EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 July 2017
EMA/HMPC/625849/2015
Committee on Herbal Medicinal Products (HMPC)

European Union herbal monograph on *Senna alexandrina* Mill. (*Cassia senna* L.; *Cassia angustifolia* Vahl) [1], folium

Draft-Revision

Initial assessment	
Discussion in Working Party on European Union monographs and list (MLWP)	Nov 2005 Jan 2006
Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation	11 January 2006
End of consultation (deadline for comments)	31 May 2006
Re-discussion in MLWP	September 2006
Adoption by HMPC Monograph (EMA/HMPC/600717/2007) AR (EMA/HMPC/3968/2008) List of references (EMA/HMPC/102303/2008) Overview of comments received during public consultation (EMA/HMPC/439318/2010) HMPC Opinion (EMA/HMPC/756918/2010)	13 July 2006
First revision	
Discussion in Working Party on European Union monographs and list (MLWP)	Sep 2015 Apr 2016 May/Jun 2016 Sep 2016 Jan 2017 May 2017

1 The botanical name of the herbal substance has been changed, see assessment report (EMA/HMPC/228759/2016) for further details.

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Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation	18 July 2017
Start of public consultation	12 October 2017
End of consultation (deadline for comments). Comments should be provided using this template to hmpc.secretariat@ema.europa.eu	12 January 2018

Keywords	Herbal medicinal products; HMPC; European Union herbal monographs; well-established medicinal use; *Senna alexandrina* Mill.(*Cassia senna* L.,; *Cassia angustifolia* Vahl), folium; Sennae folium; senna leaf;

BG (bulgarski): Сена, лист CS (čeština): sennový list DA (dansk): Sennesblad DE (Deutsch): Sennesblätter EL (elliniká): φύλλο σέννης EN (English): Senna Leaf ES (español): Sen, hoja de ET (eesti keel): sennaleht FI (suomi): senna, lehti FR (français): Sené (feuille de) HR (hrvatski): senin list HU (magyar): Szennalevél IT (italiano): Senna foglia	LT (lietuvių kalba): Senų lapai LV (latviešu valoda): Sennu lapas MT (Malti): Werqa tal-Senna NL (Nederlands): Sennablad PL (polski): Liść senesu PT (português): Sene-da-índia, folha RO (română): frunză de siminichie, fruză de foi de mamă SK (slovenčina): List senny SL (slovenščina): list sene SV (svenska): Senna, blad IS (íslenska): NO (norsk): Sennesblad

European Union herbal monograph on *Senna alexandrina* Mill., 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 *Senna alexandrina* Mill. (*Cassia senna* L.; *Cassia angustifolia* Vahl), folium (senna leaf) i) Herbal substance Not applicable. ii) Herbal preparations Comminuted herbal substance or herbal preparations thereof, standardised	

3. Pharmaceutical form

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

2 The declaration of the active substance(s) for an individual finished product should be in accordance with relevant herbal quality guidance.

3 The material complies with the Ph. Eur. monograph (ref.: 0206).

4. Clinical particulars

4.1. Therapeutic indications

Well-established use	Traditional use
Herbal medicinal product for short-term use in cases of occasional constipation.	

4.2. Posology and method of administration[4]

Well-established use	Traditional use
Posology *Adolescents over 12 years of age, adults, elderly* Single dose: Herbal preparation equivalent to 10 – 30 mg hydroxyanthracene derivatives, calculated as sennoside B (photometric method) to be taken once daily at night. The correct individual dose is the smallest required to produce a comfortable soft-formed motion. The use in children under 12 years of age is contraindicated (see section 4.3 Contraindications). The pharmaceutical form must allow lower dosages. **Duration of use** Not to be used for more than 1 week. Usually it is sufficient to take this medicinal product up to two to three times during that week. 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. **Method of administration** Oral use.	

[4] For guidance on herbal substance/herbal preparation administered as herbal tea or as infusion/decoction/macerate preparation, please refer to the HMPC 'Glossary on herbal teas' (EMA/HMPC/5829/2010 Rev.1).

4.3. Contraindications

Well-established use	**Traditional use**
Hypersensitivity to the active substance. Cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis), abdominal pain of unknown origin, severe dehydration state with water and electrolyte depletion. Pregnancy and lactation (see section 4.6 and 5.3) Children under 12 years of age.	

4.4. Special warnings and precautions for use

Well-established use	**Traditional use**
Long-term use of stimulant laxatives should be avoided, as use for more than a brief period of treatment may lead to impaired function of the intestine and dependence on laxatives. If laxatives are needed every day the cause of the constipation should be investigated. Senna 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. 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 leaf preparations concomitantly. Like all laxatives, senna leaf preparations should not be taken by patients suffering from faecal impaction and undiagnosed, acute or persistent gastro-intestinal complaints, e.g. abdominal pain, nausea and vomiting, unless advised by a doctor, because these symptoms can be signs of potential or existing intestinal blockage (ileus). When preparations containing senna 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.	

Well-established use	Traditional use
If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted. For liquid dosage forms containing ethanol the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.	

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. Concomitant use with diuretics, adrenocorticosteroids and liquorice root may enhance loss of potassium.	

4.6. Fertility, pregnancy and lactation

Well-established use	Traditional use
Pregnancy The use during pregnancy is contraindicated because experimental data concerning a genotoxic risk of several anthranoids, e.g. emodin and aloe-emodin. **Lactation** The use during lactation is contraindicated because after administration of anthranoids, active metabolites, such as rhein, were excreted in breast milk in small amounts. **Fertility** No fertility data are available (see section 5.3 preclinical safety data)	

4.7. Effects on ability to drive and use machines

Well-established use	**Traditional use**
No studies on the effect on the ability to drive and use machines have been performed.	

4.8. Undesirable effects

Well-established use	**Traditional use**
Hypersensitivity: Hypersensitivity reactions (pruritus, urticaria, local or generalised exanthema) may occur. Gastrointestinal disorders: Senna leaf preparations 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. Furthermore, chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation. Kidney and Urinary tract symptoms: Long term use may lead to water and electrolyte imbalance and may result in albuminuria and haematuria. Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment. The frequencies are not known. 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. Treatment should	

Well-established use	Traditional use
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
Pharmacotherapeutic group: contact laxatives Proposed ATC code: A06AB06 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: stimulation of the motility of the large intestine resulting in accelerated colonic transit. 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.	

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). Aglycones 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. 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 preclinical data available for senna leaves or preparations thereof. It can be assumed that data obtained with senna pods can be transferred to senna leaf preparations. In a 90-day rat study, senna pods were administered at dose levels from 100 mg/kg of up to 1500 mg/kg (human equivalence dose of 16-242 mg/kg). In all groups epithelial hyperplasia of the large intestine of minor degree was found and was reversible within the 8-week recovery period.	

Well-established use	Traditional use
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. Senna pods, extracts thereof and several hydroxyl anthracene derivatives were mutagenic and genotoxic in several *in vitro* test systems, however for senna and aloe-emodin this was not proven in *in vivo* systems. In long term carcinogenicity studies with senna pods effects on kidneys and colon/caecum were reported.	

6. Pharmaceutical particulars

Well-established use	Traditional use
Not applicable	

7. Date of compilation/last revision

18 July 2017