV
Senna pods			
Standardised dry aqueous extract (DER 4-6:1) from Sennae fructus angustoliae; 20 mg hydroxyanthracene derivatives per coated tablet	Constipation	Coated tablet Adults and adolescents 1 coated tablet daily	WEU 1991 AT
Standardised dry aqueous extract (DER 3-5:1) from Sennae fructus acutifoliae; 8.6 mg hydroxyanthracene derivatives per film-coated tablet	Constipation	Film-coated tablet Adults and adolescents 2-4 film-coated tablets daily	WEU 1969 AT

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Standardised dry aqueous extract (3-5:1) from Sennae fructus acutifoliae	Cleaning of bowels before diagnostic purposes or surgery	Oral solution 150 mg hydroxyanthracene derivatives as single dose	WEU 1971 AT
Sennae angustifoliae fructus	Herbal medicinal product for short-term use in cases of occasional constipation. Cleaning of bowel before diagnostic endoscopic and radiological examination.	Herbal tea for oral use 1.1 g of the herbal substance) one tea spoon) equivalent to 15 – 30 mg of hydroxyanthracene derivatives, calculated as sennoside B, to be taken once daily at night. Normally it is sufficient to take this medicinal product up to two to three times a week. Use for more than 1 - 2 weeks requires medical supervision.	WEU, authorised 1995 CZ
Dry extract (DER 6-12:1) Alexandrian senna pods, extraction solvent ethanol 60% V/V; standardised to contain 7.5 to 15 mg hydroxyanthracene derivatives	Short-term use incases of occasional constipation	Daily dose: 7.5 to 30 mg hydroxyanthracene derivatives	WEU in DE (1978)
Dry extract (DER 5.6-6.9:1) Alexandrian senna pods, extraction solvent methanol 80% V/V; standardised to contain 12.5 mg hydroxyanthracene derivatives	Short-term use incases of occasional constipation	Daily dose: 12.5 to 25 mg hydroxyanthracene derivatives	WEU in DE (1978)
1 bag contains 40 g Tinnevelly-senna pods comminuted;16.0 –	Herbal medicinal product for short-term use in cases of	Ethanolic extract;adults and adolescents take 4 to 5 measuring spoons	WEU 1978 DE

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
22.4 g standardized to 561 mg sennoside B	occasional constipation	daily corresponding to 22.44 - 28.05 mg sennoside B. 1-2 weeks	
250-318 mg Tinnevelly-senna pods, comminuted, standardized to 7 mg sennoside B	Herbal medicinal product for short-term use in cases of occasional constipation	Tablets; adults and adolescents take 1 to 4 tablets corresponding to 7 - 28 mg sennoside B.	WEU 1978 DE
Sennae fructus	Herbal medicinal product for short-term use in cases of occasional constipation	drink one cup of 150 ml containing 0.5 g sennae fructus; 10-15 min preparation time. Use for more than 1 - 2 weeks requires medical supervision.	Standardzulassung BfArM 2002 DE
Comminuted herbal substance (*Cassia angustifolia* Vahl, fructus) 280 mg corresponding to 6 mg sennoside B	Herbal medicinal product for short term use in constipation	Tablets Posology: 1 - 3 tablets daily when needed. Not to be used for more than 1 week.	MA February 1997; HR
1 gram tea contains: Comminuted *Cassia angustifolia* Vahl, fructus, corresponding to 22 mg hydroxyanthracene derivates, calculated as sennoside B Same product in 2g sachets	Herbal medicinal product for short tern use in constipation	Herbal tea Posology: Adults: 2.5-5 ml (½-1 teaspoon) daily. Pour over with boiling water and wait 5-10 minutes. Not to be used for more than 1 week.	MA July 1995; MA November 1996; DK
Dry extract from *Cassia senna* L., fructus and *Cassia angustifolia* Vahl, fructus (DER 4.5-5.5 : 1), extraction solvent water corresponds to	Short-term use in the case of occasional constipation	Herbal tea 650 mg herbal tea (1 teaspoon) contains 200-333 mg extract, corresponding to 20 mg hydroxyanthracene glycozides calculated as	On the market since 14.02.2011. (WEU); HR

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
20 mg hydroxyanthracene glycozides calculated as sennoside B.		sennoside B. Adults and adolescents over 12 years of age: ½ to 1 ½ teaspoon; one week if symptoms persist or worsen during the use of the medicinal product. Use for more than 1 - 2 weeks requires medical supervision.	
Dry extract from *Cassia angustifolia* Vahl, fructus (DER 4 - 6:1), extraction solvent water corresponds to 20 mg hydroxyanthracene glycozides calculated as sennoside B.	Short-term use in the case of occasional constipation	Coated tablets 1 coated tablet contains 150 to 220 mg extract (as dry extract) from *Cassia angustifolia* Vahl, fructus (4 - 6:1), corresponding to 20 mg hydroxyanthracene glycozides calculated as sennoside B. Adults and adolescents over 12 years of age: 1 tablet daily; one week if symptoms persist or worsen during the use of the medicinal product. Use for more than 1 - 2 weeks requires medical supervision.	15.11.2011. (WEU). HR
Senna pods powdered 1 tablet contains 154 mg *Cassia senna* L. (C. acutifolia Delile) (Senna pods, Alexandrian)/*Cassia angustifolia* Vahl	As a laxative in the treatment of occasional constipation.	Tablet Adults only: 2-4 tablets in 24 hours, to be taken at night. Not to be given to children except on	Full MA; 2003; CZ

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
(Senna pods Tinnevely), standardised to contain 7.5 mg total sennosides per tablet, calculated as sennoside B.		medical advice.	
Combinations of senna leaves and senna pods			
Fruit block; comminuted Senna leaves 0.43-0.64 g, tinnevelly-senna pods 0.43-0.64 g; (corresponding to 30 mg sennoside B).	Herbal medicinal product for short-term use in cases of occasional constipation	Fruit block: adults and adolescents ½ - 1 fruit blocks.	WEU 1978 DE
Sennae folium and Sennae fructus	For short-term use in cases of occasional constipation	Each chewable tablet contains 0.71 g of Sennae folium and 0.3 g of Sennae fructus. Each tablet contains not more than 30 mg hydroanthracene glycosides expressed as sennoside B. Adults, elderly: 1 tablet once daily at night.	WEU, since 1995; LV
Sennae folium and Sennae fructus	For short-term use in cases of occasional constipation	Each chewable tablet contains 0.71 g of Sennae folium and 0.3 g of Sennae fructus. Each tablet contains not more than 30 mg hydroanthracene glycosides expressed as sennoside B. Adults, elderly: 1 tablet once daily at night. Adolescents over 12 years of age ¼ -1/2 tablets.	WEU, since 1995; LV

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		Contraindicated for use in children under 12 years of age. Use for more than 1 - 2 weeks requires medical supervision.	
10 g herbal tea contain 2.5 g senna leaves; 5-7.5 g Tinnevelly-senna pods; Alexandrine senna pods 0-2.5 g	Herbal medicinal product for short-term use in cases of occasional constipation	Herbal tea; adults and adolescents 0.5 g – 1 g ½-1 measuring spoon in 150 ml boiling water.	WEU 1978 DE
1 g granulate contains senna leaves comminuted 0.5779 g, Tinnevelly-senna pods comminuted 0.3853 g (corresponding to 26 mg sennoside B).	Herbal medicinal product for short-term use in cases of occasional constipation	Granulate: adults and adolescents take 1-2 measuring spoon of the granulate corresponding to 0.575 – 1.150 g granulate and to 15 – 30 mg Sennosid B)	WEU 1978 DE

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

Senna has been used for medicinal purposes for centuries (Lemli 1995). It was introduced into European medicine by the Arabs in the 9th or 10th century.

Tabernaemontanus (1625) (Kräuterbuch von Jacobus Theodorus 1625) mentions "Kassie" (*Cassia alata*). Different parts and preparations of the plant were used: "CASSIA FISTULA" or "CASSIA FISTULATIS", MEDULLA CASSIAE, FLORES CASSIAE and CASSIA EXTRACTUM CUM FOLIIS SENNAE. The last one was an electuary (a medicine composed of powders, or other ingredients, incorporated with some conserve, honey, or syrup, a soft solid) which was prepared from MEDULLA CASSIAE and different other herbs and senna leaves. This extract was used as a clysma. Tabernaemontanus also

mentioned the use as a purgative, which was administered in case of fever or heat. In the "American Materia Medica, Therapeutics and Pharmacognosy" of Finley Ellingwood (Ellingwood 1919) "Alexandria Senna" is described as an efficient remedy, mild, kindly, certain and uniform in its action. It is a constituent of the larger number of the proprietary laxative or cathartic compounds, syrups, cordials or elixirs. It is used in all cases of temporary constipation, however induced.

Frerichs *et al.* (1927) also mentions the use of an electuary of senna as a laxative which was sometimes used as a klysma. Combination preparations with senna are used for purification the blood, to treat obesity and gallstones. "Sennatin", an extract of senna leaves, was administered subcutaneous or intramuscular to treat constipation.

Thoms (1927) describes the use of senna in teas for purification of blood and as a laxative. He also mentioned "Sennatin" like Frerichs *et al.* (1927).

Madaus (1938) gives a review of the use of senna. Paracelsus already indicated the use as a purgative (Madaus 1976). Also Hecker in1814, Lonicerus in 1564, Bock in 1565, Matthiolus in 1626 and Clarus in 1860 described the use as a laxative (Madaus, 1976). Matthiolus also cured lues venerea (syphilis) with senna. Hoppe mentions 1949 senna leaves as a laxative in cases of acute and chronic constipation.

In Todd (1967) (Martindale) senna is described as a purgative for the treatment of constipation.

The Pharmacopoeia Austriaca (1812) lists senna leaves as "infusum laxativum".

In his "Manual of Materia Medica and Pharmacology" Culbreth (1927) described the use of "*Cassia senna*" as follows: "The Arabians used it in skin affections"; the herbal substance is "now employed for habitual constipation, haemorrhoids, fissura ani, fevers". But "its smell, taste, tendency to nauseate, injurious effects in hemorrhoids, intestinal hemorrhage, and inflammation, all lessen its popularity."

In Hungary, combinations with senna preparations are used traditionally as cholagoga. Two prescriptions can be found in Hungarian Pharmacopoiea (in Edition VI. 1967) and some in the Formulae Normales (the officinal compendium of prescriptions, Edition V. 1967) and there are some paramedicines with this indication also. But the pharmacological data available for senna do not support such use; taking into consideration the benefit-risk ratio for senna, this use cannot be accepted.

In India, senna leaves are also used in loss of appetite, abdominal pain, liver disease, splenetic extension, hepatitis, anaemia, leprosy, foul smelling breath, bronchitis and tumours (Kirtikar & Basu 1975). In his "Indian materia medica" Nadkarni (1976) describes senna leaves and pods as purgatives. Therapeutical doses stimulate intestinal peristalsis. Furthermore externally powdered leaves mixed with vinegar and made into a plaster are applied locally in certain skin diseases. Senna leaves combined with Henna are also used as a hair-dye to make the hair black.

As von Koenen described 1977, senna was used in South Africa for treatment of influenza and as secretolytic ointment. In Central Africa, senna was used in digestive complaints and to treat wounds, burns and furuncles.

The WHO monograph "Folium Sennae" (1999) mentions the following uses described in folk medicine, not supported by experimental or clinical data: as an expectorant, a wound dressing, an antidysenteric, a carminative agent; and for the treatment of gonorrhoea, skin diseases, dyspepsia, fever, and haemorrhoids.

Table 2 Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form**	**Reference**
Senna	All diseases where an easy defaecation is desirable: e.g. analfissures, haemorrhoids, after rectoanal surgery. For bowel cleansing before diagnostic procedures or surgery; constipation	Medium daily dose: 20 mg bis 60 mg hydroxyanthracene derivatives. Comminuted herbal substance, powder or dry extracts for infusion, decoction or cold mazerates. Fluid and solid pharmaceutical forms only for oral application.	Senna (Kommission E monograph, 1984)
Sennae folium	Constipation	Comminuted herbal substance, powder or dry extracts for infusion, decoction or cold mazerates. Fluid and solid pharmaceutical forms only for oral application. 20-30 mg hydroxyanthracene derivatives/day, calculated as sennoside B. The correct individual dose is the lowest to achieve a soft formed stool	Sennae folium (Kommission E monograph, 1993)
Sennae fructus	Constipation	Comminuted herbal substance, powder or dry extracts for infusion, decoction or cold mazerates. Fluid and solid pharmaceutical forms only for oral application. 20-30 mg	Kommission E Monograph, 1993)

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
		hydroxyanthracene derivatives/day, calculated as sennoside B. The correct individual dose is the smallest required to produce a comfortable soft formed motion.	
Sennae folium	For 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 15-30 mg hydroxyanthracene derivatives, calculated as sennoside B, to be taken once daily at night.	ESCOP Monographs 3rd ed. November 2003
Sennae fructus acutifoliae	For 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 15-30 mg hydroxyanthracene derivatives, calculated as sennoside B, to be taken once daily at night.	ESCOP Monographs 3rd ed. November 2003
Sennae fructus angustifoliae	For short-term use in cases of occasional	The correct individual dose is the smallest required to produce a	ESCOP Monographs 3rd ed. November

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
	constipation	comfortable soft formed motion. Adults and children from 10 years on: preparations equivalent to 15-30 mg hydroxyanthracene derivatives, calculated as sennoside B, to be taken once daily at night.	2003
Folium Sennae	Short-term use in occasional constipation	The correct individual dose is the smallest required to produce a comfortable, soft-formed motion. Powder: 1–2 g of leaf daily at bedtime. Adults and children over 10 years: standardized daily dose equivalent to 10–30mg sennosides (calculated as sennoside B) taken at night.	WHO monographs on selected medicinal plants.—Vol. 1. 1999
Fructus Sennae	Short-term use in occasional constipation	The correct individual dose is the smallest required to produce a comfortable, soft-formed motion. Powder: 1–2g of leaf daily at bedtime. Adults and children over 10 years: standardized daily dose equivalent to 10–30mg sennosides (calculated as sennoside B) taken at night.	WHO monographs on selected medicinal plants.—Vol. 1. 1999

2.3. Overall conclusions on medicinal use

From the multitude of products authorised in the European Union the 10 years of well-established use can be attributed to various herbal preparations of senna leaf and senna pods (see table 3).

Because of the standardisation and the known mode of action of anthraquinonglycosides the HMPC decided to define the herbal preparations in the monographs only by reference to the standardisation. In the posology reference a range for standardisation is mentioned which is based on the posologies from products on the market. Additionally, a reference to the calculation based on a photometric method is made because the methodology described in the respective monographs of the European Pharmacopeia is under revision. During revision of the monographs on Senna alexandrina, fructus and Senna alexandrina, folium the HMPC also decided to change the range of posology from 15-30 mg to 10 to 30 mg hydroxyl anthracene derivatives. This is supported by products in the market and follows the approach to minimise the amount used. The range is now also consistent with the posology defined in the revised monograph on *Aloe barbadensis* Mill. and on *Aloe* (various species, mainly *Aloe ferox* Mill. and its hybrids), folii succus siccatus.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Sennae folium			
Comminuted herbal substance; standardised in the finished medicinal products to contain 15-30 mg hydroxyanthracene derivatives, calculated as sennoside B	Short-term use in cases of occasional constipation	Daily dose: 0.9-2 g of herbal substance, standardised on 15-30 mg hydroxyanthracene derivatives.	Marketing authorisations in DE, CZ, LV (2005 and earlier)
Dry extract (DER 7-10:1) extraction solvent methanol 60 % V/V; standardised to contain 11.0-15.0 % hydroxyanthracene derivatives, calculated as sennoside B	Short-term use in cases of occasional constipation	Daily dose: 14 or 28 mg hydroxyanthracene derivatives.	Marketing authorisation in DE (1978)
Dry extract (DER 4.3-5.9:1) extraction solvent methanol 60 % V/V; standardised to contain 11.0-15.0 % hydroxyanthracene derivatives, calculated as sennoside B	Short-term use in cases of occasional constipation	Maximum daily dose, once: 30 mg hydroxyanthracene derivatives.	Marketing authorisation in DE (1978)
Dry extract (DER 84.4:1) extraction solvent methanol 75 % V/V; standardised to 47.5-52.5 %	Constipation	Daily dose: Corresponding to 12-24 mg hydroxyanthracene	Marketing authorisations in AT (2013 and 1985)

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
hydroxananthracene derivatives		derivatives.	
Dry extract (DER 6-12:1) Extraction solvent ethanol 60 % V/V	Symptomatic treatment of constipation	Daily dose: Corresponding to 20-30 mg hydroxyanthracene derivatives.	Marketing authorisation in BE (2002)
Sennae fructus			
Comminuted herbal substance	Short-term use in cases of occasional constipation	Herbal tea preparation Daily dose: 0.5-1.1 g of herbal substance, standardised on 15-30 mg hydroxyanthracene derivatives, calculated as sennoside B. Comminuted herbal substance in solid dosage forms: Daily dose: 6-30 mg hydroxyanthracene derivatives, once Single dose: 250-320 mg herbal substance, standardised to 6-7.5 mg hydroxyanthracene derivatives.	Marketing authorisations in CZ, DE, DK (2002 and earlier)
Dry extract (DER 4-6:1) extraction solvent water	Short-term use incases of occasional constipation	Daily dose: 20 mg hydroxyanthracene derivatives.	Marketing authorisation in HR (2011)
Dry extract (DER 3-6:1) extraction solvent water	Constipation	Daily dose: 20 mg or 17.2 to 34.4 mg hydroxyanthracene derivatives.	Marketing authorisation in AT (1991 and 1969)
Dry extract (DER 3-5:1) extraction solvent water	Cleaning of bowels before diagnostic purposes or surgery	Single dose: 150 mg hydroxyanthracene derivatives.	Marketing authorisation in AT (1971)
Dry extract (DER 6-12:1)	Short-term use	Daily dose: 7.5 to 30	Marketing authorisation

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
extraction solvent ethanol 60 % V/V; standardised to contain 7.5 to 15 mg hydroxyanthracene derivatives	incases of occasional constipation	mg hydroxyanthracene derivatives.	in DE (1978)
Dry extract (DER 5.6-6.9:1) extraction solvent methanol 80 % V/V; standardised to contain 12.5 mg hydroxyanthracene derivatives	Short-term use incases of occasional constipation	Daily dose: 12.5 to 25 mg hydroxyanthracene derivatives.	Marketing authorisation in DE (1978)

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

3.1.1. Primary pharmacodynamics

Data on herbal preparations

Senna leaves belong to the stimulant laxatives. Pharmocodynamic data regarding different forms of herbal preparations are not available.

Data derived from studies on Hydroxyanthracene Derivatives

Ishii *et al.* (1990) investigated the mechanism of action of aloe-emodin-9-anthrone in causing a significant increase in the water content of the rat large intestine. Aloe-emodin-9-anthrone inhibited rat colonic Na^+/K^+-adenosine triphosphatase *in vitro*, and increased the paracellular permeability across the rat colonic mucosa *in vivo*. Therefore, it seemed that the increase in water content of the rat large intestine produced by aloe-emodin-9-anthrone was due to both inhibition of absorption and stimulation of secretion without stimulation of peristalsis. Since, however, pretreatment with loperamide completely prevented the increase of paracellular permeability induced by aloe-emodin-9-anthrone, but did not completely reduce the concomitant increase in residual fluid volume, other multiple mechanisms of action might be involved in the increase of water content in the rat large intestine.

The effect of rhein and rhein anthrone on the transit and the transport of water and electrolytes in the large intestine were investigated by van Hoestenberghe *et al.* (1992) in germ-free rats. After intracaecal administration, neither of the two compounds was found to accelerate the transit of a colour marker through the large intestine. Both compounds reduced the net absorption of sodium and chloride in the colon and enhanced net potassium secretion. Net water absorption was decreased by rhein and even reversed into net secretion by rhein anthrone. The secretagogue activity of the compounds is not sufficient to induce laxation in germ-free rats. Furthermore rhein and rhein anthrone had no laxative properties under these experimental conditions. No laxative effect was seen in germ-free animals by Nijs *et al.* (1993) as well.

Hoenig *et al.* (1992), and Rauwald *et al*. (1992) studied the influence of 23 anthraquinones and anthrones on the regulatory volume decrease which is effected in Ehrlichs ascites tumor cells by activation of Cl^- channels. They showed that the strongest inhibition of the Cl^- channels' activity was caused by aloe-emodin-anthrone and aloe-emodin. These anthraquinones reduce the Cl^- permeability of the cells, this influence being sometimes more pronounced than that of the Cl^- channel blocker 130B. In contrast to the investigations of Ishii *et al.* (1990), both substances showed no pronounced inhibition activity of the Na^+/K^+-ATPase. Rhein, frangula-emodin and other anthraquinones with an additional phenolic hydroxyl group showed inhibition.

Results of investigations of Capasso *et al.* (1983) in rat isolated colon suggest that the laxative properties of aloin and 1.8-dioxyanthraquinone may depend, at least in part, on increased prostaglandin synthesis by the intestinal tissue.

The effect of sodium rhein on contractile activity and fluid flow in the rat complete large intestine was studied by Rumsey *et al.* (1993) *in vitro*. Contractile activity was recorded using serosal strain gauges and volume transducers recorded distal fluid flow from the segment. Luminal sodium rhein (1 mM) produced a protracted increase in caecal activity yet increased colonic contractility transiently. Fluid flow from the preparation was increased and the number of propagated complexes was elevated after the initial 10 min of exposure. The effect did not appear to be related directly to dose. Sodium rhein (0.1 mM) did not significantly stimulate contractility and a higher dose (5 mM) only produced a transient effect on propagated contractions. However, this dose had the effect of significantly reducing activity when the rhein was replaced by normal buffer. The data suggest that the action of sodium rhein is subtle; after an initial excitation, the glycoside shifts the pattern of motor activity in favour of propulsion at the expense of segmentation. The large intestine is more able, therefore, to expel luminal contents in a caudal direction following the addition of this anthraquinone laxative.

The quantity of the laxative effect is dependent on the orocaecal transit time and colonic metabolism of sennosides (Frexinos *et al.,* 1989), the dosage of sennosides, the amount and period of accompanying fluid intake (Fioramonti *et al.,* 1988, Okawa *et al.,* 1990).

Rhein anthrone (12.48 mg/kg) produces watery and mucoid diarrhoea approximately 20 min after intracaecal administration to rats. Pretreatment with the prostaglandin (PG) biosynthesis inhibitor indomethacin (10 mg/kg, i.p.) only delayed and did not completely block the onset of the induced diarrhoea. Rhein anthrone stimulated PGE2 release into the rat colonic lumen and the increased release was depressed by indomethacin. Rhein anthrone also accelerated large intestinal transit and this acceleration could be partly inhibited by indomethacin, which was probably responsible for the delay in the onset of diarrhoea. Indomethacin prevented the enhanced water, K^+ and mucus secretion and the reduced Na^+ absorption in the colon which were induced by rhein anthrone. The net water secretion could not be reversed to net absorption and the mucus secretion was only slightly depressed by indomethacin. Thus, the authors suggested that other mechanisms, together with the PG-dependent mechanism, are involved in the purgative action of rhein anthrone in rats (Yagi *et al.,* 1991).

The involvement of Ca^{2+} in the mechanism of the purgative action of rhein anthrone in rats was studied by Yamauchi *et al.* (1993). Among individual or combination pretreatments with calcium channel blockers, calmodulin antagonists and prostaglandin biosynthesis inhibitors, the combination of indomethacin and nifedipine completely blocked the diarrhoea induced by rhein anthrone and also inhibited its effects on colonic fluid and electrolyte transport, and large intestinal motility. Calmodulin antagonists were less active regarding suppression of the effects of rhein anthrone. The authors concluded that, in addition to prostaglandins, diarrhoea induced by rhein anthrone must also involve the calcium channel which can be blocked by nifedipine, but not verapamil.

After gastric administration of daily 100 mg sennosides/kg body weight, no morphological differences could be found between the colon of treated rats and the controls by Rudolph and Mengs (1988). In particular, no damage to the intramural nerve tissue could be seen under the electron microscope.

Ishii *et al.* (1994) measured the charcoal transport, as an indicator of the degree of peristalsis, and water content in the large intestine after intracaecal administration of barbaloin simultaneously in the same rat. Charcoal transport was significantly accelerated at both 3.5 and 6.5 h after the administration of barbaloin. At 6.5 h, diarrhoea instead of normal faeces was observed. Moreover, at 1 h before the acceleration of charcoal transport, a marked increase in water content of the large intestine was observed. It appeared that the increase in water content of the large intestine induced by barbaloin preceded the stimulation of peristalsis, attended by diarrhoea. The authors therefore suggested that the increase in water content is a more important factor than the stimulation of peristalsis in the diarrhoea induced by barbaloin.

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

Herbal preparation tested	**Posology**	**Experimental model**	**Reference**	**Main non-clinical conclusions**
Hydroxyanthracene derivatives				
Aloe-emodin-9-anthrone; Barbaloin, Aloeemodin and Sennoside A	10^{-3} M, 2 ml 10^{-3} M, 2 ml 10^{-3} M, 2 ml 10^{-3} M, 2 ml	*In vivo/ In vitro*	Ishii *et al.* (1990)	Increase in water content of the rat large intestine produced by aloe-emodin-9-anthrone was due to both inhibition of absorption and stimulation of secretion without stimulation of peristalsis.
Rhein and Rheinanthrone	3 mM 15-20 mg kg^{-1} Intracaecal application	*In vivo* germ-free Fisher rats	van Hoestenberghe *et al.* (1992)	No laxative effect
23 anthraquinones	No information	*In vitro*	Hoenig *et al.* (1992)	Strongest inhibition of the Cl^- channels' activity was caused by aloe-emodin-anthrone and aloe-emodin
23 anthraquinones	No information	*In vitro*	Rauwald *et al*. (1992)	Strongest inhibition of the Cl^- hannels' activity was caused by

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
				aloe-emodin-anthrone and aloe-emodin
Barbaloin	31.1 mg/10ml kg^{-1}	*In vivo*	Ishii *et al.* (1994)	The increase in water content is a more important factor than the stimulation of peristalsis in the diarrhoea induced by barbaloin
Na-rhein	1 mM (0.1-5 mM)	*In vitro*	Rumsey *et al.* (1993)	Produced a protracted increase in caecal activity yet increased colonic contractility transiently; expels luminal contents in a caudal direction
Rhein anthrone	(12.48 mg/kg) Intracaecal application	*In vivo*	Yagi *et al.* (1991)	Indomethacin prevented the enhanced water, K+ and mucus secretion and the reduced Na+ absorption in the colon which were induced by rhein anthrone. The net water secretion could not be reversed to net absorption and the mucus secretion was only slightly depressed by indomethacin.
Rhein anthrone	Rhein anthrone In 2 % sodium bicarbonate solution 12.48 mg/kg i.c. Indomethacin 10	*In vivo*	Yamauchi *et al.,* 1993	Among individual or combination pretreatments with calcium channel blockers, calmodulin antagonists and

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
	mg/kg i.p. Trifluoperazine 10mg/kg oral W-7 10 mg/kg oral Dilthiazem 30mg/kg i.p. Nicardipine 15mg/kg i.p. Nifedipine 20mg/kg i.p. Verapamil 20 mg/kg i.p.			prostaglandin biosynthesis inhibitors, the combination of indomethacin and nifedipine completely blocked the diarrhoea induced by rhein anthrone and also inhibited its effects on colonic fluid and electrolyte transport, and large intestinal motility.

3.1.2. Secondary pharmacodynamics

Data on herbal preparations

In the study, folium sennae was firstly extracted by various solvents to obtain five folium sennae extracts by Lin *et al.* (2014). Then, five folium sennae extracts were evaluated for the protective effects against •OH^- induced DNA damage, antioxidant abilities *in vitro*, and chemical contents using various methods. On this basis, the correlation graphs between the pharmacological effects and chemical contents were plotted to obtain the correlation coefficients (R values). Finally, in order to obtain biological evidence, ethyl acetate extract of folium sennae was investigated for the protective effect against oxygen radical induced mesenchymal stem cells damage using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl) assay.The pharmacological assays indicated that five folium sennae extracts could effectively protect against oxygen radical induced DNA damage. The correlation analysis suggested that the average R values of total phenolics, total anthraquinones, aloe-emodin, rhein, and emodin were respectively 0.843, 0.833, 0.753, 0.820, and 0.784, while those of total sugars and total saponins were respectively 0.103 and 0.0068. The mechanistic analysis revealed that five folium sennae extracts could also scavenge free radicals, and reduce Cu^{2+} to Cu^{+}. MTT assay revealed that the viability of mesenchymal stem cells which were treated with oxygen radicals has been effectively protected by ethyl acetate extract of folium sennae (3 and 30 μg/ml). On this basis, the authors concluded that: (i) Folium sennae exhibits a protective effect against oxygen radicals induced damages to DNA and mesenchymal stem cells; (ii) The effects may be attributed to phytophenols (especially aloe-emodin, rhein, and emodin), not sugars or saponins; (iii) They exert the protective action via hydrogen atom transfer and/or sequential electron proton transfer mechanisms which make phenolic –OH moiety be oxidized to stable semiquinone form; (iv) The stability of semiquinone form can ultimately be responsible for the protective or antioxidant effect of phytophenols.

Data on hydroxyanthracene derivatives

Rhein (4,5-dihydroxyanthraquinone-2-carboxylic acid), the primary anthraquinone in the roots of *Cassia alata* L., is a naturally occurring quinone which exhibits a variety of biologic activities including anti-cancer activity. However, the effect of rhein on endothelial or cancer cells under hypoxic conditions has never been delineated. Therefore, the aim of this study was to investigate whether rhein inhibits angiogenesis and the viability of hormone-dependent (MCF-7) or -independent (MDA-MB-435s) breast cancer cells *in vitro* under normoxic or hypoxic conditions. Rhein inhibited vascular endothelial growth factor-stimulated human umbilical vein endothelial cell tube formation, proliferation and migration under normoxic and hypoxic conditions. In addition, rhein inhibited *in vitro* angiogenesis by suppressing the activation of phosphatidylinositol 3-kinase, phosphorylated-AKT (p-AKT) and phosphorylated extracellular signal-regulated kinase (p-ERK) but showed no inhibitory effects on total AKT or ERK. Rhein dose-dependently inhibited the viability of MCF-7 and MDA-MB-435s breast cancer cells under normoxic or hypoxic conditions, and inhibited cell cycle in both cell lines. Furthermore, Western blotting demonstrated that rhein inhibited heat shock protein 90alpha (Hsp90α) activity to induce degradation of Hsp90 client proteins including nuclear factor-kappa B (NF-κB), cyclooxygenase 2, and human epdiermal growth factor receptor 2. Rhein also inhibited the expression of hypoxia-inducible factor-1 alpha, vascular endothelial growth factor, epidermal growth factor, and the phosphorylation of inhibitor of NF-κB (I-κB) under normoxic or hypoxic conditions. Therefore, further studies including *in vivo* and pre-clinical experiments concerning rhein as a promising anti-angiogenic compound for breast cancer cell viability and growth need to be performed. (Fernand *et al.* 2011)

3.1.3. Safety pharmacology

In theory, it is possible that reflex stimulation might occur, involving not only the colon but also uterine muscles and then might lead to the development of hyperaemia in the pelvic region and to miscarriage as a result of neuromuscular stimulation of uterine muscles (Blaschek *et al.* 2003).

Data on studies with the herbal substance

The toxic effects of diet containing 10 % of *C. senna* fruits or 10 % of *N. oleander* leaves or their 1:1 mixture (5 % + 5 %) on male Wistar rats, treated for 6 weeks, were investigated. Diarrhea was a prominent sign of *C. senna* toxicosis. In both groups (*C. senna* fruits vs*. N. oleander* leaves), there were decreases in body weight gains, inefficiency of feed utilization, dullness and enterohepatonephropathy. These findings accompanied by leukopenia and anemia were correlated with alterations of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities and concentrations of total protein, albumin, urea and other serum constituents. In both phytotoxicities, the ability of the liver to excrete bilirubin remained unchanged (Al-Yahya *et al.* 2002).

Data on studies with hydroxyanthracene derivatives

Rats were treated with sennosides (6 x 10, 6 x 40 or 2 x 30 mg/kg weekly) or with danthron (6 x 500 mg/kg weekly) for 6 months. The laxative effect as measured by faecal wet weight during the first 10 h after treatment increased 3- to 4-fold by the higher sennoside doses (daily or intermittently) and 1- to 3-fold by danthron. The low sennoside dose had no measurable effect except on the 1st day (2 fold) compared with the control group. Mean faecal water content increased from 53 % (controls) to 66-79 % in rats treated with high sennoside doses and to 57 (1st day) -69 % in danthron-treated rats. Serum aldosterone levels and mucosal Na(+)-K(+)-ATPase activities in the small intestine and colon did not change with treatment. There were no signs of habituation or secondary hyperaldosteronism due to sennosides or danthron in spite of chronic diarrhoea over 6 months (Leng-Peschlow *et al.,* 1993).

3.1.4. Pharmacodynamic interactions

For interactions see section 5.5.4.

3.1.5. Conclusions

In vitro data show a dose dependent absortion and secretion of dianthrones and their aglycones (Waltenberger *et al.,* 2008). Increase in water content of the rat large intestine produced by aloe-emodin-9-anthrone was due to both inhibition of absorption and stimulation of secretion without stimulation of peristalsis (Ishii *et al.,* 1990). In germ-free Fisher rats rhein and rheinanthrone induced no laxative effect (van Hoestenberghe *et al.,* 1992). The strongest inhibition of the Cl-channels' activity was caused by aloe-emodin-anthrone and aloe-emodin (Hoenig and Rauwald 1992). Na-rhein induced a transient increase of peristalsis (Rumsey *et al.,* 1993). Among individual or combination pretreatments with calcium channel blockers, calmodulin antagonists and prostaglandin biosynthesis inhibitors, the combination of indomethacin and nifedipine completely blocked the diarrhoea induced by rhein anthrone and also inhibited its effects on colonic fluid and electrolyte transport, and large intestinal motility (Yamauchi *et al.,* 1993). These data on hydroxyanthracenes support the efficacy of the standardised senna extracts of the monograph under well established use.

Rhein-9-anthrone is the most important metabolite, which 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 and reduced fluid absorption. 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 (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), results in enhanced concentrations of fluid and electrolytes in the lumen of the colon.

These findings are based on investigations with different anthrones including also other anthranoid-containing herbal substances, but the results of these investigations are not always consistent.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Data on herbal preparations from animal studies

The kinetics of anthraquinones were investigated following oral administration of senna-containing products to rats (Mengs *et al*., 2004; Mitchell *et al*., 2006). Concentrations of rhein and aloe-emodin were determined in the blood of rats at various time points on days 90 and 91 of a 13-week gavage study (100 to 1,500 mg/kg) of powdered Tinnevelly senna fruit (Mengs *et al*., 2004). The concentrations in plasma were proportional to dose from 100 to 750 mg/kg, and were generally higher in females than in males. Chrysophanol was detected in some plasma samples. Blood was sampled at 6, 12, and 24 months in a 2-year oral carcinogenicity study in rats receiving powdered Tinnevelly senna fruit (25 to 300 mg/kg) (Mitchell *et al*., 2006). In the study, emodin and chrysophanol were generally not detected and aloe-emodin was only detected in the plasma of the high-dose group. Concentrations of rhein were higher in females at 6 and 12 months, but were similar to males at 24 months. In a radiolabeled study of aloe-emodin in gavaged rats, the ^{14}C was absorbed, distributed to all assayed tissues, and 30 % of the total dose was excreted in urine as rhein, an unidentified metabolite, and their conjugates (Lang 1993). The remainder of the dose was excreted in feces. The biotransformation of emodin and chrysophanol were investigated in induced liver microsomes from

male and female rats (Mueller *et al*., 1998). Emodin was metabolized to omega-hydroxyemodin and 2-hydroxyemodin; whereas chrysophanol was metabolized to emodin. (NTP 2012)

Data on hydroxyanthracenes from animal studies

The glycosidic sennosides are not absorbed. They are hydrophilic and do not pass the gastrointestinal tract membranes (Westendorf 1993). Neither the gastric acid nor the α-glycosidase of the small intestine is able to hydrolyse the β-O-glycosidic linkages of the sennosides. Only the β-glycosidase of the bacteria of the large intestine is able to hydrolyse them to sennidins. These sennidins are further cleaved to the active metabolite (rhein anthrone) by the bacteria (Blaschek *et al*., 2003). Aglycones are absorbed in the upper gut.

Until now it is unclear how much of the rhein anthrone is absorbed. The absorbed rhein anthrone is glucuronidised in the liver. One part of the glucuronides is excreted via the urine and cause the yellow or redbrown discolouration of the urine. The other part is excreted via the bile (Lemli *et al*., 1980). Animal experiments with radio-labeled rhein anthrone administered directly into the caecum of rats demonstrated absorption < 10 % (De Witte and Lemli 1988).

Excretion of sennosides and their known metabolites is mainly by faeces. According to different analysing methods, sennosides are recovered from faeces in up to 92.8 % in unbound or bound polymerised forms (Hietala *et al.,* 1988). In experimental animal studies, nearly 6 % of the amount of the oral administered anthranoids could be found unchanged in the urine and faeces (Lemli *et al*., 1980, Lemli, 1988).

The *in vitro* microbial degradation and the urinary excretion and biliary secretion in rats of two anthraquinone glycosides (sennosides A and B) and four aglycones (sennidins A and B, rhein, and danthron) were studied using a high performance liquid chromatographic system with gradient elution and amperometric detection. Microbial degradation of sennosides A and B occurred almost exclusively in the presence of mice caecum inoculae and was associated with the release of sennidins A and B. Rhein and danthron were indiscriminately metabolized by bacteria sampled from all regions of mice intestine, whereas sennidins lacked stability in biological media. The fraction of the dose administered orally to rats and recovered as aglycones or as glucuronides in bile and urine after 48 hours was five times greater for rhein (15 %) and danthron (13.4 %) than for sennosides A (1.8 %) and B (2.8 %) excreted or secreted as sennidins (Moreau *et al.,* 1985).

The pharmacological activity of senna is associated with sennosides A and B, the most abundant anthranoids and the precursors of the active metabolite, rhein anthrone (also known as rhein-9-anthrone) (Breimer and Baars 1976; Sasaki *et al.,* 1979; Lemli and Lemmens 1980, Hietala *et al.,* 1987; de Witte 1993; Franz 1993). The *in vivo* fate of the sennosides and the other senna anthranoids are described as follows. Sennosides are not readily absorbed from the mammalian gut; therefore, the activity depends on formation of rhein anthrone following deconjugation and reduction by microflora in the large intestine (Breimer and Baars 1976; Sasaki *et al.,* 1979; Lemli and Lemmens 1980. Lemli and Lemmens (1980) postulated that rhein anthrone arises through formation of a free radical following reduction of sennidin in the gastrointestinal tract. The systemic bioavailability of rhein anthrone is low, putatively due to limited absorption associated with binding to gut contents and rapid oxidation to rhein and sennidin once it is absorbed (Lemli and Lemmens 1980; Grimminger and Leng-Peschlow 1988; de Witte 1993). Lemli and Lemmens (1980) recovered less than 4 % of an oral dose. Small amounts of free anthraquinones and their glycosides are present in senna (Franz 1993; Newall *et al.,* 1996), including rhein. Absorption of rhein from the rat gut appears to be greater than absorption of rhein anthrone (de Witte and Lemli 1988). The cumulative urinary excretion of a single dose of ^{14}C-labeled rhein or ^{14}C-labeled rhein anthrone over 5 days was 37.1 % and 2.8 %, respectively. Rhein

was primarily excreted as glucuronide and/or sulfate conjugates. Most of the rhein anthrone-derived ^{14}C excreted in urine was recovered as rhein following oxidative hydrolysis and extraction of the urine. In a separate study, rhein-derived ^{14}C was highest in the tissues of the gastrointestinal tract in gavaged rats (Lang 1993). Other tissues contained low levels of radioactivity 7 days following dosing, probably due to protein binding in the blood. The total absorbed dose was estimated to be 50% and was excreted in urine, primarily as conjugates. In a study conducted by Dahms *et al.* (1997), specific metabolites, mostly glucuronide and sulfate conjugates, were identified in other at 10 to 11 hours. The authors postulated that the first peak arose from the presence of free or glycosylated rhein in the products and the second peak represented rhein derived from sennosides. In addition to work in animals, Dahms *et al*. (1997) investigated the metabolism of rhein in human volunteers receiving an oral dose of ^{14}C-labeled diacetylrhein. Diacetylrhein was converted to rhein by gut microflora. Some rhein-derived glucuronide and sulfate conjugates excreted in the urine of humans were common to the urine of rats, rabbits, and dogs receiving oral doses of ^{14}C rhein. However, potentially reactive metabolites (i.e., quinoids and diglucuronides) observed in some animals were not present in human urine, and the radioactivity in human serum was highly extractable over time indicating little potential for protein binding. (NTP 2012)

Intracaecal administration of an equimolar mixture of aloe-emodin anthrone and rhein anthrone produced a synergistic laxative effect in female albino mice (Yagi *et al*., 1991). A laxative effect is driven by increasing peristalsis and reduced absorption of water and electrolytes (Leng-Peschlow, 1993). In female Wistar rats, oral administration of 50 mg/kg sennosides reduced large intestinal transit time. Intracecal administration of equimolar doses of sennosides A+B, sennidins A+B, and rhein-9-anthrone produced similar responses in reduced large intestine transit time and increased soft feces (Leng-Peschlow 1988). Application of rhein anthrone on mucosa of isolated guinea pig ileum dose-dependently increased parameters of peristaltic reflex (longitudinal muscle tension, intraluminal pressure, and volume displacement) (Nijs *et al*., 1993). In isolated large intestine from male Wistar rats, application of rhein (1 mM) in the lumen increased contractility in the colon, the number of migrating contractions, and fluid flow (Rumsey *et al.,* 1993). (NTP 2012)

Oral administration of sennosides in rats *in vivo*, as well as application of rhein on the mucosal side of isolated rat colon *in vitro*, decreased absorption of water and sodium; enhanced secretion of water, sodium, and potassium; and reduced Na+, K+-ATPase activity (Leng-Peschlow 1993). In addition, in humans, perfusion with rhein reversed absorption of water and sodium into secretion in the jejunum and colon, increased chloride secretion in the jejunum, reduced chloride absorption in the colon, and enhanced potassium secretion in the jejunum and colon (Ewe 1993). (NTP 2012)

Detailed information concerning the metabolism and pharmacokinetic characteristics of anthranoid derivatives had been available only in a few cases. After oral administration, sennoside is degraded only in the lower parts of the gastrointestinal tract, releasing its active metabolite rhein anthrone. Nowadays, this process is understood at the molecular level. A study with ^{14}C-labelled rhein anthrone administered intracecally to rats, revealed that the compound is scarcely absorbed. Since on the contrary its anthraquinone equivalent is absorbed to a much larger extent, it is inferred that dianthrone- or anthrone-glycosides exhibit a lower systemic availability than anthraquinone O-glycosides. (de Witte 1993)

Because of previously observed species differences in rhein tolerability, with rabbits being very susceptible to kidney disturbances, *in vivo* and *in vitro* biotransformation studies were performed to find out whether the differences in the undesired effects of rhein are associated with qualitative, species-dependent differences in its metabolism. First hints on species-dependent biotransformation profiles were obtained from *in vivo* experiments with ^{14}C-labeled rhein in rat, rabbit, dog, and man.

TLC-analysis of urine samples obtained after oral administration of ^{14}C-rhein to rabbits revealed an additional, hydrophilic metabolite fraction in rabbit urine as compared with dog and human urine, all of which contain phenolic monoglucuronide and monosulfate as major metabolites. An investigation of urine samples (obtained from dogs, rabbits, rats, and human volunteers after oral application of unlabeled rhein) was conducted by means of mass spectrometric tandem techniques including on-line HPLC-MS/MS. *In vitro* experiments with subcellular liver fractions of rats and rabbits revealed the presence of three monohydroxylated metabolites of rhein, their quinoid oxidation products, and a bishydroxylated derivative of rhein. The hydroxylated phase I metabolites were detected as glucuronides in urine samples of all investigated species, whereas the quinoid product was present only in rabbit urine. Moreover, two regioisomeric phenolic glucuronides and sulfates or glucosides of rhein were found as major phase II metabolites in urine of all species. Furthermore, acyl glucuronides of rhein and monohydroxylated rhein and their respective isomeric acyl migration products were identified in human urine. In rabbit urine different bisglucuronides (bisphenolic glucuronide, mixed ether/ ester glucuronides) were identified, whereas in rats only the bisether/ether glucuronide was present. In addition, the investigations of dog and human urine showed the formation of two regioisomeric phenolic glucosides. With respect to a potential reactivity with endogenous macromolecules the quinoid metabolites as well as the bisester/ether glucuronides appear most relevant (Dahms *et al.,* 1997).

In experiments with rats, chrysophanol showed a cytochrome P450-dependent conversion to aloe-emodin. In turn, aloe-emodin can be metabolized to rhein in the liver (Mueller *et al.,* 1998; Lang 1993).

Animal experiments demonstrated that placental passage of rhein in rats was small. Senna leaves act within 8 to 12 hours due to the time taken for transport to the colon and metabolisation into the active compound.

In order to measure the serum concentrations of senna anthranoids (sennosides, aloe-emodin, and rhein), Sprague-Dawley rats were orally administered with single dose and multiple doses of Folium Sennae. The concentrations of anthranoids in serum were determined by HPLC method before and after hydrolysis with sulfatase and β-glucuronidase. The results showed that in the serum, aloe-emodin glucuronides and rhein glucuronides were the major metabolites. Traces of rhein free form were present transiently during the early phase, whereas the free form of aloe-emodin was not detected. The modulation effect of Folium Sennae on P-glycoprotein by using the LS 180 cell model which showed that it significantly inhibited P-glycoprotein by 16-46 % was also evaluated. Peng *et al.* concluded 2014, senna anthranoids were rapidly and extensively metabolized to rhein glucuronides and aloe-emodin glucuronides in rats. Folium Sennae ingestion inhibited the efflux function of P-glycoprotein in the intestine. (Peng *et al.* 2014)

Data on herbal preparations from human studies

Faber *et al.* (1988) investigated the excretion of rhein in 100 breast milk samples of 20 post-partum women after intake of a "standardised senna laxative", which also contains *Plantago ovata* seeds/husks as bulk substances. After daily doses of 5 g of the senna laxative containing 15 mg sennosides for 3 days, the rhein concentration in milk samples from every lactation during 24 h post-dose varied between 0 and 27 ng/ml with values below 10 ng/ml in 94 %. Based on median values, 0.007 % of the sennoside intake (calculated as rhein) was excreted in breast milk. None of the breast-fed infants had an abnormal stool consistency. Assuming theoretically a complete metabolism of sennosides to rhein in the mother, the amount of rhein delivered to the infant (ng/kg b.w.) is by the factor 10^{-3} below the rhein intake of the mother.

Data on hydroxyanthracenes from *in vitro* studies

Laxative effects of senna preparations are mainly mediated by rheinanthrone, a metabolite formed in the intestinal flora from dianthrones. Nevertheless, it was not clear whether dianthrones are bioavailable at all and contribute to the overall effects of this important medicinal plant. Using the Caco-2 human colonic cell line as an *in vitro* model of the human intestinal mucosal barrier, the bioavailability of dianthrones was studied by Waltenberger *et al.* (2008) in apical to basolateral (absorptive) and basolateral to apical (secretive) direction. Permeability coefficients (P(c)) and percent transport were calculated based on quantitations by HPLC. From the data obtained it was concluded that sennosides A and B, as well as their aglycones sennidine A and B are transported through the Caco-2 monolayers in a concentration-dependent manner and their transport was linear with time. The absorption in apical to basolateral direction was poor and P(c) values were comparable to mannitol. The transport was higher in the secretory direction, indicating a significant efflux (e.g. by efflux pumps) of the (poorly) absorbed compounds in the intestinal lumen again. The laxative effects of senna are explainable mainly by metabolites and not by the natively present dianthrones.

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 hydroxyanthracene derivatives

In mice, the estimated LD_{50} of senna extracts (calcium sennosides A+B, 20%) administered by gavage was greater than 2.5 g/kg (Marvola *et al.,* 1981) For sennosides administered by gavage the estimated LD_{50} was greater than 5 g/kg for mice and was greater than 3.5g/kg for rats (Marvola *et al.,* 1981; Mengs 1988).

Hietala *et al.* investigated 1987 the laxative effect and acute toxicity of certain fractions of senna extracts in mice. The same tests were also carried out with several pure anthraquinone derivatives common in senna pods. The results showed that the laxative and toxic components of senna pods and senna extracts can be separated. The most potent laxative components, sennosides A + B and fraction V (relative potencies 1 and 0.9 respectively), have the lowest toxicity (relative intravenous toxicities 1 and less than 1). Fractions with very low laxative activity (rhein-8-glucoside and fraction IV, relative potencies 0.56 and 0.05) have the highest acute toxicity (relative toxicities 10 and 32 respectively).

3.3.2. Repeat dose toxicity

Data on the herbal substance

Male Wistar rats fed a diet containing 10 % senna (pods, powdered) for 3 or 6 weeks exhibited diarrhea, decreased food intake, and decreased body weight gain compared to controls. The result showed an increased serum index of liver toxicity (alanine aminotransferase and aspartate aminotransferase) and increased urea in serum along with slight degenerative changes in the liver, kidney, and intestines but decreased calcium levels in serum and decreased white blood cell counts compared to controls (Al-Yahya *et al*. 2002).

Oral administration of senna (750 mg/kg or greater; powdered Tinnevelly senna pods diluted with 0.1% carboxymethylcellulose) to Sprague-Dawley rats for 13 weeks increased soft feces and water consumption in males and females and reduced body weight gain in males (Mengs *et al.* 2004). Administration of up to 1500 mg/kg senna for 13 weeks decreased sodium in urine and increased kidney weights in 1500 mg/kg male and 750 and 1500 mg/kg female Sprague-Dawley rats compared

to controls (Mengs *et al*. 2004). Minimal to slight hyperplastic changes in the mucosa of the large intestine in rats receiving more than 100 mg/kg of senna and minimal to slight hyperplastic epithelium of the forestomach in rats receiving 1500 mg/kg were observed. These hyperplastic changes were reversible. Hyperplastic changes were not observed in animals 8 weeks after the 13 weeks of senna administration ended.

Groups of five male and five female mice (C57BL/6NTAC mice) were exposed to 0, 625, 1250, 2500, 5000, or 10000 ppm senna (equivalent to average daily doses of approximately 115, 245, 490, 975, or 2075 mg senna/kg body weight to males and 160, 310, 625, 1190, or 2570 mg/kg to females) in feed for 5 weeks. All mice survived to the end of the study. Mean body weights of exposed groups were similar to those of the controls. No differences in feed consumption were noted between exposed and control groups. Significantly increased incidences of epithelial hyperplasia of the cecum occurred in males exposed to 10000 ppm and females exposed to 5000 or 10000 ppm; significantly increased incidences of epi-thelial hyperplasia of the colon occurred in males and females exposed to 5000 or 10000 ppm (NTP 2012).

Groups of 25 male and 25 female mice (heterozygous F1 P53+/− mice) were exposed to 0, 100, 300, 1000, 3000, or 10000 ppm senna (equivalent to average daily doses of approximately 12, 36, 120, 365, or 1260 mg/kg to males and 14, 42, 140, 435, or 1520 mg/kg to females) in feed for 40 weeks. Mean body weights of exposed male and female mice were within 10% of those of the controls throughout the study. Feed consumption by exposed mice was generally similar to that by the controls. Significant increases in the incidences of epithelial hyperplasia of the colon and cecum occurred in 10000 ppm males and females, and the incidence of epithelial hyperplasia of the colon was significantly increased in 3000 ppm females (NTP 2012).

Several studies in the literature have examined the relationship between the use of senna and damage in the enteric nervous system of the colon. For example, a study by Smith observed 1968 damage to intestinal nerves of mice given senna syrup. However, other rodent studies failed to show damage in the enteric nervous system of the colon after ingestion of senna or sennosides (Dufour and Gendre 1984, Rudolph and Mengs 1988, Mengs *et al*. 2004, Mitchell *et al*. 2006, NTP 2012).

Data on other *Senna* species

Silva *et al.* (2011) performed a pre-clinical safety evaluation of hydroalcoholic extract of *Cassia occidentalis* stem and leaf in male and female Wistar rats. In acute toxicity tests, four groups of rats (n = 5/group/sex) were orally treated with doses of 0.625, 1.25, 2.5 and 5.0 g/kg and general behavior, adverse effects and mortality were recorded for up to 14 days. In subacute toxicity assays, animals received *Cassia occidentalis* by gavage at the doses of 0.10, 0.50 or 2.5 g/kg/day (n = 10/group/sex) for 30 days and biochemical, hematological and morphological parameters were determined. *Cassia occidentalis* did not produce any hazardous symptoms or death in the acute toxicity test, showing a LD_{50} higher than 5 g/kg. Subacute treatment with *Cassia occidentalis* failed to change body weight gain, food and water consumption and hematological and biochemical profiles. In addition, no changes in macroscopical and microscopical aspect of organs were observed in the animals. The results showed that acute or subacute administration of *Cassia occidentalis* is not toxic in male and female Wistar rats, suggesting a safe use by humans.

Data on hydroxyanthracene derivatives

In male and female Wistar rats, administration of 25 mg/kg sennosides produced a laxative effect and administration of 100 mg/kg for 6 months induced diarrhea and decreased body weight gain by approximately 50% compared to controls. Single administration of sennosides (2 to 7.5 g/kg) to male

and female Wistar rats produced diarrhea, sedation, hunched posture, piloerection, and death (Mengs 1988).

Male Sprague-Dawley rats fed a diet containing 0.2 % sennosides for 56 days had diarrhea, reduced body weight gain, and decreased survival compared to controls (Mereto *et al.,* 1996). In NMRI mice, oral administration of 9.35 mg/kg of sennosides induced a laxative effect and 2.5 g/kg of sennosides induced diarrhea (Dufour and Gendre 1984; Mengs 1988). A mild laxative effect was induced in male NMRI mice fed a diet containing 0.03 % sennosides (86 % sennosides) for 20 weeks (Siegers *et al.,* 1993a). Mild kidney effects of sennosides have been observed.

In male and female Wistar rats treated with 2 to 20 mg/kg sennosides for 4 weeks, no changes in hematological, biochemical, or urinary parameters were observed (Mengs 1988). However, in 20 mg/kg rats, mean kidney weights were higher than that of the control group and small sudanophilic globules within the convoluted tubules of the kidney were observed. In male Wistar rats administered 25 or 100 mg/kg sennosides for 6 months, no hematological or urinary changes were observed, but increased kidney weights as well as dose-related basophilia of convoluted renal tubules were observed.

In male F344 rats fed sennoside A (0.006 % to 0.05 %) for 7 days, cell proliferation in the colorectum was increased and inflammatory changes in the large intestine were observed (Toyoda *et al*., 1994).

However, in female Wistar rats, administration of 30 mg/kg sennosides for 12 weeks did not affect cell proliferation in the large intestine (Geboes *et al.,* 1993). Administration of 50 mg/kg sennosides did not affect lactic acid dehydrogenase release into the colon lumen of female Wistar rats (Leng-Peschlow 1993). In male Wistar rats, administration of sennosides (10 or 40 mg/kg) for 23 weeks did not affect the duration or frequency of the long-spike burst in the large intestine (Fioramonti *et al.,* 1993; NTP 2012).

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:

16-day study in F344/N rats

Groups of 5 male and 5 female rats were fed diets containing 0, 600, 2000, 5500, 17000, or 50000 ppm emodin. This corresponds in males to average daily doses of approximately 50, 170, 480, 1400, or 3700 mg emodin/kg bw and in females to 50, 160, 460, 1250, or 2000 mg/kg bw. Three female rats died before the end of the study. Mean body weights of males and females exposed to 5500 ppm or greater were significantly less than those of the controls. Feed consumption by males and females receiving 17000 or 50000 ppm was decreased throughout the study. Macroscopic lesions were present in the kidney of rats exposed to 17000 or 50000 ppm.

16-day study in B6C3F1 mice

The size of the groups and the administered concentrations were the same as described above. The concentrations correspond in males to average daily doses of approximately 120, 400, 1200 or 3800 mg/kg bw and in females to 140, 530, 1600 or 5000 mg/kg bw. 50000 ppm equivalents were not calculated due to high mortality. All mice exposed to 50000 ppm died before the end of the study. Mice in the 17000 ppm groups lost weight during the study. Feed consumption by 5500 ppm females was greater than that by the controls. Macroscopic lesions were present in the gallbladder and kidney of mice exposed to 17000 ppm.

14-week study in rats

Groups of 10 male and 10 female rats were fed diets with 0, 312.5, 625, 1250, 2500 or 5000 ppm emodin. This corresponds to average daily doses of approximately 20, 40, 80, 170, or 300 mg/kg bw in males and females. Among others, relative kidney weights of rats exposed to 1250 ppm or greater and relative lung weights of rats exposed to 625 ppm or greater were significantly increased compared to the control groups. Relative liver weights were increased in females exposed to 625 ppm or greater. The estrous cycle length was significantly increased in females exposed to 1250 or 5000 ppm. All male rats exposed to 1250 ppm or greater and all exposed female rats had pigment in the renal tubules; and the severity of pigmentation generally increased with increasing exposure concentration. The incidences of hyaline droplets in the cortical epithelial cytoplasm were increased in all groups of exposed males and in females exposed to 312.5, 625, or 1250 ppm.

14-week study in mice

The size of the groups and the administered concentrations were the same as described above. This corresponds to average daily doses of approximately 50, 100, 190, 400, or 800 mg/kg to males and 60, 130, 240, 500, or 1100 mg/kg to females. Relative kidney weights of male mice exposed to 1250 ppm or greater, relative lung weights of males exposed to 625 ppm or greater, and relative liver weights of female mice exposed to 625 ppm or greater were increased. The incidences and severities of nephropathy were increased in males and females exposed to 1,250 ppm or greater. The incidences of renal tubule pigmentation were significantly increased in males exposed to 625 ppm or greater and in females exposed to 1250 ppm or greater.

3.3.3. Genotoxicity

Data on herbal preparations

In a chromosome aberration assay in bone marrow cells of the rat, micronucleus test in rats, mouse xpot test no cytotoxic, toxic, embryotoxic or genotoxic effect could be found (Kommission E monograph of Sennae folium 1993). Therefore use during pregnancy can not be recommended for such a specified extract, because of the experimental data concerning a genotoxic risk of several anthranoids.

Sandnes *et al.* (1992) investigated the mutagenicity of senna glycosides and extracts of senna folium and senna fructus in the *Salmonella typhimurium* reversion assay. Senna glycosides were inactive in all strains, except for a slight, but significant increase in mutant frequency in TA102 in the absence and presence of liver microsomes. Extracts of senna fructus and senna folium demonstrated weak activity in TA97a, TA100 and TA102 in the presence of liver microsomes, and in TA97a and TA102 in the absence of liver microsomes. A strong increase in mutant frequency (3- to 5-fold above background frequency) was observed with all extracts in TA98 in the presence of liver microsomes. This activity increased further following enzymatic hydrolysis with hesperidinase of extracts of senna fructus from one source, and could be correlated to the release of the flavonol aglycones kaempferol and quercetin.

Genotoxicity tests were performed by several laboratories with fructus sennae, senna extract, sennosides, rhein and aloe-emodin. Fructus sennae, the sennosides and rhein did not increase mutation frequencies in the following test systems: bacterial systems (*Salmonella* reverse mutation test and/or *Escherichia coli* forward mutation test); mammalian cell cultures [hypoxanthine guanine phosphoribosyl transferase (HGPRT) test; mouse lymphoma test; chromosome aberration test with Chinese hamster ovary cells]; bone marrow (micronucleus test; chromosome aberration test); melanoblast cells (mouse spot test) of rodents. With aloe-emodin mutagenic effects were observed only i*n vitro* in the chromosome aberration test with CHO cells and in the *Salmonella* reverse mutation test (frameshift mutations in strains TA 1537, TA 1538 and TA 98). In the *in vitro* gene mutation test

with V79 cells (HGPRT test) no mutagenic potential of aloe-emodin was observed. In *in vivo* studies (micronucleus test with bone marrow cells of NMRI mice, chromosome aberration test with bone marrow cells of Wistar rats, mouse spot test (crossing DBA/2J x NMRI) no indication for a mutagenic activity of aloe-emodin was found. The relevance of the absence of a mutagenic potential in *in vivo* test systems was strengthened by the fact that aloe-emodin could be found in the blood serum after oral administration. Additional information on the interaction of aloe-emodin with DNA was obtained from an ex vivo unscheduled DNA synthesis test performed with hepatocytes of male Wistar rats: aloe-emodin did not induce unscheduled DNA synthesis as expression of DNA damage. (Heidemann *et al.,* 1993)

Four different samples of senna, including three samples of the same lot (0.7 % sennoside A, 1.3 % sennoside B, 0.06 % sennidin A, and 0.03 % sennidin B) were tested for mutagenicity in bacterial test systems. In two samples, no evidence of mutagenicity was seen in several strains of *S. typhimurium* and *E. coli*, with or without exogenous metabolic activation. In the other two samples, mutagenic activity was seen in *S. typhimurium* strains TA98 and TA100, with variable requirements for exogenous metabolic activation. *In vivo*, no increases in the frequencies of micronucleated erythrocytes were seen in male mice exposed for 40 weeks to senna via dosed feed. No significant changes in the percentage of reticulocytes among erythrocytes were observed in male mice, suggesting that exposure to senna did not induce bone marrow toxicity (NTP 2012).

Data on hydroxyanthracene derivatives

Toxicological data indicate that two hydroxyanthraquinones, emodin and aloe-emodin, present as minors component in senna, might represent a genotoxic or carcinogenic risk (Mori *et al.,* 1990, Siegers *et al.,* 1992, Brusick *et al.,* 1997). While most studies gave negative responses, results from some studies suggest a genotoxic activity by both (Wölfle *et al.,* 1990, Westendorf *et al.,* 1990, Westendorf 1993). These were Ames tests showing an interaction with Salmonella DNA resulting in the production of frameshift mutations (Westendorf *et al.,* 1990, Sandnes *et al.,* 1992, Heidemann *et al.,* 1993). Other sennosides and rhein were mostly negative in the respective tests. In three *in vivo* studies the crude senna herbal substance at a concentration of 1 or 1.5 g/kg body weight showed no evidence of any genetic effects (Heidemann *et al.,* 1993). *In vitro* assays overestimate the potential hazard from exposure and must be reevaluated by *in vivo* experiments.

Westendorf *et al.* (1990) reported that in the Ames test aloe-emodin was mutagenic in *S. typhimurium* strain TA1537 and furthermore active against TA98, TA1538 and TA97 (all frameshift mutant sites). The activity was independent of metabolic activations; in fact, the addition of S9 mix tended to suppress the mutagenicity.

In the Mammalian Cell Mutation Test, Westendorf *et al.* reported that aloe-emodin was mutagenic to V79 cells. However, other scientists question this conclusion. The highest concentration employed was 30 µg/ml and did not show much, if any toxicity. This indicates the possibility of a problem, since mutagenic effects in this assay are typically associated with toxicity. The apparent positive response was based on a very low spontaneous mutant frequency. Numerous laboratories have recognised that the spontaneous background for HGPRT-mutants (hypoxanthine-guanine phosphoribosyl transferase) is quite variable and increase of at least 3-5 fold are required in duplicate tests to confirm an effect.

In the *in vitro* unscheduled DNA synthesis (UDS) assay, also conducted by Westendorf *et al.* (1990), aloe-emodin was associated with a significant increase in net grains/nucleus. Two trials were reported. The concentrations range in both covered 6.3 µg/ml to 100 µg/ml. At a concentration of 25 µg/ml, the net grains/nucleus reached the criteria to call the response positive.

The three *in vivo* studies by Heidemann *et al.* (1993) which showed no evidence of any genetic effects, were the Chromosome Aberration Test, the Mouse Spot Test, and the *in vivo/in vitro* UDS test in rat hepatocytes:

Chromosome Aberration Test (Heidemann *et al.,* 1993): Each of NMRI mice or Wistar rats, conventionally housed, received aloe emodin orally via stomach tube. They were suspended in either 0.3 – 0.5 % tragacanthe in aqua dest. or aqua dest. The volume administered was 15 ml/kg. 2.5 h prior to sacrifice the animals were injected intraperitoneally with the spindle inhibitor Colcemid (2 mg/kg) to arrest cells in metaphase. The preparation intervals were 6, 24 and 48 h after treatment. After flushing out of the bone marrow from the femora with hypotonic potassium chloride solution the cells were fixed, spread by flame drying and stained with Giemsa solution. The mitotic index from 1,000 cells was determined in each experimental group, and scoring of chromosomal aberrations was done in 50 metaphases per animal on coded slides of each 5 males and females per group. A test substance was classified positive if it induced either a dose-related increase in the number of structural chromosomal aberrations or a statistically significant (Mann-Whitney test) positive response for at least one of the test points.

Mouse Spot Test (Heidemann *et al.,* 1993): Housing of the animals and treatment with aloe-emodin were as described above. In the spot test embryos were exposed to the test substances at an appropriate stage of development, mostly day 9, and allowed to grow up. The target cells in the developing embryos were melanoblasts, and target genes were those which control the pigmentation of the coat hairs. The embryos were heterozygous for three coat colour genes. A mutation in or loss of the dominant allele of such genes resulted in the expression of the recessive genotype forming a spot of altered colour in the black coat of the F1 mouse. The F1 offspring were examined for coat colour spots 3 weeks after birth. Brownish or greyish pigmented spots and non-midventral white spots were regarded to have genetic relevance. A test substance was classified as positive if it induced either a dose-related increase in the frequency of genetically relevant spots or a statistically significant (exact Fisher Yates test) positive response for at least one of the test points.

In vivo/in vitro UDS Test in Rat Hepatocytes (Heidemann *et al.,* 1993): Housing of the animals and treatment with the test substances were as described above. After a treatment period of 4 and 16 h, the animals were anaesthetised and sacrificed during liver perfusion. Primary hepatocyte cultures were set up and exposed for 4 h to 3H-thymidine, which is incorporatedinto the DNA if UDS occurs. The uptake of 3H-thymidine by the hepatocytes was determined by autoradiography. For each test group hepatocytes from 3 animals were assessed for the occurrence of UDS. The number of silver grains above the nuclear area was counted using Artek 880 or 982 counter. In addition, the number of grains of one nuclear-sized cytoplasmic area adjacent to the nucleus was counted. At least two slides per animal and 50 cells per slide were evaluated. A test substance was classified as positive if it induced either a dose-related increase in 3H-thymidine incorporation expressed as grains per nuclear area (=nucleus) or a statistically significant (Mann-Whitney test) positive response for at least one of the test points.

In the following study, Aviello *et al.* evaluated 2010 the cytotoxicity of rhein, the active metabolite of senna, on human colon adenocarcinoma cells (Caco-2) and its effect on cell proliferation. Cytotoxicity studies were performed using 3-(4.5-dimethylthiazol-2-yl)-2.5-diphenyltetrazolium bromide (MTT), neutral red (NR) and trans-epithelial electrical resistance (TEER) assays whereas (3)H-thymidine incorporation and Western blot analysis were used to evaluate the effect of rhein on cell proliferation. Moreover, for genoprotection studies Comet assay and oxidative biomarkers measurement (malondialdehyde and reactive oxygen species) were used. Rhein (0.1-10 µg/ml) had no significant cytotoxic effect on proliferating and differentiated Caco-2 cells. Rhein (0.1 and 1 µg/ml) significantly

reduced cell proliferation as well as mitogen-activated protein (MAP) kinase activation; by contrast, at high concentration (10 µg/ml) rhein significantly increased cell proliferation and extracellular-signal-related kinase (ERK) phosphorylation. Moreover, rhein (0.1-10 microg/ml): (i) did not adversely affect the integrity of tight junctions and hence epithelial barrier function; (ii) did not induce DNA damage, rather it was able to reduce H(2)O(2)-induced DNA damage and (iii) significantly inhibited the increase in malondialdehyde and reactive oxygen species (ROS) levels induced by H(2)O(2)/Fe(2+). Rhein was devoid of cytotoxic and genotoxic effects in colon adenocarcinoma cells. Moreover, at concentrations present in the colon after a human therapeutic dosage of senna, rhein inhibited cell proliferation via a mechanism that seems to involve directly the MAP kinase pathway. Finally, rhein prevents the DNA damage probably via an anti-oxidant mechanism.

Emodin was mutagenic in *Salmonella typhimurium* strain TA100 in the presence of S9 activation; no mutagenicity was detected in strain TA98, with or without S9. Chromosomal aberrations were induced in cultured Chinese hamster ovary cells treated with emodin, with and without S9. Three separate *in vivo* micronucleus tests were performed with emodin. A male rate bone marrow micronucleus test, with emodin administerd by 3 intraperitoneal injections, gave negative results. Results of acute-exposure (intraperitoneal injection) micronucleus tests in bone marrow and peripheral blood erythrocytes of male and female mice were negative. In a peripheral blood micronucleus test on mice from the 14-week study, negative results were seen in male mice, but a weakly positive response was observed in similarly exposed females. The studies give no evidence of carcinogenic activity of emodin in male rats and female mice, and equivocal evidence in female rats and male mice. In view of conflicting results on genotoxicity, it was noted the first pass effect and need for metabolic activation suggesting a metabolite as the genotoxic form. The metabolite 2-hydroxyemodin acts as the genotoxin (Masuda *et al.,* 1985).

The NTP (2012) tested rhein (a component of senna) for mutagenicity in *S. typhimurium strains* TA98 and TA100; dose-related increases in mutant colonies were seen with both strains in the presence of rat or hamster liver S9, at lower concentrations than were required for the positive responses seen with senna samples. Another component of senna, chrysophanic acid, was tested for mutagenicity in TA98, TA100, and TA1535; weak and inconsistent responses were seen in TA100 with rat and hamster liver S9. Sennosides A and B were also tested for mutagenicity in bacterial test systems; neither compound was mutagenic, with or without S9 metabolic activation.

3.3.4. Carcinogenicity

Data on herbal preparations

Mascolo *et al*. (1999) investigated the influence of senna extract on the growth and initiation of malignant tumours in rat colon. In the dose of 10 mg of extract/kg, which just produced a slight laxative effect, no carcinogenic or tumourigenic effects were observed. Only the second dose level of 100 mg/kg given for 13 – 28 weeks together with azoxymethane produced a higher rate of tumours compared to the control group (only given azoxymethane). The authors concluded that, under therapeutic dosage, senna extracts have no carcinogenic effects whatever. The dose of 100 mg/kg led to permanent diarrhoea in the animals for 3 months and was thus clearly too high and of no therapeutic relevance.

Mengs *et al.* conducted 2004 a toxicity study on senna in male and female rats. The administered senna preparation were powdered Tinnevelly senna pods containing 1.829 % of sennosides A-D, 1.596 % of potential rhein, 0.111 % of potential aloe-emodin, 0.014 % of total emodin, and 0.004 % of total chrysophanol (sum of potential hydroxyanthraquinones 1.725 %). Senna was administered by gavage to Sprague Dawley rats once daily at dose levels of 0, 100, 300, 750 or 1,500 mg/kg for up to

13 consecutive weeks followed by an 8-week recovery period for selected animals. There was a dose-dependent laxative effect at 300 mg/kg per day and above. Animals receiving 750 or 1,500 mg/kg per day had significantly reduced body weight gain (males only) and, related to the laxative properties of senna, increased water consumption and notable electrolyte changes in blood and urine. At both the terminal and recovery phase necropsy, an increase in absolute and relative kidney weights was seen for male and female animals receiving 750 and/or 1,500 mg/kg per day. A dark discolouration of the kidneys was observed at necropsy along with histopathological changes (slight to moderate tubular basophilia and pigment deposits) at 300 mg/kg and above. Although the pigmentation decreased towards the end of the recovery period, it still remained to a lesser degree. However, there were no indications in laboratory parameters of any renal dysfunction. In addition, for all treated groups, minimal to slight hyperplasia was recorded in the forestomach and large intestine, which was reversible within the 8-week recovery period. The histological changes were considered a physiological adaptation to the laxative substance. Under the conditions of the study, there were no alteration seen in the colonic nervous plexus. Even in the highest dose group, there was no indication of any pigment deposits in the mucous membranes of the large intestine. The authors concluded that senna did not cause any notable target organ toxicity up to the highest dose tested. A no-observable-effect-level (NOEL) could not be obtained, but the changes seen were considered to represent a physiological adaptation to treatment and not a true toxic response.

To determine the potential toxic effects of senna, a 40-week toxicology and carcinogenesis study in the C3B6.129F1-Trp53 (tm1Brd) N12 haploinsufficient (p53(+/-)) mouse were conducted within the NTP Programm (Surh *et al*. 2013; see also NTP, 2012). Groups of 25 male and 25 female mice were exposed to 0, 100, 300, 1,000, 3,000, or 10,000 ppm senna (equivalent to average daily doses of approximately 12, 36, 120, 365, or 1,260 mg/kg to males and 14, 42, 140, 435, or 1,520 mg/kg to females) in feed for 40 weeks. Mean body weights of exposed male and female mice were within 10 % of those of the controls throughout the study. Feed consumption by exposed mice was generally similar to that by the controls. Significant increases in the incidences of epithelial hyperplasia of the colon and cecum occurred in 10,000 ppm males and females, and the incidence of epithelial hyperplasia of the colon was significantly increased in 3,000 ppm females.

To evaluate the carcinogenic potential of anthraquinones, the effect of long-term senna pod extract treatment on either healthy rats or rats treated with an initiating tumor agent (azoxymethane) has been studied. Senna pod extract (30 and 60mg/kg), administered for 110 weeks, did not induce the development of aberrant crypt foci and tumors in healthy rats. The development of aberrant crypt foci and tumors in rats treated with azoxymethane were significantly reduced by senna pod extract (30 and 60 mg/kg) (Borelli *et al.* 2005)

In vivo/in vitro UDS test in rat hepatocytes: A carcinogenicity study was done by Lyden-Sokolowski *et al.* (1993) in rats receiving for 2 years a purified senna extract, that contained approximately 40.8 % anthranoids, of which 35.7 % were total sennosides, corresponding to approximately 25.2 % calculated potential total rhein, 2.3 % potential aloe-emodin and 0.007 % potential emodin. Besides the control group, 3 dosages groups (5, 15 and 25 mg/kg) were tested, which showed clinical signs of chronic electrolyte loss, mostly in the high-dosage 25 mg/kg group. No treatment-related increase in tumours of the gastro-intestinal tract, liver or kidneys could be found. The highest dose level was approximately 20-25 times the recommended clinical dose.

Data on hydroxyanthracene derivatives

Mereto *et al.* (1996) found that senna glycosides acted as weak promoters of rat colon carcinogenesis. The doses used were considerably above those taken by humans and which are usually used in therapy.

Induction of cell proliferation by laxatives and related compounds in rat intestines was analysed by BrdU-labelling and compared with histopathological changes in the mucosa and findings for feces by Toyoda *et al*. (1994). Male F344 rats were fed a diet containing danthron, sennosid A, bisacodyl, 1-hydroxyanthraquinone, magnesium sulfate, dextran sulfate sodium, pectin, carboxymethylcellulose sodium (CMC-Na) or sodium chloride (NaCl) for 7 days. The stimulant laxatives, danthron, sennosid A and bisacodyl, significantly induced cell proliferation in almost the entire intestinal epithelia in a clear dose-dependent manner. DSS also induced cell proliferation in some portions at high doses. Increase in BrdU-labelling indices was correlated well with the severity of inflammatory changes in the intestinal mucosa as well as with purging effects of stimulant laxatives and dextran sulfate sodium. In contrast, the bulk-forming laxative CMC-Na did not consistently enhance cell proliferation nor cause apparent cytotoxicity in the intestine despite exerting remarkable purging effects. 1-hydroxyanthraquinone and magnesium sulfate slightly induced cell proliferation in the cecum and the colorectum, although there was little or no intestinal cytotoxicity. Pectin and NaCl did not influence cell kinetics of the epithelia, nor cause any inflammatory changes in the mucosa. The results thus indicate that diarrhea caused by laxatives is not necessarily correlated with induction of cell proliferation, as in the intestinal mucosa, and that inflammatory changes followed by regenerative process could be responsible for enhancing cell kinetics.

The carcinogenic activities of anthraquinone and six derivatives were compared and contrasted. Studies included representatives of amino, alkyl, nitro, hydroxy, or halogen-containing anthraquinones, with the purpose of uncovering general structure-activity relationships. Anthraquinone, 2-aminoanthraquinone, 1-amino-2-methylanthraquinone, 2-methyl-1-nitroanthraquinone,1-amino-2,4-dibromoanthraquinone, 1,4,5,8-tetraaminoanthraquinone, and 1,3,8-trihydroxy-6-methylanthraquinone (of varying purities) were administered via feed to Fischer 344/N rats and B6C3F, mice. In rats, anthraquinone induced tumors in the liver, kidney, and urinary bladder. A 2-amino substitution narrowed the carcinogenicity to the liver, while multiple amino substitutions led to a carcinogenic response in the urinary bladder alone. A methyl substitution ortho to a 1-aminogroup preserved the hepatic and renal neoplasms seen with the parent anthraquinone, but did not induce urinary bladder tumors; amino or bromo substitutions para to a 1-amino group were related to urinary bladder neoplasms. The intestine may have been a target organ for bromine-substituted anthraquinones. The presence of a nitro group altered the targets of carcinogenicity, and skin tumors may have been associated with this particular functional group in both rats and mice. Over-all for mice, the findings were somewhat different and limited by the small number of common target organs. The parent anthraquinone was clearly carcinogenic only to the liver. There were no other effects of single amino substitutions, in the presence or absence of an additional methyl group, on the carcinogenicity or the site of carcinogenesis of anthraquinone in mice. Multiple amino substitutions diminished, while bromine substitutions enhanced the carcinogenicity induced by anthraquinone and extended the target organs to include forestomach and lung (Doi *et al.* 2005).

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.

2-year (105 weeks) study in rats: Groups of 65 male and 65 female rats were fed diets containing 0, 280, 830, or 2,500 ppm emodin (equivalent to average daily doses of approximately 110, 320, or 1,000 mg/kg to males and 120, 370, or 1,100 mg/kg to females). Three Zymbal's gland carcinomas were observed in female rats exposed to 2,500 ppm. This incidence exceeded the range observed for current historical controls and was considered an equivocal finding. At the 6- and 12-month interim evaluations and at 2 years, emodin-related increases in the incidences of renal tubule hyaline droplets occurred in all exposed groups. The incidences of renal tubule pigmentation were significantly increased in all exposed groups of males at 2 years. There were negative trends in the incidences of

mononuclear cell leukaemia in male and female rats, and the incidences in the 2,500 ppm groups were significantly decreased. In females exposed to 2,500 ppm, the incidence was below the historical control range; the incidence in males exposed to 2,500 ppm was at the lower end of the historical control range.

2-year (105 weeks) study in mice: Groups of 60 male mice were fed diets containing 0, 160, 312, or 625 ppm emodin (equivalent to average daily doses of approximately 15, 35, or 70 mg/kg). Groups of 60 female mice were fed diets containing 0, 312, 625, or 1,250 ppm emodin (equivalent to average daily doses of approximately 30, 60, or 120 mg/kg). Low incidences of renal tubule adenoma and carcinoma occurred in exposed male mice; these incidences included one carcinoma each in the 312 and 625 ppm groups. Renal tubule neoplasms are rare in male mice, and their presence in these groups suggested a possible association with emodin exposure. At the 12-month interim evaluation, the severity of nephropathy was slightly increased in males exposed to 625 ppm. Also at 12 months, the severity of nephropathy increased from minimal in the lower exposure groups to mild in females exposed to 1,250 ppm; the incidence in this group was significantly increased compared to the control group. At 2 years, the severities of nephropathy were slightly increased in males exposed to 625 ppm and females exposed to 1,250 ppm. The incidences of nephropathy were significantly increased in all exposed groups of females. At the 12-month interim evaluation, the incidences of renal tubule pigmentation were significantly increased in all exposed groups of males and in females exposed to 625 or 1,250 ppm. The severities increased with increasing exposure concentration. At 2-years, the incidences of renal tubule pigmentation were significantly increased in all exposed groups; severities also raised with increasing exposure concentration.

3.3.5. Reproductive and developmental toxicity

Garcia-Villar evaluated in 1988 the effects of sennosides on uterine motility in the pregnant ewe. Repeated intracolonic administration of laxative doses of sennosides A+B (60mg/kg) between the 70th and 120th day of the pregnancy had no effect on cervical motility but significantly reduced uterine motility in some ewes. Pregnancy maintenance was normal (Blaschek *et al.* 2003).

3.3.6. Local tolerance

There are no studies available regarding local tolerance.

3.3.7. Other special studies

Interactions between widely used anthranoid laxatives and other simultaneously administered drugs were studied by Laitinen *et al* 2007. In this paper, the influence of rhein, danthron, sennidins A/B, sennosides A/B, and senna leaf infusion was investigated on the permeability of furosemide, ketoprofen, paracetamol, propranolol, verapamil, digoxin, and Rhodamine 123 across Caco-2 monolayers. The effects on monolayer integrity ([(14)C]mannitol permeability, trans-epithelial electrical resistance) were also determined. The *in vitro* absorption of highly permeable drugs was not strongly affected during co-administration of the laxatives. Furosemide permeability was enhanced by rhein and danthron (3.6 and 3.0-fold), which may partly be due to opening of the paracellular spaces and/or effects on active efflux. However, the secretory permeability of digoxin and Rho 123 was not strongly affected by rhein and danthron, suggesting that inhibition of MDR1 was not responsible for the increased permeation of furosemide. The absorptive permeability of digoxin was decreased by rhein and danthron, offering evidence for effects on apical membranes. According to the authors the effects on monolayer integrity were detectable, but reversible. According to presented experiments, daily use

of laxatives with well-absorbing drugs would seem unlikely to affect drug permeability, but the effects on the absorption of poorly permeable drugs cannot be excluded.

3.3.8. Conclusions

Genotoxicity tests were performed by several laboratories with the herbal substance Sennae fructus, senna extract, sennosides, rhein and aloe-emodin. The herbal substance Sennae fructus, the sennosides and rhein did not increase mutation frequencies in the following test systems: bacterial systems (*Salmonella* reverse mutation test and/or *Escherichia coli* forward mutation test); mammalian cell cultures [hypoxanthine guanine phosphoribosyl transferase (HGPRT) test; mouse lymphoma test; chromosome aberration test with Chinese hamster ovary cells]; bone marrow (micronucleus test; chromosome aberration test); melanoblast cells (mouse spot test) of rodents. In *in vivo* studies [micronucleus test with bone marrow cells of NMRI mice, chromosome aberration test with bone marrow cells of Wistar rats, mouse spot test (crossing DBA/2J x NMRI)] no indication for a mutagenic activity of aloe-emodin was found.

No increase in tumours of the gastro-intestinal tract, liver or kidneys could be found in rats in a 2 year carcinogenicity study with a purified senna extract (40.8 % anthranoids). There was some potassium loss in the high dose group covering 20-25 fold the clinically recommended dose (Lyden-Sokolowski *et al.,* 1993).

Cassia occidentalis did not produce any hazardous symptoms or death in the acute toxicity test, showing a LD_{50} higher than 5 g/kg. The results showed that acute or subacute administration of *Cassia occidentalis* is not toxic in male and female Wistar rats, suggesting a safe use by humans Silva *et al.* 2011. In mice, the estimated LD_{50} of senna extracts (calcium sennosides A+B, 20%) administered by gavage was greater than 2.5 g/kg (Marvola *et al.,* 1981). For sennosides administered by gavage the estimated LD_{50} was above 5 g/kg for mice and was above 3.5 g/kg for rats (Marvola *et al.,* 1981;Mengs 1988).

In a 2-year (105 weeks) study in mice fed with emodin (equivalent to average daily doses of approximately 15, 35, or 70 mg/kg) low incidences of renal tubule adenoma and carcinoma occurred in exposed male mice; these incidences included one carcinoma each in the 312 and 625 ppm groups. Renal tubule neoplasms are rare in male mice, and their presence in these groups suggested a possible association with emodin exposure. At 2-years, the incidences of renal tubule pigmentation were significantly increased in all exposed groups of rats and mice; severities also raised with increasing exposure concentration (NTP 2001).

Male Wistar rats fed a diet containing 10% senna for 3 or 6 weeks had an increased serum index of liver toxicity and increased urea in serum along with slight degenerative changes in the liver, kidney, and intestines but decreased calcium levels in serum and decreased white blood cell counts compared to controls. Some authors observed damage to intestinal nerves of mice given senna syrup. Other rodent studies failed to show damage in the enteric nervous system of the colon after ingestion of senna or sennosides (Dufour and Gendre 1984, Rudolph and Mengs 1988, Mengs *et al*. 2004, Mitchell *et al*. 2006, NTP 2012.

Sprague Dawley rats showed a dose-dependent laxative effect at 300 mg/kg per day and above, had significantly reduced body weight gain, and an increased water consumption and notable electrolyte changes in blood and urine. A dark discolouration of the kidneys was observed. A no-observable-effect-level (NOEL) could not be obtained, but the changes seen were considered to represent a physiological adaptation to treatment and not a true toxic response (Mitchell and Mengs 2006).

The review of Morales *et al.* (2009) summarizes that there is no convincing evidence that the chronic use of senna has, as a consequence, a structural and/or functional alteration of the enteric nerves or the smooth intestinal muscle, there is no relation between long-term administration of a senna extract and the appearance of gastrointestinal tumors or any other type in rats, senna is not carcinogenic in rats even after a two-year daily dose of up to 300 mg/kg/day, and the current evidence does not show that there is a genotoxic risk for patients who take laxatives containing senna extracts or sennosides.

The HMPC decided to follow the strategy to condens information given in section 5.3 of the monographs as far as possible. A short summary of the 90-day study in rats is presented as well as a remark on the different data on genotoxicity and cancerogenicity.

3.4. Overall conclusions on non-clinical data

Preclinical data show the laxative pharmacodynamic effects of preparations containing senna leaves and pods.

Rhein-9-anthrone is the most important metabolite, which 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 and reduced fluid absorption. 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 (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), results in enhanced concentrations of fluid and electrolytes in the lumen of the colon.

The use during pregnancy is contraindicated in the monograph because experimental data concerning a genotoxic risk of several anthranoids, e.g. emodin and aloe-emodin.

4. Clinical Data

4.1. Clinical pharmacology

Constipation is said to be present when passed stools are of hard consistency and when evacuation of faeces is too difficult, too infrequent and irregular. The physiological range for frequency of bowel movements is wide, extending from three times daily to once every 2 to 3 days. In the pathogenesis of constipation the colon plays a key role because this is where the contents of the gut remain for 24 – 48 hours. During this period the liquid contents from the small intestine are converted into faeces by absorption of water and electrolytes in response to the action of bacteria. These functions are dependent on the interplay of peristaltic processes, which mix the contents and the normal coordination of the anorectal muscles during defaecation. A disturbance involving any of these individual areas may lead to constipation. In this context, functional disturbances are far more common than those of an organic origin. In addition, assessment is problematic because the symptoms are perceived differently by the individuals affected (Ewe 1994, Gabler 1994), due to different concepts of what normal bowel habits are.

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

Ewe *et al.* (1993) measured gastric emptying, small and large intestinal transit in 24 healthy volunteers using a metal detector method. Twelve persons taking a normal diet received loperamide in a dose sufficient to double the individual transit time. All subjects measured gastrointestinal transit

time under normal conditions (A) and with a product containing purified sennosides 20 mg (B), a fibre product containing 20 g Plantago ovata seeds/husks (C), or a combination of 5.4 g Plantago ovata seeds/husks + 1.2 g senna pod with a sennoside content of 30 mg (D). Colonic transit was reduced by (B) and (D) from 39 +/- 4 h to 17 +/- 3 h ($p<0.005$). (C) did not influence colonic transit (39 +/- 3 h). Loperamide prolonged colonic transit from 27 +/- 0.7 to 72 +/- 12 h. This effect was abolished by (B) (30 +/- 5 h) and (D) (27 +/- 1 h) ($p<0.005$), but not by (C) (64 +/- 13 h). The same effects were seen when right and left colonic transit were analysed separately. Neither gastric emptying nor small intestinal transit was affected by either substance. All three investigated medicinal products increased stool weight significantly ($p<0.05$). When stool frequency and consistency were compared, the effects were less clear. (D) caused the greatest, (C) the least changes of these parameters. Oroanal transit times measured by the metal detector and by the Hinton method using 20 radiopaque markers were similar (43 +/- 6 and 47 +/- 6 h, respectively).

Buhmann *et al.* (2005a) enrolled 15 healthy individuals (8 males, 7 females, 20 to 45 years old) with no history or present symptoms of bowel disorders in a functional cine-MRI examination at 6 a.m. after a starving phase for at least eight hours before and after oral administration of senna leaves tea. Two consecutive sets of repeated measurements of the entire abdomen were performed using a 1.5T MRI system with coronal T2-weighted HASTE sequences anatomically adjusted to the course of the large bowel. A navigator technique was used for respiratory gating at the level of the right dorsal diaphragm. The changes in diameter (given in cm) were measured at 5 different locations of the ascending (AC), transverse (TC) and descending colon (DC), and assessed as parameters for the bowel motility. The mean values as a statistical measure for large bowel relaxation were determined. Before ingestion of senna tea, the mean diameter measured 3.41 cm (AC), 3 cm (TC) and 2.67 cm (DC). After the ingestion of senna tea, the mean diameter increased to 3.69 cm (AC), to 3.4 cm (TC) and to 2.9 cm (DC). A statistically significant difference was demonstrated with the Wilcoxon test (level of confidence 0.05). For the determination of dynamic increase, the changes of the statistical scatter amplitude to the mean value were expressed as percentage before and after the ingestion of senna tea. Thereby, an increase in variation and dynamic range was detected for the AC (112.9 %) and DC (100 %), but a decrease in the dynamics for the TC (69 %). This study investigated a non-invasive method for the assessment of bowel motility for the first time. The results have therefore to be regarded with caution. Further studies have to determine whether the results of this technique are clinical relevant.

Buhmann *et al.* (2005b) sought to assess large bowel motility, induced by 2 prokinetic agents, senna leaves tea and erythromycin, using functional cine magnetic resonance imaging (MRI). Twelve volunteers underwent functional cine MRI before and after the administration of senna tea or erythromycin. The protocol consisted of 2 sets of repeated measurements using coronal T2-weighted HASTE sequences, adjusted to the course of the colon. For the assessment of large bowel motility, the changes of the luminal diameter were measured at 5 defined locations in the ascending, transverse, and descending colon. In all examined volunteers after senna tea, the mean number of significant changes in the ascending colon was 8.6 and after erythromycin, 7.2. In the transverse colon, 9.6 diameters changed significantly for senna tea and 7.2 for erythromycin. In the descending colon, 6.6 diameters changed after senna tea and 7.2 after erythromycin. Senna tea and erythromycin proved to induce large bowel motility; senna tea was more effective. Functional cine MRI is a reliable, noninvasive method for the assessment of colonic motility.

In a pharmacological study the jejunum and the colon of humans were perfused with 15 mg and 20 mg rhein, respectively, via tube. The fluid absorption was turned into a fluid secretion. The net transport of sodium changed and there was a loss of potassium (Symposium Antrachinon-Laxantien, 1985).

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

Kobashi *et al.* demonstrated 1980 that sennosides could be converted to rhein anthrone by specific cultured bacteria strains from the human intestine. Further, Hattori *et al.* demonstrated 1993 cleavage of the O-glucosyl bond of sennoside B, reduction of sennidin B, and accumulation of rhein anthrone in a coculture of two bacteria strains isolated from human feces. (NTP 2012)

Concentrations of rhein and aloe-emodin were determined over time in plasma of human volunteers receiving four daily therapeutic doses of either of two senna-containing laxatives (Krumbiegel and Schulz, 1993). No aloe-emodin was detected in any samples. Two peak concentrations of rhein were observed in plasma following each dose, one at 3 to 5 hours and the anthrone has a weaker laxative effect than rhein anthrone. In humans, intraluminal introduction of senna, which was preincubated with feces or *Escherichia coli*, produced peristalsis within 1 hour. Intraluminal application of rhein anthrone also produced peristalsis within 1 hour (Hardcastle and Wilkins 1970; NTP 2012).

Therapeutic doses of two laxatives were repeatedly administered to 10 healthy volunteers in a two-way change-over design (Krumbiegel and Schulz*,* 1993). One laxative contained purified sennosides 20 mg, and the other was a combination of Plantago ovata seeds/husks and senna pod. Blood samples were collected up to 96 h after the first dose, and plasma levels of total aloe-emodin and rhein were determined simultaneously with a sensitive (lower limit of quantification: 0.5 ng aloe-emodin and 2.5 ng rhein per millilitre plasma) and specific fluorometric HPLC method. Aloe-emodin was not detectable in any plasma sample of any subject. Rhein concentration time courses showed highest levels of 150 – 160 ng/ml, mean 81.8 ng/ml (combination) and 49.6 ng/ml (purified sennosides), and peak maxima at 3 – 5 h and 10 – 11 h after dosing probably according to absorption of free rhein and rhein released from prodrugs (e.g. sennosides) by bacterial metabolism, respectively.

Hattori *et al.* (1988) reported that during the course of studies on the metabolism of sennosides by human intestinal bacteria, an enzyme which takes part in the reduction of sennosides and sennidins could be originally isolated from Peptostreptococcus intermedius. This enzyme catalysed the electron transfer from NADH (nicotinamide adenine dinucleotide) to FAD (flavin adenine dinucleotide), FMN (riboflavine 5'phosphate) or benzyl viologen, which reduced nonenzymatically sennosides and sennidins to 8-glycosyl-rhein anthrone and rhein anthrone, respectively.

A gas chromatography-mass spectrometry (GC-MS)-based screening procedure was developed for the detection of stimulant laxatives and/or their metabolites in human urine after enzymatic cleavage of conjugates followed by extractive methylation. The part of the phase-transfer catalyst remaining in the organic phase was removed by solid-phase extraction on a diol phase. The compounds were separated by capillary GC and identified by computerized MS in the full scan mode. By use of mass chromatography with the ions m/z 305, 290, 335, 320, 365, 350, 311, 326, 271, and 346, the possible presence of stimulant laxatives and/or their metabolites could be indicated. The identity of positive signals in such mass chromatograms was confirmed by comparison of the peaks underlying full mass spectra with the reference spectra. This method allowed the detection of the diphenol laxatives bisacodyl, picosulfate, and phenolphthalein and of the anthraquinone laxatives contained in plant extracts and/or their metabolites in human urine samples. The overall recoveries of the stimulant laxatives and/or their metabolites ranged between 33 % and 89 % with a coefficient of variation of less than 15 %, and the limits of detection ranged between 10 and 25 ng/ml (S/N 3) in the full scan mode. After ingestion of the lowest therapeutic dose of a senna extract, the main metabolite of sennosides, rhein, was detectable in urine samples for 24 hours (Beyer *et al.* 2005).

Diacerhein is a drug for the treatment of patients with osteoarthritis. This drug is administered orally as 50 mg twice daily. Diacerein is entirely converted into rhein before reaching the systemic circulation. Rhein itself is either eliminated by the renal route (20 %) or conjugated in the liver to rhein glucuronide (60 %) and rhein sulfate (20 %); these metabolites are mainly eliminated by the kidney. The pharmacokinetics characteristics of diacerein are about the same in young healthy volunteers and elderly people with normal renal function, both after a single dose (50 mg) or repeated doses (25 to 75 mg twice daily). Rhein kinetics after single oral doses of diacerein are linear in the range 50 to 200 mg. However, rhein kinetics are time-dependent, since the nonrenal clearance decreases with repeated doses. This results in a moderate increase in maximum plasma concentration, area under the plasma concentration-time curve and elimination half-life. Nevertheless, the steady-state is reached by the third administration and the mean elimination half-life is then around 7 to 8 hours. Taking diacerein with a standard meal delays systemic absorption, but is associated with a 25 % increase in the amount absorbed. Mild-to-severe (Child Pugh's grade B to C) liver cirrhosis does not change the kinetics of diacerein, whereas mild-to-severe renal insufficiency (creatinine clearance <2.4 L/h) is followed by accumulation of rhein which justifies a 50% reduction of the standard daily dosage. Rhein is highly bound to plasma proteins (about 99 %), but this binding is not saturable so that no drug interactions are likely to occur, in contrast to those widely reported with nonsteroidal anti-inflammatory drugs. Except for moderate and transient digestive disturbances (soft stools, diarrhoea), diacerein is well tolerated and seems neither responsible for gastrointestinal bleeding nor for renal, liver or haematological toxicity (Nicolas *et al.,* 1998).

4.2. Clinical efficacy

4.2.1. Dose response studies

There are no dose-finding studies available.

The recommended dosage as a laxative for adults, elderly and adolescents over 12 years of age (15 – 30 mg hydroxyanthracene derivatives only once daily at night) is supported by experts' opinions (Kommission E, 1984; Kommission E 1993) and by clinical investigations as reported below. This recommendation is also given in consideration of the toxicological data, which were evaluated and led to pharmacovigilance actions in Germany for anthranoid-containing laxatives in 1996 (BfArM 1996). This dosage corresponds to the recommendation given in the above-mentioned ESCOP monographs (2003). The WHO monographs referred above (WHO monographs on selected medicinal plants 1999) recommend 10 – 30 mg sennosides (calculated as sennoside B).

Through the individual product information (especially the package leaflet), patient should be informed that the correct individual dose is the smallest required to produce a comfortable soft-formed motion.

It is normally sufficient to take an anthranoid-containing laxative up to two to three times a week (Hitzenberger *et al.,* 1999).

4.2.2. Clinical studies (case studies and clinical trials)

The efficacy of senna preparations has been evaluated in clinical trials in the treatment of constipation, for bowel cleansing before radiological investigations or colonoscopy, in chemotherapy induced constipation, in postoperative constipation, in opioid-induced constipation after orthopaedic surgery and in opioid-induced constipation in palliative care. In some of the studies, combinations of senna with fibre were investigated. For bowel cleansing high doses of a senna preparation were tested.

Constipation

Pers *et al.* (1983) treated 20 elderly in-patients (above 60 years old) suffering from severe constipation, once daily for 2 weeks with combination (A) ("2.6 g Semen plantaginis ovata, 0.11 g Ispaghula husk and 0.62 g Sennae fructus angustifolie equivalent to 15 mg glycoside A+B per sachet of 5 g") or combination (B) ("3.3 g Testa ispaghula 'Tika' and 25 mg glycoside sennae A+B per sachet"). The patients were allocated randomly into the two treatment groups, one starting with (A), the other with (B). The investigation comprised three periods. The first one was the week prior to the treatment with either of the two preparations. During that week the patients received the medication routinely used at the department. The second period comprised 2 weeks treatment with one or the other of the 2 preparations. During the third period, of another 2 weeks, the preparations were changed. The periods were strictly consecutive. The dosage was one sachet in the evening. Nineteen patients completed the trial. In one patient diarrhoea from sources obviously not related to the medication occurred and this patient was classified as a drop-out. The defaecation frequency was higher during the (B) treatment than during the (A) one. This was expected as the given dose of (B) contained 10 mg glycosides more than that of (A). Precise data are not given in the publication. Large differences were seen both between individuals and for the same individual during treatment. Enemas were given to a few patients during the first period as well as during the second and third period. There were no differences between the two treatments. Concerning ease of administration, ease of swallowing and taste, there were also no differences. No-side effects were seen. The authors concluded that both preparations worked well, even if they have differences in senna glycoside content in the given dosage.

A study was conducted by Marlett *et al*. (1987) involving 42 adults with chronic constipation who remained constipated after a week of single-blind placebo treatment. Qualifying patients were than randomised to receive ispaghula husk (7.2 g/day) or psyllium plus senna (6.5 g + 1.5 g/day) for 1 week. The ingested amount of sennosides is not mentioned in the publication. Because the psyllium and senna preparation is a granular formulation ingested with a cold liquid, and the ispaghula husk product is a powder that must be mixed with a liquid before ingestion, no attempt was made to blind the identity of the treatment. Both preparations significantly increased stool frequency ($p<0.001$). In the ispaghula husk group stool frequency increased from 2.3 +/- 0.1 during placebo to 3.6 +/- 0.3 stools/wk during laxative ingestion and in the combination group from 2.0 to 6.8 stools/wk. Both treatments also significantly increased mean wet and dry stool weights, although the added effect of senna was clearly evident. Ispaghula husk treatment increased the mean wet stool weight from 254.2 g to 444.8 g/7 day and the mean dry stool weight from 75.4 g to 126.5 g/7 day. The combination treatment increased the mean wet stool weight from 277.7 g to 982.1 g/7 day and the mean dry stool weight from 79.9 g to 190.8 g/7 day. Overall relief of constipation was reported by 90 % of patients on the combination therapy and by 85 % of patients on ispaghula husk alone. Interestingly, the objective improvement in stool frequency in both groups did not attain the high level of subjective improvement; 63 % of the combination group and 48 % of the ispaghula husk group had more than three bowel movements during the week of treatment. Reports of gastrointestinal side effects (pain and cramping) were predominant in the combination group (32 % versus 14 % for ispaghula husk alone). Three of the 22 patients treated with ispaghula husk reported side effects of cramping and gas. Seven of the 22 patients treated with the combination experienced 11 episodes of side effects, which included mainly cramps, uncomfortable diarrhoea, as well as bloating, gas, and nausea. After completion of the protocol and evaluation of the data, two distinct responses to the combination therapy were evident. These two groups were designated as normal responders and high responders. The subpopulation of high responders was responsible for most of the increases in stool frequency and wet weight and all of the effect on dry stool weight. All seven high responders classified their bowel movements as too

frequent. Despite significant positive results from the objective faecal parameters, including an increase to more than 3 bowel movements per week after treatment, and despite the fact that 85 % of patients reported relief of constipation, the authors concluded that a dose higher than 7 g psyllium per day or a period of treatment longer than 7 days might be necessary to produce an effect in a chronically constipated population. The single daily dose of "senna plus psyllium" had two distinct effects; approximately one-third of the subjects had a marked response, which included gastrointestinal side effects, while two-thirds had a mild response not significantly different from those given by ispaghula husk alone. The authors suggested that doses of psyllium + senna be individualised, given the higher incidence of undesirable side effects with combination therapy.

Passmore *et al*. (1993 a, b) compared the efficacy of a senna-fibre combination, a ispaghula-senna combination (ispaghula 54.2 %, senna 12.4 % (m/m)) and lactulose in 77 elderly patients (average age: 82.9 years) with a history of chronic constipation in long-term hospital or nursing home care in a randomised, double-blind, crossover study. The patients received active senna-fibre combination 10 ml daily with lactulose placebo 15 ml twice daily, or active lactulose 15 ml twice daily with senna-fibre placebo 10 ml daily for two 14 day periods. Doses could be increased or decreased according to response. The maximum daily dose for active or placebo senna-fibre was 20 ml (10 ml twice daily) and for lactulose or lactulose placebo 60 ml. Before entry into the first phase, and between treatments, subjects had a three to five day period free of laxatives. The number of stools and their consistency and ease of evacuation, together with any other symptoms or adverse effects were noted daily. Mean daily bowel frequency was greater with the senna-fibre combination (0.8, 95 % confidence interval 0.7 to 0.9) than with lactulose (0.6 (0.5 to 0.7); $t=3.51$, $p< 0.001$). Scores for stool consistency and ease of evacuation were significantly higher for the senna-fibre combination than for lactulose ($p< 0.005$, $p=0.02$ respectively). The recommended dose was exceeded more frequently with lactulose than the senna-fibre combination. Compared with the recommended daily dose, this equates to a dose per stool of 1.52 for lactulose and 0.97 for the senna-fibre combination. Twenty one patients had adverse effects with lactulose: 7 cramps, 7 urgency, 8 wind or flatulence, 3 bloating, 1 headache, 4 anorexia. Twenty four patients had adverse effects with the combination: 7 cramps, 13 urgency, 10 wind or flatulence, 2 nausea, 3 bloating, 1 anorexia. There was no difference between treatments when adverse effects were analysed, individually or overall. The authors concluded that both treatments were effective and well tolerated for chronic constipation in long stay elderly patients. The senna-fibre combination was significantly more effective than lactulose at a lower cost.

Kinnunen O *et al.* compared 1993 the efficacy of a senna-fibre combination and lactulose in 30 long stay elderly patients aged 65 – 94 years (mean 81.8 years) in the treatment of chronic constipation. The trial was an open, randomised and controlled crossover study. A week's run-in without laxatives was followed by a 5-week period (I) of a daily dose of 14.8 mg (20 ml) senna-fibre combination or 20.1 g (30 ml) lactulose. The senna-fibre combination contained Plantago ovata seed 521.6 mg (bulk forming), Fructus cassiae angustifoliae 138 mg (stimulant) and atsulen 70 g (anti-inflammatory). Period I ended with a week's wash-out, which was followed by another 5-week period with crossed medicines (period II). If over 4 days had elapsed since the last defaecation, 10 mg bisacodyl was given per rectum. The bowel frequency, bisacodyl use and stool consistency were recorded. In period I, 21 patients received senna-fibre combination and 9 patients lactulose; in period II, 7 patients received Agiolax® and 18 patients Levolac®. Bowel frequency/week was significantly higher on senna-fibre combination treatment during both periods, mean (SD) in period I: 4.5 (2.3); period II: 4.5 (2.4), compared to lactulose. Bowel frequency on lactulose treatment was in period I 2.2 (0.9) ($p=0.0006$) and in period II 1.9 (0.9) ($p=0.027$). There was a tendency for the number of bisacodyl doses to be greater when lactulose was used. During both periods bulk plus senna tended to produce more frequently hard, normal or watery stools but the differences did not reach any statistical significance.

The frequency of loose stools was greater ($p<0.05$) during the bulk plus senna period. No complications or such changes in laboratory parameters which could be indicated as medicinal product related could be found. The authors concluded that bulk laxatives plus senna was more efficient than lactulose.

A systematic review of the efficacy and safety of traditional medical therapies for chronic constipation was undertaken, making evidence-based recommendations. Ramkumar and Rao searched 2005 the English literature for drug trials evaluating treatment of constipation by using MEDLINE and PUBMED databases from 1966 to 2003. Only studies that were randomized, conducted on adult subjects, and published as full manuscripts were included. Studies were assigned a quality score based on published methodology. Standard forms were used to abstract data regarding study design, duration, outcome measures, and adverse events. By using the cumulative evidence of published data for each agent, recommendations were made regarding their use following the United States Preventive Services Task Force guidelines. Good evidence (Grade A) was found to support the use of polyethylene glycol (PEG) and tegaserod. Moderate evidence (Grade B) was found to support the use of psyllium, and lactulose. There was a paucity of quality data regarding many commonly used agents including milk of magnesia, senna, bisacodyl, and stool softeners. There is good evidence to support the use of PEG, tegaserod, lactulose, and psyllium. Surprisingly, there is a paucity of trials for many commonly used agents. These aspects should be considered when designing trials comparing new agents with traditional therapies because their use may not be well validated.

Irritable Bowel Syndrome

Hübner and Moser (2002) enrolled 284 patients between 19 and 70 years suffering from irritable bowel syndrome (IBS) in a 12-week double blind, controlled, randomised, multicentre and prospective clinical trial to compare the efficacy as well as the tolerance of tablets (containing as active ingredients "180 mg Carbo ligni", i.e. vegetable, non-activated charcoal, "105 mg Fol. Sennae, 25 mg rhubarb extract") (CL+) to Carbo ligni (CL) containing tablets. Men and women who met the Rome criteria for IBS (all forms) for at least 3 months were eligible. 145 patients received CL+ and 139 patients Carbo ligni. During the first 4 weeks, the physician was allowed to adapt the dosage to a patient's individual needs, from one to eight tablets per day. No dosage changes were allowed after the fourth week. The number of tablets prescribed daily (1-3, 4-6, or >6) was similar between groups, although a tendency to use fewer tablets was evident in the Eucarbon® group. After the 12-week treatment period, 262 patients were available for intention-to-treat (ITT) analysis and 144 for per-protocol (PP) analysis whereby changes of the disease were evaluated with scores based on the Francis IBS system (Francis *et al*., 1997) modified with an open upper boundary (a patient-administered questionnaire that uses a visual analogue scale (VAS) (0%-100%) to score the severity of pain, distension, bowel dysfunction, and quality of life/global well-being) as the primary efficacy parameter. Scores on the VAS for overall well-being decreased in the PP population from 48 with CL+ and 46 with CL before treatment (ITT, 47 and 47) to 18 and 20 after 12-week treatment (ITT, 19 and 22). This translates to an amelioration of symptoms in the PP population by 62.5% with CL+ and 56.5% with CL; respective values in the ITT population were 59.6% and 53.2%. The relative gain in efficacy with CL+ compared with its basic component (charcoal) was therefore only about 8% to 9% without statistical significance. Differences in the Francis score became more prominent in some subgroups selected for exploratory analysis. The patients, who described "often normal stools" at baseline achieved significantly greater overall well-being after treatment with CL+ ($p=0.038$, Wilcoxon test, PP population). Similar improvement in the subgroup admitting to "movements often hard" was more pronounced with CL+ than with CL (not statistically significant). Both treatments were well tolerated, adverse events occurred with similar frequency in both groups (22% of patients treated with CL+ vs. 17% treated with CL). In most cases, it was not possible to distinguish the event from symptoms of IBS. The ingested dose of

hydroxyanthracene derivatives is not mentioned in the publication. The package leaflet obtained from the chemical-pharmaceutical factory F. Trenka, Vienna, Austria, indicates an amount of 2.65 – 3.95 mg anthraquinone per tablet. This study cannot prove the efficacy of senna leaves in irritable bowel syndrome. The study treatment was a combination product and the differences between the groups concerning the primary efficacy parameter were not statistically significant. Based on the results of this study, it is not possible to recommend the specific indication "irritable bowel syndrome".

Bowel cleansing

Colonoscopy plays an important role in the diagnosis and treatment of gastrointestinal illness in both Western countries and Japan. However, preparative bowel cleansing for colonoscopy is frequently troublesome for elderly and/or constipated patients, since they must drink larger volumes of lavage solution for adequate cleansing.

Most of these studies were conducted with a product containing 1.26 - 1.85 g dry extract from Senna fructus acutifoliae corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B; DER 3-5:1,extraction solvent water, per single dose.

In the sixties, seventies and eighties, several studies were conducted with product PX alone or in comparison with other cleansing methods. From the eighties onwards, studies compared product PX with the newly developed electrolyte solutions. The more recent studies are presented.

First clinical trials using standardized herbal medicinal products (150 mg hydroxyanthracene glycoside per day) for **bowel cleansing without additional enema** are presented.

Attempts have been made to further improve the widely performed colonoscopy preparation with lavage. In a prospective study, 120 outpatients and inpatients scheduled for total colonoscopy were randomized to two preparatory regimens. The day before endoscopy either extractum sennae (N = 60) or a placebo solution (N = 60) was given. Just before examination all patients underwent whole gut irrigation with a polyethylene glycol electrolyte lavage solution (PEG-ELS). Adequacy of preparation, patient tolerance, and the necessary amount of PEG-ELS were assessed. Physician assessment of colon cleansing showed superiority in the group with additional laxative. The colon was free of solid debris in 66.7% of patients after PEG-ELS and in 90% after senna/PEG-ELS administration (p less than 0.01). Patient tolerance was similar in both groups with 86.7% vs. 83.3% of subjects rating the preparation as tolerable. Severe adverse events were not observed. In the senna/PEG-ELS group, significantly less (p less than 0.05) lavage fluid was needed. Ziegenhagen *et al.,* 1991 conclude that the combination of senna and PEG-ELS is more effective than PEG-ELS in cleansing the colon for colonoscopy.

Frigerio *et al*. (1996) compared two doses of senna (product containing 1.26 - 1.85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1,extraction solvent water , per single dose) for colon cleansing. 473 patients (225 males and 248 females with a mean age of 59.7 years, range 14 – 96 years) referred for colonoscopy participated in the randomised, single-blind study. 250 patients (group A) received a dose of the solution equivalent to 150 mg sennosides in a single administration the evening before the examination. 223 patients (group B) received two doses, one at mid-day and one on the evening prior to the examination, equivalent to 300 mg sennosides. All patients were advised to consume liquids orally according to need, and no enema was given. At the end of the colonoscopy the following scores were attributed: 0 = perfect examination, possible to observe the entire colon mucosa; 1 = acceptable examination, capable of responding to the diagnostic problem but with insufficient observation of some areas; 2 = examination impossible, requiring repetition. Colonoscopy was impossible (and had to be repeated) in 44 patients (M/F = 22/22), 38 of these (15.2%) belonged to group A (150 mg) and 6 (2.7%) belonged to group B. The observed difference was highly significant (p=0.000006). The

examination was acceptable in 148 patients (M/F = 79/69), 85 (34.0%) belonging to group A and 63 (28.3%) to group B (p=0.02). A perfect examination could be carried out in 281 patients, 127 patients (51%) belonging to group A and 154 patients (69%) belonging to group B. 48 patients (M/F = 22/26), 23 (9.2%) belonging to group A and 25 (11.2%) to group B (p=0.568 NS) complained of side effects: group A: abdominal pain 19, nausea 2, fainting 3; group B: abdominal pain 17, nausea 5, fainting 1, headache 1. The authors concluded that 300 mg of senna was more efficacious than 150 mg and that both doses were well tolerated.

Schanz *et al*. (2008) compared different bowel cleansing modalities referring to tolerability (primary aim), cleanliness and acceptance (secondary aims). 355 consecutive out-patients between 18 and 75 years undergoing colonoscopy were randomised to 3 groups (A, B, C). Group A received a sodium phosphate solution. Group B received a sodium phosphate solution and a senna preparation (1,26 - 1,85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B; DER 3-5:1,extraction solvent water, calculated as sennoside B, per single dose). Group C received PEG-ELS and the same senna preparation. Gastroenterologists performing colonoscopy were blinded to the type of preparation. All patients documented tolerance and adverse events. Vital signs, premedication, completeness, discomfort and complications during the procedure were recorded. A quality score (0 – 4) of cleanliness was generated: 0 = excellent to 4 = repeated examination necessary. The 3 groups (A = 128, B = 133, C = 94) were similar with regard to age, sex, Body Mass Index (BMI), indication for colonoscopy and comorbidity. Drinking volumes (L) (A = 4.33+1.2, B = 4.56+1.18, C = 4.93+1.71) were different (p=0.005). Discomfort from ingested fluid was recorded in A = 39.8 % (vs. C: p=0.015), B = 46.6 % (vs. C: p=0.147) and C = 54.6 %. No differences in adverse events and the cleanliness effects occurred in the three groups (p=0.113). Tolerability in group A was bad in 6.4 %, moderate in 21.6 % and good in 72 %, in group B 7.5 %, 20.3 % and 72.2 %, respectively, in group C 5.4 %, 10.9 % and 83.7 %, respectively. The cleanliness quality scores 0 – 2 were calculated in A: 77.7 %, B: 86.7 % and C: 85.2 %. Acceptance between the 3 groups was not different: refusal for repeated equal preparation procedure reported in A: 14.8 %, B: 18.5 % and C: 17 % (p=0.737). Alternative bowel preparation would prefer in A: 30.2 %, B: 30 %, C: 37.2 % (n.s.). These data do not demonstrate significant differences in tolerability, preparation quality and acceptance between the 3 types of bowel preparation for colonoscopy. Cleansing with the sodium phosphate solution was not superior to PEG-ELS.

One hundred and thirty four patients, who needed elective colonoscopy, were randomly allocated to take 180 mg senna tablets (24 tablets of 7.5 mg /tab, Senokot) or 95 ml sodium phosphate solution on the day before colonoscopy. The efficacies of both laxatives were compared using the mean difference of colon-cleanliness score of the rectum, sigmoid segments, descending colon, transverse colon and cecum. The scores were rated by two observers who were blinded to the laxatives administered. The higher score means that the colon is cleaner. The efficacy of both laxatives was equivalent if the 95% confidence interval of the mean difference of the score of colon lie within -1 to +1. On intention-to-treat analysis, the mean cleanliness scores in the four segments of colon except the cecum were higher in the sodium phosphate group than those in senna group (7.9 +/- 1.7 vs 8.3 +/- 1.5, 8.0 +/- 1.8 vs 8.5 +/- 1.4, 7.9 +/- 2.0 vs 8.5 +/- 1.3, 7.9 +/- 2.0 vs 8.2 +/- 1.4 and 7.2 +/- 1.7 vs 6.9 +/- 1.4, respectively). The 95 % confidence intervals (95 % CI) of mean difference in each segment of colon were not found to lie within 1 point which indicated that their efficacies were not equivalent. The taste of senna was better than sodium phosphate solution. Also, senna had fewer side effects. The efficacy of senna is not equivalent to sodium phosphate solution in bowel preparation for colonoscopy, but senna may be considered an alternative laxative. (Kositchaiwat *et al.* 2006)

Valverde *et al.* (1999) included 523 patients with colonic or rectal carcinoma or sigmoid diverticular disease, undergoing elective colonic or rectal resection followed by immediate anastomosis in a

prospective, randomised, observer-blind, parallel, multicentre study. 262 patients received senna (sennosides corresponding to 120 mg or 240 mg in obese patients) in the evening before surgery. 261 patients received polyethylene glycol (PEG) (2 packages diluted in 2 – 3 l of water) in the evening before surgery. All patients received 5% povidone iodine antiseptic enemas (2 l) the evening and the morning before surgery. Criteria of evaluation were the surgeons' assessment of bowel cleanliness by a 3-stage score according to Hollender *et al.* (0 = no faecal matter, + = small amount of faecal matter, ++ = faecal matter bothersome to the surgery). Other criteria were consistency of faecal matter, rate and magnitude of intraoperative faecal soiling, rate of abdominal infective complications and patient tolerance. Colonic cleanliness was better (p=0.006), faecal matter in the colonic lumen was less fluid (p=0.001), and the risk for moderate or large intraoperative faecal soiling was lower (p=0.11) with senna. Overall, clinical tolerance did not differ significantly between groups, but 20 patients receiving PEG (vs 16 with senna) had to interrupt their preparation. Adverse reactions with senna were reported as follows: discomfort 55 patients (21 %), vomiting 12 (4.6 %), abdominal pain 35 (13.4 %), distension 8 (3 %), malaise 23 (8.8 %). In the other group the following adverse reactions were reported: discomfort 55 patients (21.1 %), vomiting 7 (2.7 %), abdominal pain 30 (11.5 %), distension 15 (5.7 %), malaise 15 (5.7 %). Senna was better tolerated (p=0.03) in the presence of stenosis. There was no statistically significant difference found in the number of patients with postoperative infective complications (14.7 % vs 17.7 %) or anastomotic leakage (5.3 % vs 5.7 %) with senna and PEG, respectively. The authors concluded that mechanical preparation before colonic or rectal resection with senna is better and easier than with PEG. An analysis of the subgroups receiving either 120 mg or 240 mg sennosides is not given. All patients additionally received two enemas.

Additional data are presented from clinical trials using standardized herbal medicinal products for **bowel cleansing with an additional enema**

In a prospective randomized clinical trial, three colon cleansing methods for colonoscopy were compared with regard to a) side effects, b) patient acceptance, c) residual liquid and stool during colonoscopy, and d) quality of the examination. The patients were randomly assigned to one of the following three groups for colon preparation: Group 1 (n = 100) 4 liters of Golytely, group 2 (n = 102) 2 liters of Golytely combined with Cascara-Salax, and group 3 (n = 98), senna preparation (1,26 - 1,85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1,extraction solvent water) combined with an enema. Group 3 caused significantly more abdominal cramps than 4 liters of Golytely (group 1) or 2 liters of Golytely with Cascara-Salax (group 2) (p less than 0.001). Vomiting was most frequent in group 1 (p less than 0.05 vs. group 3). The patients therefore preferred senna preparation to 4 liters of Golytely (p less than 0.01). The cleanest colon was obtained with 4 liters of Golytely, while 2 liters of Golytely with Cascara-Salax was least efficacious. The quality of the examination was equal in groups 1 and 3, and clearly better than in group 2 (p less than 0.01). We thus conclude that while 4 liters of Golytely and senna preparation plus enema have equivalent cleansing efficacy for colonoscopy, patients judged the senna preparation to be less unpleasant (Hanggartner *et al.,* 1989).

Krakamp *et al.* tested 1996 three different colonoscopy preparation methods in 150 out-patients, who received colonoscopies, 50 in each group, in a randomised simple-blind study. The original Golytely-recepture (polyethylene glycol 3350 and electrolytes for oral solution) with 3 litres of liquid between 5 and 8 a.m. on the day of colonoscopy (group 1) was tested against PEG-ELS, which was dissolved in four litres of liquid and administered between 3 and 7 p.m. on the day before colonoscopy (group 2). Both receptures had the same isotonic salt solutions. The third group was a method with a laxative (a senna fruit dry extract preparation corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B, per single dose) administered at 1 p.m. on the day before colonoscopy including eating restriction lasting three days (for 3 days diet easy to digest, the day before colonoscopy clear liquid

diet) and an enema one hour before colonoscopy. The mean age was 57 +/- 19 years in group 1, 55 +/- 15 years in group 2 and 57 +/- 17 years in group 3. The judgement criteria were the cleanliness of the bowel by a 4-stage score ('excellent' to 'colonoscopy not possible'), the formation of foam by a 4-stage score ('no foam' to 'examination strongly restricted') and the subjective sensitivity of the patient during the preparation phase. The preparation with the three bags containing 3 litres of Golytely solution according to the original recepture proved to be the least troublesome for the patients and was the most efficient method when it came to cleanliness and the formation of foam. The costs of this preparation method were lower than those of the other methods.

Bokemeyer 2000 compared in an open prospective study different colonoscopy preparations in more than 300 outpatient colonoscopies. Endoscopists assessed the bowel cleanliness by a score 1 (best) – 6 (worse). Patients assessed the tolerance and acceptance by a score 1 (best) – 6 (worse). Following colonoscopy preparation with Golytely (2 l on the day before colonoscopy and 2 l on the day of colonoscopy p.o.), Golytely-RSS (3 l on the day of colonoscopy p.o.) and Phospho-Soda (45 ml on the day before and 45 ml on the day of colonoscopy p.o.) mainly good or excellent cleansing results were found: score for Golytely 2.1, for Golytely-RSS 2.1 and for Phospho-Soda 1.9. Colonoscopy preparation with a smaller volume of PEG-lavage solution in combination with a laxative (1.26 - 1.85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1, extraction solvent water, per single dose, and an enema and 2 l Golytely on the day before colonoscopy p.o. and an enema in the morning before colonoscopy) produced significantly worse results: score 3.0. The questioning of the patients before and after endoscopy demonstrated the sufficient tolerance of colonoscopy preparation and colonoscopy overall. Problems resulted from a relative large volume of remaining fluid in the bowel especially after 1-day preparation with PEG-lavage solutions. By using an additional dose of cisaprid the remaining fluid could be reduced and the cleansing result was better. In patients prepared with Phospho-Soda, disturbing bubbles were found more often and in most cases significant changes were observed in serum electrolyte levels (97.6 %).

Clinical studies using **calcium sennosides in a daily dose of 120 mg – 300 gm HAD for bowel cleansing** are presented as supportive data

Arezzo compared 2000 a randomised observer-blind, parallel study effectiveness and tolerance of different bowel preparations. 300 patients were randomised into three groups, to be administered either a senna compound (group 1; 12 tablets each containing 12 mg sennosides A+B at 10 a.m. and magnesium sulfate 15 g at 5 p.m. on the day before colonoscopy p.o.), a PEG lavage (group 2; 4 l at 4 p.m. on the day before colonoscopy p.o.), or an oral sodium phosphate solution (group 3; 40 ml at 6 p.m. on the day before and 40 ml at 6 a.m. on the day of colonoscopy). After each colonoscopy, the endoscopist blindly scored cleansing for each bowel segment ('good', 'medium', 'scarce') and defined the quality of the examination as 'optimal', 'acceptable' or 'to be repeated'. Bowel cleanliness was scored as 'good' in 38 (group 1), 50 (2), 68 (3) patients. Bowel cleanliness was scored as 'good' or 'medium' in 73 (group 1), 77 (2) and 95 (3) patients. Bowel cleanliness was scored as 'scarce' in 27 (group 1), 23 (2) and 5 (3) patients. Significant more patients in group 3 (68 %) achieved a good cleansing compared with group 2 (50 %) ($p<0.0001$) and group 1 (38 %) ($p<0.005$). Significant more patients in group 3 achieved a 'good' or 'medium' cleansing compared with group 2 and group 1. 63% of constipated patients obtained a good preparation in group 3, which was significantly higher than in group 1 (28 %, $p<0.05$) and than in group 2 (42 %, $p<0.02$). Feasibility of the examination was considered 'optimal' significantly more in group 3 (80 patients) than in group 2 (62 patients, $p<0.005$)) and in group 1 (59 patients, $p<0.005$). There was however no difference between the groups when 'optimal' and 'acceptable' examinations were considered together (96 patients group 1, 96 patients group 2 and 100 patients group 3). There was no statistically significant difference

between the three groups with regard to patient tolerance. Eighty seven patients (group 1), 85 patients (2) and 93 patients (3) rated the preparation as 'good' (no symptoms), 10 patients (group 1), 10 patients (2) and 5 patients (3) as 'medium' (nausea, mild abdominal pain) and 3 patients (group 1), 5 patients (2) and 2 patients (3) as 'scarce' (vomiting, severe abdominal pain, severe diarrhoea). The author believed that the sodium phosphate solution should be the standard preparation for elective colonoscopy.

Tasci *et al*. conducted 2003 a prospective randomised trial to assess the cleansing ability and tolerance of bowel preparations for colonoscopy in a group of 953 patients. Of the 1021 patients enrolled, 68 were excluded from analysis because of intolerance to the solutions or medicinal products, improper use of the regimen, electrolyte imbalance, cardiac disorders or vomiting. The bowel cleansing methods were: i) sennoside calcium (300 ml of a 1 mg/ml solution given 2 days prior to colonoscopy), ii) PEG lavage (3 l given 1 day prior to colonoscopy), iii) oral sodium phosphate solution in one 90 ml-dose 1 day prior to colonoscopy, iv) oral sodium phosphate solution in 2 doses (90 ml 1 day prior to colonoscopy + 45 ml 5 h prior to colonoscopy), v) oral sodium phosphate solution in 2 doses (45 ml + 90 ml), vi) oral sodium phosphate solution in 2 doses (45 ml + 90 ml) plus 10 mg cisapride, and vii) oral sodium phosphate solution in 2 doses (45 ml + 90 ml) plus 10 ml domperidone. All patients were recommended to take clear liquid diet one day before starting the bowel cleansing regimen. Sodium phosphate enema was applied to the patients on the morning of colonoscopy. The efficiency of the different procedures was evaluated according to a 5-point scale. The cisapride-containing procedure was abandoned partially through the study because of its adverse effects. Overall, bowel cleansing was effective in 890 (93%) patients. Procedures using sodium phosphate solution and either cisapride or domperidone were effective in all patients, while the other 5 protocols led to insufficient bowel preparation in some patients ($p<0.05$). Among these first 5 protocols, those using 2 doses of sodium phosphate solution were superior to the single treatments of the first 3 groups ($p<0.05$). Tolerance to sennoside calcium and PEG lavage in comparison to other groups was significantly worse ($p<0.05$). Of the patients who received sodium phosphate-based treatments, 72%-78% stated that they would undergo the procedure again if necessary, while only 21 % of patients in the sennoside calcium group and 11% in the PEG group were so willing ($p<0.05$). The authors concluded that 2 doses of the sodium phosphate solution (45 ml +90 ml) plus domperidone for colon cleansing is a safe, effective, rapid, inexpensive and well tolerated procedure.

The trial of Radaelli *et al.* (2005) compared the efficacy and patient acceptance of an oral high dose of senna to conventional polyethylene glycol-electrolyte lavage solution (PEG-ES) in adults undergoing elective colonoscopy. Consecutive outpatients referred for elective colonoscopy were prospectively randomly assigned to receive, the day before the procedure, either 24 tablets of senna (12 mg extract of sennoside A and B), divided into two doses at 1 p.m. and 9 p.m. (senna group, n=191), or standard 4-L PEG-ES (PEG-ES group, n=92). The overall quality of colon cleansing (primary outcome measure) and cleansing in the right colon were evaluated using the Aronchick scoring scale (1=excellent to 4=inadequate; Aronchick *et al*. 2000) by the investigator/endoscopist who was blinded to the treatment assignment. Patient acceptance and the safety of the preparation were assessed by a nurse, using a structured questionnaire covering compliance with the dosing, overall tolerance of the preparation (1=none or mild discomfort to 4=severely distressing), and adverse events. The quality of colon cleansing, overall tolerance of the preparation, and compliance were significantly better with senna; overall cleansing was excellent or good in 90.6% of patients in the senna group and in 79.7 % in the PEG-ES group ($p= 0.003$). The percentage of procedures rescheduled because of insufficient colon cleansing was 7.3% in the PEG-ES group and 2.6 % in the senna group ($p=0.035$). Multivariate logistic regression modeling showed the PEG-ES preparation as negative independent predictor of unsuccessful bowel cleansing. The incidence of adverse reactions was similar in the two groups;

patients who received senna experienced significantly less nausea and vomiting, but more abdominal pain. An oral high dose of senna is a valid alternative to standard PEG-ES for outpatient colonoscopy preparation.

Patients' compliance with and tolerance of large-volume polyethylene glycol electrolyte solution (PEG-ES) have prompted continuous investigation with alternative forms of cleansing. High-dose senna is superior to PEG-ES for the quality of bowel cleansing, patient compliance, and tolerance, but its acceptance may be influenced by the incidence of abdominal pain. Amato *et al.* hypothesized 2010 that a combination of half doses of PEG-ES and senna could minimize the incidence of abdominal pain without affecting the quality of bowel preparation.This randomized, investigator-blinded trial has been conducted on consecutive outpatients scheduled for elective colonoscopy at a single community-based hospital. Patients were randomly assigned to receive either 12 tablets of 12 mg senna and 2 l of PEG-ES (half-dose group, HDG) or 24 tablets of senna divided in two doses (senna group, SG) the day before colonoscopy. The main outcome measures were the quality of colon cleansing (Aronchick scoring scale) and the incidence of preparation-related abdominal pain. Secondary outcome measures were patients' compliance with the cleansing regimen, overall tolerability, prevalence of predefined side effects, and quality of right colon cleansing. A total of 296 patients were enrolled (HDG=151 and SG=145). Overall cleansing was excellent to good in 90.1 and 88.3 % patients in HDG and SG, respectively (P=0.62). Preparation-related moderate-to-severe abdominal pain was reported by 6 % patients in HDG and 15.2% in SG (P=0.009). No significant differences were observed for secondary outcomes. The regimen combining half doses of PEG-ES and senna provides high-quality bowel preparation and acceptable patient tolerance, with less abdominal pain compared to high-dose senna.

High-quality video colonoscopy requires adequate preparation of the bowel to ensure both adequate procedure completion rates and polyp detection rates. A prospective audit of the efficacy, safety, and acceptability of low-volume polyethylene glycol (2 L) versus standard volume polyethylene glycol (4-L) versus magnesium citrate plus stimulant laxative as bowel preparation for colonoscopy was published by Kelly *et al.* 2012. A total of 258 (female: 138; 53.5 %) patients were recruited, 91 in the polyethylene glycol 4-L group (female: 45, 49.5 %), 86 patients in the polyethylene glycol 2-L group (female: 45; 52.3 %), and 81 in the Senna/ magnesium citrate group (female: 44; 54.3 %). Significantly more patients were unable to take the prescribed dose of polyethylene glycol 4-L when compared with the other 2 regimes (19.6 %; P<0.0001 vs. polyethylene glycol 2-L; P<0.0001 vs. Senna/ magnesium citrate). A total of 45.65 % of patients reported polyethylene glycol 4-L as tasting unpleasant. This was significantly more than both polyethylene glycol 2-L (10.47 %; P=0.008) and Senna/ magnesium citrate (9.88 %; P<0.0001). The overall cleansing efficacy across the 3 groups (those with grades A or B) was 73.9 %, 74.5 %, and 86.5 % for polyethylene glycol 4-L, polyethylene glycol 2-L, and Senna/ magnesium citrate, respectively. In this series Senna/ magnesium citrate proved significantly better at bowel cleansing than polyethylene glycol 4-L (P<0.05) and it showed a trend toward better cleansing when compared with polyethylene glycol 2-L (P=0.08). In summary, low-volume PEG and Senna/ magnesium citrate combination were better tolerated than large volume PEG with Senna/ magnesium citrate providing superior mucosal cleansing.

The patients were prospectively randomized to 2 arms of sodium phosphate versus Sennoside A+B calcium preparation (medicinal product not mentioned) for the investigation of Manukyan *et al.* (2011). Laboratory assessment, body weight, height, and vital signs were obtained at baseline and before colonoscopy. A self-administered questionnaire was completed by the patients. The time taken to complete the colonoscopy and the segment of the colon examined were recorded. The patients in the Sennoside A+B calcium group were more comfortable with the taste of the solution. Patients using sodium phosphate faced more nausea and significantly lower Ca levels and P values. The pulse rate was significantly higher in this group. Patients in the sennoside group had better grades of bowel

cleansing in sigmoid and descending segments of the colon. Sennoside A+B calcium is more effective in some of the colonic segmental cleansing, causes fewer changes on serum electrolyte levels, and is better tolerated. Split-dosing regime for morning and afternoon lists may have confounded results.

Inadequate bowel cleaning leads to a suboptimal colonoscopic examination. Gum chewing has been reported to have a favorable effect on postoperative bowel functions. We conducted this study to establish if gum chewing added to high-dose senna before colonoscopy promotes bowel cleaning. In this randomized controlled study, consecutive outpatients scheduled for elective colonoscopy were randomized into two groups. Group 1 patients (n = 65) used senna solution 150 ml (300 mg senna) the night before colonoscopy. The patients also used sennoside tablet 80 mg daily for 3 days before the colonoscopy. Patients in group 2 (n = 64) were additionally advised to chew sugarless gum half an hour three-times daily after meals for these 3 days. The overall quality of colonoscopy cleaning was evaluated using the Aronchick scale by a single endoscopist who was blinded to the intervention. Difficulty of procedure, patients' tolerance, and adverse events were also evaluated. A total 129 patients were enrolled in the study. Superior cleaning was found in gum chewing group when compared with other group particularly in the cecum and ascending colon. Cecal intubation time was significantly shorter in the gum-chewing group (8.6 ± 5.1 and 7.1 ± 2.8 min, P = 0.03). Adverse events were more common in group 1 compared to the gum-chewing group. The authors concluded that gum chewing enhances colonoscopy bowel preparation quality (Ergül *et al.* 2014).

Even though polyethylene glycol-electrolyte lavage (PEG-EL)-based regimes have become the gold standard in recent years, to finish drinking 4 L of PEG-EL solution can be difficult. The quality of sennoside-based bowel-cleansing regimes used in Turkey has been known for some time. Therefore, the authors aimed to investigate the efficacy of both bowel-cleansing regimes. Patients over 18 years old undergoing elective colonoscopic procedures between January and March 2011 were included in the study. The patients were divided into 2 groups; in Group 1, 91 patients were given sennoside a + b calcium 500 mg/250 ml, and in Group 2, 94 patients were given 4 L of PEG-EL. The mean age of the patients and the male distribution were similar in the 2 groups. Both inadequate bowel cleansing and the best cleansed bowels were seen in Group 1. The number of inadequate colonoscopies declined when using a whole bowel-cleansing regime from 24.5 % to 19.3 % in Group 2, but it did not decline in Group 1. The best bowel cleansing can be achieved with sennoside-based regimes, whereas a greater proportion of adequate results via colonoscopy were reached with the PEG-EL-based regimes (Altinbaş *et al.,* 2015).

To establish the optimum barium-based reduced-laxative tagging regimen prior to CT colonography (CTC) 95 subjects underwent reduced-laxative (13 g senna/18 g magnesium citrate) CTC prior to same-day colonoscopy and were randomised to one of four tagging regimens using 20 ml 40 % w/v barium sulphate: regimen A: four doses, B: three doses, C: three doses plus 220 ml 2.1 % barium sulphate, or D: three doses plus 15 ml diatriazoate megluamine. Patient experience was assessed immediately after CTC and 1 week later. Two radiologists graded residual stool (1: none/scattered to 4: >50 % circumference) and tagging efficacy for stool (1: untagged to 5: 100 % tagged) and fluid (1: untagged, 2: layered, 3: tagged), noting the HU of tagged fluid. Preparation was good (76-94 % segments graded 1), although best for regimen D (P = 0.02). Across all regimens, stool tagging quality was high (mean 3.7-4.5) and not significantly different among regimens. The HU of layered tagged fluid was higher for regimens C/D than A/B (P = 0.002). Detection of cancer (n = 2), polyps > or =6 mM (n = 21), and < or =5 mM (n = 72) was 100, 81 and 32% respectively, with only four false positives > or =6 mm. Reduced preparation was tolerated better than full endoscopic preparation by 61 %. Reduced-laxative CTC with three doses of 20 ml 40 % barium sulphate is as effective as more complex regimens, retaining adequate diagnostic accuracy (Taylor *et al.* 2008).

The effectiveness of polyethylene glycol solutions (PEG) for colon cleansing is often limited by the inability of patients to drink adequate portions of the 4 L solution. The aim of the study of Hookey *et al.* (2006) was to determine whether a reduced volume of PEG combined with stimulant laxatives would be better tolerated and as or more effective than the standard dose. Patients undergoing outpatient colonoscopy were randomly assigned to receive either low-volume PEG plus sennosides (120 mg oral sennosides syrup followed by 2 L PEG) or the standard volume preparation (4 L PEG). The subjects rated the tolerability of the preparations and their symptoms. Colonoscopists were blind to the colonic cleansing preparation and graded the cleansing efficacy using the Ottawa scale (Rostom *et al.* 2004). The low-volume PEG plus sennosides preparation was significantly better tolerated than the standard large volume PEG (P<0.001) but was less efficacious (P=0.03). Thirty-eight per cent of patients in the large volume PEG group were unable to finish the preparation, compared with only 6% in the reduced volume group. There were no adverse events reported. Although the low-volume PEG plus sennosides preparation was better tolerated, it was not as effective as standard large-volume PEG. However, in view of the significant difference in tolerance, further research investigating possible improvements in the reduced-volume regimen seems warranted.

Senna has also been investigated in combination with low-volume PEG solutions in three trials (Lemli *et al.,* 1983, Iida *et al*., 1992, Ziegenhagen *et al.,* 1991). Although Iida *et al*. reported 1992 increased efficacy with 2 L of PEG combined with sennosides (36 mg), this trial was nonrandomized, used a historical control group, and data collection from both patients and endoscopists was incomplete. Another approach was reported by Ziegenhagen *et al.* (1991), in which PEG was administered by mouth or nasogastric tube the morning of colonoscopy until rectal effluent was clear. The addition of senna the night before significantly reduced the amount of PEG required for an adequate preparation. Recently, 2 L of PEG and 120 mg of sennosides syrup were compared with 4 L of PEG, and results showed that although the lower volume preparation was better tolerated, it was less efficacious (Lemli *et al.,* 1983). In the present review, the sennosides were given just before the ingestion of PEG and altering the timing of the sennosides from 30 min to 60 min before the PEG may be more beneficial.

Iida *et al.* (1992) reported increased efficacy with 2 L of PEG combined with sennosides (36 mg). This trial was non-randomized, used a historical control group, and data collection from both patients and endoscopists was only partially complete. Senna has also been investigated in combination with low-volume PEG solutions in different trials. Another approach was reported by Ziegenhagen *et al.* (1991), in which PEG was administered orally or by nasogastric tube the morning of colonoscopy until rectal effluent was clear. The addition of senna the night before significantly reduced the amount of PEG required for an adequate preparation. In another study, 2 L of PEG and 120 mg of sennosides syrup were compared with 4 L of PEG, and results showed that the lower volume preparation was better tolerated, though it was less efficacious (Hookey *et al.* 2006). In the review of Hookey *et al. (*2007), the sennosides were given just before the ingestion of PEG and altering the timing of intake of sennosides from 30 min to 60 min before the PEG may be more beneficial.

PEG-ELS, which is the goldstandard agent for precolonoscopic bowel preparation, has an important problem to be overcome: its large volume. In accordance with the literature, only 70 % of patients were able to finish the whole PEG-EL solution before the colonoscopic procedure. For this reason, investigators have worked on therapeutic options to reduce the PEG-EL solution volume in recent years (Altinbas *et al.* 2015).

Clinical trials using **senna and sennoside preparations below 80 mg HAD/day** are described below.

In an uncontrolled study Iida *et al.* already investigated 1992 a colon cleansing preparation regimen in which examinees had to drink 2 l of Golytely on the day of examination by taking 36 mg of sennosides

(no further information of the formulation) orally in the evening before colonoscopy. Bowel preparation was carried out in 297 examinees (219 male and 78 female; mean age 57 years). No special diet was recommended. 97 % of the patients were able to drink the total dose of 2 l Golytely. Bowel cleanliness was assessed as 'excellent' or 'good' in 90 % to 97 % of the patients at all sites in the colon and rectum. There was a tendency for better irrigation to be achieved in the proximal colon compared with the distal colon. With regards to foam and peristalsis, there were no problems in 85 % respectively 92 % of the patients. No severe adverse reactions were noted. During the drinking of Golytely, 1 % of patients complained of abdominal pain, 10 % of chills or nausea and 24 % of abdominal fullness. 54 % of patients had no adverse reactions.

Chilton *et al.* compared 2000 in a randomised, observer-blind, parallel study a novel low-dose, low-volume triple regimen with Phospho-soda. A blinded, experienced colonoscopist examined 132 consecutive patients randomly allocated to receive i) either a triple regimen consisting of 75 mg sennoside A+B at 10 a.m. + sodium picosulphate 10 mg at 2 p.m. + Golytely 1 l at 6 p.m. on the day before colonoscopy when colonoscopy took place before 12 a.m. or 75 mg sennosides A+B at 2 p.m. + sodium picosulphate 10 mg at 6 p.m. + Golytely 1 l at 7 a.m. on the day of colonoscopy when colonoscopy took place after 12 a.m. (n=81), ii) or sodium phosphate solution 45 ml at 8 a.m. and 45 ml at 8 p.m. on the day before colonoscopy when colonoscopy took place before 12 a.m. or sodium phosphate solution 45 ml at 8 p.m. and at 8 a.m. in the morning of the colonoscopy when colonoscopy took place after 12 a.m. (n=51). Endoscopists assessed bowel cleanliness by a 4-stage score (excellent, good, intermediate, poor). Further on time taken to reach the caecum and completeness of examination were assessed. In the triple regimen group, 73 % of the patients were scored 'excellent' or 'good' compared with 57 % in the other group (p=0.037 Mann-Whitney U-test). Examination of the caecum was achieved in 95 % of patients of the triple regimen group and in 89 % of the other group. Among those examined as far as the caecum, the time to reach the caecum was 11 minutes (range 5 – 50 min) in the triple regimen group compared with 16 minutes (range 5 – 65 min) in the other group (p=0.08, Mann-Whitney U-test). Patient tolerability was not assessed in this study. The authors concluded that this novel triple regimen produces a cleaner colon than Phospho-soda, is associated with a trend towards a quicker and more efficient colonic examination, and is also 30 % cheaper per patient.

Four liters or more of orally taken polyethylene glycol solution (PEG) has proved to be an effective large-bowel cleansing method prior to colonoscopy. The problem has been the large volume of fluid and its taste, which is unacceptable to some examinees. The authors aimed to investigate the effectiveness of 2 l PEG combined with senna compared with 4 l PEG for bowel preparation. The design was a single-center, prospective, randomized, investigator-blinded study with parallel assignment, in the setting of the Endoscopy Unit of Umeå University Hospital. Outpatients (n = 490) scheduled for colonoscopy were enrolled. The standard-volume arm received 4 l PEG, and the low-volume arm received 36 mg senna glycosides in tablets and 2 l PEG. The cleansing result (primary endpoint) was assessed by the endoscopist using the Ottawa score. The patients rated the subjective grade of ease of taking the bowel preparation. Analysis was on an intention-to-treat basis. There were significantly more cases with poor or inadequate bowel cleansing after the low-volume alternative with senna and 2 l PEG (22/203) compared with after 4 l PEG (8/196, p = 0.027). The low-volume alternative was better tolerated by the examinees: 119/231 rated the treatment as easy to take compared with 88/238 in the 4 l PEG arm (p = 0.001). 4 l PEG treatment is better than 36 mg senna and 2 l PEG as routine colonic cleansing before colonoscopy because of fewer failures (Haapamäki *et al.* 2011).

Capsule endoscopy (CE) is limited by incomplete small-bowel transit and poor view quality in the distal bowel. Currently, there is no consensus regarding the use of bowel purgatives or prokinetics in CE. To evaluate the usefulness of bowel purgatives and prokinetics in small-bowel CE. The cited study is a

prospective single-blind randomized controlled study by Postgate *et al*. (2009). A total of 150 patients were prospectively recruited. Patients were randomized to 1 of 4 preparations: "standard" (fluid restriction then nothing by mouth 12 hours before the procedure, water and simethicone at capsule ingestion [S]); "standard" + 10 mg oral metoclopramide before the procedure (M); magnesium citrate + senna bowel-purgative regimen the evening before CE (CS); magnesium citrate + senna + 10 mg metoclopramide before the procedure (CSM). The primary outcome measures were gastric transit time (GTT) and small-bowel transit time (SBTT), completion rates (CR), view quality, and patient acceptability. Secondary outcome measures: positive findings, diagnostic yield. No significant difference was noted among groups for GTT (median [minutes] M, CS, and CSM vs S: 17.3, 24.7, and 15.1 minutes vs 16.8 minutes, respectively; P = .62, .18, and .30, respectively), SBTT (median [minutes] M, CS, and CSM vs S: 260, 241, and 201 vs 278, respectively; P = .91, .81, and .32, respectively), or CRs (85 %, 85 %, and 88 % vs 89 % for M, CS, and CSM vs S, respectively; P = .74, .74, and 1.00, respectively). There was no significant difference in view quality among groups (of 44: 38, 37, and 40 vs 37 for M, CS, and CSM, vs S, respectively; P = .18, .62, and .12, respectively). Diagnostic yield was similar among the groups. CS and CSM regimens were significantly less convenient (P<.001), and CS was significantly less comfortable (P = .001) than standard preparation. Bowel purgatives and prokinetics did not improve CRs or view quality at CE, and bowel purgatives reduce patient acceptability. (No posology for senna; two packets of senna)

As with colonoscopy, adequate bowel cleansing is essential prior to colon capsule endoscopy (CCE). Because CCE requires that the capsule traverse the entire gastrointestinal tract during the examination, laxative 'boosters' are used. The objective of this prospective, single-center, single-arm study by Kashyap *et al.* (2015) was to evaluate the safety of a bowel preparation consisting of polyethylene glycol (PEG) plus an oral sulfate solution. Subjects were healthy volunteers aged 50-75 years old with normal baseline serum chemistry. The bowel preparation consisted of 4 Senna tablets, 4 liters of PEG (split dose), 10 mg metoclopramide, 2 oral sulfate solution boosters (6 oz. and 3 oz.), and 10 mg bisacodyl. Serum chemistry was performed at baseline, following PEG intake, 24 hours after bisacodyl administration, and at 7 days post procedure (in subjects with abnormal 24 hour results). The primary endpoints were the percentage of subjects with a clinically significant change in serum chemistry at the last test and the adverse event (AE) rate. A total of 25 subjects were enrolled. The serum chemistry was normal in all subjects at the final evaluation. One subject showed a slight elevation in creatinine (1.08 mg/dl 7 days post procedure from 0.84 mg/dl at baseline), deemed not clinically significant. Another subject had a transient elevation in serum creatinine (from 1.01 mg/dl at baseline to 1.45 mg/dl at 24 hours after the bowel preparation); values returned to near baseline at 7 days post procedure (1.06 mg/dl). There were no serious adverse events (AEs), three moderate AEs related to the bowel preparation (nausea, headache, elevated creatinine) and two mild unrelated AEs (chills, abdominal cramping). A bowel cleansing regimen of PEG plus an oral sulfate solution can be used in healthy volunteers. These data provide support for the continued study of this regimen in future CCE clinical trials and in medical practice.

The aim of the present study was to compare the efficacy, adequacy, side effects, and patient compliance of sodium phosphorus (NaP) and senna solutions when preparing the colon before colonoscopy. A total of 137 consecutive patients who were considered for colonoscopy evaluation had randomly received one of two premeditated regimens: 90 ml of oral NaP (NaP group) or 500 ml of 1,000 mg of sennosides A and B calcium +66.6 g of sorbitol (senna group). Patients' compliance with the bowel-cleansing method was determined using a questionnaire prior to the colonoscopic examination. On the other hand, the adequacy of the bowel-cleansing method was evaluated by the colonoscopist who was blind to the bowel-cleansing regimen used prior to the examination of the colon from the rectum to the cecum. Nausea and vomiting complaints were seen more frequently in the NaP

group than in the senna group (47 vs 28 and 31 vs 10; P<0.05 and P<0.01, respectively). The response to the question of whether the patients would like to use the same regimen again or not was similar in both groups. The acceptable bowel-cleansing rate was also comparable across both groups. Nevertheless, the number of patients that experienced excellent bowel cleansing in terms of general appraisal of the colonoscopic evaluation was significantly greater in the NaP group than in the senna group (46 vs 25; P<0.001). Although bowel cleansing was better in the NaP group, both cleansing regimens were comparable regarding the admissibility of the preparations for the procedure. The senna regimen is, however, superior to the NaP regimen in terms of application compliance and its side effects, and it may be an effective alternative for cleansing the bowel prior to colonoscopic examination (Poyrazoglu and Yalniz 2015).

To prospectively investigate the effectiveness and patient's tolerance Vradelis *et al.* investigated 2009 two low-cost bowel cleansing preparation protocols based on magnesium citrate only or the combination of magnesium citrate (1 sachet contains 11.6 g magnesium carbonate and 17.8 g anhydrous citric acid) and senna (1 sachet; no further information). A total of 342 patients who were referred for colonoscopy underwent a colon cleansing protocol with magnesium citrate alone (n = 160) or magnesium citrate and senna granules (n = 182). The colonoscopist rated the overall efficacy of colon cleansing using an established score on a 4-point scale. Patients were questioned before undergoing colonoscopy for side effects and symptoms during bowel preparation. The percentage of procedures rescheduled because of insufficient colon cleansing was 7 % in the magnesium citrate group and 4% in the magnesium citrate/senna group (P = 0.44). Adequate visualization of the colonic mucosa was rated superior under the citramag/senna regimen (P = 0.004). Both regimens were well tolerated, and did not significantly differ in the occurrence of nausea, bloating or headache. However, abdominal cramps were observed more often under the senna protocol (29.2 %) compared to the magnesium citrate only protocol (9.9 %, P < 0.0003). The addition of senna to the bowel preparation protocol with magnesium citrate significantly improves the cleansing outcome.

Conclusions on herbal preparations of senna pods for bowel cleansing:

In the European Union there have been medicinal products with senna pod herbal preparations as active substance with an indication in the therapeutic area of bowel cleansing before diagnostic investigations or surgery.

The safety and efficacy of senna pods in this indication has as well been investigated in more than 20 clinical trials. A series of clinical trials with an extract of senna pods (e. g. Ziegenhagen *et al*., 1991; Frigerio *et al*., 1996; Schanz *et al*. 2008; Kosichaiwat *et al*. 2006; Valverde *et al*., 1999) proved an effectiveness for bowel cleansing. Some of these trials compared efficacy with treatment with sodium phosphate solution and it was concluded that treatment with senna extract was not absolutely equivalent to the treatment with sodium phosphate.

However, especially the clinical studies by Ziegenhagen *et al*. (1991, senna/PEG-ELS-group with significantly less lavage fluid needed in comparison to PEG-ELS-placebo group), Valverde *et al*. (1999, better cleansing for senna group compared to PEG-group) and Krakamp *et al*. (1996, 90 % of senna group adequately prepared in comparison with Golytely and Klean Prep) clearly support well-established use. The results of further clinical trials with isolated sennosides are additionally contributing to the evidence. When higher dosages of senna pod preparations (equivalent to about 300 mg sennosides) were compared with lower dosages (equivalent to about 150 mg sennosides), higher dosages were slightly more effective, but revealed more adverse effects (e. g. Amato *et al*. 2010).

The HMPC concluded that the requirements for well-established use with the indication "Herbal medicinal product for bowel cleansing prior to clinical procedures requiring bowel preparations" are fulfilled. A dosage equivalent to 150 mg sennosides is sufficient. It is up to the health care professional to integrate the use of senna pod preparations into an adequate preparatory scheme such as for instance described by Krakamp *et al*. (1996: "The preparation starts with a three days diet of clear fluids, the herbal preparation is to be applied between 2 pm and 4 pm of the day before the examination followed by a glass of water and drinking of 2 l of clear fluids until bedtime. No solid food intake until examination."). When deciding about appropriateness of application of senna pod preparations, in this indication, it must be considered that standard therapies with sodium phosphate or PEG-solutions was slightly more effective, but senna preparations were better tolerated (Amato *et al*. 2010; Manukyan *et al*. 2011; Hookey *et al*. 2006). For senna preparations less vomiting but more frequent spasms have been observed. Application of senna pod preparations may be a reasonable and effective therapeutic option for patient groups with limitations in intake of high volumes of fluids.

Postoperative constipation

The objective of the study of Patel *et al.* (2010) was to compare time to first bowel movement (BM) after surgery in subjects randomized to placebo or senna with docusate. Ninety-six subjects completed a baseline 7-day bowel diary before and after surgery. After pelvic reconstructive surgery, the subjects were randomized to either placebo (n=45) or senna (8.6 mg) with docusate (50 mg) (n=48). Time to first BM and postoperative use of magnesium citrate were compared. There was a significant difference in the time to first BM in those receiving senna with docusate vs placebo (3.00+/-1.50 vs 4.05+/-1.50 days; P<.002). More subjects in the placebo group needed to use magnesium citrate to initiate a bowel movement (43.6 % vs 7.0 %; P<.001). The use of senna with docusate decreases time to first BM in those undergoing pelvic reconstructive surgery compared with placebo. Subjects using senna with docusate are also significantly less likely to use magnesium citrate.

Postoperative opiod-induced constipation

Marciniak *et al*. (2014) investigated the efficacy of lubiprostone compared to senna on bowel symptoms and constipation in post-operative orthopedic patients treated with opioids. In this double blind, randomized, active comparator trial, adults who required opioids for analgesia following orthopedic procedures and who were admitted in inpatient rehabilitation were randomized following baseline assessments to lubiprostone , orally twice a day or senna (generic; no further information) two capsules administered daily for six days. Subjects were assessed using the patient assessment of constipation (PAC)-symptoms (PAC-SYM) and the PAC-quality of life (PAC-QOL) scales measured at baseline and Day 7; Subjects were assessed daily for secondary measures included the Bristol stool scale bowel consistency, specific bowel symptom score (Nausea, cramping, straining, completeness, abdominal pain, time per lavatory attempt, assistance needed), adverse events and rescue medications required. Function was measured using the functional independence measure (FIM) at admission and discharge; length of stay (LOS) and missed treatments due to gastrointestinal symptoms were also assessed. 64 adults were enrolled; 56 participants (28 in each group) had baseline and follow up measures and were included in the intention to treat (ITT) analyses. 43 participants completed the study, 21 in the active lubiprostone and 22 in the active Senna group. The mean age of the participants was 71.5 years (SD = 11.4 years, range: 28-96 years). In the ITT analyses, participants showed significant improvement in bowel symptoms as measured by the PAC-SYM (mean ± SD, -0.28 ± 0.60, range: -1-2.33) and PAC-QOL (mean ± SD, 0.33 ± 0.81, range: -1.5-2.0) over time, but there were no significant differences between the lubiprostone and Senna groups in mean change in the PAC-SYM (-0.20 ± 0.60 vs -0.36 ± 0.61, P = 0.61 respectively) or the PAC-QOL (0.29 ± 0.76 vs 0.37 ± 0.87, P = 0.61 respectively). The mean change in each bowel symptom also did not significantly differ between treatment groups on ITT analyses, except for completeness of

bowel movement, with the Senna group showing greater negative mean change in bowel movement completeness (-0.56 ± 1.01 vs -2.00 ± 1.41, P = 0.03) and for reduction of abdominal pain, favoring Senna (-0.14 ± 0.73 vs -0.73 ± 1.08, P = 0.04). Fifteen (75 %) participants in the lubiprostone and in the Senna group requested rescue treatments. Participants made significant functional improvement from admission to discharge over a median LOS of 12 d, with a mean FIM change of 29.13 ± 13.58 and no significant between group differences (27.0 ± 9.2 vs 31.5 ± 16.6, P = 0.27). The authors concluded, both lubiprostone and senna improved constipation-related symptoms and QOL in opioid-induced constipation, with no significant between-group differences.

Chemotherapy-induced constipation

In the following study 82 patients suffering from constipation after chemotherapy were assigned to Group AB and Group BA. Group AB referred to patients who first took senna extract (extraction solvent: no information available) in the 1st chemotherapeutic course and the crude fiber diet in the 2nd chemotherapeutic course. But the sequence was just the opposite in Group BA. The effective rates of relieving chemotherapy-induced constipation by senna extract and by the crude fiber diet were observed. The differences of the digestive tract reaction and the hematotoxicity reaction were compared. The conditions of patients' abdominal pain and stool properties were observed after they took senna extract.The effective rate of constipation by taking senna extract was 92.68 % and that by the crude fiber diet was 10.93 %, with statistical difference shown (P<0.01). There was no statistic difference in adverse reaction rate such as decreased neutrophils over degree II, decreased hemoglobin, decreased platelet, nausea, vomit, etc. (P>0.05). The occurrence rate of abdominal pain over degree II after taking senna was 8.54 %. In the distribution of stool properties, the rate of loose stool was 35.53 % (Tao *et al.* 2012).

Constipation in people receiving palliative care

Constipation is a frequent cause of distress in advanced cancer. A palliative care unit in Kerala, a southern state of India, conducted a controlled trial comparing a liquid Ayurvedic (herbal) preparation with a conventional laxative tablet (purified senna extract 60 mg containing 12 mg senna glucocides as calcium salts) in the management of opioid-induced constipation in 50 patients with advanced cancer. Sofsena tablets were given in increasing amounts (2 tabs at night; 4 tabs at night; 2 tabs in the morning + 4 tabs at night every 2 days; n=25); Misrakasneham in 2,5 ml; 5 ml ;10 ml. Although there was no statistically significant difference in the apparent degree of laxative action between the two, the results indicate that the small volume of the drug required for effective laxative action, the tolerable taste, the once-daily dose, the acceptable side effect profile, and the low cost make Misrakasneham a good choice for prophylaxis in opioid-induced constipation. There is a need for further studies of Ayurvedic medicines in palliative care (Ramesh *et al.,* 1998).

Agra *et al.* (1998) enrolled 91 terminal cancer patients treated with opioids in a randomised, open, parallel group trial to determine treatment and cost efficiency for senna derivatives and lactulose and to determine their efficacy at different opioid doses. Constipation is a frequent condition in terminal cancer patients, approximately 80 % of whom need laxatives to counteract it. The period of the study was 7 days to assess laxative efficacy on defaecation days and laxative efficacy at variable opioid dosage and 27 days to assess the mean morphine dose at which a laxative was necessary. Both laxative and opioid treatments were initiated simultaneously. Laxative dosage increases were determined as a function of the patient’s intestinal rhythm, irrespective of opioid dose variation. Initial daily intake in two doses was 0.4 ml (12 mg) for senna (no other information of the formulation are given) and 15 ml (10 g) for lactulose, with increments of 0.4 ml and 15 ml, respectively, every 3 days, according to clinical response. Maximum doses were 1.6 ml (48 mg) for senna and 60 ml (40 g) for lactulose. When a patient reached the ceiling of his respective laxative and had a defaecation-free

period of 3 days, he was maintained on that dose and, in the absence of side effects, he was also given the initial dose of the other laxative, which could then be increased at 3-day intervals until reaching the experimental maximum. Forty three patients were assigned to senna and 48 to lactulose. Sixteen patients dropped out during the first 4 days. By the end of the 27 days, 37 patients were lost: 21 in the senna group and 16 in the lactulose group. Three developed vomiting, five refused to continue in the protocol, 17 died, and 12 were hospitalised. No significant differences were found regarding the number of defaecation-free 72-hr periods, mean number of defaecation days, or the general state of health between the experimental groups. There were no differences in the respective defaecation-free 72-hr intervals as a function of opioid. The number of defaecation days was similar in both groups (senna: mean 8.9 days; SD 6.6 days; lactulose: mean 10.6 days, SD 7.3 days). 37.5 % of patients tracked until the end of the study period required both laxatives. During the first 7 days, 6 patients (3 treated with senna and 3 treated with lactulose) presented adverse effects (diarrhoea, vomiting, and cramps) easy to manage with conventional therapy. Fifteen patients, 8 with senna and 7 with lactulose, required laxatives from days 12 – 27 of the study. The mean morphine dose at which laxatives proved necessary was 84.1 mg (SD 72.3 mg).

To evaluate the evidence for clinically established pharmacological therapies for constipation in palliative care, a systematic literature review was performed by Bader *et al*. (2012) in different databases (Cochrane Library, Embase, PubMed, Ovid MEDLINE, CINAHL), textbooks, and publications.Whereas 130 randomized controlled trials were found with patients outside of palliative care settings, only 10 controlled studies with patients in end-of-life situations were identified: three RCTs with methylnaltrexone and one with the combination of oxycodone and naloxone showed the effect and safety of opiate antagonists for patients who are not at risk of gastrointestinal perforation. There have been no studies which test methylnaltrexone against the optimization of therapy with conventional laxatives. Six other controlled studies of limited quality in design and execution and with only few participants tested naloxone, senna, lactulose, co-danthramer, an Ayurvedic preparation, magnesium hydroxide, fluid paraffin, sodium picosulfate and docusate without finding statistically significant differences in efficacy or side effects. Most patients in these studies had cancer. Only case studies with few patients in palliative care were found for meglumine, neostigmine, and other substances mentioned above. Evidence on medical treatment of constipation in palliative care is sparse and guidelines have to refer to evidence from outside the palliative care setting and to expert opinions. Results from studies with other patient groups can only be transferred with limitations to very ill patients at the end of life who might have a higher risk for potential side effects such as gastrointestinal perforation in case of abdominal tumor manifestation. Therefore further studies are required to evaluate the medical treatment of multiple reasons for constipation in these patients. These studies should focus on feasibility, clinical relevance and quality of life.

Constipation is reported in 52 % of people with advanced malignancy. This figure rises to 87 % in people who are terminally ill and taking opioids. Constipation may be the most common adverse effect of opioids. There is no reason to believe that people with chronic non-malignant disease who take opioids will be any less troubled by this adverse effect. Ahmedzai and Boland (2010) conducted a systematic review and aimed to answer the following clinical questions: What are the effects of: oral laxatives, rectally applied medications, and opioid antagonists for constipation in people prescribed opioids? They searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2009. They included harms alerts from relevant organisations such as the US Food and Drug Administration and the UK Medicines and Healthcare products Regulatory Agency. The authors found 23 systematic reviews, RCTs, or observational studies that met the inclusion criteria. They performed a GRADE evaluation of the quality of evidence for interventions. In this systematic review information relating to the effectiveness and safety of the following interven-tions were presented: arachis oil

enemas, bisacodyl, co-danthrusate/co-danthramer, docusate, glycerol suppositories, ispaghula husk, lactulose, liquid paraffin, macrogols plus electrolyte solutions, magnesium salts, methylcellulose, opioid antagonists, phosphate enemas, senna, sodium citrate micro-enema, and sodium picosulfate. The RCT they found suggested that the outcomes after senna are similar to those of lactulose. The agent of choice therefore depends on patient preference and local cost. Despite the lack of strong RCT evidence, senna is used commonly in the UK in people taking opioids. Senna is recommended in the UK over lactulose as it is similar in terms of benefits and adverse effects but is less expensive. Further RCTs are needed. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

A second update of a Cochrane review on the effectiveness of laxatives for the management of constipation in people receiving palliative care was published in 2015. Previous versions were published in 2006 and 2010 where we also evaluated trials of methylnaltrexone; these trials have been removed as they are included in another review in press. In these earlier versions, the authors drew no conclusions on individual effectiveness of different laxatives because of the limited number of evaluations. This is despite constipation being common in palliative care, generating considerable suffering due to the unpleasant physical symptoms and the availability of a wide range of laxatives with known differences in effect in other populations. To determine the effectiveness and differential efficacy of laxatives used to manage constipation in people receiving palliative care. The Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library), MEDLINE, EMBASE, CINAHL and Web of Science (SCI & CPCI-S) for trials to September 2014 were searched. Randomised controlled trials (RCTs) evaluating laxatives for constipation in people receiving palliative care were included. Two authors assessed trial quality and extracted data. The appropriateness of combining data from the studies depended upon clinical and outcome measure homogeneity. Five studies involving the laxatives lactulose, senna, co-danthramer, misrakasneham, docusate and magnesium hydroxide with liquid paraffin were identified. Overall, the study findings were at an unclear risk of bias. As all five studies compared different laxatives or combinations of laxatives, it was not possible to perform a meta-analysis. There was no evidence on whether individual laxatives were more effective than others or caused fewer adverse effects. This second update found that laxatives were of similar effectiveness but the evidence remains limited due to insufficient data from a few small RCTs. None of the studies evaluated polyethylene glycol or any intervention given rectally. There is a need for more trials to evaluate the effectiveness of laxatives in palliative care populations. Extrapolating findings on the effectiveness of laxatives evaluated in other populations should proceed with caution. This is because of the differences inherent in people receiving palliative care that may impact, in a likely negative way, on the effect of a laxative (Candy *et al.* 2015).

Table 5: Clinical studies on humans in constipation

References	Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Comments
Pers *et al.* (1983)	Prospective randomized	("2.6 g Semen plantaginis ovata, 0.11 g Ispaghula husk and 0.62 g Sennae fructus angustifolie equivalent to 15 mg glycoside A+B per sachet of 5 g") ("3.3 g testa ispaghula and 25 mg glycoside sennae A+B per sachet"). 1 week prior 2 weeks Prep A 2 weeks Prep B	20; 1 dropout diarrhoea of unknown origin	severe constipation	No difference between the preparation	No information	Supportive data for constipation
Marlett *et al*. (1987)	Controlled, Randomised, single-blind	-ispaghula husk (7.2 g/day) n=20 -psyllium plus senna (6.5 g + 1.5 g/day) for 1 week n=22	42 adults	No information available	No relevant outcome	No information available	Limited relevance for assessment
Passmore *et al*. (1993 a, b)	randomised, double-blind, crossover study	(ispaghula 54.2 %, senna 12.4 % (m/m)) and lactulose senna-fibre combination 10 ml daily with lactulose -- active senna-fibre combination 10 ml daily with	77 elderly patients (average age: 82.9 years)	history of chronic constipation	Mean daily bowel frequency was greater with the senna-fibre combination (0.8, 95 % confidence interval 0.7 to 0.9) than with lactulose (0.6 (0.5 to 0.7); t=3.51, p<	No information available	The senna-fibre combination was significantly more effective than

References	Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Comments
		lactulose placebo 15 ml twice daily active lactulose 15 ml twice daily with senna-fibre placebo 10 ml daily for two 14 day periods. - maximum daily dose for active or placebo senna-fibre was 20 ml (10 ml twice daily) and for lactulose or lactulose placebo 60 ml.			0.001).		lactulose at a lower cost.
Kinnunen *et al.*, 1993	open, randomised and controlled crossover study In period I, 21 patients received A and 9 patients B; in period II, 7 patients received A	A:Plantago ovata seed 521.6 mg (bulk forming), Fructus cassiae angustifoliae 138 mg (stimulant) B: 30 ml lactulose	30 long stay elderly patients aged 65 – 94 years (mean 81.8 years) 65 – 94 years (mean 81.8 years)	chronic constipation	bowel frequency/week ignificantly higher on A treatment during both periods mean (SD): in period I: 4.5 (2.3) period II: 4.5 (2.4), compared to B bowel frequency on B treatment in period I 2.2 (0.9) (p=0.0006) and in period II 1.9 (0.9) (p=0.027).	No information available	Limited relevance for assessment

References	Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Comments
	and 18 patients B.				Bowel frequency/week significantly higher on A treatment during both periods, mean (SD) in period I: 4.5 (2.3); period II: 4.5 (2.4), compared to B. Bowel frequency on B treatment in period I 2.2 (0.9) (p=0.0006) and in period II 1.9 (0.9) (p=0.027)		

Table 6: Clinical studies on humans in irritable bowel syndrome.

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Hübner and Moser (2002) compare the efficacy as well as the tolerance	12-week double blind, controlled, randomised, multicentre and prospective clinical trial	tablets CL+(containing as active ingredients "180 mg Carbo ligni", i.e. vegetable, non-activated *charcoal, "105 mg Fol. Sennae, 25 mg rhubarb extract" 2.65 – 3.95* mg anthraquinone per tablet)(n=145) to Carbo ligni (CL) containing tablets (n=139). Adaptation from one to eight tablets per day	284 patients between 19 and 70 years	irritable bowel syndrome (IBS) Rome criteria for IBS	1.changes of the disease were evaluated with scores based on the Francis IBS system modified with an open upper boundary (a patient-administered questionnaire that uses a visual analogue scale (VAS) (0%-100%) to score the severity of pain, distension, bowel dysfunction, and quality of life/global well-being)	262 patients were available for intention-to-treat (ITT) analysis 144 for per-protocol (PP) analysis	Amelioration of symptoms in the PP population by 62.5% with CL+ and 56.5% with CL; respective values in the ITT population were 59.6% and 53.2%.

Table 7: Clinical studies on humans, in bowel cleansing

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
150 mg – 300 mg HAD without enema							
Ziegenhagen *et al.* (1991)	Prospective randomized investigator blinded	The day before endoscopy either extractum sennae 1.26 - 1.85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1,extraction solvent water;n = 60) or a placebo solution (N = 60) was given.	120 outpatients, all patients underwent whole gut irrigation with 2 l polyethylene glycol electrolyte lavage solution (PEG-ELS)	referred for colonoscopy	Bowel cleanliness	p=0,05; CI 95%	senna/PEG-ELS group, significantly less (p less than 0.05) lavage fluid was needed. Study contributes to evidence for well-established use.
Frigerio *et al.* (1996)	randomised, single-blind study	-1 dose of senna 1.26 - 1.85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1,extraction solvent water) for colon cleansing (n=250). -two doses, one at mid-day and one on the evening prior to the examination, equivalent to 300 mg senna (n=223)	473 patients (225 males and 248 females with a mean age of 59.7 years, range 14 – 96 years) liquids orally according to need, no enema	referred for colonoscopy	Score 0 = perfect examination, possible to observe the entire colon mucosa; 1 = acceptable examination, capable of responding to the diagnostic problem but with insufficient observation of some areas; 2 = examination impossible, requiring repetition.	Colonoscopy was impossible (and had to be repeated) in 44 patients (M/F = 22/22), 38 of these (15.2%) belonged to group A (150 mg) and 6 (2.7%) belonged to group B. (p=0,000006) The	300 mg of senna was more efficacious than 150 mg and that both doses were well tolerated. Supportive evidence for well-established use.

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
						examination was acceptable in 148 patients (M/F = 79/69), 85 (34.0%) belonging to group A and 63 (28.3%) to group B (p=0.02). A perfect examination could be carried out in 281 patients, 127 patients (51%) belonging to group A and 154 patients (69%) belonging to group B.	
Schanz *et al.* (2008)	Randomised, multicenter, observer-blinded	-A: sodium phosphate solution n=128 - B:sodium phosphate solution and sennosides 1,26 - 1,85 g dry extract	355 consecutive out-patients (18 and 75 years). Drinking volumes (L) (A	referred to colonoscopy	quality score (0 – 4) of cleanliness was generated: 0 = excellent to 4 = repeated examination necessary	No information available	No differences in adverse events and the cleanliness effects occurred in the three groups

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1,extraction solvent water n=133 - C: PEG-ELS and sennosides n=94	= 4.33+1.2, B = 4.56+1.18, C = 4.93+1.71) were different (p=0.005)				(p=0.113). Supportive evidence for well-established use
Kositchaiwat *et al.* (2006)	Prospective randomized single blinded	-180 mg senna tablets (24 tablets of 7.5 mg /tab), n=67 -95 ml sodium phosphate solution on the day before colonoscopy n=67	134	referred for elective colonoscopy	The efficacy of both laxatives were equivalent	ITT; CI 95%	Limited relevance for monograph.
Valverde *et al.* (1999)	prospective, randomised, observer-blind, parallel, multicentre study	dry extract Senna fructus acutifoliae standardized to 120 mg sennosides A et B evening before surgery n=262 - polyethylene glycol (PEG) (2 packages a 59 g diluted in 2 – 3 l of water,	523 patients in 2 strata, ie, those with carcinoma and those with sigmoid diverticular disease 5 % povidone	colonic or rectal carcinoma or sigmoid diverticular disease undergoing elective colonic or rectal	3-stage score according to Hollender *et al.* (0 = no faecal matter, + = small amount of faecal matter, ++ = faecal matter bothersome to the surgery) Other criteria were consistency of faecal	χ^2 test for categorical values and the Student *t* test for continuous variables	Colonic cleanliness was better (p=0.006), faecal matter in the colonic lumen was less fluid (p=0.001), and the risk for moderate or large intraoperative

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		ColoPeg®) n=261	iodine antiseptic enemas (2 l) the evening and the morning before surgery	resection followed by immediate anastomosis	matter, rate and magnitude of intraoperative faecal soiling, rate of abdominal infective complications and patient tolerance. Adverse reactions with senna were reported as follows: discomfort 55 patients (21%), vomiting 12 (4.6%), abdominal pain 35 (13.4%), distension 8 (3%), malaise 23 (8.8%). In the other group the following adverse reactions were reported: discomfort 55 patients (21.1%), vomiting 7 (2.7%), abdominal pain 30 (11.5%), distension 15 (5.7%), malaise 15 (5.7%). Senna was better tolerated (p=0.03) in the presence of stenosis.		faecal soiling was lower (p=0.11) with senna. There was no statistically significant difference found in the number of patients with postoperative infective complications (14.7% vs 17.7%) or anastomotic leakage (5.3% vs 5.7%) with senna and PEG.
150 mg HAD with an enema							
Hangartner *et al.*	prospective	- 4 liters of Golytely; n=100	300 patients	referred for	1 bowel cleanliness:	descriptive	4 liters of Golytely and Senna extract

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
(1989)	randomized	- 2 liters of Golytely combined with Cascara-Salax n=102 - (1.26 – 1.85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1, extraction solvent water) for colon cleansing) combined with an enema n=98	Exclusion of prior colonic surgery	colonoscopy	-no stool residue -Stool liquid mixture -Solid stool -Frequency of endoscope blockage 2 side effects patients acceptance quality of examination		plus enema have equivalent cleansing efficacy for colonoscopy, patients judged senna extract to be less unpleasant. Supportive evidence for well-established.
Krakamp *et al.* (1996)	prospectiver andomised simple-blind study	-Golytely-recepture 3l; 3 h n=48 -PEG-ELS, 4l; 4h; n=48 - 1.26 – 1.85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1,extraction solvent water n=50	150 out-patients 57 +/- 19 years in group 1, 55 +/- 15 years in group 2 and 57 +/- 17 years in group 3 three days eating restrictions; 1 day clear fluids 1 enema 1 h before	Referred for colonoscopy	4-stage score (‘1 excellent’ dry colon or clourless fluid; 2 fluid residiue in feces like colour; 3 sufficient inimal solid fecal residueto 4‘colonoscopy not possible’), the formation of foam by a 4-stage score (‘no foam’ to ’examination strongly restricted’)	descriptive	90% of the senna group was adequately prepared, 3 litres of Golytely the most efficient method when it came to cleanliness and the formation of foam. Contributes to evidence for well-

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
			procedure.				established use.
Bokemeyer *et al.* 2000	open prospective study	-Golytely (2 l on the day before colonoscopy and 2 l on the day of colonoscopy p.o. n=41 - Golytely-RSS (3 l on the day of colonoscopy p.o.) n=40 - Phospho-Soda 45 ml on the day before and 45 ml on the day of colonoscopy p.o.) n=44 - 1,26 - 1,85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1,extraction solvent water, per single dose, and an enema and 2 l Golytely on the day before colonoscopy p.o. and an enema in the morning before colonoscopy) n=40	165 outpatients	Referred for colonoscopy	Endocopist: bowel cleanliness by a score 1 (best) – 6 (worse). Patients assessed the tolerance and acceptance by a score 1 (best) – 6 (worse).	Senna extract produced significantly worse results: score 3.0.	Problems resulted from a relative large volume of remaining fluid in the bowel especially after 1-day preparation with PEG-lavage solutions. By Using an additional dose of cisaprid the remaining fluid could be reduced and the cleansing result was better Supportive evidence for well-established use.

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Calcium sennosides 120 - 300 mg HAD							
Arezzo (2000) Compare effectiveness and tolerance of different bowel preparations	randomised observer-blind, parallel study	(group 1; 12 tablets, each containing 12 mg calciumsalts of sennosides A+B from a standardized extract of senna leaves extraction solvent: methanol 66% (V/V) at 10 a.m. and magnesium sulfate 15 g at 5 p.m. on the day before colonoscopy p.o. + 2l water=100 - PEG lavage (group 2; 4 l at 4 p.m. on the day before colonoscopy p.o. n=100 - an oral sodium phosphate solution (group 3; 40 ml at 6 p.m. on the day before and 40 ml at 6 a.m. on the day of colonoscopy n=100	300 patients avoid foods with seeds for five days before colonoscopy; the day before colonoscopy, patients were asked to avoid solid food after noon.	Referred for colonoscopy	Endocopist: blindly scored cleansing for each bowel segment ('good', 'medium', 'scarce') and defined the quality of the examination as 'optimal', 'acceptable' or 'to be repeated'	descriptive	Bowel cleanliness was scored as 'good' in 38 (group 1), 50 (2), 68 (3) patients. Significant more patients in group 3 (68%) achieved a good cleansing compared with group 2 (50%) ($p<0.0001$) and group 1 (38%) ($p<0.005$). Feasibility of the examination was considered 'optimal' significantly more in group 3 (80 patients) than in group 2 (62 patients, $p<0.005$)) and in group 1 (59 patients,

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
							p<0.005). the sodium phosphate solution should be the standard preparation for elective colonoscopy
Tasci *et al*. (2003)	prospective randomised trial	-sennoside calcium (300 ml of a 1 mg/ml solution given 2 days prior to colonoscopy), n=150 -PEG lavage (3 l given 1 day prior to colonoscopy), n= 145 -oral sodium phosphate solution in one 90 ml-dose 1 day prior to colonoscopy, n= 141 -oral sodium phosphate solution in 2 doses (90 ml 1 day prior to colonoscopy + 45 ml 5 h prior to colonoscopy), n= 136 -oral sodium phosphate solution in 2 doses (45 ml +	953; 1021 patients enrolled, 68 were excluded from analysis because of intolerance to the solutions or medicinal products, improper use of the regimen, electrolyte imbalance, cardiac disorders or vomiting. -clear liquid diet one day before starting the	efficiency of the different procedures was evaluated according to a 5-point scale.	Bowel cleansing was effective in 890 (93%) patients. Tolerance to sennoside calcium and PEG lavage in comparison to other groups was significantly worse (p<0.05). Of the patients who received sodium phosphate-based treatments, 72%-78% stated that they would undergo the procedure again if necessary, while only 21% of patients in the sennoside calcium group and 11% in the PEG group were so willing (p<0.05)	Differences per ANOVA t-test; CI 95%	Tolerance to sennoside calcium and PEG lavage in comparison to other groups was significantly worse (p<0.05). Of the patients who received sodium phosphate-based treatments, 72%-78% stated that they would undergo the procedure again if necessary, while only 21% of patients in the sennoside calcium group and 11% in

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		90 ml), n=147 -oral sodium phosphate solution in 2 doses (45 ml + 90 ml) plus 10 mg cisapride, n= 82 -oral sodium phosphate solution in 2 doses (45 ml + 90 ml) plus 10 ml domperidone; n= 152.	bowel cleansing regimen - Sodium phosphate enema was applied to the patients on the morning of colonoscopy.				the PEG group were so willing ($p<0.05$)
Radaelli *et al.* (2005)	prospective randomized single blinded	-oral high dose of senna 24 tablets of senna (tablet, each containing 12 mg calciumsalts of sennosides from a standardized extract of senna leaves extraction solvent: methanol 66% (V/V)) contains 12 mg of concentrated extract of sennoside A and B as calcium salts divided into two doses at 1 p.m. and 9 p.m. + 2 l clear liquid (n=191), -conventional polyethylene	283 low-fiber diet and encouraged to increase water intake (at least 1.5 L) on the fourth through second pre-procedural days. On the day before the procedure, they were advised to eat a normal breakfast in the morning and a	referred for elective colonoscopy	Aronchick scoring scale (1=excellent to 4=inadequate)	Multivariate logistic regression modeling	The quality of colon cleansing, overall tolerance of the preparation, and compliance were significantly better with senna; overall cleansing was excellent or good in 90.6% of patients in the senna group and in 79.7% in the PEG-ES group (p= 0.003). Supportive

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		glycol-electrolyte lavage solution (PEG-ES) (n=92)	light liquid lunch; afterward, only clear liquids were allowed until 2 h before colonoscopy.				evidence for well-established use.
Amato *et al.* (2010)	prospectiver andomizedin vestigator-blinded	- 12 tablets ,each containing 12 mg calciumsalts of sennosides A+B from a standardized extract of senna leaves; extraction solvent: methanol 66% (V/V) contains 12 mg of concentrated extract of sennoside A and B as calcium salts and 2 l of PEG-ES (half-dose group, HDG) n=151 -24 tablets of senna divided in two doses (senna group, SG) the day before colonoscopy.n=145	296	referred for elective colonoscopy	1. Aronchick scoring scale) and the incidence of preparation-related abdominal pain. 2. Patients' compliance with the cleansing regimen, overall tolerability, prevalence of predefined side effects, and quality of right colon cleansing	descriptive	half doses of PEG-ES and senna provides high-quality bowel preparation and acceptable patient tolerance, with less abdominal pain compared to high-dose senna. Supportive evidence for well-established use.
Kelly *et al.* (2012) bowel	prospective	-low-volume polyethylene glycol (2-L); n=86 -standard volume	258 (female,138; 53.5%)	referred for elective colonoscopy	Overall cleansing grades of preparations used: patient compliance, taste, and	Fisher exact test Unpaired t	The overall cleansing efficacy across the 3 groups (those with

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
preparation for colonoscopy		polyethylene glycol (4 L) n=91 -magnesium citrate plus 1 sachet Senna (no further information) n=81			acceptability.	testing P value was <0.05.	grades A or B) was 73.9%, 74.5%, and 86.5% for polyethylene glycol 4-L, polyethylene glycol 2-L, and Senna/ magnesium citrate. Senna/ magnesium citrate proved significantly better at bowel cleansing than polyethylene glycol 4-L (P<0.05) and it showed a trend toward better cleansing when compared with polyethylene glycol 2-L (P=0.08).
Manukyan *et al.* (2011)	Prospective randomised	-Sodium phosphate 2 x 45 ml phosphor-soda n=53 -Sennoside A+B 150 ml =	99	referred for elective colonoscopy	time taken to complete the colonoscopy and the segment of the colon examined were recorded	SPSS 10.0 Chi^2 Test Student t-test, Fisher exact	Sennoside A+B calcium is more effective in some of the colonic segmental

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		150 mg (HAD) n=46				test	cleansing, causes fewer changes on serum electrolyte levels, and is better tolerated.
Ergül *et al.* (2014) gum chewing added to high-dose senna before colonoscopy promotes bowel cleaning?	randomized controlled, single blinded	- sennoside tablet 80 mg daily for 3 days;senna solution 150 ml (300 mg senna) the night before colonoscopy n=65 - to chew sugarless gum half an hour three-times daily after meals for these 3 days sennoside tablet 80 mg daily for 3 days;senna solution 150 ml (300 mg senna) the night before colonoscopy n=64	129	scheduled for elective colonoscopy	Aronchick scale	CI 95%	Cecal intubation time was significantly shorter in the gum-chewing group (8.6 ± 5.1 and 7.1 ± 2.8 min, P = 0.03). Gum chewing enhances colonoscopy bowel preparation quality
Altinbas *et al.* (2015)	Retrospective single blinded	- sennoside a + b calcium 500 mg/250 ml n=91 - 4 L of PEG-EL n=94	185 patients; 53.4 ± 13.4 years (53.7 ± 15.0 in Group 1, 52.42 ± 11.8 in Group 2, P =	elective colonoscopy	Ottawa Bowel preparation Scale Score	SPSS 13.0 (SPSS Inc., Chicago, IL, USA). P < 0.05 was accepted as the cut-off	A large proportion of patients (75.3%) in Group 1 and half the patients in Group 2 (46.2%) would agree to

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
			0.255), and 89.3% and 95.8% of the patients in the groups were male, respectively (P = 0.545).			value for statistical significance. Chi-square, Kruskal–Wallis, and Mann–Whitney U tests	drink the same regime again.
Taylor *et al.* (2008) optimum barium-based reduced-laxative tagging regimen prior to CT colonography	Controlled randomised	reduced-laxative (13 g sachet of senna granules /18 g magnesium citrate) CTC prior to CT colonography tagging regimens: -20 ml 40%w/v barium sulphate: regimen A: four doses, -B: three doses, -C: three doses plus 220 ml 2.1% barium sulphate, or -D: three doses plus 15 ml diatriazoate megluamine	95 patients (50 female, mean age 64 years, range 50–85 years) two days of low residue diet	scheduled to undergo afternoon diagnostic colonoscopy for symptoms suggestive of colorectal neoplasia	Two radiologists graded residual stool (1: none/scattered to 4: >50% circumference) and tagging efficacy for stool (1: untagged to 5: 100% tagged) and fluid (1: untagged, 2: layered, 3: tagged), noting the HU of tagged fluid.	Questionnaire responses compared using Fischer's exact test. False-positive numbers were compared using one-way ANOVA.	Preparation was good (76-94% segments graded 1), although best for regimen D (P = 0.02). Across all regimens, stool tagging quality was high (mean 3.7-4.5) and not significantly different among regimens. Reduced-laxative CTC with three doses of 20 ml 40% barium sulphate is as effective as more

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
							complex regimens, retaining adequate diagnostic accuracy.
Hookey *et al.* (2006)	prospectiver andomizedin vestigator-blinded	- 120 mg (HAD) oral sennosides syrup followed by 2 L PEG n=79 -4 L PEG n=81	171 patients a clear fluid diet the day before colonoscopy	referred for elective colonoscopy	1.Ottawa scale 2. Patients' compliance with the cleansing regimen, overall tolerability, prevalence of predefined side effects	tolerance and efficacy in a χ^2 test, to detect a 20% difference in effectiveness of colon cleansing and patient tolerance, with an alpha of 0.05 and 80% confidence level, 80 patients/group	A significant difference between the two preparations in the quality of colon cleansing was seen in favour of PEG (P=0.03) low-volume PEG plus sennosides was better tolerated than PEG (P<0.001)
<80 mg HAD							
Iida *et al.* (1992)	uncontrolled	-drink 2 l of Golytely on the day of examination by taking 36 mg of sennosides (no further information of the formulation) orally in the evening before colonoscopy.	297 examinees (219 male and 78 female; mean age 57 years)	referred for colonoscopy	Bowel cleanliness was assessed as 'excellent' or 'good' in 90% to 97% of the patients at all sites in the colon and rectum.	No information available	Uncontrolled therefore only weakly supportive to well-established use
Chilton *et*	Randomised,	-75 mg syrup; 50 ml	132 consecutive	Referred for	Endoscopists assessed	Nonparametric	The triple regimen

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
al. (2000)	single blinded	contains sennoside B, 7.5 mg/5 ml. + sodium picosulphate 10 mg at 2 p.m. + Golytely 1 l at 6 p.m. on the day before colonoscopy when colonoscopy took place before 12 a.m n=81 -75 mg sennosides A+B at 2 p.m. + sodium picosulphate 10 mg at 6 p.m. + Golytely 1 l at 7 a.m. on the day of colonoscopy when colonoscopy took place after 12 hours. n=81, - sodium phosphate solution 45 ml at 8 a.m. and 45 ml at 8 p.m. on the day before colonoscopy when colonoscopy took place before 12 hours; n=51 - sodium phosphate solution 45 ml at 8 p.m. and at 8 a.m. in the morning of the colonoscopy when colonoscopy took place after	patients; Low residue diet for 48 h; liquid only 24 h prior to examination The doubling of the groups is due to the time frame of examination	colonoscopy	bowel cleanliness by a 4-stage score (excellent, good, intermediate, poor). "Time to caecum"	statistics, the chi-squared test was used to compare proportions	patients had significantly cleaner colons than patients who received Phospho-soda (p = 0.037, Mann-Whitney U-test). Although the median (range) cleanliness scores were identical for both groups, 73 % of the triple regimen group scored 1 or 2, compared with 57 % of the Phospho-soda group Median time to caecum was 11 minutes (range 5 - 50) in the triple regimen group and 16 minutes (range 5 - 65) in the Phospho-soda group, (p = 0.08).

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		12 a.m. (n=51).					
Haapamäki *et al.* (2011)	single-center, prospectiver andomizedin vestigator-blinded study	-2 l PEG combined with 36 mg senna glycosides in tablets n=244; ITT=203 -4 l PEG for bowel preparation; n=246; ITT=196	n = 490 avoid solid food after 3 pm the day before colonoscopy and were allowed to drink clear liquids	referred for elective colonoscopy	1. Ottawa score 2. subjective grading of patients of ease of taking the large-bowel preparation, frequency of need for repeated colonoscopy because of insufficient view, and frequency of incomplete intake of bowel preparation.	Differences in categorical data between groups were tested with the two-sided chi-square test. Statistical analysis was carried out using SPSS version 16.0 (SPSS, Chicago, IL, USA).ITT; CI 95%	significantly more cases with poor or inadequate bowel cleansing after the low-volume alternative with senna and 2 l PEG (22/203) compared with after 4 l PEG (8/196, p = 0.027). Patients' subjective grading of ease of taking the bowel preparation: Difficult and impossible 25/231 senna 55/238 4 l PEG
Postgate *et al*. (2009) To evaluate the	prospective single-blind randomized controlled	-"standard" (fluid restriction then nothing by mouth 12 hours before the procedure, water and simethicone at	150 volunteers	healthy	1.gastric transit time (GTT); small-bowel transit time (SBTT), completion rates (CR), view quality,	descriptive	Bowel purgatives and prokinetics did not improve CRs or view quality at CE, and bowel

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
usefulness of bowel purgatives and prokinetics in small-bowel Capsule Endoscopy CE		capsule ingestion [S]); -"standard" + 10 mg oral metoclopramide before the procedure (M); -Citramag + senna bowel-purgative regimen the evening before CE (CS); n=40 -Citramag + senna + 10 mg metoclopramide n=37 before the procedure (CSM).			and patient acceptability 2. positive findings, diagnostic yield		purgatives reduce patient acceptability
Kashyap *et al.* (2015)	prospective, single-center, single-arm	-4 Senna tablets, no further specification -4 liters of PEG (split dose), -10 mg metoclopramide, -2 oral sulfate solution boosters (6 oz. and 3 oz.), and -10 mg bisacodyl.	25 volunteers to colon capsule endoscopy (CCE)	healthy	the percentage of subjects with a clinically significant change in serum chemistry at the last test and the adverse event (AE) rate.	SQL Server8, SQL, and SPSS Version 20. Data were summarized by descriptive statistics (for continuous variables)	no serious AEs, three moderate AEs related to the bowel preparation (nausea, headache, elevated creatinine) and two mild unrelated AEs (chills, abdominal cramping
Poyrazoglu and Yalniz	Prospective randomised	-90 ml of oral NaP (NaP group) ITT= 66	137 consecutive patients	Referred for colonoscopy	Patients questionnaire Bowel cleansing	ITT;CI=95% descriptive	the number of patients with excellent bowel

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
(2015)	Single-blinded	- senna solution (500 ml, 1,000 mg of sennosides A and B calcium +66.6 g of sorbitol) in two divided doses 1 day before the procedure: 250 ml at 4 pm and 250 ml at 6 pm. ITT=62	Drop out 9 senna 5 NaP		The patients' compliance to the bowel-cleansing regimen, as well as any gastrointestinal or other unfavorable symptoms (nausea, vomiting, abdominal pain, and dizziness) induced by these regimens, was assessed, and patients' responses were graded using a four-point scoring system: 1= no trouble; 2= mild; 3= moderate; and 4= severe.		cleansing according to the general appraisal of colonoscopic evaluation was significantly higher in the NaP regimen group than in the senna group (46 [78%] vs 25 [43.1%], P<0.001)
Vradelis *et al.* (2009)	prospective	-magnesium citrate 2 sachets á 11.6 g magnesium carbonate and 17.8 g anhydrous citric acid n=160 - 2 sachets á 11.6 g magnesium carbonate and 17.8 g anhydrous citric acid 1 sachet senna granules no further information	345 consecutive adult out patients low-fiber diet for 2 days; clear fluids 1 day	referred to the endoscopy	The combined citramag/senna regimen proved superior in bowel cleansing as it achieved "adequate" colon visualization (quality of colon cleansing rated as "good" or "satisfactory" in 148/182 (81.3 %) compared to 108/160 (67.5 %) colonoscopies using the citramag	χ^2-test CI 95	The combined citramag/senna regimen proved superior in bowel cleansing as it achieved "adequate" colon visualization (quality of colon cleansing rated as "good" or "satisfactory" in 148/182 (81.3%)

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		n=182			protocol (*P* = 0.004		compared to 108/160 (67.5%) colonoscopies using the citramag protocol (*P* = 0.004;

Table 8: Clinical studies on humans, in postoperative constipation

Reference	**Study Design**	**Test Product(s):**	**Number of subjects**	**Type of subjects**	**Outcomes**	**Statistical analysis**	**Clinical relevance**
Patel *et al.* (2010)	Prospective randomized	- placebo n=45 - senna 8.6 mg with docusate 50 mg n= 48	96 patients after pelvic reconstructive surgery	after pelvic reconstructive surgery	first bowel movement (BM) postoperative use of magnesium citrate were compared	CI=95%	There was a significant difference in the time to first BM in those receiving senna with docusate vs placebo (3.00+/-1.50 vs 4.05+/-1.50 days; P<.002). More subjects in the placebo group needed to use magnesium citrate to initiate a bowel movement (43.6% vs 7.0%; P<.001).

Table 9: Clinical studies on humans, in postoperative opioid-induced constipation

Reference	**Study Design**	**Test Product(s):**	**Number of subjects**	**Type of subjects**	**Outcomes**	**Statistical analysis**	**Clinical relevance**
Marciniak *et al*. (2014) the efficacy of lubiprostone compared to Senna on bowel symptoms and constipation in post-operative orthopedic patients treated with opioids	double blind, randomized, active comparator trial randomisation: 1:1 ratio in blocks of 4	-lubiprostone , orally twice a day 24 µg - senna (generic) two capsules administered daily for six days.	64 adults 56 participants (28 in each group) had baseline and follow up measures and were included in the intention to treat (ITT) analyses. 43 participants completed the study, 21 in the active	No information available	1.Patient assessment of constipation (PAC)-symptoms (PAC-SYM) and the PAC-quality of life (PAC-QOL) scales measured at baseline and Day 7 2. Bristol stool scale bowel consistency, specific bowel symptom score (Nausea, cramping, straining, completeness, abdominal pain, time per lavatory attempt, assistance needed), adverse events and rescue medications required.	ITT; CI 95%	Both lubiprostone and senna improved constipation-related symptoms and QOL in opioid-induced constipation, with no significant between-group differences.

Table 10: Clinical studies on humans, in chemotherapy-induced constipation

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Tao *et al.*(2012)	no data available	-senna extract in the 1st chemotherapeutic course and the crude fiber diet in the 2nd chemotherapeutic course. -vice versa	82 patients	constipation after chemotherapy	effective rates of relieving chemotherapy-induced constipation by senna extract and by the crude fiber diet; the differences of the digestive tract reaction and the hematotoxicity reaction were compared	CI 95%	The effective rate of constipation by taking senna extract was 92.68% and that by the crude fiber diet was 10.93%, with statistical difference shown (P < 0.01).

Table 11: Clinical studies on humans, in constipation in people receiving palliative care

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Ramesh *et al.* (1998)	Controlled open	-purified senna extract 60 mg containing 12 mg senna glycosides as calcium salts(2 tabs at night;4 tabs at night;2 tabs in the morning + 4 tabs at night every 2 days n=25; step1: 2 tabl. night; step2:4 tab. At night; step 3: 2 tab. Morning; 4 tab. night -a liquid Ayurvedic (herbal) preparation (Misrakasneham; 21 herbs) n=25 Increasing in 3 steps; 2,5 ml; 5 ml; 10 ml	50 patients (30-70years), 9 dropouts (senna: 4 irreg. admin; 2 lost follow-up; 2 morphine withdrawal; 1 bowel movement spontaneous) 5 drop outs (Misrakasneham : 2†; 2 lost follow-up; 1 irregular administration)	management of opioid-induced constipation in advanced cancer	Bowel movement.	descriptive	No difference
Agra *et al.* (1998)	randomised, open, parallel – group trial	-senna derivatives 0.4 ml (12 mg) for senna (no other information of the formulation are given) intake in two doses;every 3 days;	91; By the end of the 27 days, 37 patients were lost: 21 in the senna group and 16 in the lactulose group.	terminal cancer patients treated with opioids; When a patient reached the ceiling of his respective laxative and had a defaecation-free period of 3 days,	The mean morphine dose at which laxatives proved necessary was 84.1 mg (SD 72.3 mg). no differences in the	The mean morphine dose at which laxatives proved necessary	Not relevant for establishment of the monograph

Reference	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		maximum doses were 1.6 ml (48 mg)n=43 -lactulose15 ml (10 g) every 3 days; maximum doses 60 ml (40 g) n=48	Three developed vomiting, five refused to continue in the protocol, 17 died, and 12 were hospitalised.	he was maintained on that dose and, in the absence of side effects, he was also given the initial dose of the other laxative, which could then be increased at 3-day intervals until reaching the experimental maximum	respective defaecation-free 72-hr intervals as a function of opioid	was 84.1 mg (SD 72.3 mg). no differences in the respective defaecation-free 72-hr intervals as a function of opioid	

4.3. Clinical studies in special populations (e.g. elderly and children)

Children

Constipation within childhood is an extremely common problem. Despite the widespread use of osmotic and stimulant laxatives by health care professionals to manage constipation in children, there has been a long standing paucity of high quality evidence to support this practice.

Twenty-one children under 15-years' old with chronic constipation were treated in a crossover trial lasting 3 weeks. In the first week they received either lactulose (10-15 ml) or senna (a standardized syrup, no further information 10-20 ml) in the next week no treatment, and in the third week the alternative treatment. Patient diaries were kept by parents on the number and character of stools passed, and of side-effects reported, during the 3 weeks. There was a significant difference, in favour of lactulose, in the number of days on which normal stools were passed during the treatment weeks. The number and frequency of the side-effects reported in the senna treatment week were very much higher (p less than 0.001) than in the lactulose week. Lactulose is recommended as an effective and very well tolerated treatment for the constipated child (Perkin 1977).

In an open controlled trial Nolan *et al.* (1991) randomly allocated 169 children with encopresis and evidence of stool on plain abdominal radiograph to receive multimodal (MM) therapy (laxatives plus behaviour modification; n=83) or behaviour modification only (BM; n=86). The protocol for the MM group used laxative therapy in two phases. The initial disimpaction phase consisted of 3-day cycles of 5 ml (sodium citrate 90 mg, sodium lauryl sulphoacetate 9 mg, sorbic acid 5 mg, glycerol, sorbitol, distilled water) on day 1, one 5 mg bisacodyl suppository after school and one in the evening on day 2, and a 5 mg bisacodyl tablet after school and one in the evening on day 3. Up to 4 cycles (12 days) were undertaken. Further cycles were prescribed if there was later evidence of stool reaccumulation. The subsequent maintenance phase consisted of a mixture (liquid paraffin, phenolphthalein, benzoic acid, sorbic acid) 5-30 ml once or twice each day, senna granules, and/or bisacodyl tablets. Doses were adjusted to maintain at least daily defaecation and were increased if there was persistent or recurrent stool retention. By 12 months follow-up 42 (51 %) of the MM group and 31 (36 %) of the BM group (p=0.079) had achieved remission (at least one 4 week period with no soiling episodes) and 52 (63 %) vs 37 (43 %) (p=0.016) had achieved at least partial remission (soiling no more than once a week). MM subjects achieved remission significantly sooner than BM subjects. The authors concluded that this study shows a clear advantage overall for the use of laxative medication, although the benefit may not be as great for children, who are able to maintain regular bowel habits. Only poor information concerning senna is given in the publication. No evaluation of the efficacy nor of the safety or tolerability is possible. Furthermore, this is a special study population, which cannot be compared with constipated children.

Bliesener *et al.* (1978) reported his experiences with a senna preparation in children. 111 patients between 0.5 and 15 years undergoing bowel cleansing before radiological examination were enrolled and 107 completed this prospective uncontrolled study (44 patients between 0.5 – 5 years; 47 between 6 – 10; 20 between 11 – 15). They received 1 ml = 2 mg/kg body weight of the senna preparation (1.26 - 1.85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B; DER 3-5:1, extraction solvent water),) at 7 p.m. in the evening prior to radiological examination. According to the authors, the preparation method was well accepted even by the younger (< 5 years) children. Excellent radiographic visualisation was obtained in most patients (87 %) and diagnosis was possible in all patients. The preparation method was well tolerated.

Despite proper technique, pull-through operations for Hirschsprung's disease (congenital aganglionic megacolon) sometimes fail to deliver normal or effective bowel evacuation. Ten patients, described herein, had had a pull-through procedure (minimally invasive approach to treat Hirschsprung's disease uses only four to five small incisions. The procedure is done with an endoscope. Sometimes this approach is used only to remove the blockage and tissue that is missing nerves. The healthy sections of bowel are then reconnected.). The procedures had been performed by various pediatric surgeons. Five cases had been diagnosed in the newborn period and had undergone colostomies. The remainder had been diagnosed later (at 2 months to 2 years of age). They too had undergone colostomy initially, and all had an elective pull-through procedure. The techniques varied; two had Soave procedures, seven had Duhamel procedures, and one had a Kimura-Soave procedure (the only case of total colonic Hirschsprung's disease in the series). All the patients had manifested difficulty in passing stools after the pull-throughs. The problem was described as "severe constipation," "obstipation," or "fecal retention." Four patients had been treated with many laxatives, suppositories, enema routines, and diet regimens for years, with no success. All had been examined radiographically to detect megarectum or megacolon. All had additional biopsies to confirm the presence of ganglia in the pulled-through segments. At 21 months to 12 years of age, these patients underwent full posterior internal sphincterotomies. Nine of the 10 had a good or excellent outcome, with resolution of the megarectum or megacolon. Three patients still require small doses of senna compound, which are being decreased continuously. Therapy failed for a patient with Down's syndrome and a, Duhamel pull-through, and a stoma was required (Blair *et al.,* 1996).

Dahshan *et al.* (1999) performed a prospective, randomised, single-blind study in children undergoing colonoscopy to evaluate the acceptance and efficacy of three different bowel preparations. 70 patients (ages 3 – 20 years, 38 male) were randomly assigned to one of the three study preparations: Group A: Magnesium citrate with a senna preparation, 1.26 - 1.85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1,extraction solvent water and clear liquid diet for 2 days. Group B: bisacodyl for 2 days and enema without dietary restriction. Group C: Golytely 20 ml/kg (up to 1 l) per hour for 4 h with clear liquid diet for 1 day. Endoscopists blinded to bowel preparation graded the adequacy of colon cleansing. The preparations were rated by patients for tolerance, willingness to retake them, adverse effects, and compliance. Data analysis using Fisher exact test and trend test showed that colon cleansing in groups A and C was superior to that in group B ($p<0.0001$) and better in group C than A ($p<0.075$). Overall tolerance and compliance were significantly better for groups A and B than group C ($p<0.003$), but not different between A and B. More of group B patients were willing to retake the preparation than in group C ($p<0.002$) and group A ($p<0.05$), but this was not different between groups A and C. Adverse effects were reported more frequently by patients in group C than in groups A and B ($p<0.01$). The authors concluded that although the least well tolerated, Golytely provided the best cleansing. Bisacodyl without dietary restriction provided unsatisfactory colon cleansing. Magnesium citrate with senna preparation was acceptable and provided good cleansing. This investigation cannot prove the efficacy of senna because it was given in combination with magnesium citrate and the study groups were very small.

There are several reports of local intolerance of a senna extract (1,26 .- 1.85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B; DER 3-5:1, extraction solvent water) on skin in children wearing napkins. These skin irritations were bullous and comparable with skin irritations caused by scalds (Sitzmann *et al.,* 1979).

The majority of children who experience constipation and whose caregivers seek medical care are seen by primary care physicians such as pediatricians or family physicians. Little is known about how

primary care physicians treat childhood constipation or the success of their treatments. With this study, Borowitz *et al.* prospectively examined 2005 which treatments primary care physicians prescribe to children who present for the first time with constipation and how effective those treatments are in a observational study. A total of 119 children who were between 2 and 7 years of age (mean: 44.1 +/- 13.6 months) and presented to 26 different primary care physicians (15 pediatricians and 11 family physicians) for the treatment of constipation for the first time participated in this study. Parents completed daily diaries of their child's bowel habits for 2 weeks before starting treatment recommended by their primary care physician and again 2 months after treatment. The prescribed treatment was identified by reviewing office records of the treating physicians. After 2 months of treatment, 44 (37 %) of 119 children remained constipated. In the majority (87 %) of cases, physicians prescribed some form of laxative or stool softener. The most commonly prescribed laxatives were magnesium hydroxide (77 %), senna syrup (23 %), mineral oil (8 %), and lactulose (8 %). In nearly all cases, a specific fixed dose of laxative was recommended; in only 5 % of cases were parents instructed clearly to adjust the dose of laxative up or down to get the desired effect. In approximately half of the cases, physicians recommended some sort of dietary intervention. Some form of behavioral intervention was mentioned in the office records of approximately one third of cases; however, in most cases, little detail was provided. In 45 % of cases, physicians prescribed disimpaction using oral cathartics, enemas, or suppositories followed by daily laxatives. In 35 % of cases, physicians prescribed daily laxatives without any disimpaction procedure. In the remainder, physicians prescribed only dietary changes (5 %), the use of intermittent laxatives (9 %), or no therapy (7 %). Treatment success corresponded to how aggressively the child was treated. Specifically, children who underwent some form of colonic evacuation followed by daily laxative therapy were more likely to have responded to treatment than were those who were treated less aggressively. Primary care physicians tend to undertreat childhood constipation. After 2 months of treatment, nearly 40 % of constipated children remain symptomatic.

A prospective study of 62 children was performed using a standard questionnaire (onset-age, regular toilet use, encopresis, complications, dietary habits and environmental and psychological factors) and physical and anthropometric assessment.Functional constipation (FC) was defined as a stool frequency of less than 3 bowel movements/week, with passage of large or scybalous stools, with or without 2 or more soiling episodes per week, without underlying disease. Treatment included demystification, behavioral modification and drugs (mineral oil and senna). Each child was periodically re-evaluated, and treatment was considered successful when the defecation rate was 3 or more bowel ovements/week, discomfort was absent, and fecal soiling frequency was 2 or fewer episodes/ month. FC accounted for 13 % of all first consultations (60 % boys, 40 % girls; mean age at diagnosis 6.1 years). The most frequent manifestations were painful defecation (60 %), rectorrhagia (42 %), obstructive episodes (34 %) and anal fissure or hemorrhoids (17 %); 19 patients (31 %) had encopresis. Nutritional assessment revealed that 84 % of the patients was well nourished and 16 % was overweight. Fiber intake was deficient in more than 60 %. Sixteen (26 %) patients underwent successful relief of impaction with senna (20-30 mg/dose; no more information on senna available) combined with mineral oil. Maintenance treatment included mineral oil (15-30 ml/day) and senna at the minimum effective dose (5-15 mg /day, no more information on senna available). Satisfactory results were achieved 1 month later in 32 % of the children, 3-6 months later in 71 %, and 6-12 months later in 85 %; successful response was closely related to regular toilet habits, dietary modification and a shift in the family's attitude (Martinez-Costa *et al.* 2005).

Many protocols of bowel preparation are available for use in children; however, none of them is commonly accepted. The aim of the study was to evaluate the efficacy and acceptability of high-volume polyethylene glycol (PEG) versus low-volume PEG combined with bisacodyl (BPEG) versus

sennosides for colonoscopy preparation in children. Participants ageed 10 to 18 years were randomly assigned to receive either PEG 60 or PEG 30 ml/kg/day plus oral bisacodyl 10 to 15 mg/day or sennosides 2 mg/kg/day for 2 days. A blinded assessment of bowel cleansing was made by the endoscopist according to the Aronchick and Ottawa scales. Patient acceptability was evaluated with the visual-analog scale. Analysis was done on an available case analysis basis. Of 240 patients enrolled in the study 234 patients were available for analysis of the efficacy of colon cleansing. There were no significant differences found among the 3 groups for the proportions of participants with excellent/good (PEG: 35/79, BPEG: 26/79, sennosides 25/76) and poor/inadequate (PEG: 20/79, BPEG: 28/79, sennosides 28/76) bowel preparation evaluated with the Aronchick scale and for the mean Ottawa total score (PEG: 5.47±3.63, BPEG: 6.22±3.3, sennosides: 6.18±3.53). Acceptability of bowel cleansing protocol was similar in all of the groups (P=0.8). All 3 cleansing methods showed similar efficacy and tolerability; however, none of them was satisfactory (Kierkus *et al.* 2013).

Safety and effectiveness of large-volume polyethylene glycol-based solution (PEG-ES) have been documented, but the taste and volume can be barriers to successful colonoscopy preparation. Efficacy and safety of small-volume electrolyte-free (PEG-P) preparation for colonoscopy preparation have been rarely studied, although presently used at many pediatric centers. The primary objective of the present study was to determine whether PEG-P results in a more efficacious and safe colonoscopy preparation as compared with senna. The study design was prospective, randomized, and single-blinded. Patients ages 6 to 21 years were randomized to a 2-day clean-out regimen of PEG-P at a dose of 1.5 g/kg divided twice per day for 2 days versus senna 15 ml daily (ages 6-12) (26,4 mg sennosides) or 30 ml daily (ages 12-21)(52,8 mg sennosides) for 2 days. Both preparations required 1 day of clear liquids whereas senna preparation required an additional day of full liquid diet. A blinded endoscopist graded the quality of preparation with a standardized cleanliness tool (Aronchick scale). Serum chemistry panels were obtained. Patients or parents rated symptoms and ease of preparation. The anticipated number of subjects was 166; however, the interim analysis demonstrated inferiority of senna preparation. Thirty patients were evaluated in the present study. Of the patients in the PEG-P arm, 88% (14/16) received an excellent/good score compared with 29% (4/14), with the senna preparation (P = 0.0022). Both preparations were well-tolerated by patient-graded ease of preparation. Demographics and laboratory values did not differ significantly across the 2 groups. No serious adverse events were noted. PEG-P is an effective colonoscopy preparation whereas senna preparation was insufficient. Both were well-tolerated and appear safe in a pediatric population (Terry *et al.* 2013).

The authors of the Cochrane review set out to evaluate the efficacy and safety of osmotic and stimulant laxatives used to treat functional childhood constipation. The search in 2012 was standardised and not limited by language and included electronic searching (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group Specialized Trials Register), reference searching of all included studies, personal contacts and drug companies. Randomised controlled trials (RCTs) which compared osmotic or stimulant laxatives with either placebo or another intervention, with patients aged 0 to 18 years old were considered for inclusion. The primary outcome was frequency of defecation. Secondary endpoints included faecal incontinence, disimpaction, need for additional therapies and adverse events. Relevant papers were identified and the authors independently assessed the eligibility of trials. Methodological quality was assessed using the Cochrane risk of bias tool.The Cochrane RevMan software was used for analyses. Patients with final missing outcomes were assumed to have relapsed. For continuous outcomes a mean difference (MD) and 95 % confidence interval (CI) was calculated using a fixed-effect model. For dichotomous outcomes an odds ratio (OR) and 95 % confidence intervals (95 % CI) was calculated using a fixed-effect model. The chi square and I(2) statistics were used to assess statistical heterogeneity. A random-effects model was used in situations of unexplained heterogeneity.

Eighteen RCTs (1643 patients) were included in the review. Nine studies were judged to be at high risk of bias due to lack of blinding, incomplete outcome data and selective reporting. Meta-analysis of two studies (101 patients) comparing polyethylene glycol (PEG) with placebo showed a significantly increased number of stools per week with PEG (MD 2.61 stools per week, 95 % CI 1.15 to 4.08). Common adverse events in the placebo-controlled studies included flatulence, abdominal pain, nausea, diarrhoea and headache. Meta-analysis of 4 studies with 338 participants comparing PEG with lactulose showed significantly greater stools per week with PEG (MD 0.95 stools per week, 95 % CI 0.46 to 1.44), although follow up was short. Patients who received PEG were significantly less likely to require additional laxative therapies. Eighteen per cent of PEG patients required additional therapies compared to 30 % of lactulose patients (OR 0.49, 95 % CI 0.27 to 0.89). No serious adverse events were reported with either agent. Common adverse events in these studies included diarrhoea, abdominal pain, nausea, vomiting and pruritis ani. Meta-analysis of 3 studies with 211 participants comparing PEG with milk of magnesia showed that the stools/wk was significantly greater with PEG (MD 0.69 stools per week, 95% CI 0.48 to 0.89). However, the magnitude of this difference is quite small and may not be clinically significant. One child was noted to be allergic to PEG, but there were no other serious adverse events reported. Meta-analysis of 2 studies with 287 patients comparing liquid paraffin (mineral oil) with lactulose revealed a relatively large statistically significant difference in the number of stools per week favouring paraffin (MD 4.94 stools per week, 95 % CI 4.28 to 5.61). No serious adverse events were reported. Adverse events included abdominal pain, distention and watery stools. No statistically significant differences in the number of stools per week were found between PEG and enemas (1 study, 90 patients, MD 1.00, 95% CI -1.58 to 3.58), dietary fibre mix and lactulose (1 study, 125 patients, P = 0.481), senna and lactulose (1 study, 21 patients, P>0.05), lactitol and lactulose (1 study, 51 patients, MD -0.80, 95% CI -2.63 to 1.03), and PEG and liquid paraffin (1 study, 158 patients, MD 0.70, 95 % CI -0.38 to 1.78). The pooled analyses suggest that PEG preparations may be superior to placebo, lactulose and milk of magnesia for childhood constipation. GRADE analyses indicated that the overall quality of the evidence for the primary outcome (number of stools per week) was low or very low due to sparse data, inconsistency (heterogeneity), and high risk of bias in the studies in the pooled analyses. Thus, the results of the pooled analyses should be interpreted with caution because of quality and methodological concerns, as well as clinical heterogeneity, and short follow up. However, PEG appears safe and well tolerated. There is also evidence suggesting the efficacy of liquid paraffin (mineral oil), which was also well tolerated.There is no evidence to demonstrate the superiority of lactulose when compared to the other agents studied, although there is a lack of placebo controlled studies. Further research is needed to investigate the long-term use of PEG for childhood constipation, as well as the role of liquid paraffin (Gordon *et al.* 2013).

Conclusion on clinical studies in special populations

The data available are not sufficient to show the efficacy and safety of senna leaves or pods to treat constipated children, if change of nutrition and increase of daily fibre intake is not effective. The Cochrane (Gordon *et al.* 2013) review showed the vast amount of data regarding the use of osmotic laxatives whereas the data on senna containing stimulants are marginal. They do not provide strong evidence supporting a recommendation for bowel cleansing for colonoscopy in children.

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no recent clinical studies available, which evaluate senna leaves or fruits alone and not in combination with other laxatives in a representative study population in the indication constipation.

The postulated laxative effect is mainly based on the pharmacological data, experts' opinions and clinical experiences. The results of the studies mentioned above show a clear laxative effect additionally to fibre intake.

The study of Hübner and Moser (2002) cannot prove the efficacy of senna leaves in irritable bowel syndrome. The study treatment was a combination product and the differences between the groups concerning the primary efficacy parameter were not statistically significant. Based on the results of this study, it is not possible to recommend the specific indication "irritable bowel syndrome".

Adequate bowel cleansing before a colonoscopic procedure is necessary in order not to miss small colonic lesions, leading to a proper diagnosis (Froehlich *et al.* 2005). Sodium phosphate (NaP)-based precolonoscopic preparation regimes were determined to have at least similar effectiveness in bowel cleansing as polyethylene glycol electrolyte lavage (PEG-EL)-based regimes, and they also have better patient tolerance than that observed with PEG-EL (Thomson *et al.,* 1996). PEG-EL has minimum side effects, while, in contrast, NaP-based regimes can be dangerous for patients with chronic systemic illness (Liebermann *et al.,* 1996). On the other hand, inadequate bowel cleansing of patients is not infrequent under PEG-based regimes, probably because of its huge volume and unpleasant taste. For this reason, reducing the amount of PEG-EL, splitting the whole dose, and adding medications (such as prokinetics or laxatives) have been investigated by researchers in recent years.

PEG-EL, which is the goldstandard agent for precolonoscopic bowel preparation, has an important problem to be overcome: its large volume. In accordance with the literature, only 70 % of patients were able to finish the whole PEG-EL solution before the colonoscopic procedure. For this reason, investigators have worked on how to reduce the PEG-EL solution volume in recent years (Altinbas *et al.* 2015).

The indication for preexaminative bowel cleansing and the method of administration (3 days of clear soups or fluids, 150 mg HAD ± enema is especially supported by the trial of Krakamp *et al.* (1996).

There are 6 different clinical trials in the indication of bowel cleansing with additional supply of 2 l fluid (saline or not) ± enema. Three of them have been performed done with a dry extract (1.26 – 1.85 g dry extract from senna fructus acutifoliae standardised to 150 mg hydroxyanthracene derivatives calculated as sennoside B. DER 3-5:1 extraction solvent water) covering 150 mg hydroxyanthracene derivatives (Ziegenhagen *et al.,* 1991; Schanz *et al.* 2008; Bokemeyer *et al.* 2000*)*, with 120 mg hydroxyanthracene derivatives as calcium sennosides (Hookey *et al.* 2006), three further trials are done with Pursennid (1 tablet: corr. to 12 mg sennaglycosides as calciumsalts from a concentrated extract of senna leaves (extraction solvent: methanol 66 % (V/V)) receiving 144 mg hydroxyanthracene derivatives (Amato *et al.* 2010*;* Arezzo *et al.* 2000) and taking 288 mg hydroxyanthracene derivatives (Amato *et al.* 2010; Radaelli *et al.* 2005), which was less tolerable.

In the trial from Radaelli *et al.* (2005) 90.6 percent of the patients taking 144 mg hydroxyanthracene derivatives as calcium sennosides were excellently or well prepared.

All of these patients had to drink additionally 2 l of Golytely, PEG-ELS, Magnesium sulphate or clear liquid. Therefore, also the following indication for a single usage of higher dosages supported:

"Herbal medicinal product for bowel cleansing prior to clinical procedures requiring bowel preparation".

Because of the unique therapeutic approach with a single dose and the very rare application to an individuum, the higher amount of exposure to hydroxyanthracene derivatives can be accepted for a single application.

Regarding the database of 430 patients from the different studies the recommended single dose is: 150 mg HAD (Ziegenhagen *et al.,* 1991; Bokemeyer *et al.* 2000; Hookey *et al.* 2006; Amato *et al.* 2010*;* Arezzo *et al*. 2000). Basically 30 % of the patients are not able to complete the bowel cleansing with 4 l of cleansing fluid. The preparation with senna preparations is slightly inferior but better tolerable. Actually the additional indication is especially to be considered for therapy of elderly patients with heart insufficiency, patients suffering from renal insufficiency, as far as they are restricted in fluid uptake, patients with a migraine and those who are not able to drink 4 l of fluid in the recommended time.

The potential indications of postoperative or opioid-induced constipation including palliative care are not uptaken into the monographs due to too heterogenous indications and study conditions in different patientgroups with immanent high drop out rates within the palliative care patients.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

Bowel cleansing

The following table of tolerability is exemplarily showing the differences in tolerability (senna n=190; PEG-ES n=191) in bowel cleansing trials:

Radaelli *et al.* (2005): Tolerability of procedure

	Mean Score (±SD)	Easy	Bothersome	Distressing	Severely distressing
Senna	1.66 ±0.74	91 (47.9)	77 (40.5)	18 (9.5)	4 (2.1)
PEG-ES	2.13 ±0.82 (p<0.001)	44 (23.0)	87 (45.6)	51 (26.7)	9 (4.7)

Colorectal cancer

Satia *et al*. (2009) evaluated whether education, physical activity, smoking status, BMI, fruit and vegetable consumption, use of nonfiber laxatives (never/<1 per year, 1-4 times per year, 5-11 times per year, 1-3 times per month, ≥1 time per week), NSAID use, sigmoidoscopy use in the past 10 years (yes, no), current multivitamin use, previous history of cancer, and first-degree family history of colorectal cancer (yes, no) were confounders of the herbal/specialty supplement-colorectal cancer associations in models already adjusted for age and gender. Colorectal cancer patients used non-fiber laxatives more frequently (14% vs. 9% at 1-4 times per year) than controls. There was no further specification of substances. The final model for all the herbal and specialty supplements included age, gender, education, physical activity, BMI, fruit and vegetable consumption, NSAID use, and sigmoidoscopy. Glucosamine, chondroitin, and methylsulfonylmethane (MSM) were further adjusted for history of arthritis.

Dukas *et al*. (2000) prospectively examined the association between bowel movement frequency, laxative use, and the risk of colorectal cancer in 84,577 women of the Nurses' Health Study living in the United States, 36-61 years of age and free of cancer in 1982. Between 1984 and 1996, 611 incident cases of colorectal cancer were documented. After controlling for age, body mass index, fiber intake, postmenopausal status and hormone use, physical activity, and use of laxatives, the relative risks associated with having bowel movements every third day or less, compared with those with

bowel movements once daily, were 0.94 (95 % confidence interval (CI): 0.69, 1.28) for colorectal cancer, 0.88 (95 % CI: 0.62, 1.26) for colon cancer, and 1.18 (95 % CI: 0.63, 2.20) for rectal cancer. Compared with women who never used laxatives, the multivariate relative risks associated with weekly to daily laxative use were 1.00 (95 % CI: 0.72, 1.40) for colorectal cancer, 1.09 (95 % CI: 0.76, 1.57) for colon cancer, and 0.68 (95 % CI: 0.29, 1.57) for rectal cancer. These findings do not support an association between infrequent bowel movement, laxative use, and risk of colorectal cancer and indicate that simple questions directed at bowel movement frequency are unlikely to enhance our ability to predict colorectal cancer risk.

Urothelial cancer

Bronder *et al*. reported 1999 on 766 cases of urothelial cancers (98 % confirmed by histology) in Berlin, Germany, between 1990 and 1994. A control group (1:1) was obtained by sampling, from the West Berlin Population Registry, persons of German nationality who had lived in Germany for at least 20 years and matched with the patients for sex and age. Through a standardized questionnaire completed by 648 patients and 647 controls, social class was recorded as well as consumption of analgesics, laxatives and tobacco. After adjustment for tobacco use and social class, the risk of urothelial carcinoma was increased in laxative users. Use of contact laxatives was reported by 63 urothelial cancer patients versus 29 controls (odds ratio, 2.5; 95 % CI, 1.5–4.2) and 13 renal pelvis and ureter cancer patients versus two controls (odds ratio, 9.3; 95 % CI, 1.1–83.3). For different laxatives, the corresponding figures (urothelial cancer patients versus controls) were: chemical and anthranoid laxatives, five versus two (odds ratio, 2.7; 95 % CI, 0.47–16); anthranoid laxatives alone, 37 versus 20 (odds ratio, 2.0; 95 % CI, 1.1–3.7); aloe, 16 versus 11 (odds ratio, 1.6; 95 % CI, 0.66–3.7); senna, 26 versus 13 (odds ratio, 2.4; 95 % CI, 1.1–5.0); and rhubarb, eight versus four (odds ratio, 2.6; 95 % CI, 0.68–9.6). The Working Group noted that no results for laxatives adjusted for use of analgesics were presented.

Table 12: Clinical safety data from clinical trials

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
Pharmacological studies						
Ewe *et al.* (1993)	prospective	-Loperamid to double transit time (A) -purified sennosides 20 mg (B) -a fibre product containing 20 g Plantago ovata seeds/husks 30 g (C) - a combination of 5.4 g Plantago ovata seeds/husks + 1.2 g senna pod with a sennoside content of 30 mg (D)	24 volunteers	healthy	none	Loperamide prolonged colonic transit from 27 +/- 0.7 to 72 +/- 12 h. This effect was abolished by (B) (30 +/- 5 h) and (D)(27 +/- 1 h) ($p<0.005$), but not by (C) (64 +/- 13 h). Colonic transit was reduced by (B) and by (D) from 39 +/- 4 h to 17 +/- 3 h ($p<0.005$).
Buhmann *et al.* (2005a)	prospective	180 ml warm Senna tea (1.7 g Sennes leaves = 30 mg Hydroxyanthra-cene glycoside	15 volunteers	healthy	None	The use of functional cine MRI utilizing a prokinetic stimulus allowed visualisation and quantification of large bowel motility.
Emeriau *et al.* (1983)	observational	Sennosides 20 mg daily	14 elderly	constipation	none	Long-term laxative treatments do not necessarily induce significant intestinal protein and potassium losses.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
Constipation						
Pers *et al.* (1983)	Prospective randomized	-2.6 g Semen plantaginis ovata, 0.11 g Ispaghula husk and 0.62 g Sennae fructus angustifolie equivalent to 15 mg glycoside A+B per sachet of 5 g") -("3.3 g Testa ispaghula 'Tika' and 25 mg glycoside sennae A+B per sachet"). 1 week prior 2 weeks Prep A 2 weeks Prep B	20; 1 drop out	severe constipation	No AEs	Due to small number of patients only limited information.
Marlett *et al*. (1987)	Controlled, Randomised, single-blind	ispaghula husk (Metamucil ® 7.2 g/day) n=20 psyllium plus senna (6.5 g + 1.5 g/day) for 1 week n=22	42 adults	Constipation	11/22 psyllium plus senna; cramps; bloating; nausea	The adverse reactions observed are reflecting the known spectrum of adverse events.
Passmore *et al*. (1993)	randomised, double-blind, crossover study	ispaghula 54.2 %, senna 12.4 % (m/m)) and lactulose senna-fibre combination 10 ml daily with lactulose -- active senna-fibre combination 10 ml daily with lactulose placebo 15 ml twice daily	77 elderly patients (average age: 82.9 years)	history of chronic constipation	cramps, urgency,flatulence, Nausea, bloated headache; no difference between groups	The adverse reactions observed are reflecting the known spectrum of adverse events.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
		active lactulose 15 ml twice daily with senna-fibre placebo 10 ml daily for two 14 day periods. - maximum daily dose for active or placebo senna-fibre was 20 ml (10 ml twice daily) and for lactulose or lactulose placebo 60 ml.				
Kinnunen *et al.* (1993)	open, randomised and controlled crossover study In period I, 21 patients received sennes combination and 9 patients lactulose; in period II, 7 patients received senna combination and 18	- Plantago ovata seed 521.6 mg (bulk forming), Fructus cassiae angustifoliae 138 mg (stimulant) -Levolac 30 ml lactulose	30 long stay elderly patients aged 65 – 94 years (mean 81.8 years) 65 – 94 years (mean 81.8 years)	chronic constipation	No AEs	No AEs; seems to be a problem of definition

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
	patients lactulose.					
Irritable Bowel Syndrome						
Hübner and Moser (2002)	12-week double blind, controlled, randomised, multicentre and prospective clinical trial	CL+ (containing as active ingredients "180 mg Carbo ligni", i.e. vegetable, non-activated charcoal, "105 mg Fol. Sennae, 25 mg rhubarb extract" 2.65 – 3.95 mg anthraquinone per tablet)(n=145) to Carbo ligni (CL) containing tablets (n=139). Adaptation from one to eight tablets per day	284 patients between 19 and 70 years	irritable bowel syndrome (IBS) Rome criteria for IBS	50 AEs CL+ 42 Carbo ligni; as in IBS	The adverse reactions observed are reflecting the known spectrum of adverse events.
Bowel cleansing 150 – 300 mg HAD without enema						
Ziegenhagen *et al.* (1991)	Prospective randomized investigator blinded	The day before endoscopy either extractum sennae (n = 60) or a placebo solution (n = 60) was given.	120 outpatients, all patients underwent whole gut irrigation with a polyethylene glycol electrolyte lavage solution (PEG-	referred for colonoscopy	Patient tolerance was similar in both groups with 86.7 % vs. 83.3 % of subjects rating the preparation as tolerable. Severe adverse events were not observed.	The adverse reactions observed are reflecting the known spectrum of adverse events.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
			ELS)			
Frigerio *et al.* (1996)	randomised, single-blind study	-1 dose of senna fruit dry extract preparation corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B, per single dose) for colon cleansing (n=250). -two doses, one at mid-day and one on the evening prior to the examination, equivalent to 300 mg sennosides (n=223)	473 patients (225 males and 248 females with a mean age of 59.7 years, range 14 – 96 years) liquids orally according to need, no enema	referred for colonoscopy	150/300 mg HAD abdominal pain 19/17 nausea 2/5 fainting 3/1 headache 0/1	The adverse reactions observed are reflecting the known spectrum of adverse events.
Schanz *et al.* (2008)	Randomised, multicenter, observer-blinded	-sodium phosphate solution n=128 (A) - sodium phosphate solution and a senna fruit dry extract preparation corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B, per single dose) n=133 (B) - PEG-ELS and senna preparation n=94 (C)	355 consecutive out-patients (18 and 75 years). Drinking volumes (L) (A = 4.33+1.2, B = 4.56+1.18, C = 4.93+1.71) were different (p=0.005)	referred to colonoscopy	Discomfort of fluid 39.8 % A; 46.6 % B 54.5 % C Tolerability A: good 72 %, moderate 21.6 % bad 6.4 % B: 72.2 % good, mod: 20.3 % bad 7.5 % C: good:83.7 % mod: 10.9 %, bad 5.4 %	The adverse reactions observed are reflecting the known spectrum of adverse events.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
Kositchaiwat *et al.* (2006)	Prospective randomized single blinded	-180 mg senna tablet -95 ml sodium phosphate solution on the day before colonoscopy	134	referred for elective colonoscopy	4 AEs ; senna 1sigmoid perforation, 1 polypectomy bleeding	The mentioned AEs are the usual risks of colonoscopy, they are not to be associated with the application of senna
Valverde *et al.* (1999)	prospective, randomised, observer-blind, parallel, multicentre study	- sennosides A + B 120 mg or 240 mg in obese patients, senna preparation evening before surgery n=262 - polyethylene glycol (PEG) (2 packages diluted in 2 – 3 l of water, ColoPeg®) n=261	523 patients 5% povidone iodine antiseptic enemas (2 l) the evening and the morning before surgery	colonic or rectal carcinoma or sigmoid diverticular disease undergoing elective colonic or rectal resection followed by immediate anastomosis	Sennoside group 262 Complete tolerance 206; vomiting 12; abd.pain 35; distension 8	The adverse reactions observed are reflecting the known spectrum of adverse events. The higher incidence correlates to the daily doses.
Bowel cleansing 150 mg HAD with enema						
Hanggartner *et al.* (1989)	prospective randomized	- 4 liters of Golytely; n=100 - 2 liters of Golytely combined with Cascara-Salax n=102 - 1,26 - 1,85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthra-cene glycosides, calculated as sennoside B; DER 3-5:1, extraction solvent water	300 patients Exclusion of prior colonic surgery	referred for colonoscopy	Vomiting 6/98 Nausea 39/98 Abd.cramps 62/98 Hunger 57/98 Vertigo 22/98 Sleeplessness 30/98	The adverse reactions observed are reflecting the known spectrum of adverse events.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
		for colon cleansing combined with an enema, n=98				
Krakamp *et al.* (1996)	randomised simple-blind study	-Golytely-recepture 3l; 3 h n=50 -PEG-ELS, 4l; 4h; n=50 - Senna preparation 150mg HAD n=50	150 out-patients Group 3 three days eating restrictions; 1 day clear fluids 1 enema 1 h before procedure. 57 +/- 19 years in group 1, 55 +/- 15 years in group 2 and 57 +/- 17 years in group 3	referred for colonoscopy	Cramps abdominal fullness no frequency	The adverse reactions observed are reflecting the known spectrum of adverse events.
Bokemeyer *et al.* (2000)	open prospective study	-Golytely, 2 l on the day before colonoscopy and 2 l on the day of colonoscopy p.o. n=41 - Golytely-RSS, 3 l on the day of colonoscopy p.o.) n=40 - Phospho-Soda (45 ml on the day before and 45 ml on the day of colonoscopy p.o.) n=44	300 outpatient	Referred for colonoscopy	1-6; tolerability around 2 for all groups	The adverse reactions observed are reflecting the known spectrum of adverse events.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
		- a senna fruit dry extract preparation corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B, per single dose, and an enema and 2 l Golytely on the day before colonoscopy p.o. and an enema in the morning before colonoscopy) n=40				
Calcium sennosides 120 - 300 mg HAD						
Arezzo (2000)	randomised observer-blind, parallel study	- senna compound (group 1; 12 tablets each containing 12 mg sennosides A+B at 10 a.m. and magnesium sulfate 15 g at 5 p.m. on the day before colonoscopy p.o. n=100 - PEG lavage (group 2; 4 l at 4 p.m. on the day before colonoscopy p.o. n=100 - an oral sodium phosphate solution (group 3; 40 ml at 6 p.m. on the day before and 40 ml at 6 a.m. on the day of colonoscopy n=100	300 patients	Referred for colonoscopy	Senna tolerability Good 87; medium 10; scarce 3	The adverse reactions observed are reflecting the known spectrum of adverse events.
Tasci *et al*.	prospective	sennoside calcium (300 ml of a	953; 1021	referred to	No information	As no information on

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
(2003)	randomised trial	1 mg/ml solution given 2 days prior to colonoscopy), -PEG lavage (3 l given 1 day prior to colonoscopy), -oral sodium phosphate solution in one 90 ml-dose 1 day prior to colonoscopy, -oral sodium phosphate solution in 2 doses (90 ml 1 day prior to colonoscopy + 45 ml 5 h prior to colonoscopy), -oral sodium phosphate solution in 2 doses (45 ml + 90 ml), -oral sodium phosphate solution in 2 doses (45 ml + 90 ml) plus 10 mg cisapride, -oral sodium phosphate solution in 2 doses (45 ml + 90 ml) plus 10 ml domperidone.	patients enrolled, 68 were excluded from analysis because of intolerance to the solutions or medicinal products, improper use of the regimen, electrolyte imbalance, cardiac disorders or vomiting. -clear liquid diet one day before starting the bowel cleansing regimen - Sodium phosphate enema was applied to the patients on	colonoscopy		adverse reaction, study allows no further conclusion

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
			the morning of colonoscopy.			
Radaelli *et al.* (2005)	prospective randomized single blinded	-oral high dose of senna 24 tablets of senna (12 mg extract of sennoside A and B divided into two doses at 1 p.m. and 9 p.m. (n=191), -conventional polyethylene glycol-electrolyte lavage solution (PEG-ES) (n=92)	283 patients	referred for elective colonoscopy	Senna Nausea 54/190 vomiting13/190 Abd. Pain 141/190 Headache 27/190 Dizziness 37/190 Tolerability see before the table	The adverse reactions observed are reflecting the known spectrum of adverse events.
Amato *et al.* (2010)	Randomized investigator-blinded	- 12 tablets of 12 mg senna and 2 l of PEG-ES (half-dose group, HDG) n=151 -24 tablets of senna divided in two doses (senna group, SG) the day before colonoscopy.n=145	296	referred for elective colonoscopy	Nausea 31/151 Vomiting15/151 Abd. Pain 60/151 Headache 33/151 Dizziness 25/151 Nausea 41/145 Vomiting13/145 Abd. Pain 66/145	The adverse reactions observed are reflecting the known spectrum of adverse events.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
					Headache 30/145 Dizziness 18/145	
Kelly *et al.* (2012)	prospective	-low-volume polyethylene glycol (2-L Moviprep; Norgine Pharmaceuticals) n=86 -standard volume polyethylene glycol (4-L) n=91 -magnesium citrate plus stimulant laxative n=81	258 (female,138; 53.5%)	referred for elective colonoscopy	AEs (mean) 1.65 Senna citramag 1,94 Klean Prep 1,89 Moviprep	The adverse reactions observed are reflecting the known spectrum of adverse events.
Manukyan *et al.* (2011)	prospective	-Sodium phosphate n=53 -Sennoside A+B n=46	99	referred for elective colonoscopy	Nausea 26% Vomiting 6% Abd. Pain 52% Headache 14%	The adverse reactions observed are reflecting the known spectrum of adverse events.
Ergül *et al.* (2014)	randomized controlled, single blinded	- sennoside tablet 80 mg daily for 3 days;senna solution 150 ml (300 mg senna) the night before colonoscopy n=65 (1) - to chew sugarless gum half an hour three-times daily after meals for these 3 days sennoside tablet 80 mg daily for 3 days;senna solution 150 ml (300 mg senna) the night	129	scheduled for elective colonoscopy	Nausea 7.7 % 3.2 % Vomiting 1.5 % 1.6 % Abd. Pain 9.2 % 4.7 % Fatigue 1.5 % - Dizziness 4.6 %	The adverse reactions observed are reflecting the known spectrum of adverse events.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
		before colonoscopy n=64 (2)			1.6 %	
Altinbas *et al.* (2015)	Retrospective single blinded	- sennoside a + b calcium 500 mg/250 ml n=91 4 L of PEG-EL n=94	185 patients; 53.4 ± 13.4 years (53.7 ±15.0 in Group 1, 52.42 ± 11.8 in Group 2, P = 0.255), and 89.3% and 95.8% of the patients in the groups were male, respectively (P = 0.545).	elective colonoscopy	No statistical differences Nausea 1-2 % Abdominal cramps 9-14 %	Single administration without specific AE
Taylor *et al.* (2008)	Controlled randomised	reduced-laxative (13 g sachet of senna granules HAD/18 g magnesium citrate) CTC prior to CT colonography tagging regimens: -20 ml 40%w/v barium sulphate: regimen A: four doses,	95 patients (50 female, mean age 64 years, range 50–85 years) two days of low residue diet	scheduled to undergo afternoon diagnostic colonoscopy for symptoms suggestive of colorectal neoplasia	Red prep: Nausea Vomiting 29% Dizziness 29% Abd. Pain 55% Soreness 49%	Single administration without specific AE,

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
		-B: three doses, -C: three doses plus 220 ml 2.1% barium sulphate, or -D: three doses plus 15 ml diatriazoate megluamine				
Hookey *et al.* (2006)	Prospective randomized investigator-blinded	- 120 mg oral sennosides syrup followed by 2 L PEG -4 L PEG	171 patients a clear fluid diet the day before colonoscopy	referred for elective colonoscopy	no significant differences in symptom scores for nausea, vomiting, chest or abdominal pain, dizziness or bloating.	The adverse reactions observed are reflecting the known spectrum of adverse events.
< 80 mg HAD						
Iida *et al.* (1992)	uncontrolled	-drink 2 l of Golytely on the day of examination by taking 36 mg of sennosides (no further information of the formulation) orally in the evening before colonoscopy.	297 examinees (219 male and 78 female; mean age 57 years)	referred for colonoscopy	Nausea 10%; abdominal fullness 24%; 54 no symptoms	The adverse reactions observed are reflecting the known spectrum of adverse events.
Haapamäki *et al.* (2011)	single-center, prospective randomized investigator-blinded study	-2 l PEG combined with 36 mg senna glycosides in tablets -4 l PEG for bowel preparation	490	referred for elective colonoscopy	No information	As no information on adverse reactions, study allows no further conclusion.
Kashyap *et*	prospective,	-4 Senna tablets,	25 volunteers	Healthy; colon	no serious AEs,	Single administration

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
al. (2015)	single-center, single-arm	-4 liters of PEG (split dose), -10 mg metoclopramide, -2 oral sulfate solution boosters (6 oz. and 3 oz.), and -10 mg bisacodyl.		capsule endoscopy (CCE)	three moderate AEs related to the bowel preparation (nausea, headache, elevated creatinine) and two mild unrelated AEs (chills, abdominal cramping	without specific AE,
Poyrazoglu and Yalniz (2015)	Prospective randomised single-blinded	-90 ml of oral NaP (NaP group) n=66 -500 ml of 1,000 mg of sennosides A and B calcium +66.6 g of sorbitol (sennagroup) N=62	137 consecutive patients; 5 NaP; 4 senna excluded	Referred for colonoscopy	Nausea and vomiting less in sennagroup p=0,05; no differences in abdominal pain; dizziness; headache	Single administration with the usual AEs; less nausea and vomiting in Senna group.
Vradelis *et al.* (2009)	prospective	-magnesium citrate 2 sachets á 11.6 g magnesium carbonate and 17.8 g anhydrous citric acid n=160 - 2 sachets á 11.6 g magnesium carbonate and 17.8 g anhydrous citric acid 1 sachet senna granules no	345 consecutive adult out patients low-fiber diet for 2 days; clear fluids 1 day	referred to the endoscopy	Nausea vomiting bloating and headache Abdominal cramps were less in the citramag group	The adverse reactions observed are reflecting the known spectrum of adverse events.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
		further information n=182				
Postoperative constipation						
Patel *et al.* (2010)	Prospective randomized	- placebo n=45 - senna 8,6 mg with docusate 50 mg n= 48	96 patients after pelvic reconstructive surgery	after pelvic reconstructive surgery	Cramping bloating 6/39	The adverse reactions observed are reflecting the known spectrum of adverse events.
Postoperative opioid-induced constipation						
Marciniak *et al.* (2014)	double blind, randomized, active comparator trial randomisation : 1:1 ratio in blocks of 4	-lubiprostone , orally twice a day 24 µg - senna (generic) two capsules administered daily for six days.	64 adults 56 participants (28 in each group) had baseline and follow up measures and were included in the intention to treat (ITT) analyses. 43 participants completed the study, 21 in the active	postoperative opioid-induced constipation	Nausea 0.46 ??? Cramping 0.11 ??? Straining 0.75 ??? Abd. Pain 0.04 ??? No differences	The adverse reactions observed are reflecting the known spectrum of adverse events.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
Chemotherapy-induced constipation						
Tao *et al.* (2012)		-senna extract in the 1st chemotherapeutic course and the crude fiber diet in the 2nd chemotherapeutic course. -vice versa	82 patients	constipation after chemotherapy	Abd. Pain 8.54 % No differences between groups	The adverse reactions observed are reflecting the known spectrum of adverse events.
Constipation in people receiving palliative care						
Ramesh *et al.* (1998)	Controlled open	-purified senna extract 60 mg containing 12 mg senna glucosides as calcium salts(2 tabs at night;4 tabs at night;2 tabs in the morning + 4 tabs at night every 2 days n=25; step1: 2 tabl. night; step2:4 tab. At night; step 3: 2 tab. morning; 4 tab. night -a liquid Ayurvedic (herbal) preparation (Misrakasneham; 21 herbs) n=25 Increasing in 3 steps; 2,5 ml; 5 ml; 10 ml	50 patients (30-70years), 9 dropouts (senna: 4 irreg. admin; 2 lost follow-up; 2 morphine withdrawal; 1 bowel movement spontaneous) 5 drop outs (Misrakasneham: 2†; 2 lost follow-up; 1 irregular administration	management of opioid-induced constipation in advanced cancer	No nausea and vomiting in Senna group	The adverse reactions observed are reflecting the known spectrum of adverse events.

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
			)			
Agra *et al.* (1998)	randomised, open, parallel –group trial	-senna derivatives 0.4 ml (12 mg) for senna (no other information of the formulation are given) intake in two doses;every 3 days; maximum doses were 1.6 ml (48 mg)n=43 -lactulose15 ml (10 g) every 3 days; maximum doses 60 ml (40 g) n=48	91 terminal cancer patients 16 patients dropped out during the first 4 days 37 patients were lost: 21 in the senna group and 16 in the lactulose group.3 vomiting;5 refusals; 17 deaths; 12 hospitalised	terminal cancer	first 7 days, 6 patients (3 treated with senna and 3 treated with lactulose) presented adverse effects (diarrhoea, vomiting, and cramps)	The adverse reactions observed are reflecting the known spectrum of adverse events.
Urothelial cancer						
Bronder *et al.* (1999)	retrospective case-control study	Aanalgesics and laxatives as risks for the induction of urothelial cancer in renal pelvis, ureter and bladder Phenacetin, Paracetamol,	-766 cases of urothelial cancers (98% confirmed by histology)	standardized questionnaire 648 patients and 647 controls social class was recorded	Use of contact laxatives was reported by 63 urothelial cancer patients versus 29	Further studies are needed; no results for laxatives adjusted for use of analgesics

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
		Acetylsalicylic acid (ASA) and Pyrazolones	-control group (1:1) was obtained by sampling, from the West Berlin Population Registry, persons of German nationality who had lived in Germany for at least 20 years and matched with the patients for sex and age	as well as consumption of analgesics, laxatives and tobacco	controls (odds ratio, 2.5; 95% CI, 1.5–4.2) and 13 renal pelvis and ureter cancer patients versus two controls (odds ratio, 9.3; 95% CI, 1.1–83.3). For different laxatives, the corresponding figures (urothelial cancer patients versus controls) were: chemical and anthranoid laxatives, five versus two (odds ratio, 2.7; 95% CI, 0.47–16); anthranoid laxatives alone, 37 versus 20 (odds ratio, 2.0; 95% CI, 1.1–3.7); aloe, 16 versus 11 (odds ratio, 1.6; 95% CI, 0.66–3.7); senna, 26 versus 13 (odds ratio, 2.4; 95% CI, 1.1–5.0);	

Reference	Study	Test Product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
					and rhubarb, eight versus four (odds ratio, 2.6; 95% CI, 0.68–9.6)	

Children

No data are available on the safety of senna use in children <6 years of age, to describe the clinical outcomes of exposure to unintentional ingestion of senna-containing laxatives in young children. All ingestion exposures of senna-containing laxatives in children <5 years of age from 6 poison centers over a 9-month period were evaluated. Inclusion criteria required 24-hour follow-up and the presence of diarrhea to confirm ingestion. Parents were told routinely that severe diaper rash was possible and to protect the perianal area with frequent cleansing and a barrier ointment if the child was wearing diapers. During the study period, 111 cases were reported: 19 children experienced no diarrhea, 4 were lost to follow-up, and 88 exposures were evaluated. Fifty-two children (59 %) were </=2 years old. Fifty children remained in diapers, 28 children were fully toilet trained, and 10 wore diapers (pull-up pants) overnight. Twenty-nine children (33 %) experienced severe diaper rash. The mean +/- SD time to recognition of the diaper rash was 15.6 +/- 8.6 hours. Ten children (11 %) had blisters and skin sloughing. There was a significant increase in severe diaper rash ($p < 0.05$) and onset of blisters and skin breakdown ($p < 0.05$) in children wearing diapers versus those who were fully toilet trained. The mean time to onset of blisters was 14.5 +/- 6.8 hours. Skin burns and loss were seen primarily on the buttocks and perineum, loosely following the diaper area. Unintentional ingestion of senna-containing laxatives in young children may potentially cause severe diaper rash, blisters, and skin sloughing (Spiller *et al.* 2003).

5.2. Patient exposure

The IARC Monograph of WHO Vol 82 describes the naturally occurring glycoside derivatives of 1,8-dihydroxyanthraquinone are the pharmacologically active constituents of a herbal purgative (laxative) preparation, senna, which is obtained from the dried leaflets or seed pods of the subtropical shrubs, Cassia (Senna) acutifolia and Cassia (Senna) angustifolia (Brunton, 1996). Aside from its market presence and the data from clinical studies in humans (3939 patients treated with different posologies from 30 mg HAD to 300 mg HAD from the studies mentioned in this assessment report) the mostly mentioned adverse events are headache, nausea, vomiting, abdominal cramps, fatigue and dizziness, to be estimated in the category of very common >1/10) to common (>1/100 to<1/10).

Siegers *et al*. (1993 b) reported about a retrospective study of 3,049 patients, who underwent diagnostic colorectal endoscopy. The incidence of pseudomelanosis coli, which is regarded as a reliable indicator of chronic anthranoid laxative abuse (use for more than nine to 12 months), was 3.13 % in patients without pathological changes. In those with colorectal adenomas, the incidence increased to 8.64 % ($p<0.01$), and in those with colorectal carcinomas it was 3.29 %. This lower rate was probably caused by incomplete documentation of pseudomelanosis coli in those with carcinoma. In a prospective study of 1,095 patients, the incidence of pseudomelanosis coli was 6.9 % for patients with no abnormality seen on endoscopy, 9.8 % ($p=0.068$) for patients with adenomas and 18.6 % for patients with colorectal carcinomas. From these data a relative risk of 3.04 (1.18, 4.9; 95 % confidence interval) can be calculated for colorectal cancer as a result of chronic anthranoid laxative abuse.

Kune *et al*. (1988) and Kune (1993) reported about the "Melbourne Colorectal Cancer Study". Commercial laxative use as a risk factor in colorectal cancer was investigated as one part of this large population based epidemiological study of colorectal incidence, aetiology and survival. Commercial laxative use was similar in 685 colorectal cancer patients and 723 age/sex matched community based controls. Also, when laxatives were subdivided into various groups containing anthraquinones, phenolphthalein, mineral salts and others, previous laxative intake was similar between cases and controls. Previous use of anthraquinone laxatives and of phenolphthalein containing laxatives was not associated with the risk of colorectal cancer. Furthermore the results of this study suggest that chronic

constipation, diarrhoea, and the frequency and consistency of bowel motions are unlikely to be etiologic factors in the development of colorectal cancer. They indicate that it is the diet and not the constipation that is associated with the risk of large-bowel cancer. Additionally, a highly statistically significant association (p=0.02) with the risk of colorectal cancer was found in those who reported constipation and also had a high fat intake.

In a retrospective study a cohort of 2,277 patients was defined by colonoscopy. Among other factors Nusko *et al*. (1993) tested whether in these patients laxative use or the endoscopically diagnosed presence of melanosis coli were risk factors related to colorectal neoplasm. In comparison to patients taking no laxatives, there was no significant increase in colorectal cancer rate either in laxatives users or in patients with melanosis coli. However, there was a statistically significant association between the occurrence of colorectal adenomas and laxative use (relative risk of all patients exposed to laxatives = 1.72; of patients exposed to laxatives without melanosis coli = 1.47). The relative risk of adenoma development in patients with melanosis coli was 2.19. Taking into account that polyps can be diagnosed in the dark mucosa of melanosis coli patients more easily, the authors concluded that even this relative risk of 2.19 seems to be related to a generally enhanced risk of laxative intake rather than to a special group of (anthranoid-containing) laxatives.

Jacobs and White examined 1998 the associations of colon cancer with constipation and use of commercial laxatives in a case control study among men and women aged 30 – 62 years (424 incident cases and 414 random-digital-dial controls). Constipation was defined by "feeling constipated to the point of having to take something". The adjusted relative risk (RR) was 2.0 [95 % confidence interval (CI) = 1.2-3.6] for constipation 12-51 times per year, and 4.4 (95 % CI = 2.1-8.9) for constipation 52 or more times a year. Cumulative lifetime use of commercial laxatives was also associated with increased risk of colon cancer. When adjusted for constipation, commercial laxative use was no longer associated with increased risk (RR = 0.3, 95 % CI = 0.1-0.9 for less than 350 uses; RR = 0.9, 95 % CI = 0.4-2.3 for 350 or more uses). The association with constipation remained. In this study, no subject reported use of anthranoid-containing laxatives.

Van Gorkom *et al*. (2000) performed a controlled study to evaluate the effects of a senna extract (1,26 - 1.85 g dry extract Senna fructus acutifoliae corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B; DER 3-5:1, extraction solvent water) on cell proliferation and crypt length in the entire colon and to clarify the mechanism of the suggested cancer-promoting effects of long-term senna ingestion. 171 outpatients were randomised into 2 groups. 84 patients received 1 ml/kg (maximum 75 ml) senna extract taken orally 18 h before colonoscopy. This was followed 3 h later by the oral intake of 2 litres lavage solution containing polyethylene glycol and electrolytes. Another 1 – 3 litres of this lavage solution were given on the morning of the colonoscopy. The same bowel preparation, but without senna, was given to 87 patients. From 32 randomised patients (15 with senna, 17 without senna) biopsies were taken. A massive acute loss of cells was found in the senna group (presumably due to induced, uninhibited apoptosis), with a shortening in the crypts and an increase in cell proliferation. The authors interpreted these effects as possible signs of a carcinogenic effect, but also pointed out that in this study patients were treated with a single high dose of senna extract, which is normally not used for repeated treatment. Furthermore the study population was very small. Others found no such effects (Hallmann 2000).

In his review Hallmann (2000) summarises toxicological data of stimulant laxatives and other freely available compounds such as lactulose. He reported on possible connections between the increased incidence of (colon) cancer and the use of senna preparations. In retrospective studies, only a relationship with long-term use of the laxative could be demonstrated.

Since individual case-control studies have failed to resolve the question whether constipation and use of cathartics represent significant risk factors of colorectal cancer, a meta-analysis was performed. The method by Peto was used to calculate pooled odds ratios of the cancer risk among exposed and unexposed subjects. The analysis of 14 previously published case-control studies revealed statistically significant risks for colorectal cancer associated with both constipation and use of cathartics, the pooled odds ratios and their 95 percent confidence intervals being 1.48 (1.32-1.66) and 1.46 (1.33-1.61), respectively. The increased risk applied similarly to both sexes, it was higher in cancer of the colon than rectum. Since constipation and cathartics are associated with much lower odds ratios than various dietary components, such as fat, meat, alcohol, and low-vegetable or low-residue diets, it appears that their risk reflects the confounding influence of underlying dietary habits (Sonnenberg and Mueller 1993).

Nusko *et al*. performed 2000 a prospective case control study at the University of Erlangen to investigate the risk of anthranoid laxative use for the development of colorectal adenomas or carcinomas. A total of 202 patients with newly diagnosed colorectal carcinomas, 114 patients with adenomatous polyps, and 238 patients (controls) with no colorectal neoplasm who had been referred for total colonoscopy were studied. The use of anthranoid preparations was assessed by standardised interview, and endoscopically visible or microscopic melanosis coli was studied by histopathological examination. There was no statistically significant risk of anthranoid use for the development of colorectal adenomas (unadjusted odds ratio 1.0; 95 % CI 0.5-1.9) or carcinomas (unadjusted odds ratio 1.0; 95 % CI 0.6-1.8). Even after adjustment for the risk factors age, sex, and blood in the stools by logistic regression analysis the odds ratio for adenomas was 0.84 (95% CI 0.4-1.7) and for carcinomas 0.93 (95 % CI 0.5-1.7). Also, there were no differences between the patient and control groups for duration of intake. Macroscopic and high grade microscopic melanosis coli were not significant risk factors for the development of adenomas or carcinomas.

Roberts *et al.* conducted 2003 a population-based, case control study with equal representation by white and black men and women aged 40 – 80 years. Constipation, defined as fewer than three reported bowel movements per week, was associated with a greater than two-fold risk of colon cancer (OR 2.36; 95 % CI = 1.41-3.93) adjusted for age, race, sex, and relevant confounders. The OR for constipation was slightly higher for distal than for proximal colon cancers. There was no association with laxative use (OR 0.88; 95 % CI = 0.69-1.11). The authors did not explicitly mention anthraquinone-containing laxatives. They mentioned the group "stimulants, fibers, natural remedies, stool softeners, oils, osmotic agents, enemas, suppositories, and unknown". They mentioned in particular phenolphthalein and magnesium.

Nilsson *et al*. examined 2004 the impact of constipation and laxative treatment on the blood levels of homocysteine, folate and cobalamine in a population-based sample of aged people. Elevated plasma homocysteine secondary to reduced supply of folate and cobolamine might indicate an increased risk of cancer, and cardiovascular and neurological diseases. The homocysteine level depends on the supply of folate and cobalamine, which constipation and/or laxative treatment might compromise. The study was based on biochemical tests in 341 females and 183 males aged 82 years and older. The concentrations of homocysteine (plasma), folate, cobalamine and urea (serum) were measured in subjects with and without ongoing treatment with laxative substances. Values were adjusted for age, gender and frailty, as well as for clinical diagnoses and medicinal therapies known to affect homocysteine levels. Homocysteine levels were increased and those of folate reduced in aged subjects on laxatives. Homocysteine remained elevated after adjusting for frailty and various neurological disorders. There was no significant effect on homocysteine and folate in constipated subjects without laxatives.

5.3. Adverse events, serious adverse events and deaths

Farah *et al.* (2000) published a review article where they presented details of reported adverse events with herbal medicines received at the Uppsala Monitoring Center of the WHO during the period from 1968 – 1997 (8985 individual reports). 101 cases were reported in connection with senna products. The symptoms listed were epileptic seizures (5 times), circulatory disorders (4), death (3), intestinal perforation (4), vomiting (6), facial oedema (3), hypertension (3), apnoea (2), hepatitis (2), bloody stools (2), anaphylactic reaction/shock (2), diarrhoea (11), abdominal pain (9), nausea (8), pruritus (7), erythema (7), skin rash (5), syncope (5), urticaria (5), vesicular eruption (4).

Due to poor information the data do not permit any meaningful analysis. It is not clear whether these adverse events occurred with mono-preparations or with combination products; furthermore the combination partners are not known. A further problem in analysing the database arises from the use of incomplete or incorrect names for the herbal medicines. In addition, the review article provides no information about dosage and the patients' medical history. Adverse events like abdominal pain, nausea and allergic reactions are known (see above).

Reports of adverse events of epileptic seizures, circulatory disorders and anaphylactic reactions/shocks were also received by the German Health Authority. These adverse reactions only occurred after ingestion of high doses of senna preparations for bowel cleansing.

Since 1990 the German Health Authority received 41 reports of adverse events concerning mono-preparations and 4 reports concerning combination products of senna leaves and fruits.

- Twenty three reports concern ingestion of high dose of senna preparations for bowel cleansing. In 6 reports, where the senna preparation was administered without co-medication, hypersensitive reactions (angiooedema, skin irritations, dyspnoea) occurred. Hypersensitive reactions are not depending on the administered dose in principle, These adverse reactions have therefore to be also mentioned in case of low dose as administered for short-term use in cases of occasional constipation.

- The remaining 22 reports concern the use for constipation. In 19 cases co-medication was administered and an objective evaluation is therefore not possible. The other 3 reports concern laxative abuse: albuminuria and haematuria (nephrolithiasis known), vomiting (gastrointestinal infection was diagnosed later on), abdominal pain (suspicion of ileus, colonoscopy showed melanosis coli).

Senna leaves and pods

Administration of senna leaves and pods can cause adverse effects such as abdominal cramps and diarrhea in humans (Langmeade and Rampton 2001).

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 adrenocorticosteroids 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

Beuers *et al.* (1991) reported a case of toxic hepatitis related to abuse of senna glycosides in a 26-year old female, who had taken an extract of senna fruits corresponding to 100 mg of sennoside B daily in addition to the usual dose of 10 g senna leaves twice a week in a laxative tea. When the patient stopped taking senna, aminotransferases fell by 70% within a week and ranged from 20 – 40 U/l subsequently. When the patient took senna alkaloids again, 2 months later, liver function rapidly deteriorated and improved once more when the product was stopped.

Vanderperren *et al.* (2005) reported a case of a 52-year-old woman who had ingested, for >3 years, one liter of an herbal tea each day made from a bag containing 70 g of dry senna fruits, developed acute hepatic failure and renal impairment requiring intensive care therapy. The severity of the hepatic failure was reflected by the increase in prothrombin time (international normalized ratio >7) and the development of encephalopathy. Relevant laboratory data included blood glucose 40 mg/dL, hemoglobin 17.9 g/dL, urea 63 mg/dL, creatinine 3.2 mg/dL, uric acid 6.7 mg/dL, sodium 138 mEq/L, chloride 96 mEq/L, calcium 10.2 mg/dL, phosphorus 6 mg/dL, aspartate aminotransferase (AST) 6640 IU/L, alanine aminotransferase (ALT) 9160 IU/L, γ-glutamyl transferase 160 IU/L, bilirubin 6.2 mg/dL, international normalized ratio (INR) 5.27, and factor V 19%. Arterial blood gas analysis revealed pH 7.18, pCO2 23 mmHg, total CO2 8 mmol/L, base deficit 19 mmol/L, and lactate 14.8 mmol/L. Urine analysis showed pH 5.5, density 1020, ++ protein, glucose 1.5 g/L, and granular casts. She was admitted to the intensive care unit (ICU). Common causes of acute hepatitis were ruled out by laboratory investigations. She had been consuming, for >3 years, one liter of an herbal tea containing 70 g of dry senna products that were made from the fruit of *Cassia angustifolia*, also known as Tinnevelly Senna. Liver transplantation was discussed, but the patient ultimately recovered with supportive therapy. Renal impairment was consistent with proximal tubular acidosis, also with marked polyuria refractory to vasopressin administration. Suprisingly, large amounts of cadmium were transiently recovered in the urine.

Severe hepatotoxicity after senna use is unusual. The cause of senna-related hepatotoxicity is unclear but could be explained by the exposure of the liver to unusual amounts of toxic metabolites of anthraquinone glycosides. To asses these two cases of liver impairment, the Roussel UCLAF causality assessment method was used. In 1993, an international group of experts published the so-called Rucam score to evaluate cases of hepatotoxicity (Danan *et al.,* 1993). The score was validated and the results published (Benichou *et al.,* 1993).

Beuers *et al.* (1991)

Rucam Score +10 highly probable: Patient had an hepatocellular type hepatitis. One month before the first signs of hepatitis, the patient had increased the dose of senna alkaloids by taking an extract of senna fruits corresponding to 100 mg sennoside B daily on top of her usual dose of 10 g folia sennae twice a week in a laxative tea. At this time she was taking 10 times the recommended dose. When she stopped taking senna ALT decreased by 70 % within a week. When she took senna again 2 months later, ALT again increased (> 280 U/l; normal range < 19 U/l). ALT decreased once more when the drug was again stopped. No concomitant use of other medication could be detected. There was no evidence for viral, autoimmune, or metabolic disease (rated with +2 points within the Rucam Score). The histological picture suggested toxic damage.

Vanderperren *et al.* (2005)

Rucam Score +4 possible: Although the value of alkaline phosphatase (AP) is not given, it is assumed that it was an hepatocellular type of hepatitis (ALT = 9160 IU/l; normal range 14 – 63 IU/l). ALT decreased > 50 % within 8 days. The authors were unable to document chronic hepatotoxicity prior to this episode because the patient had never consulted a physician and had no laboratory workup. The

patient regularly took vitamin supplements. Common causes of acute hepatitis were ruled out by laboratory investigations (no special information). Interpretation is that the non-drug related causes of the first group were ruled out (rated with +1 point within the Rucam Score).

A 42-year-old woman was admitted to the emergency department with a five-day history of worsening epigastric pain, anorexia, episodic vomiting, and intermittent fever. She reported that she had boiled dried senna leaves (unreported daily dose) she had bought from herbalists and drank approximately 200 ml daily for two years. Color Doppler screening found an echogen thrombus obliterating portal vein bifurcation and the right branch. The lumen was obstructed at this level and there was no blood flow through it. Treatment with thrombolytics was unsuccessful.Chronic use of *Cassia angustifolia* may rarely be associated with portal vein thrombosis (Soyuncu *et al.* 2008).

Assessor's comment

According to the Rucam score, the hepatotoxic cases are related to the chronic ingested overdoses.

Nephritis

Nephritis as a response to large doses of anthraquinones is mentioned by Brunton (1996) without any further information or references.

As mentioned above, Vanderperren *et al.* reported 2005 one case with acute liver failure and renal impairment related to the abuse of senna anthraquinone glycosides. The renal dysfunction in this patient had the characteristics of secondary mixed proximal and distal renal tubular acidosis. It is caused by an impairment of bicarbonate reabsorption in the proximal tube. This defect is either hereditary or secondary to administration of drugs or toxin e.g. cadmium. The tubular defect in this case is transient. Significant amounts of cadmium were found in the patient's urine. In the present case the source of cadmium remained unknown. The authors did not identify metals in a sample of the herbal tea drunken by the patient.

Assessor's comment

The relationship between this abuse of senna and the renal impairment is too weak to be mentioned in the European Union herbal monograph.

Finger clubbing

Silk *et al*. (1975) reported a case of a 26-year old female, who was investigated for severe diarrhoea, which occurred after laparotomy with division of the ligament of Treitz because of a duodenal ileus and a second laparotomy with a duodenojejunostomy because of persisting vomiting. No organic cause could be revealed. During the course of her illness the patient had developed finger clubbing. During a recent hospitalisation more than 2,000 tablets of Senokot® (standardised senna concentrate; each tablet contains 8.6 mg sennosides) were found in her bedside locker, and a subsequent analysis of her urine showed that high concentrations of anthranquinone excretion products were present. After this finding the psychiatric assessment revealed that the patient exhibited many features typically associated with anorexia nervosa. On stopping the purgatives, her diarrhoea improved and her finger clubbing regressed. But vomiting and diarrhoea recurred and she admitted to take 100 to 200 Senokot® tablets a day. Her finger clubbing also returned 2 to 3 months after she admitted to reingesting purgatives.

Prior *et al*. (1978) reported on a 24-year old woman with anorexia nervosa. Over the past 4 years she was taking increasing quantities of senna (up to 50 tablets daily) to produce a regular stool. She denied diarrhoea. The patient was thin. She had scoliosis and the fingers and toes were clubbed. She

presented tetany, probably caused by a combination of hypokaliaemia and hyperventilation. The patient refused to cease laxative abuse.

Malmquist *et al*. reported 1980 the case of a young woman with a previous history of anorexia nervosa (body weight minimum 26 kg, height 1.56 m) and of abuse of alcohol and sedatives presented with severe finger clubbing. Urine samples intermittently contained significant amounts of aspartylglucosamine. Liver biopsy showed abnormal cytoplasmic inclusions in phagocytic cells. The patient reluctantly admitted the daily intake of 2 to 5 tablets of a senna preparation (each containing 12 mg calciumsalts of sennosides A+B from a standardized extract of senna leaves extraction solvent: methanol 66 % (V/V)) continuously for 10 years. Although she was strongly advised to discontinue, she could not because attempts to do so cause severe constipation according to what the patient said.

Levine *et al*. reported 1981 the case of a 64-year old woman, who had lost more than 45 % of her healthy weight loss. She had had repeated urinary infections with renal stones over many years, but diarrhoea had been the chief symptom since 1972. Finger clubbing and hypokaliaemia were observed in 1975. Hypogammaglobulinaemia and a B-cell deficit were diagnosed. When hospitalised over 200 Senokot® tablets were found in her locker. Stopping ingestion of senna and increasing food intake with enteral proprietary supplements led to rapid weight gain. Serum levels of immunoglobulins rose and a repeat lymphocyte analysis showed B cells in normal numbers. In an interview with a clinical psychologist, she gave a history of probable anorexia nervosa in early adult life, since when she had apparently retained the idea that a low bodyweight was desirable.

Armstrong *et al*. presented in 1981 a case of a 21-year old woman with a 9-month history of painful swelling of both ankles followed by painful swelling and morning stiffness affecting proximal and distal interphalangeal joints of both hands without rheumatic family history. She had intermittent diarrhoea of three years' duration. On examination she weighed 49.1 kg. There was clubbing of fingers and toes with pronounced periungual erythema. Both ankles were swollen, red, and tender, and there was tenderness of interphalangeal joints of fingers. Radiographs of knees and ankles showed striking symmetrical bilateral periosteal new bone formation, affecting particularly the ends of the long bones. The patient confessed to habitually taking at least 3 senna tablets daily to control her weight. She also admitted to a period of secondary amenorrhoea of several months' duration a year before. Her weight subsequently increased to 57.2 kg when she stopped taking the laxatives. Within 6 months the clubbing had disappeared. Her rheumatic symptoms were less severe and controlled by NSAID, though the radiological bone abnormalities did not regress.

Assessor's comment

These cases only show symptoms of an overdose and abuse. But all these reported cases have in common a history of anorexia nervosa with an abuse of senna to control weight. The causality of the finger clubbing and all other disturbances with this misuse seems to be dubious. The main disease is anorexia nervosa, which can cause life-threatening disturbances. At this moment, available data are not strong enough and these effects are not introduced in the European Union herbal monograph.

Melanosis coli

Willems *et al.* described 2003 a case of melanosis coli, which occurred in a 39-year old liver transplant patient, who took an over-the-counter product containing aloe, rheum and frangula. The typical brownish pigmentation of the colonic mucosa developed in a period of ten months. The anthranoid medication was stopped and follow-up colonoscopy one year later showed normal looking mucosa once more. However, in contrast to previous examinations, a sessile polypoid lesion was found in the transverse colon. Histology showed tubulovillous adenoma with extensive low-grade dysplasia. Since

there had been preliminary reports suggesting a possible role of anthranoid-containing laxatives in the development of colorectal adenomas and cancer, the authors discouraged their use.

Ewing *et al*. reported 2004 the case of an 83-year old man, who underwent a left hemicolectomy for colonic adenocarcinoma and was found incidentally to have melanosis coli associated with long-term use of a herbal laxative, a senna leaves preparation, not only in his colonic mucosa, but also in the colonic submucosa and in his pericolonic lymph nodes. Four more cases were described in the literature (Hall and Eusebi 1978) in which spindle-shaped, yellow-brown bodies were seen in the mesentric lymph nodes of patients with melanosis coli. The authors concluded that this implies that the melanosis pigment-laden macrophages formed in the lamina propria of the colon pass to the regional lymph nodes and may explain the observation of similar pigment-laden macrophages in other sites. In addition the authors demanded further studies to determine whether there is a relation between the prolonged use of this herbal laxative and colonic adenocarcinoma.

5.4. Laboratory findings

No specific data available. The laboratory data from some of the clinical trials show no critical changes neither in the indication constipation nor in bowel cleansing.

5.5. Safety in special populations and situations

Elderly

In order to check the long-term tolerance of a laxative treatment, Emeriau *et al.* supervised 1983 during six months a group of 14 elderly people (12 women and 2 men) with a mean age of 81.3 years suffering from long-standing constipation without any organic cause. The laxative was given in a daily dosage corresponding to 20 mg of sennosides. Alpha 1-antitrypsin (alpha 1-AT) clearance and exchangeable potassium pool (PPE) were measured, at the beginning (T0), and at the end of the third (T3) and the sixth (T6) months of the study. No abnormal variation of intestinal protein loss (alpha 1-AT: T0, 6.74 +/- 3.16; T3, 2.96 +/- 1.35; T6, 4.15 +/- 1.45 ml/24 h; T0-T3; p less than 0.05, T0-T6, T3-T6: NS) and exchangeable potassium pool (PPE: T0, 19.54 +/- 2.55; T3, 20.29 +/- 3.46, T6, 23.56 +/- 4.92 mEq/kg; T0-T3, T0-T6, T3-T6: NS) was observed. Long-term laxative treatments do not necessarily induce significant intestinal protein and potassium losses.

5.5.1. Use in children and adolescents

The use in children is contraindicated (see section 5.5.2)

5.5.2. Contraindications

During processing steps such as drying, cutting, weighing and filling, senna occasionally causes an inhalation allergy involving the mucous membranes of the respiratory organs (Roth *et al.,* 1988). Isolated cases of various anaphylactic reactions have also been reported in connection with senna administration. Senna leaves and pods should therefore not be used by patients with known hypersensitivity to senna leaves or pods.

Furthermore, senna leaves and pods 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; BfArM-Bekanntmachung 1996). Sossai *et al.* reported 2007 a case report of an

85 year old man suffering from constipation who took a tisane containing *Cassia angustifolia* leaves and fruits liquorice, mallow, fennel, balm and caraway in unreported doses from a health food store. He suffered at hospital admission from a paralytic ileus. After suspension of the cassia containing product and conventional therapy including enema, nose tube and fuid supply with potassium supplementation the patient recovered fully. Colonoscopy showed a colic melanosis.

Senna leaves and pods preparations are contraindicated in children under 12 years of age, because lack of data regarding constipation and bowel cleansing in children and because of general safety concerns.

The use of preparations containing senna leaves and pods are contraindicated in pregnant and lactating women, because of the potential of cancerogenicity 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

Senna leaves preparation 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).

Mueller-Lissner (2005) concluded in his review that the arguments in favour of laxative-induced damage to the autonomous nervous system of the colon are based on poorly documented experiments and that, in contrast, the investigations that do not support such damage are well done. The studies in the cited references (Smith 1968; Riemann *et al.,* 1980 and 1982; Berkelhammer *et al.* 2002; Meisel *et al.,* 1977; Pockros *et al.,* 1985) showed abnormalities observed in humans (damage to enteric nerves, smooth muscle atrophy; distension or ballooning of axons, reduction of nerve-specific cell structures and increase in lysosomes, and sometimes a total degeneration of whole nerve fibers; short-lived superficial damage to the mucosa). These were uncontrolled observations and the author therefore concluded that the cause of these damages can also be the constipation itself or pre-existing changes of unknown aetiology.

The only study comparing the morphology of the autonomous nervous system of constipated patients taking anthraquinones (aloe) to that of an appropriate control group of constipated patients without laxative intake (Riecken *et al.,* 1990) did not support the hypothesis that anthraquinone-containing laxatives are able to provoke relevant degenerative changes in the colonic nerve tissue. But this investigation was conducted in 11 matched pairs only.

It cannot be assessed definitely if a longer than a brief period of treatment with stimulant laxatives leads to dependence requiring increasing quantities of the medicinal product, to an atonic colon with impaired function and to aggravation of the constipation. Precautionally 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. Senna pod 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 senna leaves concomitantly.

Like all laxatives, senna leaves 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 senna leaves are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces (Sitzmann *et al.,* 1979; Spiller *et al.* 2003*)*.

Patients with kidney disorders should be aware of possible electrolyte imbalance.

5.5.4. Drug interactions and other forms of interaction

Seybold *et al*. (2004) reported a case of a 28-year-old woman, who presented a 2-week history of fatigue, myalgias, epigastric pain, pyrosis, and nausea. For 2 days, she had noted yellowish eyes and dark urine. Recently, she had been consuming 3 to 4 l of beer per week. The patient declined liver biopsy. Ultrasonography showed only increased hepatic echogenicity. After the patient stopped drinking alcohol, liver function levels initially decreased but, after 4 weeks, increased again. The patient recalled that she had been found to be homozygous for the CYP2D6*4 variant while participating in a scientific study. She also reported drinking an herbal tea containing senna leaves. She stopped drinking the tea, and her laboratory results gradually returned to normal. Twelve months later, a controlled tea reexposure was performed. Within 7 days, liver function levels increased dramatically. The tea was withdrawn, and the values slowly decreased. One month later, another increase in liver function levels was noted after moderate alcohol consumption. Without further senna or alcohol ingestion, all laboratory values normalised after 7 more weeks. Rhein levels in stored serum samples were as follows: 330 ng/ml after 11 months of tea consumption, 130 ng/ml 2 weeks after the patient stopped drinking the tea, 200 ng/ml at 2 weeks after 1 week of reexposure, and less than 100 ng/ml (lower limit of quantification) 3 weeks later. Serum rhein levels in this patient 24 hours after the last senna dose were 2 to 10 times higher than in the investigation of Krumbiegel *et al.,* 1993. The authors assumed that the toxic effects in this patient were caused by a small dose of sennosides that would not have harmed persons with normal metaboliser status. Furthermore, the exact amount of ingested sennosides is not given in the publication and the first duration of administration was 11 months. The role of the alcohol consumption cannot be evaluated definitely. On the other side, a reexposition again resulted in an increase in liver function levels. It cannot be assessed if CYP2D6*4 played a key role. This can be regarded as a signal. Until there are further data available, no information referring to this publication is given in the European Union herbal monograph.

The monograph makes reference to the particular effects, which may arise from interaction with potassium metabolism in sections 4.4 and 4.5. The wording in the revised monographs is based on the data presented here, development of the wording from the first versions and consideration of consistency with other revisions of monographs on hydroxyanthracene containing herbal substances.

Chronic use or abuse of senna leaves may lead to hypokalaemia. 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 (Haverkamp *et al*. 2002). 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 diuretics and by 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 dangerous or not.

5.5.5. Fertility, pregnancy and lactation

There are no recent investigations available.

There are also no new, systematic preclinical tests for senna leaves or preparations thereof. There are some preclinical data that refer to an extract of senna pods containing 1.4 to 3.5 % of anthranoids, corresponding to 0.9 to 2.3 % of potential rhein, 0.05 to 0.15 % of potential aloe-emodin and 0.001 to 0.006 % of potential emodin or to isolated active constituents, rhein or sennosides A and B. The following *in vivo* studies were conducted using this extract:

Bauer (1977) administered a combination to 95 pregnant women suffering from constipation: 3 g of this preparation contain 0.9 g methyl cellulose, 0.3 g frangula bark (13.5 mg hydroxyanthracene derivatives), 0.3 g senna leaves (7.5 mg hydroxyanthracene derivatives), 0.15 g rhubarb root (6.75 mg hydroxyanthracene derivatives) and 0.015 g achillea extract. Fourteen pregnant women were in the first trimester, 15 in the second one, and 66 women in the third trimester. On average the combination was administered for 61.4 days and the complaints disappeared in 3.9 days with a daily dose of 3.9 g. Efficacy was very good in 55 patients, good in 31 patients, satisfactory in 7 patients and insufficient in 2 patients. This result was not analysed with regard to the different trimesters. 4 patients (4.2 %) complained about adverse reactions. Twelve women in the second group were gynaecologically treated because of a threatening abortion. Only one of these women miscarried. There is no information about the state of the new-borns. This investigation cannot prove the safe use of senna preparations in general in pregnancy.

Shelton reported 1980 that successful treatment of constipation in the immediate postpartum period in 93 % of white patients and 96 % of coloured patients was achieved in a clinical randomised controlled trial of "standardised senna tablets". The time of the first spontaneous normal bowel action was taken as the criterion. If this occurred within the first 24 hours after delivery or on the following day (i.e. within 48 hours of delivery) the response was regarded as successful. This result was significantly better than the success rates of 51 % and 59 % in white and coloured patient controls treated with placebo. Minor abdominal cramps occurred in some 13 % of the patients treated with senna and in 4 % of the controls given the placebo. Furthermore the author reported that there was no evidence to suggest that standardised senna had any effect whatsoever on a breast-fed baby if taken by the mother.

Faber *et al.* (1988) investigated the excretion of rhein in 100 breast milk samples of 20 post-partum women after intake of a "standardised senna laxative", which also contains *Plantago ovata* seeds/husks as bulk substances. After daily doses of 5 g of the senna laxative containing 15 mg sennosides for 3 days, the rhein concentration in milk samples from every lactation during 24 h post-dose varied between 0 and 27 ng/ml with values below 10 ng/ml in 94 %. Based on median values, 0.007 % of the sennoside intake (calculated as rhein) was excreted in breast milk. None of the breast-fed infants had an abnormal stool consistency. Assuming theoretically a complete metabolism of sennosides to rhein in the mother, the amount of rhein delivered to the infant (ng/kg b.w.) is by the factor 10^{-3} below the rhein intake of the mother.

The possible teratogenic effect of frequently used laxative drug had not been checked in case-control epidemiological study, previously. Therefore, the objective of the study of Ács *et al.* (2009) was the comparison of cases with congenital abnormalities (CAs) and their matched controls without CAs in the

population-based large data set of the Hungarian Case-Control Surveillance System of Congenital Abnormalities. Of 22,843 cases with CA, 506 (2.2 %) had mothers with senna treatment, while of 38,151 control newborn infants without CA, 937 (2.5 %) were born to mothers with senna treatment (adjusted OR with 95% CI: 1.0, 0.9-1.1), and of 834 malformed controls with Down syndrome, 26 (3.1 %) had mothers with the use of senna (OR with 95 % CI: 0.7, 0.5-1.1). The range of senna doses was between 10 mg and 30 mg, but most pregnant women used 20 mg daily. The mothers with senna treatment showed the characteristics of pregnant women with constipation (elder with larger proportion of primiparae). There was no higher risk for 23 different CA groups after the senna treatment during the second and/or third gestational month of 260 mothers, i.e. in the critical period of most major CAs, compared with their 500 matched controls. Gestational age at delivery was somewhat longer (0.2 week) and the rate of preterm birth was lower (6.6 % vs. 9.2%) in newborn infants without CA born to mothers with senna treatment compared with babies born to mothers without senna treatment. In conclusion, senna treatment did not associate with a higher risk of CAs in the offspring of pregnant women with constipation.

Conclusion on fertility, pregnancy and lactation.

Use during pregnancy and lactation is contraindicated due to preclinical data regarding potential genotoxicity and carcinogenicity of anthranoids as well as there are insufficient data on the excretion of metabolites in breast milk, respectively. Small amounts of active metabolites (rhein) are excreted in breast milk. A laxative effect in breast fed babies has not been reported.

No fertility data available.

5.5.6. Overdose

The section overdose of the monographs refers to major symptoms of chronic use and abuse such as griping pain and severe diarrhoea with consequent losses of fluid and electrolytes and also the 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 conclusion on clinical safety

Because of the possible genotoxic or cancerogenic potential in experimental investigations and the results of Siegers (1993 b), pharmacovigilance actions for anthranoid-containing laxatives (BfArM-1996) were initiated in Germany. By this pharmacovigilance actions the daily dose and the duration of administration were limited. The use in children and nursing mothers was contraindicated. The use during pregnancy was linked to special conditions.

The results of the more recent clinical studies are inconsistent and the question of a possible carcinogenic risk of long-term use of anthranoid-containing laxatives is still open. Some studies revealed a risk for colorectal cancer 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. Therefore the conditions determined in the pharmacovigilance actions for anthranoid-containing laxatives have to be maintained for the moment.

Long-term administration of anthranoid-containing medicinal products over a period of 4 – 13 months leads to the development of pseudomelanosis coli – pigmentation of the gut wall in the caecum and colon. This condition is produced by the accumulation of macrophages that have stored a brown pigment from the breakdown products of anthranoid (probably lipofuscin) and consequently cause the mucosa to appear brown to blackish-brown in colour. Prevalence among patients with chronic constipation is reported to be 12 – 31 %, and 62 % following chronic ingestion of anthraquinone-containing laxatives. This finding disappears 6 – 12 months after stopping chronic laxative administration (Mascolo *et al*., 1998).

6. Overall conclusions (benefit-risk assessment)

Senna leaf preparations and senna pods preparations fulfil 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

for bowel cleansing prior to clinical procedures requiring bowel preparation

WHO ATC: A06AB06 and V04CZ01/05

The efficacy of senna preparations has been evaluated in clinical trials in the treatment of constipation and for bowel cleansing before radiological investigations or colonoscopy. In the majority of the studies on constipation combinations of senna with fibre were investigated. For bowel cleansing high doses of a senna preparation were tested. In the European Union herbal medicinal products have been authorised for more than ten years. There have been over hundred scientific publications during the last ten years and the data on effects and efficacy are coherent.

There is no well-designed non-experimental descriptive study with a mono-preparation of senna leaves and pods available which investigates the short-term use of occasional constipation. Evidence is obtained from pharmacological data, experts' reports and opinions and extensive clinical experiences.

Well-designed clinical studies are available for combination products for occasional constipation and for high doses of senna preparations for bowel cleansing.

Furthermore pharmacological studies in humans are available (Ewe *et al*., 1993; Buhmann *et al*. 2005; Symposium Antrachinon-Laxantien, 1985), even if they show some shortcomings, e.g. a not validated technique (Buhmann *et al*. 2005). The studies with combination products clearly identify the additional effect of the senna fraction in the combination products.

The results of the studies with combination preparations show a clear laxative effect additionally to fibre intake.

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 consider adverse effects of long-term misuse and also the potential carcinogenicity.

An indication concerning bowel cleansing prior to clinical procedures is added under well-established use. In total, 23 clinical trials have been performed with different settings of preparations for bowel cleansing prior to any clinical procedures requiring a clean bowel e.g. bowel endoscopy or radiology.

The data available on use for bowel cleansing in a high dose are consistent. (see section 4.2.2., subsection Conclusions on application of herbal preparations of senna pods for bowel cleansing)

The HMPC concluded that the requirements for well-established use with the indication "Herbal medicinal product for bowel cleansing prior to clinical procedures requiring bowel preparations" are fulfilled. A dosage equivalent to 150 mg sennosides is sufficient. It is up to the health care professional to integrate the use of senna pod preparations into an adequate preparatory scheme such as for instance described by Krakamp *et al*. (1996, "The preparation starts with a three days diet of clear fluids, the herbal preparation is to be applied between 2 pm and 4 pm of the day before the examination followed by a glass of water and drinking of 2 l of clear fluids until bedtime. No solid food intake until examination."). When deciding about appropriateness of application of senna pod preparations in this indication it must be considered that standard therapies with sodium phosphate or PEG-solutions was slightly more effective, but senna preparations were better tolerated. For senna preparations less vomiting but more frequent spasms have been observed. Application of senna pod preparations may be a reasonable and effective therapeutic option for patient groups with limitations in intake of high volumes of fluids.

In the indications described in the European Union monograph the benefit/risk ratio is considered positive.

Hydroxy anthracene derivatives are considered by the HMPC as constituents with known therapeutic activity.

Annex

List of references