European Medicines Agency
Evaluation of Medicines for Human Use

London, 27 April 2007
Doc. Ref. EMEA/HMPC/51868/2006 *Corr*.

COMMITTEE ON HERBAL MEDICINAL PRODUCTS

ASSESSMENT REPORT ON *CASSIA SENNA* L. AND *CASSIA ANGUSTIFOLIA* VAHL, FOLIUM

Herbal substance	*Cassia senna* L. (*C. acutifolia* Delile) [Alexandrian or Khartoum senna] or *Cassia angustifolia* Vahl [Tinnevelly senna], folium (senna leaf) or a mixture of the two species
Herbal preparation	dried leaflets, standardised; standardised herbal preparations thereof
Pharmaceutical forms	Herbal substance for oral preparation
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I. Introduction

This assessment report reviews the scientific data available for senna leaves (*Cassia senna* L. (*C. acutifolia* Delile) *et Cassia angustifolia* Vahl), primarily the clinical data. The core-SPC for Sennae folium established in 1994 by the Committee for Proprietary Medicinal Products (CPMP) was taken into consideration. This report was prepared on the basis of the expert-reports presented in 2002 for an herbal medicinal product containing senna leaves as the active pharmaceutical ingredients. The report , reviews also the literature presented by the European Scientific Cooperative on Phytotherapy (ESCOP) to support the monographs "Sennae folium (Senna Leaf)" (94), "Sennae fructus acutifoliae (Alexandrian Senna Pods)" (95) and "Sennae fructus angustifoliae (Tinnevelley Senna Pods)" (96) (ESCOP Monographs, second edition 2003). The report takes also into account the literature presented by the World Health Organization (WHO) for the monographs "Folium Sennae" and "Fructus Sennae".
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).

Constipation is a common complaint in 1 – 6% of the middle-aged population and 20 – 80 % of the elderly people, and may be treated by laxatives. Constipation also tends to be more prevalent among women. Functional constipation is the most common type without any specific aetiology (1). The most commonly used laxatives are either stimulant preparations (containing anthracenic derivatives from senna, frangula or cascara), lubricant laxatives (e.g mineral oils) or bulk forming agents.

Preparations based on senna plants are among the most commonly used herbal laxatives (2, 3). Senna has been used for medicinal purposes for centuries (4). It was introduced into European medicine by the Arabs in the 9^{th} or 10^{th} century. Its laxative properties were already known at that time. The leaves and fruits of the senna plant were used to an equal extent (5).

According to the CPMP core-SPC, senna leaves are intended "for short-term use in cases of occasional constipation". This indication is substantiated by extensive empirical data (derived from research into the constituents and their pharmacology) and by clinical data.
Senna leaves preparations have to be regarded as herbal medicinal products with a "well-established medicinal use" in this indication with respect to the application of Directive 2001/83/EC of the Parliament and of the Council on the Community code relating to medicinal products for human use as amended.

II. CLINICAL PHARMACOLOGY

II.1 Pharmacokinetics

II.1.1 Phytochemical characterisation

Senna leaves consist of the dried leaflets of *Cassia senna* L. (*Cassia acutifolia* Delile), known as Alexandrian or Khartoum senna, or *Cassia angustifolia* Vahl, known as Tinnevelly senna, or a mixture of the two species. 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 %) (6). The amount of anthranoids of the emodin and aloe-emodin type is generally higher in the leaves than in the fruits (7).
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" (ref.01/2005:0206).

The herbal substance also contains small quantities of other dianthrone diglycosides, monoanthraquinone glycosides and aglyka. The amount of aglyka increases during storage. Aglyka are classified as toxic substances. Preparations produced with heat like teas contain aglyka whereas preparations produced without heat like cold macerations do not contain these constituents. The amount of aglyka is limited by specific requirements for the quality and the storage of the medicinal

herbal substance. Furthermore the amount of aglyka has to be determined during tests of stability. Adverse events are caused by overdose rather than by the aglyka themselves. Therefore, a higher risk for teas than for cold preparations cannot be postulated and the Community herbal monograph also covers senna teas.

The naphthalene glycosides are without pharmacological significance but are important for differentiating the two species of senna: tinnevellin glycoside is found only in *Cassia angustifolia* Vahl, and 6-hydroxymusizin glycoside only in the mature plants of *Cassia senna* L. (8, 9).

II.1.2 Absorption, metabolism and excretion

The glycosidic sennosides are not absorbed. They are hydrophilic and do not pass the gastrointestinal tract membranes (10). 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 (11). Aglyka 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 (12).
Animal experiments with radio-labeled rhein anthrone administered directly into the caecum demonstrated absorption < 10 % (14).
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 (15). In experimental animal studies, nearly 6 % of the amount of the oral administered anthranoids could be found unchanged in the urine and faeces (12, 13).

Therapeutic doses of two laxatives were repeatedly administered to 10 healthy volunteers in a two-way change-over design (16). Sennatin® contains purified sennosides 20 mg, and Agiolax® is 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 (Agiolax®) and 49.6 ng/ml (Sennatin®), 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 M et al. 1988 (17) 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.

Faber P. et al. 1988 (18) 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 (Agiolax®). 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.

Animal experiments demonstrated that placental passage of rhein is small.

II.1.3 Progress of action

Senna leaves act within 8 to 12 hours due to the time taken for transport to the colon and metabolisation into the active compound.

II.2 Pharmacodynamics

II.2.1 Mode of action

- **Laxative effect**

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 (19, 20), due to different concepts of what normal bowel habits are.

Senna leaves belong to the stimulant laxatives. 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 deriving also from other anthranoid-containing herbal substances, but the results of these investigations are not always consistent.

Ishii Y et al. 1990 (99) 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 (ATPase) *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.

Hoenig J, Rauwald HW et al. 1992 (100, 101) studied the influence of 23 anthraquinones and anthrones on the regulatory volume decrease (RVD) 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 Y et al. 1990 (99), 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.

Ishii Y et al. 1994 (102) 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.

Results of investigations of **Capasso F et al. 1983** (103) 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 quantity of the laxative effect is dependent on the orocaecal transit time and colonic metabolism of the herbal substance (21), the dosage of the herbal substance, the amount and period of accompanying fluid intake (22, 23).
No laxative effect was seen in germ-free animals (24, 25).

Ewe K et al. 1993 (26) 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 and with Sennatin® containing purified sennosides 20 mg, Agiocur® (30 g) as a fibre product containing 20 g *Plantago ovata* seeds/husks, or Agiolax® (10 g) as a combination of 5.4 g *Plantago ovata* seeds/husks + 1.2 g senna pod with a sennoside content of 30 mg. Colonic transit was reduced by Sennatin® and by Agiolax® from 39 +/- 4 h to 17 +/- 3 h ($p<0.005$). Agiocur® 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 Sennatin® (30 +/- 5 h) and Agiolax® (27 +/- 1 h) ($p<0.005$), but not by Agiocur® (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. Agiolax® caused the greatest, Agiocur® 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 S et al. 2005 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 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 (27).

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 (28).

II.2.2 Interactions

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 (105). 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 SPC, the doctor can decide whether the concomitant use of a given diuretic is dangerous or not.

Seybold U et al. 2004 (92) 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 G et al.1993 (16). 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 assessed as a signal, not more and not less. Until there are further data available, no information referring to this publication is given in the Community herbal monograph.

III. CLINICAL EFFICACY

III.1 Dosage

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 (7) 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 (29). This dosage corresponds to the recommendation given in the above-mentioned ESCOP monographs. The WHO monographs referred above (65) 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 (104).

III.2 Clinical studies

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, combinations of senna with fibre were investigated. For bowel cleansing high doses of a senna preparation were tested.

III.2.1 Constipation

Pers M et al. 1983 (30) treated 20 elderly in-patients (above 60 years old) suffering from severe constipation, once daily for 2 weeks with either Agiolax® ("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 Lunelax comp® ("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 Agiolax®, the other with Lunelax comp®. 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 Lunelax comp® treatment than during the Agiolax® one. This was expected as the given dose of Lunelax comp® contained 10 mg glycosides more than that of Agiolax®. 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 JA et al. 1987** (31) 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 (Metamucil ® 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 AP et al. 1993 (32, 33) compared the efficacy of a senna-fibre combination (Manevac®, Agiolax®: 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); $t=3.51$, $p \leq 0.001$). 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. 1993 (34) compared the efficacy of a senna-fibre combination (Agiolax®) and lactulose (Levolac®) 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) Agiolax® or 20.1 g (30 ml) Levolac ®. "Agiolax® contains *Plantago ovata* seed 521.6 mg (bulk forming), Fructus cassiae angustifoliae 138 mg (stimulant) and atsulen 70 µg (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 (Metalax®) was given per rectum. The bowel frequency, bisacodyl use and stool consistency were recorded. In period I, 21 patients received Agiolax® and 9 patients Levolac®; in period II, 7 patients received Agiolax® and 18 patients Levolac®. Bowel frequency/week was significantly higher on Agiolax® treatment during both periods, mean (SD) in period I: 4.5 (2.3); period II: 4.5 (2.4), compared to Levolac®. Bowel frequency on Levolac® 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.

Agra Y et al. 1998 (35) 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).
The ingested dose of hydroxyanthracene derivatives is not defined in the publication.

Conclusion

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.
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.

III.2.2 Irritable bowel syndrome

Moser EH and Hübner WD 2002/2003 (36, 37) 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 Eucarbon® tablets (containing as active ingredients "180 mg Carbo ligni", i.e. vegetable, non-activated charcoal, "105 mg Fol. Sennae, 25 mg rhubarb extract") 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 Eucarbon® 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 (38) 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 Eucarbon® 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 Eucarbon® and 56.5% with CL; respective values in the ITT population were 59.6% and 53.2%. The relative gain in efficacy with Eucarbon® 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 Eucarbon® (p=0.038, Wilcoxon test, PP population). Similar improvement in the subgroup admitting to "movements often hard" was more pronounced with Eucarbon® 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 Eucarbon® 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.

Conclusion

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".

III.2.3 Bowel cleansing

Most of these studies were conducted with X-Prep®, a senna fruit dry extract preparation corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B, per single dose.

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

Frigerio G et al. 1996 (39) compared to doses of senna (X-Prep®, a senna fruit dry extract preparation corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B, 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.

Krakamp B et al. 1996 (40) tested 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 Klean Prep®**,** 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 the laxative X-Prep® (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.

Valverde A et al. 1999 (41) 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 A + B 120 mg or 240 mg in obese patients, X-Prep Sarget®) in the evening before surgery. 261 patients received polyethylene glycol (PEG) (2 packages diluted in 2 – 3 l of water, ColoPeg®) 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.

Bokemeyer B 2000 (42) 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 (Klean-Prep®, 2 l on the day before colonoscopy and 2 l on the day of colonoscopy p.o), Golytely-RSS (Endofalk®, 3 l on the day of colonoscopy p.o.) and Phospho-Soda (Fleet®, 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 (X-Prep®, 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) 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 (Propulsin®) 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%).

Arezzo A 2000 (43) compared 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; Fleet®, 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.

Chilton AP et al. 2000 (44) compared in a randomised, observer-blind, parallel study a novel low-dose, low-volume triple regimen with Fleet® 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 (Picolax®) 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 (Picolax®) 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 (Fleet® Phospho-soda) 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 (Fleet® Phospho-soda) 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 Fleet® Phospho-soda, is associated with a trend towards a quicker and more efficient colonic examination, and is also 30% cheaper per patient.

Schanz S et al. 2003 (45) 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 (Fleet® Phospho-soda). Group B received a sodium phosphate solution and

sennosides (X-Prep®, a senna fruit dry extract preparation corresponding to 150 mg hydroxyanthracene glycosides, calculated as sennoside B, per single dose). Group C received PEG-ELS (Klean-Prep®) and sennosides (X-Prep®). 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.

Tasci I et al. 2003 (46) conducted 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 (X-M, Yenisehir Ilac) given 2 days prior to colonoscopy), ii) PEG lavage (3 l given 1 day prior to colonoscopy), iii) oral sodium phosphate solution (Fleet ® Phosphosoda) 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.

In an uncontrolled study **Iida Y et al. 1992** (93) already investigated 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.

Conclusion

The more recent studies do not unequivocally prove that bowel cleansing with high doses of senna is superior to other preparations like a polyethylene glycol lavage or an oral sodium phosphate solution. An adequate bowel cleansing can be achieved by other preparation methods than with a high dose of senna with a less favourable benefit-risk-ratio. In particular, if different methods are combined, lower doses of senna seem to be effective enough. But up to now there is no clear evidence to recommend a specific dose nor a specific combination of different bowel cleansing methods. No recommendation concerning the use of senna for bowel cleansing is therefore made in the Community herbal monograph, even not for a special patient group, who is not able to ingest high amounts of fluid, e.g. patients suffering from cardiac insufficiency.

III.3 Clinical studies in special populations

III.3.1 Use in children

In an open controlled trial **Nolan T et al. 1991** (47) 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 Microlax ® (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 Agarol® (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 JA et al. 1978 (48) reported his experiences with X-Prep® 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 X-Prep® (150 mg/75 ml sennosides A+B) 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 ($\leq$ 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.

Dahshan A et al. 1999 (49) 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 X-Prep® and clear liquid diet for 2 days. Group B: Dulcolax® (bisacodyl) for 2 days and Fleet® 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. Dulcolax® without dietary restriction provided unsatisfactory colon cleansing. Magnesium citrate with X-Prep® 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 X-Prep® on skin in children wearing napkins. These skin irritations were bullous and comparable with skin irritations caused by scalds (51).

Conclusion

First of all, change of nutrition is recommended in constipated children with an increase in daily fibre intake. According to the recommendations from a conference on dietary fibre in childhood, children older than 2 years of age should increase their intake of dietary fibre (increased consumption of a variety of fruits, vegetables, cereal and other grain product) to an amount equal or greater than their age plus 5 g (e.g. 8 g/day at age 3) (50). Change in nutrition should be accompanied with behaviour modification, e.g. increased physical exercise.
The data mentioned above are not sufficient to show the efficacy and safety of senna leaves to treat constipated children, if change of nutrition and increase of daily fibre intake is not effective (see chapter IV.2 Contraindications).
They do not represent strong evidence supporting a recommendation for bowel cleansing for colonoscopy in children.
According to the 'Note for guidance on clinical investigation of medicinal products in the paediatric population' (CPMP/ICH/2711/99) of 27 July 2000, the age limit between 'children' and 'adolescents' is set to 12 years of age.

III.3.2 Use during pregnancy and lactation

There are no recent investigations available.
Up to now there are no reports of undesirable or damaging effects during pregnancy or on the foetus associated with senna preparations when used in accordance to the recommended dosage schedule.

Bauer H 1977 (106) administered Laxariston® 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 Laxariston® 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. One of these women only 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.

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. This extract is one of the ingredients of Agiolax®, a combination of *Plantago ovata* seeds/husks and senna pods. The following *in vivo* studies were conducted using this extract:

Chromosome Aberration Assay in Bone Marrow Cells of the Rat, Micronucleus Test in Rats, Mouse Spot Test. No cytotoxic, toxic, embryotoxic or genotoxic effect could be found. (7). Therefore use during pregnancy can only be recommended for such a specified extract but with the advice that the use is to be avoided during the first trimester, because of the experimental data concerning a genotoxic risk of several anthranoids. Senna leaves should only be used intermittently and if other actions like behavioural modification, dietary changes and use of bulk forming agents have failed (53).

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 (11). **Garcia Villar R 1988** (54) evaluated 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 (11).

Shelton MG 1980 (55) reported 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" (Senokot®). 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 P et al. 1988 (18) (see also chapter II.1.2 Absorption, metabolism and excretion) reported that based on median values, 0.007 % of the mothers' sennoside intake (calculated as rhein) was excreted in breast milk. None of the breast-fed infants had an abnormal stool consistency.

Conclusion

Use during lactation is not recommended as there are insufficient data on the excretion of metabolites in breast milk. Small amounts of active metabolites (rhein) are excreted in breast milk. A laxative effect in breast fed babies has not been reported.

III.4 Traditional use

As already mentioned in chapter I Introduction, senna has been used for medicinal purposes for centuries (4). It was introduced into European medicine by the Arabs in the 9th or 10th century.

Tabernaemontanus 1625 (56) mentions "Kassie" (Cassis 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 1919** (57) "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.

Hager 1927 (58) 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 (59) describes the use of senna in teas for purification of blood and as a laxative. He also mentioned “Sennatin” like Hager 1927.

Madaus 1938 (60) gives a review of the use of senna. Paracelsus already indicated the use as a purgative, as well Hecker 1814. Lonicerus 1564, Bock 1565, Matthiolus 1626 and Clarus 1860 described the use as a laxative. Matthiolus also cured lues venerea (syphilis) with senna. Other described indications are as an emmenagogue agent and in acidosis in diabetics, in congestion by night, in fever and scurf and in lung and liver diseases.

Hoppe 1949 (119) mentions senna leaves as a laxative in cases of acute and chronic constipation.

In **Martindale 1967** (61) senna is described as a purgative for the treatment of constipation.

The **Austrian Pharmacopoeia 1812** (120) lists senna leaves as “infusum laxativum”.

In his “Manual of Materia Medica and Pharmacology” **Culbreth 1927** (62) 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 Hungary, the use for slimming cure is also described in paramedicines. The Hungarian competent authority limited the quantities of anthranoids in such products to 15 mg/day and the duration of use was limited to maximum one month. The use of either an anthranoid-containing laxative or any other laxative during a slimming cure must be regarded as obsolete. An effective and lasting body weight reduction cannot be reached with such substances. They do not reduce adipose tissue.

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 KR et al. 1975** (63)). In his “Indian materia medica” **Nadkarni KM 1976** (121) 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 **Koenen 1977** (64) described, senna was used in South Africa in grippe (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” (65) 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.

Conclusion

Besides the use in occasional constipation in Europe and America, senna was used for purification of the blood, bowel and other organs. In former times such a purification was often the first step to treat a lot of diseases. Such a procedure is now obsolete. Furthermore there are no plausible pharmacological data for the purification of the blood and other organs than the bowel, as well as for the use as cholagoga.
The other indications described for India and Arabia are not traditional one for Europe. The use in skin affections is surprising because senna can cause skin irritations by itself.
Furthermore the possible risks as described in chapter IV have to be taken into account.
None of the above-mentioned uses can therefore be accepted for inclusion in the 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products'.

IV. SAFETY

IV.1 Toxic, genotoxic and cancerogenic risk

IV.1.1 Preclinical Data

Toxicological data indicate that two hydroxyanthraquinones, emodin and aloe-emodin, present as minors component in senna, might represent a genotoxic or carcinogenic risk (**Mori H 1990** (66), **Siegers CP 1992** (67), **Brusick D 1997** (68)). While most studies gave negative responses, results from some studies suggest a genotoxic activity by both (**Wölfle D 1990** (69), **Westendorf J et al. 1990** (70), **Westendorf J 1993** (71)). These were Ames tests showing an interaction with Salmonella DNA resulting in the production of frameshift mutations (Westendorf J et al. 1990 (70), **Sandnes D et al. 1992** (72), **Heidemann A 1993** (73)). 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 A 1993 (73)). *In vitro* assays overestimate the potential hazard from exposure and must be reevaluated by *in vivo* experiments.

Westendorf J et al. 1990 (70) 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 J 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 (see publication). 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 J 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.

Sandnes D et al. (72) 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 aglyka kaempferol and quercetin.

The three *in vivo* studies by Heidemann A 1993 (73) 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

Each of NMRI mice or Wistar rats, conventionally housed, received the test substances orally via stomach tube. They were suspended in either 0.3 – 0.5% tragacanth 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

Housing of the animals and treatment with the test substances 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 F_1 mouse. The F_1 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

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 ^{3}H-thymidine, which is incorporated into the DNA if UDS occurs. The uptake of ^{3}H-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 ^{3}H-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.

A carcinogenicity study was done by **Lyden-Sokolowski A et al. 1993** (74) 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.

Mereto E et al.1996 (75) 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.

Mascolo N et al. 1999 (76) 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 U et al. 2004 (97) conducted 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.

Mitchell JM, Mengs U et al. 2006 (98) conducted an oral carcinogenicity and toxicity study of senna in rats. The administered senna preparation was the same preparation described above. Senna was administered by gavage to Sprague Dawley rats once daily at dose levels of 0, 25, 100 and 300 mg/kg/day for up to 104 consecutive weeks. Based upon clinical signs related to the laxation effect of senna, the highest dose (300 mg/kg/day) was considered to be a maximum tolerated dose. The primary treatment-related clinical observation was mucoid faeces seen at 300 mg/kg/day. In the highest dose group animals had slightly reduced body weights, increased water consumption and notable electrolyte changes in serum and urine. At necropsy, dark discolouration of the kidneys was observed in all treated groups. Histological changes were seen in the kidneys of animals of all treated groups and included slight to moderate tubular basophilia and tubular pigment deposits like already described above. For all treated groups, minimal to slight hyperplasia was evident in the colon and caecum. 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. No treatment-related neoplastic changes were observed in any of the examined organs. The authors concluded that senna did not reveal any evidence of carcinogenicity in this study.

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 (107).

- 16-day study in F344/N rats

Groups of 5 male and 5 female rats were fed diets containing 0, 600, 2,000, 5,500, 17,000, or 50,000 ppm emodin. This corresponds in males to average daily doses of approximately 50, 170, 480, 1,400, or 3,700 mg emodin/kg bw and in females to 50, 160, 460, 1,250, or 2,000 mg/kg bw. Three female rats died before the end of the study. Mean body weights of males and females exposed to 5,500 ppm or greater were significantly less than those of the controls. Feed consumption by males and females receiving 17,000 or 50,000 ppm was decreased throughout the study. Macroscopic lesions were present in the kidney of rats exposed to 17,000 or 50,000 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, 1,200 or 3,800 mg/kg bw and in females to 140, 530, 1,600 or 5,000 mg/kg bw. 50,000 ppm equivalents were not calculated due to high mortality. All mice exposed to 50,000 ppm died before the end of the study. Mice in the 17,000 ppm groups lost weight during the study. Feed consumption by 5,500 ppm females was greater than that by the controls. Macroscopic lesions were present in the gallbladder and kidney of mice exposed to 17,000 ppm.

- 14-week study in rats

Groups of 10 male and 10 female rats were fed diets with 0, 312.5, 625, 1,250, 2,500 or 5,000 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 1,250 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 1,250 or 5,000 ppm. All male rats exposed to 1,250 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 1,250 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 1,100 mg/kg to females. Relative kidney weights of male mice exposed to 1,250 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 1,250 ppm or greater.

- 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.

- Genetic toxicology

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.

Conclusion by the "National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee":

- 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 (108).

IV.1.2 Clinical Data

Siegers C-P et al. 1993 (77) 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 GA et al. 1988 (78) and **Kune GA 1993** (79) 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 G et al. 1993** (80) 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 EJ et White E 1998 (109) examined 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 B et al. 2000 (81) performed a controlled study to evaluate the effects of a highly purified senna extract (X-Prep®, 2 mg/ml sennoside A and B) 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 (max. 75 ml) X-Prep® 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 (Klean-Prep®). 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 F 2000 (82)).

In his review **Hallmann F 2000** (82) 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.

Nusko G et al. 2000 (83) performed 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.

Willems M et al. 2003 (84) described 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.

Roberts MC et al. 2003 (110) conducted 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.

Ewing CA et al. 2004 (85) reported 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 the herbal laxative Swiss Kriss®, 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 (86) 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 require further studies to determine whether there is a relation between the prolonged use of this herbal laxative and colonic adenocarcinoma.

Nilsson SE et al. 2004 (87) examined 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.

IV.1.3 Conclusion

Because of the possible genotoxic or tumourigenic risk in experimental investigations and the results of Siegers 1993, pharmacovigilance actions for anthranoid-containing laxatives (52) were initiated in Germany in 1996. The daily dose and the duration of administration were limited. Use in children and nursing mothers was contraindicated. Use during pregnancy was linked to special conditions (see chapter III.3 Clinical studies in special populations).

Results of toxicity and carcinogenicity studies in 2004 and 2005 in rats did not reveal any evidence of carcinogenicity and did not show any notable toxicity. But rats as well as mice and dogs do not develop a pseudomelanosis coli like humans and guinea pigs and it is therefore questionable if these results can be extrapolated to humans.
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 (90). 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. Further investigations are needed to determine the carcinogenic risk definitely. 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 leads to the development over a period of 4 – 13 months 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 (5).

IV.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 (88). Isolated instances of various anaphylactic reactions have also been reported in connection with senna administration (89). Senna leaves should therefore not be used by patients with known hypersensitivity to senna leaves.

Furthermore, senna leaves 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 (7, 52).

Finally, senna leaves preparations are contraindicated in children under 12 years of age.

IV.3 Special warnings and precautions for use

The following warnings and precautions for use are recommended:

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 (see chapter II.2.2 Interactions).

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 a potential or existing intestinal blockage (ileus).

If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of laxatives should be avoided.
Use for more than 1 - 2 weeks requires medical supervision, as outlined in the posology section of the Community herbal monograph.

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 (7).

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.

Müller-Lissner SA 2005 (111) 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 B 1968 (112); Riemann JF et al. 1980 (113) and 1982 (114); Berkelhammer C et al. 2002 (115); Meisel JL et al. 1977 (116); Pockros PJ et al. 1985 (117)) 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 EO et al. 1990** (118)) 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.

In the light of existing safety concerns, further warnings and precautions for use are recommended:

If stimulant laxatives are taken for longer than a brief period of treatment, this may lead to impaired function of the intestine and dependence on laxatives.

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

When senna leaves preparations are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces (see chapter III.3.1 Use in children).

IV.4 Undesirable effects

Senna leaves may produce abdominal pain and colickly gastrointestinal symptoms and passage of liquid stools, in particular in patients with irritable colon. However, these symptoms may also occur generally as a consequence of individual overdosage. In such cases dose reduction is necessary. The correct individual dose is the smallest required to produce a comfortable soft-formed motion (7, 52).

As mentioned above, hypersensitive reactions (pruritus, urticaria, local or generalised exanthema) may occur (see chapter IV.2 Contraindications).

Chronic use may lead to disorders in water equilibrium and electrolyte metabolism, and may result in albuminuria and haematuria.
Furthermore, use over a long period may lead to pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation.
Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment (see chapter II.1.2 Absorption, metabolism and excretion).

Farah MH et al. 2000 (89) 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).

IV.5 Interactions

See chapter II.2.2

IV.6 Overdose

The 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).

<u>Hepatitis</u>

Beuers U et al. 1991 (91) 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 B et al. 2005 (122) reported a case of a 52-year old woman, who had ingested, for more than 3 years, one litre of an herbal tea each day made from a bag containing 70 g of dry senna fruits. She developed renal impairment and acute hepatic failure with increase in prothrombin time (international normalised ratio > 7) and development of encephalopathy. The patient recovered with supportive therapy. Surprisingly, large amounts of cadmium were transiently recovered in the urine.

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 G et al. 1993** (123)). The score was validated and the results published (**Benichou C et al. 1993** (124)).

Assessment

- Beuers U 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 100mg 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 $\leq$ 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 B 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 $\geq$ 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).

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 LL 1996** (125) without any further information or references.

As mentioned above, Vanderperren B et al. 2005 (122) reported 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. The relationship between this abuse of senna and the renal impairment is too weak to be mentioned in the Community herbal monograph.

Finger clubbing

Silk DBA et al. 1975 (126) 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 J et al. 1978 (127) 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 J et al. 1980 (128) reported 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 (Pursennid®, containing 12 mg senna glycoside per tablet) 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 D et al. 1981 (129) reported 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 RD et al. 1981 (130) presented 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 (Senokot®) 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.

Assessment
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 Community herbal monograph.

V. Overall conclusion

Well-established use: short-term use in cases of occasional constipation

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 combinations of senna with fibre were investigated. For bowel cleansing high doses of a senna preparation were tested.

There is no well-designed non-experimental descriptive study with a mono-preparation of senna available which investigates the short-term use of occasional constipation. Evidence is obtained from 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 and they clarify the pharmacodynamics. Furthermore pharmacological studies in humans are available (26, 27, 28), even if they show some shortcomings, e.g. a not validated technique (27). The studies with combination products clearly identify the additional effect of the senna fraction in the combination products.

Therefore in consideration of all these data the current level of evidence[1] of the available scientific data for "the short-term use in cases of occasional constipation" can be identified as level III. The results of the studies with combination preparations show a clear laxative effect additionally to fibre intake.

The conditions determined in the pharmacovigilance actions for anthranoid-containing laxatives have to be maintained for the moment because further investigations are needed to clarify the carcinogenic risk. The results of the most recent studies are inconsistent. However, a risk was also revealed for constipation itself and underlying dietary habits.
The use in children under 12 years of age is contraindicated and use during lactation is not recommended.
During pregnancy only a specified extract (as described above) can be regarded as safe, but with the advice that the use is to be avoided during the first trimester. Senna leaves should only be used intermittently and if other actions like behavioural modification, dietary changes and use of bulk forming agents failed.

Provided that the correct dose and duration of administration and the advices given in the SPC are followed, senna can be regarded as a safe and effective medicinal plant for the short-term use in cases of occasional constipation. In this indication the benefit/risk ratio is positive.

The data available on use for bowel cleansing in a high dose are not consistent. An adequate bowel cleansing can be achieved as well by other preparation methods than with a high dose of senna with a less favourable benefit-risk-ratio. In particular if different methods are combined, lower doses of senna seem to be effective enough. Use at a high dose cannot therefore be recommended.
In an unpublished multicentre, prospective, controlled, randomised, two-parallel-group, observer-blind study in 133 patients, which was presented in the application procedure of a senna preparation (150 mg hydoxyanthracene glycosides, calculated as sennoside B) for bowel cleansing a statistically significant non-inferiority of this preparation in combination with 2 l PEG-ELS could not be shown in comparison to 4 l PEG-ELS. The descriptive evaluation shows a better bowel cleansing in the rectum, colon descendens, colon transversum and flexura coli dextra for 4 l PEG-ELS and an equivalent cleansing for both preparations in the colon sigmoideum , colon ascendens and caecum.

Up to now there is no clear evidence to recommend a specific dose nor a specific combination of different bowel cleansing methods. No recommendation concerning the use of senna for bowel cleansing is therefore made in the Community herbal monograph, even not for a special patient group, who is not able to ingest high amounts of fluid, e.g. patients suffering from cardiac insufficiency.

Traditional use

Senna was traditionally used for purification the blood, bowel and other organs in many diseases. In former times, such a purification was often the first step to treat a lot of diseases. Such a procedure is now obsolete. There are no plausible pharmacological data available for the purification of the blood

[1] As referred to in the HMPC 'Guideline on the assessment of clinical safety and efficacy in the preparation of Community herbal monographs for well-established and of Community herbal monographs/entries to the Community list for traditional herbal products/substances/preparations' (EMEA/HMPC/104613/2005)

and other organs than the bowel, or for use as a cholagogum. In view of possible risks, such traditional uses cannot be recommended. This is in accordance with the German pharmacovigilance actions for anthranoid-containing laxatives.