European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON PLANTAGO OVATA FORSSK., SEMEN' (EMEA/HMPC/340861/2005)

Table 1: Organisations that commented on the draft 'Community herbal monograph on Ispaghula seed (Plantago ovata, semen)' as released for consultation in October 2005 until 31 January 2006

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)
2.	Medical Products Agency (MPA), Sweden
3.	The European Scientific Cooperative on Phytotherapy (ESCOP)

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Table 2: Discussion of comments

General comment	Comment and rationale	Rapporteur's comments
	Compared to the former HMPWP core data, we appreciate the inclusion of children from 6-12 years of age for the indications given.	
Title	We would suggest adding the following and alternative way of expressing the plant name and part used: "***Plantaginis ovatae semen***".	The title was changed into `Plantago ovata Forssk., semen´, which is in line with guidance in the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMEA/HMPC/182352/2005 Rev.2).
	We suggest to use the correct Latin expression in brackets: Plantaginis ovatae semen.	
	We would suggest correcting the reference to "Article 10(1)(a)(ii)" into Article "10a" of Directive 2001/83/EC as amended.	Agreed, see 'Template for a Community herbal monograph' (EMEA/HMPC/107436/2005 Rev.2).
	We think that the expression '*bulk producer*' should be clarified and changed into '*laxative bulk producers'*.	We agree to change the wording in section 4.4 and 4.6.

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4.1. Therapeutic indications	The interested party seriously questions whether the data on clinical efficacy in the claimed indication do fulfil the criteria of "well-established medicinal use with recognised efficacy" according to Directive 2001/83/EC. However, the interested party recognises that ispaghula seed has a well-documented traditional use as a mild laxative for treatment of constipation. Based on the content of bulk material (indigestible polysaccharides) in ispaghula seed the efficacy also appears plausible in this indication. The data presented would qualify products containing ispaghula seed for registration as traditional herbal medicinal products. The future classification of ispaghula seed, well-established or traditional, will heavily depend on the scientific interpretation of criteria for recognised clinical efficacy.	The use of ispaghula seed as a laxative is based on experts' opinions and scientifically substantiated by the pharmacological data. The active ingredients are the same as in ispaghula husk, even if the amount is smaller in ispaghula seed. A higher dosage is therefore required. The clinical data on ispaghula husk support the well-established use of ispaghula seed as laxative and in conditions in which easy defecation with soft stool is desirable.
	In accordance with the ESCOP monograph, we suggest to add: "Adjuvant symptomatic therapy in cases of diarrhoea from various causes." This is also in line with the HMPC dosage recommendation, because the higher dose levels recommended (HMPC: up to 40g and ESCOP: up to 30 g) are indicated only for diarrhoea and not for laxative use.	No further data are submitted. The available data were evaluated and discussed in the Committee plenary meeting. The study **Hamouz W 1984** is uncontrolled and investigates a small and special population. Agiocur®, a combination of ispaghula husk and seed, was administered. These data are insufficient to support a well-established use for diarrhoea.
4.2. Posology	The daily dose recommended for adults and children over 12 years of age for use as laxative is of "*25-40 g in 1-3 doses*". We should like to note that this is more than twice the lower dose level recommended in the HMPWP Proposal for Core Data from the year 2003 (which recommended as posology "12-40g in 1-3 doses") and to our point of view, does not seem to be supported by scientific evidence. A lower dose level of 7 g is supported by Martindale 2002 [1]: "3.5g one to three times daily". Sölter and Lorenz [2] treated 556 patients with a mean daily dose 7.8g of Ispaghula seed and 0.26g of Ipaghula husk and 63 patients with a mean daily dose of <6.5g of Ispaghula seed and of <0.22g of Ispaghula husk. An additional evaluation of this clinical study [3] confirms that the lower daily dosage of 7 g as recommended in the ESCOP monograph is effective. Ligny [4] used a daily dose of 20g of a preparation equivalent to 13.0g of Ispaghula seed and 0.44g of Ispaghula husk. From these findings it can be concluded that a <u>minimum daily dose for adults of 7g Ispaghula seed</u> is justified for use as a laxative.	Martindale recommends the same daily dose for ispaghula seed, ispaghula husk and psyllium seed. Based on the different swelling indices, this does not seem to be plausible. But the complete recommendation in Martindale is: "The usual dose is about 3.5 g one to three times daily by mouth **although higher doses have been given**. The other mentioned references deal with a combination of ispaghula husk and seed. The amount of ispaghula husk administered by Sölters and Lorenz was very small, approximately 4 % of the minimal daily dose (7 g) recommended by the monograph on ispaghula husk. It can therefore be concluded that the main efficacy is based on the amount of ispaghula seeds and that already 8 g ispaghula seeds are effective. For ispaghula seed the Ph. Eur. indicates a swelling index of minimum 9. High-quality ispaghula seeds are capable of absorbing 14 to 19 times their own weight of water. Ispaghula seed has only between 25 % to 45 % of the water binding capacity of ispaghula

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4.2. Posology Continuation	Furthermore the dose recommendation of HMPC, i.e. 25-40 g Ispaghula seed to be taken in 1 to 3 doses, does not seem justified. It would mean that the patient is recommended to take as single dose 25g with 750ml of liquid or even up to 40g with 1200ml of liquid. For this reason we consider a dose recommendation of **7-30g in 2-3 doses** as more patient-friendly and more feasible. The lowest single dose would be 3.5g of Ispaghula seed with 105ml of liquid and the highest single dose would be 15g of Ispaghula seed with 450ml of liquid. [1] Martindale. The complete drug reference. 33rd ed. Pharmaceutical Press. London-Chicago 2002:1129. [2] Sölter H, Lorenz D. Summary of Clinical Results with Prodiem® Plain, a Bowel-Regulating Agent. Today's Therapeutic Trends 1983;1:45-59. [3] Post-evaluation of the studies with Agiocur® from the publication by Sölter and Lorenz (Today's Therapeutic Trends 1 (1983), 45-59), with reference to the effective Plantago ovata dosage in comparison to dosages published in monographs. Cologne 25 July 2005. [4] Ligny G. Therapie des Colon irritabile. Therapeutikon 1988;7:449-453. The daily dose for adults and children over 12 years of age for use as laxative is reported as follows: **HMPC draft dated 24 October 2005** **HMPWP Proposal for Core Data, 27 March 2003** **ESCOP monograph** 25-40 g in 1-3 doses (as a laxative) 12-40 g in 1-3 doses (as a laxative) 7-30 g in 2-3 doses (as a laxative), up to 40 g (in cases of diarrhoea	husk. We propose to extend the range from 8 – 40 g daily. This range covers different available qualities of seeds. The Ph. Eur. only recommends a swelling index of minimum 9. We agree to change the daily number of administration as follows: "**8 – 40 g herbal substance or corresponding amount of herbal preparation (daily dose) in 2-3 single doses**".

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4.2. Posology Continuation	From the interested party's viewpoint the dose recommendation of the HMPC draft with regard to the lower dose level of 25g is not substantiated. Compared to the "Proposal for Core Data" from the year 2003 it is more than the double amount of the lower dose level and is not supported by bibliographical evidence. ESCOP has proposed a lower dose level of 7 g which is supported by Martindale 2002: "3.5g one to three times daily". Sölter and Lorenz [2] treated 556 patients with a mean daily dose 7.8g of Ispaghula seed and 0.26g of Ispaghula husk and 63 patients with a mean daily dose of <6.5g of Ispaghula seed and of <0.22g of Ispaghula husk. An additional evaluation of this clinical study [3] confirms that the lower daily dosage of 7 g as recommended in the ESCOP monograph is effective. Ligny [4] used a daily dose of 20g of a preparation equivalent to 13.0g of Ispaghula seed and 0.44g of Ispaghula husk. From these findings it can be concluded that a daily dose for adults of 7-30g Ispaghula seed is justified for use as a laxative. Furthermore the dose recommendation of HMPC, i.e. 25-40 g Ispaghula seed to be taken in 1 to 3 doses, is not justified from the interested party's point of view. It would mean that the patient is recommended to take as single dose 25g with 750ml of liquid or even up to 40g with 1200ml of liquid. For this reason we consider the ESCOP dose recommendation with 7-30 g in 2-3 doses as much more patient-friendly and feasible. The lowest single dose would be 3.5g of Ispaghula seed with 105ml of liquid and the highest single dose would be 15g of Ispaghula seed with 450ml of liquid.	See above

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4.3. Contraindications	For clarity purpose, we suggest to shorten and reword this section as follows: "***-Known hypersensitivity (allergy) to Ispaghula seed*** ***-Unless advised by a physician, patients suffering from the following conditions should not use Ispaghula seed preparations:*** • ***Acute abdominal pain of any origin*** • ***Existing intestinal obstructions (ileus) or conditions likely to lead to intestinal obstruction***"	We maintain the recommended wording because first of all these contraindications are addressed to the patient and the patient cannot interpret the general term "conditions likely to lead to intestinal obstruction". The SPC-wording should be adjusted to the package leaflet for the patient.
	We suggest to shorten this paragraph in order to make it better understandable for the user of the medicinal product. A clearer wording could be: "Atonic and obstructive ileus, subileus or conditions likely to lead to intestinal obstruction. Acute abdominal pain of any origin (e.g. appendicitis)".	
4.4. Special warnings and precaution for use	The wording "unless advised by a doctor" should be deleted. Such a dangerous advice by a physician should be ignored. If a patient has the described symptoms, and ileus has been excluded, other treatments than ispaghula is most likely indicated.	In this section, the symptoms described can be, but must not be signs of an ileus. Therefore, the patient has to consult a physician first and then it is up to the physician to decide, whether ispaghula seed may be suitable or not. We prefer to recommend a definite amount of fluid per single dose to make sure that the amount is sufficient. However this amount may not always be 150 ml for every medicinal product. Therefore we propose to reword this statement as follows: **"Take each single dose of this product with at least x ml (x is to be replaced by the amount which corresponds to 30 ml per 1 g of the herbal substance or corresponding amount of the herbal preparation) of water or similar aqueous fluid"** The information is addressed to the patient and is necessary for the understanding and the safety of the patient.
	The wording given under "*Warnings*", 1st paragraph, is too long and would prevent the user from taking the product. We therefore suggest the following text: "… should be taken with at least 10 times the amount of fluid because otherwise bezoar formation and intestinal obstruction may occur."	
	We find that the wording given under "Warning" is too long and may deter patients from using the product. We therefore suggest the following text: "***Take this product with at least 10 times the amount of fluid in order to avoid swelling and obstruction***."	

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4.7. Effects on ability to drive and use machines	We would suggest replacing "not known" by "none known".	The wording is changed into "Not relevant." in accordance with guidance in the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMEA/HMPC/182352/2005 Rev.2). Knowledge about clinical and experimental pharmacology of ispaghula seed does not reveal any relevance in the context of the ability to drive and use machines.
5.2. Pharmaco-dynamic properties	Progress of action should be given under 5.1. Pharmacodynamic properties. The sentence on elimination is inept and should be deleted.	We agree that the paragraph on progress of action is to be moved to section 5.1 and propose to reword section 5.2 as follows: "The material hydrates and swells to form a mucilage because it is only partially solubilised. Polysaccharides, such as those which dietary fibres are made of, must be hydrolysed to monosaccharides before intestinal uptake can occur. The sugar residues of the xylan backbone and the side chains of psyllium are joined by ß-linkages, which cannot be broken by human digestive enzymes. Less than 10 % of the mucilage gets hydrolysed in the stomach, with formation of free arabinose. Intestinal absorption of the free arabinose is approximately 85 % to 93 %. To varying degrees, dietary fibre is fermented by bacteria in the colon, resulting in production of carbon dioxide, hydrogen, methane, water, and short-chain fatty acids which are absorbed and brought into the hepatic circulation. In humans, psyllium reaches the large bowel in a highly polymerised form that is fermented to a limited extent, resulting in increased faecal concentration and excretion of short-chain fatty acids."

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5.3. Preclinical safety data	The concept of "well-established medicinal use" implies that experience from clinical use is of sufficient extent and duration to ensure safety. However, due to the inherent limitations of pharmacovigilance, epidemiology and related information on safety in humans, there may be unrecognized, but important, safety issues associated with herbals with "well-established medicinal use". These include adverse effects on reproduction, possible genotoxicity as well as carcinogenicity, which are very difficult or even impossible to detect even in cases of extensive human use. Such data are usually obtained from preclinical studies. Consequently, the interested party would like to suggest that section 5.3. of Community herbal monographs focuses on reproductive toxicity (particular embryo-foetal toxicity), genotoxicity and carcinogenicity as apparent from preclinical safety studies. If no studies/data are available this should be stated. The statement "there are no preclinical concerns based on extensive human experience" makes no sense in the context of the above reasoning and should be deleted.	There are only data available for ispaghula husk and psyllium without defining the exact test preparation available. **Single dose toxicity**: The LD50 in rats was greater than the highest dose tested corresponding to 3,360 mg/kg ispaghula husk administered by gavage of an aqueous suspension. The LD50 in mice was greater than the highest dose tested corresponding to 2,940 mg/kg ispaghula husk also administered by gavage of an aqueous suspension. These studies were conducted prior to the establishment of good laboratory practices. **Subchronic toxicity:** Psyllium was fed to rats at levels high as 10 % of the diet for periods up to 13 weeks (three 28-day studies, one 13-week study). Psyllium consumption ranged from 3,876 to 11,809 mg/kg/day. Because the absorption of psyllium is very limited, histopathological evaluations were limited to the gastrointestinal tract, liver, kidneys and gross lesions without observing any treatment-related effect. Effects considered to be biologically significant and related to psyllium supplementation were lower serum total protein, albumin, globulin, total iron-binding capacity, calcium, potassium, and cholesterol; and higher aspartate transaminase (AST) and alanine transaminase (ALT) activities relative to control. Several of these effects are considered to be secondary effects to others. The reasons for the lower serum total protein, albumin and globulin are not clear, but the absence of any increases in urinary protein, any evidence of gastrointestinal pathology which could account for protein loss, and any differences in growth or feed efficiency in psyllium fed rats may give evidence that there are no adverse effect of psyllium on protein metabolism**.** **Reproductive toxicity:** A rat multigeneration reproduction/teratology study showed no evidence of any adverse effects of psyllium on reproduction or development. Psyllium as 0, 1.25, or 5.0% (w/w) of the diet was administered in a standard (NIH-07) rat and mouse meal diet *ad libitum* through gestation of the third generation.

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5.3. Preclinical safety data **continuation**		A segment II study in rabbits also showed no evidence of any adverse effect. Psyllium as 0, 2.5, 5 or 10% (w/w) of diet was administered in a purine certified rabbit chow diet for days 2-20 of gestation. **Genotoxicity and carcinogenicity:** Tests on genotoxicity and carcinogenicity have not been performed..