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COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)

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ASSESSMENT REPORT ON
CASSIA SENNA L., FRUCTUS AND CASSIA ANGUSTIFOLIA VAHL, FRUCTUS

Herbal substance	Alexandrian senna pods: Cassia senna L. (Cassia acutifolia Delile), Tinnevelly senna pods: Cassia angustifolia Vahl
Herbal preparation	dried fruits
Pharmaceutical forms	Herbal substance for oral preparation
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I. Introduction

This assessment report on senna fruits (pods) refers to the assessment report on senna leaves, because the spectrum of constituents of senna leaves is comparable to that of senna fruits.

The assessment report on senna leaves 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 core-SPC for *Sennae folium* established in 1994 by the Committee for Proprietary Medicinal Products (CPMP) was taken into consideration. The report also reviewed the literature presented by the European Scientific Cooperative on Phytotherapy (ESCOP) to support the monographs “*Sennae folium* (Senna leaf)”, “*Sennae fructus acutifoliae* (Alexandrian Senna Pods)” and “*Sennae fructus angustifoliae* (Tinnevelley Senna Pods)” (ESCOP Monographs, second edition 2003). The report on senna leaves took also into account the literature presented by the World Health Organization (WHO) for the monographs “*Folium Sennae*” and “*Fructus Sennae*”.

Finally, the CPMP core-SPC for *Sennae fructus acutifoliae* (1994) was integrated in the assessment.

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 etiology (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 9th or 10th 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 fruits are intended “for short-term use in cases of occasional constipation”.

This indication is substantiated by extensive empirical data (stemming from research into the constituents and their pharmacology) and by clinical data.

Senna fruits 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

Alexandrian senna pods (*Sennae fructus acutifoliae*) consist of the dried fruit of *Cassia senna* L. (*Cassia acutifolia* Delile). They contain not less than 3.4 % of hydroxyanthracene glycosides, calculated as sennoside B ($C_{42}H_{38}O_{20}$; M_r 863) with reference to the dried herbal substance. The material complies with the European Pharmacopoeia monograph “Senna pods, Alexandrian” (ref.01/2005:0207).

The main active constituents are sennosides A and B (ca. 4%), which are rhein-dianthrone diglycosides. Smaller amounts of other dianthrone diglycosides, monoanthraquinone glycosides and aglyca are also present.

Tinnevelley senna pods (*Sennae fructus angustifoliae*) consist of the dried fruit of *Cassia angustifolia* Vahl. They contain not less than 2.2 % of hydroxyanthracene glycosides calculated as sennoside B ($C_{42}H_{38}O_{20}$; M_r 863) with reference to the dried herbal substance. The material complies with the European Pharmacopoeia monograph “Senna pods, Tinnevelley” (ref.01/2005: 0208).

The main active constituents are sennosides A and B (ca. 2.5%), which are rhein-dianthrone diglycosides. 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 where as preparations produced without heat like cold macerations do not contain these constituents. But 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 constituents of senna leaves and fruits are comparable, only the percentage distribution seems to be different. 85 to 90 % dianthrone glycosides and 10 to 15 % anthrone glycosides were found in the fruits. Nearly 95 % of the sennosides are sennosides A, A₁ and B, and 5 % are sennosides C and D. The fraction of the naphthalene glycoside tinnevellin glycoside is only found at 0.3 %. The senna leaves contain 75 to 80 % dianthrone and 20 to 25 % anthrone, which are predominantly present as glycosides. Nearly 80 % of the sennosides are sennosides A, A₁ and B, and 20 % are sennosides C and D. In the leaves tinnevellin glycoside is present at 0.4 % (10).

The amount of anthranoids of the emodin and aloe-emodin type is generally higher in the leaves than in the fruits (7).

II.1.2 Absorption, metabolism and excretion

We refer to the assessment report on *Sennae folium*.

II.1.3 Progress of action

We refer to the assessment report on *Sennae folium*.

II.2 Pharmacodynamics

We refer to the assessment report on *Sennae folium*.

III. Clinical Efficacy

We refer to the assessment report on *Sennae folium*.

IV. Safety

We refer to the assessment report on *Sennae folium*.

V. Overall Conclusion

The conclusion from the evaluation of senna pods is concordant with the evaluation of senna leaf.

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 expert 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. 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 evidence¹ of the available scientific data for “the short-term use in cases of occasional constipation” can be identified as level III.

The question of a possible carcinogenic risk of long-term use of anthranoid-containing laxatives is still open and the results of the more recent studies are inconsistent. Therefore the conditions determined in the pharmacovigilance actions for anthranoid-containing laxatives have to be maintained.

The use in children below the age of 12 years and during lactation is not recommended.

During pregnancy only a specified extract (as described in the assessment report on *Sennae folium*) can be regarded as safe, but with the advice that the use is to be avoided during the first trimester. Senna pods 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 such a high dose use 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 hydroxyanthracen 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.

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’ (EMA/HMPC/104613/2005)

Up to now there is no clear evidence to recommend a specific dose or 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 of the blood, bowel and other organs in many diseases. In former times such 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 and other organs than the bowel, or for use as a cholagogum.

In view of the possible risks, such traditional uses cannot be recommended. This is in accordance with the German pharmacovigilance actions for anthranoid-containing laxatives.