European Medicines Agency
*Post-authorisation Evaluation of Medicines for Human Use*

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**OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *CASSIA SENNA* L . AND *CASSIA ANGUSTIFOLIA* VAHL, FOLIUM' (EMEA/HMPC/51869/2006)**

*Table 1: Organisations that commented on the draft 'Community herbal monograph on senna leaf (Sennae folium)' as released for consultation in January 2006 until 31 May 2006*

| | **Organisation** |
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| 1. | Association of the European Self-Medication Industry (AESGP) |
| 2. | Biohorma BV, NL |
| 3. | Herbapol, Poland |
| 4. | The European Scientific Cooperative on Phytotherapy (ESCOP) |
| 5. | The Herbal Forum, UK |
| 6. | The Medicines Evaluation Board of the Netherlands (MEB NL) |
| 7. | Traditional Medicinals Inc., USA |
| 8. | Italian Medicines Agency |

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## Table 2: Discussion of comments

| Comment | Comment and rationale | Rapporteur's response |
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| **2. Qualitative and Quantitative Composition** | A typing error under "Definition" should be corrected: the names of the author as part of the scientific names "Delile" and "Vahl" instead of "DELILE" and "VAHL"; and "Tinnevelly" instead of "Tinnevelley" thus without "e" before "y" at the end (see correct spelling in Ph. Eur.). Sennoside B with without "s" and with reference to the dried drug instead of with reference to the dried herbal substance (according to Ph. Eur.). | We have corrected the spelling.<br>The HMPC agreed upon using the term 'herbal substance' instead of ' herbal drug'. |
| | Senna has a long traditional use for occasional constipation in several European countries. It is used as "single" herbal product or in combination with other herbs [Hellemont 1988, Hoppe 1949, List et al 1977, Madaus 1976]. An example of a combination product is Linoforce (Senna angustifolia, Linum usitatissimum and Rhamnus frangula (13%, 43% and 1% respectively). This product has been sold for more than thirty years in the Netherlands and also for many years in other EU countries (e.g. Spain 24 years). Based upon these data and in accordance with the directive 2001/83 EC we propose to include the traditional use for Senna and mention that there are combination products with Senna and other herbs. | According to Article 16a(3) of Directive 2001/83/EC as amended, the provisions of chapter 2a shall not apply in cases where the competent authorities judge that a traditional herbal medicinal product fulfils the criteria for authorisation in accordance with Article 6 or registration pursuant to Article 14. Senna preparations fulfil these criteria and even linseed and frangula bark as a laxative.<br>On the other hand possible risks have to be taken into account. This was discussed in the HMPC with the result that a traditional use cannot be supported. |

| Comment | Comment and rationale | Rapporteur's response |
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| **2. Qualitative and Quantitative Composition**<br><br>**Continuation** | Overview:<br>Senna leaf has been used for centuries as a Traditional Medicine in both western and eastern cultures as a laxative, usually taken as a tea infusion or swallowed in a powdered form. To the extent that the Indian systems of Traditional Medicine (e.g. traditional Ayurveda, Unani, and Siddha medicine) as well as the Chinese system (Traditional Chinese Medicine (TCM)), among other traditional systems of medicine, have been, and continue to be, practiced within some Member States of the European Union (EU), the traditional use of senna leaf products within these systems of Traditional Medicine must be taken into consideration for the final draft of the monograph.<br>The interested party further gives examples from these Traditional Medicine Systems to support the traditional use of Senna leaves. | See above. |
| | We note the restriction of single ingredient Senna pods/leaf products to Well-Established Use market authorisation.<br>However, we are extremely concerned about the position of the many traditionally used combination herb products which include Senna pods/leaf amongst their ingredients – some examples as attached. In our view it should be possible to register such traditionally used products, which are unlikely to hold the level of evidence required for a Well-Established Use market authorisation, under the Traditional Herbal Medicinal Products Directive. | See above. |

| Comment | Comment and rationale | Rapporteur's response |
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| **3. Pharmaceutical form** | The use of the word standardised for crude drug is not correct. To our opinion is the crude drug not standardised but the finalized product made thereof. We suggest therefore to leave out the word "standardised". | All preparations or medicinal products with senna have to be standardised with regard to the amount of hydroxyanthracene glycosides. The crude herbal substance is the raw material for the preparation and not standardised first. The amount of hydroxyanthracene glycosides has to be identified and if this amount corresponds to the specifications the crude herbal substance can be used. Otherwise the herbal substance has to be processed to adjust the amount of the hydroxyanthracene glycosides. Therefore we maintain the term "standardised" but we rephrase at follows: "Standardised herbal substance or herbal preparation…" |
| | We would like to suggest "Crude or standardised processed herbal substance" instead of "Standardised crude or processed herbal substance" because the crude drug itself cannot be standardised (except in case of "inert" herbal material which is added to a herbal tea). | See above. |

| Comment | Comment and rationale | Rapporteur's response |
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| **4.1. Therapeutic indications** | With regard to the "short-term use" we would like to mention that, according to newer expert opinions, the use of stimulant laxatives (senna anthranoids, bisacodyl, sodium picosulphate) taken in correct dosages is permissible up to two to three times weekly, the indicator for correct use (this includes long term/chronic use) being the absence of laxative-induced diarrhoea [2,3]. | Senna preparations are not medicinal products on prescription. Without medical supervision a short-term use can only be recommended. As mentioned in the cited publications the diagnosis "constipation" has to be established before taking senna preparations for a long time. Therefore we recommend a special warning in section 4.4: "Use for more than 1 – 2 weeks requires medical supervision. …".<br>We agree to modify the wording in section 4.4 Posology and method of administration:<br>*Adolescents over 12 years of age, adults, elderly*<br>Herbal substance/preparation equivalent to 15 – 30 mg hydroxyanthracene derivatives, calculated as sennoside B, to be taken at night. The dosage refers to one administration. Normally it is sufficient to take this medicinal product up to two to three times **a week**. |
| | A consensus conference held in 1999 [4] came to the conclusion that, in most cases of constipation, giving a laxative is the best solution. The choice depends on the severity of constipation, possible side effects and patient compliance. Usually the intake of products rich in fibers is justified in first intention. Should this not achieve the desired results, a treatment with a stimulant laxative and the intake of fibres or of an osmotic laxative is required. At this Conference, senna was considered to be the oldest known, best documented laxative, which is <u>also suitable for long-term therapy</u> being non-mutagenic, non-carcinogenic, non-toxic and non-addictive. This is in accordance with the findings of Nusko et al. [5] who describe pseudomelanosis coli, a black discoloration of the colon caused by long-term senna use, as a harmless and reversible pigment deposit in enterocytes (see also our comments under 5.3.) | See above concerning long-term therapy.<br>Concerning carcinogenic risk we refer to our comments in chapter 4.4 and 5.3. |

| Comment | Comment and rationale | Rapporteur's response |
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| **4.2. Posology and method of administration** | The sentence "The dosage refers to one administration" is contradictory and should be deleted as it contradicts the statement that the pharmaceutical form must allow lower dosages with respect to the maximum daily dosage of hydroxyanthracene glycosides (30mg). Furthermore it is mentioned in the same chapter that the dose has to be taken at one time of the day, i.e. "to be taken at night". Therefore an individual dosage is required and advised. The necessary dosage should not only be administered at once but especially in combination with bulk-forming laxatives, each administration being followed by drinking plenty of liquid, and at least two or more administrations should be taken at one time of the day, i.e. "to be taken at night". | In our opinion this sentence is not contradictory. The information that the pharmaceutical form must allow lower dosages with respect to the maximum daily dosage of hydroxyanthracene glycosides (30 mg) does not mean that the maximum daily dosage can be distributed to more than one single dose. It means that the patient must have the ability to take less than the maximum daily dosage because the correct individual dose is the smallest required producing a comfortable soft-formed motion. The ESCOP monograph also recommends "to be taken once daily at night". This takes into account the fact that in general defaecation takes place after a delay of 8 – 12 hours and the patient is not disturbed in his sleep.<br>Alternatively we propose the wording corresponding to the ESCOP monograph:<br>"Herbal substance/preparation equivalent to 15 – 30 mg hydroxyanthracene derivatives, calculated as sennoside B, to be taken once daily at night. |
| | This HMPC document is an herbal monograph and can be used as guidance on harmonization criteria for the evaluation of herbal medicinal products. In this draft a maximal daily dose is given. The sentence "This is equivalent to … (dose of the preparation)" product specific sentence and indicates that a preparation is conform the monograph. Therefore, it is part of the product dossiers and can be left out here. | The maximal daily dose which corresponds to 30 mg hydroxyanthracene glycosides does not always correspond to the recommended dosage of the medicinal product. This dosage can be lower.<br>Therefore we maintain this wording. |
| | This chapter states that the pharmaceutical form must allow lower dosages (lower that the maximum daily dosage of 30mg hydroxyanthacene glycosides). The sentence "The dosage refers to one administration" is contradictory with this and should be deleted. | See above. |
| | For debilitated or older patients the therapy can be initiated with 8.5 mg sennosides. | There are no scientific data available for such a recommendation. In the monograph the patient is informed that the correct individual dose is the smallest required producing a comfortable soft-formed motion. Therefore the patient can adapt his individual dose. |

| Comment | Comment and rationale | Rapporteur's response |
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| **4.3. Contra-indications** | The remark "Not recommended for use in children under 12 years of age" is mentioned here as well as in chapter 4.2 "Posology and method of administration". However, we think this should only be mentioned in chapter 4.2. in order to avoid redundant information. | We maintain the remark and refer to the 'Guideline on Summary of Product Characteristics' from October 2005 and to the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMEA/HMPC/182352/2005 Rev.2). |
| | The remark "Not recommended for the use in children under 12 years" is already mentioned under 4.2. Beside it does not exclude the use in children under 12 and therefore it should be mentioned here again. | See above. |
| | Under the heading contraindication is the second part of the first sentence "should not use senna preparations" is double information and should be deleted. | We agree and propose the following wording:<br>"Patients with known hypersensitivity to senna." |
| | The use of Senna leaf should be contraindicated in menstruation period due to menorrhoea. | The causality is not plausible. |
| **4.4. Special warnings and precautions for use** | The remarks in the first sentence: "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." are redundant and should only be mentioned in Chapter 4.5 "Interactions with other medicinal products" since this is a description of interactions. | According to the 'Guideline on Summary of Product Characteristics' of October 2005 cross-references are possible and sometimes recommended.<br>The wording in this chapter describes the precaution which should be taken (consult a doctor when taking these medicinal products) and in chapter 4.5 the interaction is described. |

| Comment | Comment and rationale | Rapporteur's response |
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| **4.4. Special warnings and precautions for use**<br><br>**Continuation** | To our knowledge, there is no scientific evidence and no data available upon interactions of medicinal products inducing QT-prolongation and senna or hydroxyanthracene glycosides, respectively. Furthermore the concentrations of hydroxyanthracene glycosides systemically available are too low to make an interaction plausible. | Chronic use or abuse of anthranoid-containing laxatives may lead to hypokalaemia. This hypokalaemia and the increased loss of potassium may interfere with the action of medicinal products inducing QT-prolongation. Including this interaction was a decision of the HMPC (Haverkamp W et al. Medikamentenbedingte QT-Verlängerung und Torsade de pointes. Drug-induced QT Prolongation and Torsade de Pointes. Deutsches Ärzteblatt 2002; 99: A 1972-9 [Heft 28-29]. |
| | With regard to addiction, dosage increase, dysfunction through nerve damage and worsening of constipation, there is no evidence from literature on the development of tolerance. Müller-Lissner [2] states that tolerance to laxatives has not been systematically studied in humans, and the fact that, in many clinical studies, a proportion of patients with chronic laxative intake could be switched to dietary fibre or prokinetics or to behavioural treatment, is a strong argument against the development of tolerance. The author concludes that the development of tolerance to stimulant laxatives occurs in the most severe patient group with slow colonic transit in whom other types of laxatives are ineffective. Tolerance thus seems to be uncommon in the majority of users. From his point of view, the belief that chronic use of stimulant laxatives damages the colonic myenteric system is largely derived from uncontrolled observations in humans and from conflicting data obtained in prospective studies of animals, and the arguments in favour of laxative-induced damage to the autonomous nervous system of the colon have been advocated on the basis of poorly documented experiments.<br>On the contrary, investigations that do not support such damage are well done and performed by using a variety of techniques. It is therefore unlikely that stimulant laxatives at recommended doses are harmful to the colon. | Recent studies are not available. Also Müller-Lissner states that it is only **unlikely** (not safe) that stimulated laxatives at recommended doses are harmful to the colon. The cited references (Smith B 1968; Riemann JF et al. 1980 and 1982; Berkelhammer C et al. 2002; Meisel JL et al. 1977; Pockros PJ et al. 1985) show 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). They are uncontrolled observations and therefore the author concludes that the cause of these damages can also be the constipation itself or pre-existing changes of unknown etiology.<br><br>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) does not support the hypothesis that anthraquinone containing laxatives are able to provoke relevant degenerative changes in the colonic nerve tissue.<br><br>Müller-Lissner concludes 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 the investigations that do not support such damage are well done. But he ignores that the investigations by Riecken EO 1990 were conducted in 11 matched pairs only.<br>A definite assessment is not possible. Therefore we do not agree to delete information concerning this but we reword this advice as follows "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." |

| Comment | Comment and rationale | Rapporteur's response |
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| **4.4. Special warnings and precautions for use**<br><br>**Continuation** | The remarks in the first sentence: "Patients taking cardiac glycosides, … taking senna pods concomitantly." is a description of Interactions should only be mentioned under 4.5. "Interactions with other medicinal products". | See above. |
| | The interested party suggests to give in every monograph a special information for people with kidney and/ or liver disorders- even if there is no precautions for them. | In our opinion this is not necessary. Information will be given only if special concerns exist for these patients. It has to be discussed if, in the monographs of anthranoid-containing laxatives, a precaution should be given for patients with kidney disorders because the possibility of electrolyte imbalance might be greater:<br>"Patients with kidney disorders should be aware of possible electrolyte imbalance." |
| | The following warnings should be added:<br>Laxative should be used for short term use; do not use longer than 1 week. | The monograph already recommends that use for more than 1 – 2 weeks requires medical supervision. |

| Comment | Comment and rationale | Rapporteur's response |
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| **4.5. Interactions with other medicinal products and other forms of interaction** | The sentence "The absorption of orally administered medicinal products may be reduced" should be deleted. This effect is well known from bulk-forming laxatives but so far not documented and described for hydroxyanthracene glycosides in the dosage range of 15-30mg daily. | We agree to delete this sentence. Most medicinal products are absorbed in the stomach or small intestine. The anthranoid-containing laxatives develop their effect in the colon. Only some medicinal products to treat inflammatory colon diseases are expected to dissolve in the colon. These diseases are listed as contraindications and therefore such medicinal products must not be considered. |
| | Furthermore, the interaction regarding medicinal products inducing QT-prolongation should be deleted (see comment to chapter 4.4.). | QT-prolongation see above. |
| | A reduction of absorption of orally administered medicinal products is not described for hydroxyanthracene glycosides containing laxatives. However, from bulk-forming laxatives this effect is well known. Therefore, the sentence "The absorption of orally administered medicinal products may be reduced" should be deleted. | See above. |
| | Concomitant use of laxatives with medicinal products against diarrhoea should be avoided. | We take this for granted. |
| | It could be useful to give a short information that product/ preparation is intended to use in monotherapy and should not be administer with other laxatives. | We do not think that the concomitant use of other laxative (e.g. bulk producers) is contra-indicated e.g. reducing the amount of ingested hydroyanthracene-derivatives. |

| Comment | Comment and rationale | Rapporteur's response |
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| **4.6. Pregnancy and lactation** | We suggest using the wording from the ESCOP monograph on Sennae folium [1]:<br>*"Pregnancy:* There are no reports of undesirable or damaging effects during pregnancy or on the foetus when used in accordance with the recommended dosage schedule. However, in view of experimental data concerning a genotoxic risk from several anthranoids (e.g. emodin and aloe-emodin), avoid during the first trimester or take only under medical supervision." [References no. 33 and no. 43-54 from the ESCOP monograph]. | We maintain our wording. First of all there are no systematic practice data available concerning the use during pregnancy. Bauer H 1977 (ESCOP Reference 54) 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. 14 pregnant women were in the first trimester, 15 in the second, 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. 12 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. Nor missing of spontaneous reports of undesirable effects during pregnancy can prove this.<br>Furthermore the first trimester is a very sensible development phase of the unborn child.<br>The doctor treating the pregnant woman has no further information and therefore the advice "take only under medical supervision" makes no sense.<br><br>ESCOP Reference 43 is not published. |
| | We would like to propose deleting the sentence "Breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in breast milk" as this is in contradiction with the statement that a "laxative effect in breast fed babies has not been reported". | We do not think that this sentence is in contradiction to the statement that laxative effect in breast fed babies has not been reported. Even if the excretion of metabolites in breast milk is too small to cause a laxative effect, there are insufficient data to prove the overall safety in the breast fed babies. |

| Comment | Comment and rationale | Rapporteur's response |
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| **4.6. Pregnancy and lactation**<br><br>**Continuation** | Under this heading two statements are given. To keep it clear and without loosing any (important) information we suggest to use the wording from the ESCOP monograph on Sennae folium "*Pregnancy*: There are no reports of undesirable or damaging effects during pregnancy or on the foetus when used in accordance with the recommended dosage schedule. However, in view of experimental data concerning a genotoxic risk from several anthranoids (e.g. emodin and aloe-emodin), avoid during the first trimester or take only under medical supervision." | See above. |

| Comment | Comment and rationale | Rapporteur's response |
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| **4.8. Undesirable effects** | From our point of view, equating the terms "chronic use" and "abuse" is not correct. The above-mentioned consensus conference stated that in the discussion of the risks associated with laxatives, laxative abuse plays a large role. It is very often equated with chronic laxative use which is in no way justified. In comparison to many other drugs, though, the abuse can be determined very easily through the resulting diarrhoea. Compared to the large number of "normal" laxative users in the population, the "abusers" are rare and extreme exceptions that have nothing to do with the therapeutic use of laxatives. | We agree to reword this chapter and the chapter 'overdose' as follows (frequencies see below):<br>Hypersensitive reactions may occur.<br>Senna leaves may produce abdominal pain and spasm and passage of liquid stools, in particular in patients with irritable colon. However, these symptoms may also occur generally as a consequence of individual overdosage. In such cases dose reduction is necessary.<br>Chronic use may lead to disorders in water equilibrium and electrolyte metabolism and may result in albuminuria and haematuria.<br>Furthermore, chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation.<br>Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.<br><br>Overdose<br>The major symptoms of overdose / abuse are griping pain and severe diarrhoea with consequent losses of fluid and electrolyte, which should be replaced.<br>Diarrhoea may especially cause potassium depletion, which may lead to cardiac disorders and muscular asthenia, particularly where cardiac glycosides, diuretics, adrenocorticosteroids or liquorice root are being taken at the same time.<br>Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly. Chronic ingested overdoses of anthranoid containing medicinal products may lead to toxic hepatitis.<br><br>According to the 'Guideline on Summary of Product Characteristics' of October 2005 choice of frequency category is based on studies. The frequencies based on reporting rates from a spontaneous reporting system should not be used for choosing a frequency category in any situation. Because there are no studies available, we omit the frequency categories. |
| | Under this heading several effects are described. The second paragraph: "Very rarely … is necessary" describes the effects of overdose. This information is given under heading 4.9. "Overdose" and should be deleted here. | This only describes an effect of an individual overdose with the recommended dose which might be sometimes too high and does not describe the effect of a general overdose. Therefore we maintain this wording in this chapter. |

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| **4.8. Undesirable effects**<br><br>**Continuation** | The third paragraph: "Chronic use … albuminuria and haematuria." is a warning and already included under heading 4.4. Therefore, it should be left out here. | We reword this chapter and the chapter 'overdose' (see above). Especially in case of overdose disorders in electrolyte metabolism are possible which lead to the named interactions. Therefore we prefer to repeat this here. |
| | The interested party does not agree with the wording of the text of Section 4.8 Undesirable effects, second paragraph : "Very rarely senna leavess/pods may produce abdominal pain and…." . According to the Guideline on Summary of Product Characteristics "very rare" is used for an ADR frequency of ≤ 1/10,000. However, the interested party is of the opinion that this is a generally occurring symptom directly related to the mode of action of senna. Therefore, the interested party proposes to omit the words "very rarely" in the draft monograph. | We agree to omit the words "very rarely". According to the 'Guideline on Summary of Product Characteristics' of October 2005 choice of frequency category is based on studies. The frequencies based on reporting rates from a spontaneous reporting system should not be used for choosing a frequency category in any situation. |
| | Poor colonic function (cathartic colon) may result from chronic use of anthraquinone laxatives (Hebel & Burnham, 2000). | Cathartic colon is caused by chronic use which is not recommended. In the monograph such an effect is mentioned in chapter 4.4 "Special warnings and precautions for use". |
| | Large doses of anthraquinones may cause nephritis. The condition is reversible with discontinuation of the drug. (Brunton,1996). | Nephritis as a response to large doses of anthraquinones is mentioned by Brunton without any further information or references.<br>Vanderperren B 2005 (6) reported one case with acute liver failure and renal impairment related to the abuse of senna anthraquinone glycosides. A relationship between this abuse of senna and the renal impairment is too weak to mention this in the monograph. |
| | Prolonged use or abuse of senna laxatives has been associated with reversible finger clubbing, (1-4) and tetany, (1) hypertrophic osteoarthropathy, (4) intermittent urinary excretion of aspartylglucosamine, (2) hypogammaglobulinaemia, (3) reversible cachexia, (3) and hepatitis (5) or hepatic failure.<br>(1) Reference 127 of the assessment report<br>(2) Reference 128<br>(3) Reference 129<br>(4) Reference 130<br>(5) Reference 91<br>(6) Reference 122 | According to the Rucam score (see assessment report) the hepatotoxic cases (5, 6) are related to the chronic ingested overdoses and therefore they cannot be mentioned in chapter 4.8 "Undesirable effects" but in chapter 4.9 "Overdose".<br><br>The other reported cases have in common a history of anorexia nervosa with an abuse of senna to control the 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 the data available are not strong enough and we do not introduce these effects in the monograph. |

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| **4.9 Overdose** | The use of the drug is not recommended in children under 12 years (4.3. Contraindication). Last word in the final line of this heading reads "young". What did the committee mean with this word? | This is right and we omit "young". |
| **5.1 Pharmaco-dynamic properties** | A space is missing between rhein and anthrone (sixth line second paragraph). The same goes for the use of this word in heading 5.2 Pharmacokinetic properties. | Agree. |
| **5.2 Pharmaco-kinetic properties** | Passage of rhein is "low" instead of "small" (last word of this paragraph). | Agree. |

| Comment | Comment and rationale | Rapporteur's response |
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| **5.3 Preclinical safety data** | Results from in vivo studies<br><br>After the 3rd sentence "As a result of investigations .... possibly due to the content of aglyca", we suggest including the following sentence: *"In a 90-day rat study, senna pods did not induce any specific target organ toxicity at dose levels of up to 1,500 mg/kg."* This is in accordance with new safety data [6] that did not show any specific organ toxicity.<br><br>Furthermore, recent investigations [7] on the aloeemodin and emodin content of senna pods with hydroxyanthracene glycoside concentrations up to 4.6% showed no significant increase of the "impurity level" compared to the hydroxyanthracene glycoside concentrations of 1.4 to 3.5% as reported in the Community Herbal Monograph Draft.<br><br>The 5th sentence "Data for herbal substance preparations are not available." should be deleted. As described above and as presented below, new preclinical data on short-term and long-term assessment for senna preparations is now available [6, 8].<br><br>After the 10th sentence the results from a new long-term study should be included:<br>*"A 104-week study on rats of both genders did not reveal any carcinogenic effects with senna pods at oral dosages of up to 300 mg/kg. The tested drug contained 1.83 % sennosides A-D, 1.6 % potential rhein, 0.11 % potential aloe-emodin and 0.014 % potential emodin. In addition, a specified senna extract given orally for 2 years..."* [8]. | We agree to amend the results of the cited references and to reword the chapter as follows:<br>"There are no new, systematic preclinical tests for senna leaves or preparations thereof. Data derive from investigations with senna pods. Since the spectrum of constituents of senna leaf and fruit is comparable, these data can be transferred to senna leaves. Most data refer to extracts 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 isolated active constituents, e.g. rhein or sennosides A and B. The acute toxicity of senna pods, specified extracts thereof, as well as of sennosides in rats and mice was low after oral treatment. As a result of investigations with parenteral application in mice, extracts are supposed to possess a higher toxicity than purified glycosides, possibly due to the content of aglyca.<br>In a 90-day rat study, senna pods were administered at dose levels from 100 mg/kg of up to 1,500 mg/kg. The tested drug contained 1.83 % sennosides A-D, 1.6 % potential rhein, 0.11 % potential aloe-emodin and 0.014 % potential emodin. In all groups epithelial hyperplasia of the large intestine of minor degree was found and was reversible within the 8-week recovery period. The hyperplastic lesions of the forestomach epithelium were reversible as well. Dose-dependent tubular basophilia and epithelial hypertrophy of the kidneys were seen at a dose of, or greater than 300 mg/kg per day without functional affection. These changes were also reversible. Storage of a brown tubular pigment led to a dark discoloration of the renal surface and still remained to a lesser degree after the recovery period. No alterations were seen in the colonic nervous plexus. A NOEL could not be obtained in this study.<br>A 104-week study on rats of both genders did not reveal any carcinogenic effects with the same senna pods preparation at oral dosages of up to 300 mg/kg.<br>In addition a specified senna extract given orally for 2 years was not carcinogenic in male or female rats. |

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| **5.3 Preclinical safety data**<br><br>**Continuation** | After the section on the carcinogenicity study with senna extract (after the 12th sentence) the results from the NTP study on emodin should be included as follows:<br>*"In further 2-year studies on male and female rats and mice, emodin did not significantly increase the spontaneous tumor ratio in comparison to controls."*<br>This corresponds to reference no. 121 of the ESCOP monograph "Sennae folium" [1]. concludes that "all subsequent studies failed to find an association between anthranoid laxative intake and CRC." For this reason, it is incomprehensible why a statement which implies potential risk and spurs unfounded fear should be part of a new senna monograph. | The extract investigated contained approximately 40.8% of anthranoids from which 35% were sennosides, corresponding to about 25.2% of potential rhein, 2.3% of potential aloe-emodin and 0.007% of potential emodin and 142 ppm free aloe-emodin and 9 ppm free emodin.<br>Further 2-year studies on male and female rats and mice with emodin gave no evidence of carcinogenic activity for male rats and female mice, and equivocal evidence for female rats and male mice.<br>Sennosides displayed no specific toxicity when tested at doses up to 500 mg/kg in dogs for 4 weeks and up to 100 mg/kg in rats for 6 months.<br>There was no evidence of any embryolethal, teratogenic or foetotoxic actions in rats or rabbits after oral treatment with sennosides. Furthermore, there was no effect on the postnatal development of young rats, on rearing behaviour of dams or on male and female fertility in rats. Data for herbal preparations are not available.<br>An extract and aloe-emodin were mutagenic in *in vitro* tests, sennoside A, B and rhein gave negative results. Comprehensive *in vivo* examinations of a defined extract of senna pods were negative."<br>We maintain the specification "extracts containing 1.4 to 3.5% of anthranoids" because the information sent by the organisations are too poor. We have only received one page with results. For assessing these investigations more data about the investigation itself are needed. |
| | <u>No risk of colorectal cancer</u><br><br>In terms of a potential risk of colorectal cancer we strongly disagree with the closing statement concerning the risk of colorectal cancer (CRC). Amongst others, a recent study of Müller-Lissner [2] | We cannot ignore the former findings. Up to now some questions remain. Müller-Lissner cites 2 recent case-control investigations:<br>- Jacobs EJ et White E (Constipation, laxative use, and colon cancer among middle-aged adults. Epidemiology 1998; 9: 385-91) did not include subjects, who took anthraquinone-containing laxatives.<br>- Roberts MC et al. (Constipation, laxative use, and colon cancer in a North Carolina population. Am J Gastroenterol 2003; 98: 857-64) did not mention anthraquinone-containing laxatives. They mentioned the group "stimulants, fibers, natural remedies, stool softeners, oils, osmotic agents, enemas, suppositories, and unknown". In table 4 of the publication, they only listed 'phenolphthalein', 'fiber', 'magnesium', 'other commercial' and 'non-commercial or unknown'. |

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| **5.3 Preclinical safety data**<br><br>**Continuation** | Nusko et al. [5] state that 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 the duration of intake. Macroscopic and high grade microscopic melanosis coli were not significant risk factors for the development of adenomas or carcinomas. The authors came to the conclusion that neither anthranoid laxative use, even in the long term, nor macroscopic or marked microscopic melanosis coli were associated with any significant risk for the development of colorectal adenoma or carcinoma. Müller-Lissner [2] states that care should be taken when extrapolating the findings of animal studies to humans since the results have been obtained using very high doses of anthranoids for a relatively long period compared to the lifespan of animals. A large number of clinical studies failed to find an association between anthranoid laxative intake and CRC. In conclusion, although chronic constipation appears to be associated with an increased risk of CRC, there are no data to support that stimulant laxatives are an independent risk factor for CRC.<br><br>**For these reasons, the last section: "Commercial laxative use cannot be definitely assessed." should be replaced by the following sentence: *"The overall preclinical data showed the safety of senna preparations."***<br><br> | Conclusions cannot be drawn from these publications about the carcinogenic risk of anthraquinone-containing laxatives.<br>Therefore we propose the following rewording: "Laxative use as a risk factor in colorectal cancer (CRC) was investigated in some clinical trials. Some studies revealed a risk for CRC associated with the use of anthraquinone-containing laxatives, some studies did not. However, a risk was also revealed for constipation itself and underlying dietary habits. Further investigations are needed to assess the carcinogenic risk definitely." |

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| **5.3 Preclinical safety data**<br><br>**Continuation** | Results from in vivo studies<br><br>Mengs and co-workers showed senna did not induce any specific organ toxicity in rats after 13 weeks [Mengs at al 2004]. In accordance with this data we suggest to include after the third sentence "As a result … content of aglyca" the following sentence: "Daily administration senna pods (up to 1.500 mg/kg body weight for 13 weeks) to rats did not induce any specific target organ toxicity."<br><br>The results reported by Mends et al and Mitchel et al showed that there is data available and therefore the 5th sentence "Data for herbal substance preparations are not available." should be deleted [Mengs at al 2004, Mitchel et al 2006].<br><br>In forth paragraph information concerning the tested amount of extract is missing. A new studied amount oral carcinogenicity and toxicity is published recently. The results of this study should be included after the 10th sentence: "After oral administration of senna pods (up to 300 mg/kg/day for 104 consecutive weeks) to rats (male and female) no carcinogenic effects were seen" [Mitchel et al 2006].<br><br>In terms of a potential risk of colorectal cancer we respectfully note that we are in complete disagreement with the closing statement to the risk of colorectal cancer. Amongst others, a recent study of Mueller-Lissner concludes, "all subsequent studies failed to find an association between anthranoid laxative intake and colorectal cancer." For this reason, this statement should be deleted. | See above. |

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| **5.3 Preclinical safety data**<br><br>**Continuation** | Nusko and co-workers state that there was no statistically significant risk of anthranoid use for the development of colorectal adenomas or carcinomas. 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. The authors came to the conclusion that neither anthranoid laxative use, even in the long term, nor macroscopic or marked microscopic melanosis coli were associated with any significant risk for the development of colorectal adenoma or carcinoma [Nusko et al 2000].<br><br>Mueller-Lissner states that care should be taken when extrapolating the findings of animal studies to humans since the results have been obtained using very high doses of anthranoids for a relatively long period compared to the lifespan of animals. A large number of clinical studies failed to find an association between anthranoid laxative intake and colorectal cancer. In conclusion, although chronic constipation appears to be associated with an increased risk of colorectal cancer, there are no data to support that stimulant laxatives are an independent risk factor for colorectal cancer [Mueller-Lissner 2005]. | See above. |