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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

COMMUNITY HERBAL MONOGRAPH ON SENNA LEAF (SENNAE FOLIUM)

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COMMUNITY HERBAL MONOGRAPH ON SENNA LEAF (SENNAE FOLIUM)

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished products.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC, as amended **Active ingredients** Senna leaf in the crude or processed state in appropriate dosage units **Definition** Senna leaf consists 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. It contains not less than 2.5 per cent of hydroxyanthracene glycosides, calculated as sennosides B (Mr 863) with reference to the dried herbal substance.[1] **Constituents** The constituents of known therapeutic activity are sennosides A and B which are rhein-dianthrone diglycosides. There are also small quantities of other dianthrone diglycosides, monoanthraquinone glycosides and aglyca.	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 crude or processed herbal substance for oral preparation in solid or liquid dosage forms (to be specified for the individual finished product). The pharmaceutical form should be described according to the standard terms by the European Pharmacopoeia.	

[1] The herbal substance complies with the European Pharmacopoeia.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Well-established use	Traditional use
For short term use in cases of occasional constipation.	None

4.2. Posology and method of administration

Well-established use	Traditional use
Dosage 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 at night. The dosage refers to one administration. Not recommended for use in children under 12 years of age. The pharmaceutical form must allow lower dosages. **Method of administration** For oral administration	

4.3. Contraindications

Well-established use	Traditional use
Patients with known hypersensitivity to senna should not use senna preparations. Not to 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. Not recommended for use in 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 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. If stimulating laxatives are taken for longer than a brief period of treatment, this may lead to dependence requiring increasing quantities of the medicinal product, an atonic colon with impaired function and aggravation of the constipation. 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.	

4.5. Interactions with other medicinal products and other forms of interaction

Well-established use	Traditional use
The absorption of orally administered medicinal products may be reduced. 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 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 fail. *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** 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 known.	

4.8. Undesirable effects

Well-established use	Traditional use
Hypersensitive reactions (pruritus, urticaria, local or generalised exanthema) may occur very rarely. Very rarely 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.	

Chronic use/abuse may lead to disorders in water equilibrium and electrolyte metabolism. 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. Chronic use 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.	

4.9. Overdose

Well-established use	Traditional use
The major symptoms are griping pain and severe diarrhoea with consequent losses of fluid and electrolyte, which should be replaced. Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly and the young.	

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 (rheinanthrone). There are two different mechanisms of action: 1. an influence on the motility of the large intestine (stimulation of peristaltic contractions and inhibition of local contractions) resulting in accelerated colonic transit, thus reducing fluid absorption.	Not applicable as per Article 16 c(1)(a)(iii) of Directive 2001/83/EC as amended

2. an influence on secretion processes (stimulation of mucus and active chloride secretion) resulting in enhanced fluid secretion. 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.	

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 (rheinanthrone). Aglyca are absorbed in the upper gut. Animal experiments with radio-labeled rheinanthrone administered directly into the caecum demonstrated absorption < 10%. In contact with oxygen, rheinanthrone 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. Most of the sennosides (ca. 90%) are excreted in faeces as polymers (polyquinones) together with 2-6% of unchanged sennosides, sennidins, rheinanthrone and rhein. In human pharmacokinetic studies with senna pods powder (20 mg sennosides), administered orally for 7 days, a max. 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 small.	Not applicable as per Article 16 c(1)(a)(iii) of Directive 2001/83/EC as amended

5.3. Preclinical safety data

Well-established use	Traditional use
There are no new, systematic preclinical tests for senna leaves or preparations thereof. 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,	Not applicable as per Article 16 c(1)(a)(iii) of Directive 2001/83/EC as amended

possibly due to the content of aglyca. 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 are no data for herbal substance preparations available. 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 substance preparations are not available. An extract and aloe-emodin were mutagenic in *in vitro* tests, sennoside A, B and rhein gave negative results. *In vivo* examinations of a defined extract of senna pods were negative. A specified senna extract given orally for 2 years was not carcinogenic in male or female rats. The extract investigated contained approx. 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. Commercial laxative use as a risk factor in colorectal cancer was investigated in some clinical trials. The results of the more recent studies are inconsistent and therefore the possibility of a carcinogenic risk of long-term use of anthranoid-containing laxatives cannot be definitely assessed.	

6. DATE OF COMPILATION

11 January 2006