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Evaluation of Medicines for Human Use

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COMMITTEE ON HERBAL MEDICINAL PRODUCTS

COMMUNITY HERBAL MONOGRAPH ON *CASSIA SENNA* L. AND *CASSIA ANGUSTIFOLIA* VAHL, FOLIUM

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[1] Changes introduced in sections 4.9 and 5.1

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COMMUNITY HERBAL MONOGRAPH ON *CASSIA SENNA* L. AND *CASSIA ANGUSTIFOLIA* VAHL, FOLIUM

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished product.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[2, 3]

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC, as amended *Cassia senna* L. (*C. acutifolia* Delile) [known as Alexandrian or Khartoum senna] or *Cassia angustifolia* Vahl [known as Tinnevelly senna], folium (senna leaf) • Herbal substance dried leaflets, standardised • Herbal preparation standardised herbal preparations thereof	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC, as amended

3. PHARMACEUTICAL FORM

Well-established use	Traditional use
Standardised herbal substance or herbal preparation for oral use in solid or liquid dosage forms. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.	

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Well-established use	Traditional use
Herbal medicinal product for short-term use in cases of occasional constipation.	None

[2] The material complies with the Ph. Eur. monograph.
[3] The declaration of the active substance(s) should be in accordance with relevant herbal quality guidance .

4.2. Posology and method of administration

Well-established use	Traditional use
Posology The maximum daily dose of hydroxyanthracene glycosides is 30 mg. This is equivalent to ....(dose of the preparation). The correct individual dose is the smallest required to produce a comfortable soft-formed motion. *Adolescents over 12 years of age, adults, elderly* Herbal substance/preparation equivalent to 15 – 30 mg hydroxyanthracene derivatives, calculated as sennoside B, to be taken once daily at night. Normally it is sufficient to take this medicinal product up to two to three times a week. Not recommended for use in children under 12 years of age (see section 4.3 Contraindications). The pharmaceutical form must allow lower dosages. **Method of administration** As described in the package leaflet corresponding to the pharmaceutical form e.g. tea bag. **Duration of use** Use for more than 1 - 2 weeks requires medical supervision. If the symptoms persist during the use of the medicinal product, a doctor or a pharmacist should be consulted. See also section 4.4 Special warnings and precautions for use.	

4.3. Contraindications

Well-established use	Traditional use
Known hypersensitivity to the active substance. Cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis), abdominal pain of unknown origin, severe dehydration state with water and electrolyte depletion. Children under 12 years of age.	

4.4 Special warnings and precautions for use

Well-established use	Traditional use
Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, have to consult a doctor before taking senna leaves concomitantly. Like all laxatives, senna leaves should not be taken by patients suffering from faecal impaction and undiagnosed, acute or persistent gastro-intestinal complaints, e.g. abdominal pain, nausea and vomiting, unless advised by a doctor, because these symptoms can be signs of potential or existing intestinal blockage (ileus). If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of laxatives should be avoided. If stimulant laxatives are taken for longer than a brief period of treatment, this may lead to impaired function of the intestine and dependence on laxatives. Senna leaf preparations should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents. When senna leaf preparations are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces. Patients with kidney disorders should be aware of possible electrolyte imbalance.	

4.5 Interactions with other medicinal products and other forms of interaction

Well-established use	Traditional use
Hypokalaemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides and interacts with antiarrhythmic medicinal products, with medicinal products, which induce reversion to sinus rhythm (e.g. quinidine) and with medicinal products inducing QT-prolongation. Concomitant use with other medicinal products inducing hypokalaemia (e.g. diuretics, adrenocorticosteroids and liquorice root) may enhance electrolyte imbalance.	

4.6 Pregnancy and lactation

Well-established use	Traditional use
Pregnancy *Wording for extracts specified as those investigated (see section 5.3 Preclinical safety data):* There are no reports of undesirable or damaging effects during pregnancy and on the foetus when used at the recommended dosage. As a consequence of experimental data concerning a genotoxic risk of several anthranoids, e.g. emodin and aloe-emodin, 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. *Wording for all other preparations:* There are no reports of undesirable or damaging effects during pregnancy and on the foetus when used at the recommended dosage. However, as a consequence of experimental data concerning a genotoxic risk of several anthranoids, e.g. emodin and aloe-emodin, use is not recommended during pregnancy. **Lactation** Use during breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in breast milk. Small amounts of active metabolites (rhein) are excreted in breast milk. A laxative effect in breast fed babies has not been reported.	

4.7 Effects on ability to drive and use machines

Well-established use	Traditional use
Not relevant.	

4.8 Undesirable effects

Well-established use	Traditional use
Hypersensitivity reactions (pruritus, urticaria, local or generalised exanthema) may occur. 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 overdose. In such cases dose reduction is necessary. Chronic use may lead to disorders in water equilibrium and electrolyte metabolism and may result in albuminuria and haematuria. Furthermore, chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation. Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment. If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.	

4.9. Overdose

Well-established use	Traditional use
The major symptoms of overdose/abuse are griping pain and severe diarrhoea with consequent losses of fluid and electrolytes, which should be replaced. Diarrhoea may 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. Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly. Chronic ingested overdoses of anthranoid containing medicinal products may lead to toxic hepatitis.	

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Well-established use	Traditional use
Pharmaco-therapeutic group: contact laxatives ATC-code: A 06 AB 1,8-dihydroxyanthracene derivatives possess a laxative effect. The β-O-linked glycosides (sennosides) are not absorbed in the upper gut; they are converted by bacteria of the large intestine into the active metabolite (rhein anthrone). There are two different mechanisms of action: 1. stimulation of the motility of the large intestine resulting in accelerated colonic transit. 2. influence on secretion processes by two concomitant mechanisms *viz*. inhibition of absorption of water and electrolytes (Na^+, Cl^-) into the colonic epithelial cells (antiabsorptive effect) and increase of the leakiness of the tight junctions and stimulation of secretion of water and electrolytes into the lumen of the colon (secretagogue effect) resulting in enhanced concentrations of fluid and electrolytes in the lumen of the colon. Defaecation takes place after a delay of 8 - 12 hours due to the time taken for transport to the colon and metabolisation into the active compound.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

5.2. Pharmacokinetic properties

Well-established use	Traditional use
The β-O-linked glycosides (sennosides) are neither absorbed in the upper gut nor split by human digestive enzymes. They are converted by the bacteria of the large intestine into the active metabolite (rhein anthrone). Aglyca are absorbed in the upper gut. Animal experiments with radio-labeled rhein anthrone administered directly into the caecum demonstrated absorption < 10%. In contact with oxygen, rhein anthrone is oxidised into rhein and sennidins, which can be found in the blood, mainly in the form of glucuronides and sulphates. After oral administration of sennosides, 3 - 6% of the metabolites are excreted in urine; some are excreted in bile.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

Most of the sennosides (ca. 90%) are excreted in faeces as polymers (polyquinones) together with 2 - 6% of unchanged sennosides, sennidins, rhein anthrone and rhein. In human pharmacokinetic studies with senna pods powder (20 mg sennosides), administered orally for 7 days, a maximum concentration of 100 ng rhein/ml was found in the blood. An accumulation of rhein was not observed. Active metabolites, e.g. rhein, pass in small amounts into breast milk. Animal experiments demonstrated that placental passage of rhein is low.	

5.3. Preclinical safety data

Well-established use	Traditional use
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 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 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. In a 90-day rat study, senna pods were administered at dose levels from 100 mg/kg 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 no-observable-effect-level (NOEL) could not be obtained in this study.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended, unless necessary for the safe use of the product.

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. In addition a specified senna extract given orally for 2 years was not carcinogenic in male or female rats. 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. 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. 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. 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. 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. Laxative use as a risk factor in colorectal cancer (CRC) was investigated in some clinical trials. Some studies revealed a risk for CRC associated with the use of anthraquinone-containing laxatives, some studies did not. However, a risk was also revealed for constipation itself and underlying dietary habits. Further investigations are needed to assess the carcinogenic risk definitely.	

6. PHARMACEUTICAL PARTICULARS

Well-established use	Traditional use
Not applicable.	

7. DATE OF COMPILATION/LAST REVISION

1 March 2007