



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 September 2018
EMA/HMPC/265637/2018
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monographs on *Senna alexandrina* Mill., folium (EMA/HMPC/625849/2015) and *Senna alexandrina* Mill., fructus (EMA/HMPC/228761/2016)

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Senna alexandrina* Mill. (*Cassia senna* L.; *Cassia angustifolia* Vahl), folium and European Union herbal monograph on *Senna alexandrina* Mill. (*Cassia senna* L.; *Cassia angustifolia* Vahl), fructus as released for public consultation on 12/10/17 until 12/01/18.

	Organisations and/or individuals
1	AESGP, Dr Christelle Anquez-Traxler, Belgium
2	ESCOP (European Scientific Cooperative on Phytotherapy), S.Y. Mills, United Kingdom



Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	We appreciate in principle the revision of the monographs which were first published in 2006. However, we are of the opinion that there is no new evidence available that may justify a restriction of use to 1 week.	The welcome note by AESGP is appreciated.
ESCOP	From our point of view, there is no new scientific knowledge available which justifies a reduction of the daily dose and of the duration of use particularly for Senna pods. The reasons will be given in the following.	See below.
AESGP ESCOP	Comments on the assessment report Comments on the assessment report	Comments on the assessment report have been considered.

Specific comments on text

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Title of the monographs Fructus	AESGP	<p>The title of the monograph: "European Union herbal monograph on <i>Senna alexandrina</i> Mill. (<i>Cassia senna</i> L.; <i>Cassia angustifolia</i> Vahl)1, fructus" refers only to one plant part: the fruits (fructus). However, further in the monograph, reference is made to 'senna pods'.</p> <p>To us, the fruits and pods clearly differ in appearance, size, colour and structure of the seeds. Moreover, Alexandrian senna pods have an almost 50% higher content of hydroxyanthracene glycosides than Tinnevely senna pods.</p>	<p>With respect to the titles the establishment of European Union monographs is based on the respective monographs of the European Pharmacopeia. The title of the European Union monograph is following the standards defined in the template.</p> <p>English common name "senna pods" is used for the herbal substance "Sennae fructus".</p> <p>"Senna alexandrina Mill. has been identified as the correct name of the plant species, there is no longer a</p>

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		Although we are aware that the issue of definition should at first be resolved in the Ph.Eur., we consider it useful to discuss it in the context of the HMPC monograph as well.	classification into two different species. Leaves and fruits of both species contain a similar spectrum of hydroxyanthracene derivatives" (AR p.4 Introduction)
2. Composition and Description of the herbal substance(s), herbal preparation(s) or combinations thereof (Assessment Report) Fructus	AESGP	<p>The HMPC Assessment report (page 4) refers to new Ph.Eur. draft monograph "Alexandrian senna" with a limit of 3.4% hydroxyanthracene derivatives.</p> <p>According to results of analysis from a company (see also attached table) for <i>Cassia angustifolia</i> Vahl using the existing photometric Ph.Eur. method and calculated with reference to the dried drug, the following data from a period of 5 years is available:</p> <ul style="list-style-type: none"> • 2013: number of tests: 47, mean value: 3.52% • 2014: number of tests: 42, mean value: 3.32% • 2015: number of tests: 40, mean value: 3.47% • 2016: number of tests: 24, mean value: 3.46% • 2017: number of tests: 28, mean value: 3.58% <p>The mean value of these 181 is calculated with 3.47%.</p> <p>In case the Ph.Eur. monograph sets a limit of 3.4% hydroxyanthracene derivatives, 78 (43%) of the analysed samples would be out of specification. This should be taken into account when the limit is defined.</p>	<p>The European Union monographs of the HMPC give a reference to the photometric method, if this is relevant for the assay.</p> <p>The setting of limits in the monograph of the Ph. Eur. will be decided by the European Pharmacopeia Commission. The current draft monographs of the Ph. Eur. set a lower limit than cited in the AR.</p>
4.2. Posology and method of administration	ESCOP	The adult dose for occasional constipation in the valid HMPC monograph (2006) is: "Herbal preparation equivalent to 15-30mg of hydroxyanthracene derivatives calculated as	<p>Not endorsed.</p> <p>The AR explains that "the duration of use is limited to a</p>

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<p>(Duration of use)</p> <p>Fructus and Folium</p>		<p>sennoside B.” The duration of administration is 1–2 weeks.</p> <p>The 2017 HMPC draft inserts a new additional indication for bowel cleansing with a single dose of herbal preparation equivalent to 150mg of hydroxyanthracene derivatives calculated as sennoside B. The new dose for occasional constipation is: Herbal preparation equivalent to 10-30 mg of hydroxyanthracene derivatives calculated as sennoside B. And duration of administration for occasional constipation is reduced to a maximum of one week.</p> <p>There are some clinical papers published between 2006 and now which assess this new indication part (bowel cleansing) and this new single dose for bowel cleansing (150mg hydroxyanthracene derivatives) as safe and effective.</p> <p>Compared to this new dose (for bowel cleansing) a reduction of duration of administration for occasional constipation from 1-2 weeks to one week only (with a usually sufficient dosing of 2 to 3 times a week) is not justified with regard to total dosing.</p> <p>In detail: The former assessed occasional constipation dosing (HMPC 2006) with 15-30mg hydroxyanthracene derivatives (single dose) multiplied by 2-3 times dosing per week multiplied by a duration of use of 1-2 weeks is corresponding to a total dosing of 30mg–90mg hydroxyanthracene derivatives per one week and a total dosing of 60mg–180mg hydroxyanthracene derivatives per 2 weeks. This is reduced now (HMPC 2017 draft) to 10-30mg hydroxyanthracene derivatives (single dose) multiplied by 2-3 times dosing per week multiplied by a duration of use of 1 week only which</p>	<p>maximum of one week [...] to consider adverse effects of long-term misuse and also the potential genotoxicity”.</p> <p>The two indications are different and application is intended in different environments. The single dose application is accompanied by medical supervision where it is expected that the most appropriate method for bowel cleansing with respect to an individual patient is applied.</p> <p>New pre-clinical data have been published for hydroxyanthracene derivatives. The HMPC has decided to consider the totality of data. The results are taken into account for all respective monographs on herbal substances containing hydroxyanthracene derivatives. The data published for individual hydroxyanthracene derivatives were usually not sufficient to justify a differentiated final evaluation of specific hydroxyanthracene derivatives. Therefore and based on this new pre-clinical data the duration of administration is restricted to one week.</p>

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		<p>corresponds to a total dosing of 20mg–90mg hydroxyanthracene derivatives per one week.</p> <p>The maximum former occasional constipation dosing for 2 weeks with a maximum of 180mg hydroxyanthracene derivatives is more or less comparable to the single dose of 150 mg hydroxyanthracene derivatives for bowel cleansing. The new occasional constipation dosing for one week with a maximum of 90mg hydroxyanthracene derivatives is far below the single dose of 150mg hydroxyanthracene derivatives for bowel cleansing.</p> <p>From a pharmacological point of view a single high dose is a much greater stress to biological systems than several low doses over a longer period of time.</p> <p>From a scientific point of view no new arguments have been presented to reduce the duration of dosing from a maximum of 1-2 weeks which had been based on a scientific assessment of the data available until 2006 taking into account the problems of possible extended dosing periods by OTC drug products users. Therefore, the restriction of duration of administration to one week is not justified because there are no new data available requiring such a restriction.</p> <p>The lowering of the minimum single dose for occasional constipation to now 10mg compared to the former 15mg hydroxyanthracene derivatives is acceptable because it is justified by the concept of “dose titration” for individual patients (already accepted in the 2006 assessment).</p>	

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		<p>We therefore propose the following text under "Duration of use":</p> <p>Not to be used for more than 1–2 weeks. Use for more than 1–2 weeks requires medical supervision. Usually it is sufficient to take this medicinal product up to two to three times during a week.</p> <p>The option to use Senna-containing laxatives for up to 14 days is also in line with the ESCOP monographs on Alexandrian Senna Pods and Tinnevelly Senna Pods [ESCOP 2003].</p>	
<p>4.6 Fertility, Pregnancy and Lactation</p> <p>Fructus and Folium</p>	<p>ESCOP</p>	<p>In section 4.6 Pregnancy and Lactation of the valid HMPC monograph of 2006, the product texts are differentiated between extracts (preparations) identical to those investigated in section 5.3 (with respect to the impurity profile) and all other preparations. This was justified because both cancerogenicity studies available in 2006 were done with senna extract and senna pods having a well described impurity profile. Just now a further cancerogenicity study (NTP2012/Surh 2013) with senna pods has been published. The overall peer review result is:</p> <p>No evidence of cancerogenicity.</p> <p>In addition to that pharmacokinetic data are available for a senna pod preparation showing that aloe-emodin could not be detected in plasma (Krumbiegel 1993). So, there are no new scientific data available justifying the new HMPC draft 2017 wording that senna is generally contra-indicated in all phases of pregnancy.</p>	<p>Not endorsed.</p> <p>Pregnant women/fetus and newborns are sensitive patient groups. Although there are references in literature stating "No evidence of cancerogenicity." the evaluation of the data on genotoxicity and cancerogenicity lead to the conclusion to minimize exposure to pregnant and lactating woman. The references cited have been taken into account in the assessment.</p>

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		<p>Furthermore, a new population-based case-control study (Acs 2009) in pregnant women has been published which concluded that senna treatment was not associated with a higher risk of congenital abnormalities in the offspring of pregnant women with constipation.</p> <p>The HMPC did not present new scientific data which support the change of the HMPC texts in section 4.6 of the valid 2006 HMPC monograph. But there are new data available now which further support the safety of senna pod treatment during pregnancy as presented.</p> <p>Therefore, we propose to stick to the assessed texts of section 4.6 of the valid 2006 HMPC monograph and not to switch to the proposed HMPC draft 2017 texts.</p> <p>(Note: All referenced papers identified by author/year are part of the reference list of the assessment report.</p> <p>EMA/HMPC/228760/2016 dated 18 July 2017)</p>	
<p>5.3 Preclinical safety data</p> <p>Fructus and Folium</p>	AESGP	<p>The draft Assessment Report (18 July 2017 EMA/HMPC/228759/2016) under 3.3.8. Conclusions p. 45 states:</p> <p>‘The HMPC decided to follow the strategy to condense information given in section 5.3 of the monographs as far as possible. A short summary of the 90-day study in rats is presented as well as a remark on the different data on genotoxicity and cancerogenicity’.</p> <p>Regarding information about mutagenicity and genotoxicity the</p>	<p>Partly endorsed.</p> <p>The HMPC decided to follow the strategy to condense information given in section 5.3 of the monographs as far as possible. A short summary of the 90-day study in rats is presented as well as a remark on the different data on genotoxicity and cancerogenicity.</p> <p>Data are not sufficient to differentiate selected constituents. Health care professionals would not have any option for different treatments. The overall</p>

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		<p>HMPC 2017 draft monograph states:</p> <p>“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.”</p> <p>From our point of view, in in vitro test systems only extracts of senna pods or leaves are used, and not the herbal drug. In line with the existing HMPC monograph (2006) information about constituents not being mutagenic or genotoxic in standard tests should be maintained. It makes clear that the main active constituents and main metabolite of senna are not mutagenic and genotoxic, also in comparison with other anthranoid laxatives. We therefore propose to add:</p> <p>“Extracts of Senna and several hydroxyanthracene derivatives except sennosides, rhein and sennidins were mutagenic and genotoxic in several in vitro test systems, however for senna and aloe-emodin this was not proven in in vivo systems.”</p>	<p>conclusion of the HMPC was to harmonize the monographs of hydroxyanthracene containing herbal substances. In summary, there is no conclusive information.</p> <p>In order to reflect this background, the text of the monographs was modified to take the comment into account:</p> <p>“Senna pods, extracts thereof and several hydroxyl anthracene derivatives with the exception of, sennosides, rhein and sennidins, were mutagenic and genotoxic in several <i>in vitro</i> test systems, however for senna and aloe-emodin this was not proven in <i>in vivo</i> systems.”</p>
<p>5.3 Preclinical safety data</p> <p>Fructus and Folium</p>	<p>ESCOP</p>	<p>Section 5.3 of the HMPC monograph draft 2017 is introduced with the sentence: “There are only few preclinical data available for senna pods or preparations thereof.”</p> <p>It is proposed to stick more or less to the original HMPC 2006 wording by saying: “Most of the preclinical data available for senna refer to senna pods with defined quantities of hydroxyanthracene derivatives, preparations thereof or its isolated constituents.”</p> <p>Argumentation: Compared to other hydroxyanthracene</p>	<p>Not endorsed.</p> <p>The HMPC decided to follow the strategy to condense information given in section 5.3 of the monographs as far as possible. A short summary of the 90-day study in rats is presented as well as a remark on the different data on genotoxicity and cancerogenicity.</p> <p>Data are not sufficient to differentiate selected constituents. Health care professionals would not have any option for different treatments. The overall</p>

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		<p>derivatives containing laxatives a rather broad spectrum of preclinical data is available for senna and most of them refer to senna pods, preparations thereof or its constituents.</p>	<p>conclusion of the HMPC was to harmonize the monographs of hydroxyanthracene containing herbal substances.</p>
<p>5.3 Preclinical safety data</p> <p>Fructus and Folium</p>	<p>ESCOP</p>	<p>For information about mutagenicity and genotoxicity HMPC 2017 draft monograph give the following wording:</p> <p>“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.”</p> <p>The following wording for this part of section 5.3 is proposed instead:</p> <p>“Extracts of Senna and several hydroxyanthracene derivatives except sennosides, rhein and sennidins were mutagenic and genotoxic in several in vitro test systems, however for senna and aloe-emodin this was not proven in in vivo systems.”</p> <p>Argumentation: In in vitro test systems only extracts of senna pods or leaves can be used not the herbal drug itself. Just in line with the valid HMPC monograph 2006 the positive information about constituents not being mutagenic or genotoxic in the standard testing should not be suppressed. This proposed wording is preferred because it makes clear that the main active constituents and main metabolite of senna are not mutagenic and genotoxic which is a striking difference compared to other anthranoid laxatives.</p>	<p>Partly endorsed.</p> <p>The HMPC decided to follow the strategy to condense information given in section 5.3 of the monographs as far as possible. A short summary of the 90-day study in rats is presented as well as a remark on the different data on genotoxicity and carcinogenicity.</p> <p>Data are not sufficient to differentiate selected constituents. Health care professionals would not have any option for different treatments. The overall conclusion of the HMPC was to harmonize the monographs of hydroxyanthracene containing herbal substances. In summary, there is no conclusive information.</p> <p>In order to reflect this background, the text of the monographs was modified to take the comment into account:</p> <p>“Senna pods, extracts thereof and several hydroxyl anthracene derivatives with the exception of, sennosides, rhein and sennidins, were mutagenic and genotoxic in several in vitro test systems, however for senna and aloe-emodin this was not proven in in vivo systems.”</p>

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5.3 Preclinical safety data Fructus and Folium	ESCOP	<p>The draft HMPC assessment report states in section 3.3.8 (Conclusions to Toxicological data) the following: <i>"The HMPC decided to follow the strategy to condens information given in section 5.3 of the monographs as far as possible. A short summary of the 90-day study in rats is presented as well as a remark on the different data on genotoxicity and cancerogenicity."</i></p> <p>This is well taken but the sentence in the HMPC 2017 monograph draft: <i>"In long term carcinogenicity studies with senna pods effects on the kidneys and colon/caecum were reported"</i> could be misunderstood because the reader expects information on carcinogenicity. As the scientific data do not reveal cancerogenic effects on kidney and colon/caecum the HMPC 2017 draft wording seems to refer to the epithelial hyperplasia of the kidney and colon/caecum which is reversible and which is described already in detail in section 5.3 by presenting the repeat dose toxicity study (Mengs 2004). Furthermore epithelial hyperplasia after extended and high dosing seems to be a general effect for stimulant laxatives and not specific for hydroxyanthracene derivatives containing herbal laxatives (Toyoda 1994).</p> <p>It is therefore proposed to take the following wording for overall conclusions of the existing cancerogenicity studies with senna pods (i.e. Lyden-Sokolowski 1993, Borelli 2005, Mitchell 2006, NTP 2012/Surh 2013) as summarized by Morales 2009 and Surh 2013: No evidence of carcinogenicity.</p> <p>If the HMPC is of the opinion that the epithelial hyperplasia</p>	<p>Not endorsed.</p> <p>The HMPC decided to follow the strategy to condense information given in section 5.3 of the monographs as far as possible. A short summary of the 90-day study in rats is presented as well as a remark on the different data on genotoxicity and cancerogenicity.</p> <p>The wording in section 5.3 reflects the lack of conclusive information.</p>

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		<p>observed in the cancerogenicity studies has to be mentioned separately in any case then it is proposed to insert in section 5.3 after the presentation of the 90-day study a further last sentence: “Respective epithelial hyperplasia is observed in the long term carcinogenicity studies as well.”</p> <p>(Note: All referenced papers identified by author/year are part of the reference list of the assessment report</p> <p>EMA/HMPC/228760/2016 dated 18 July 2017)</p>	