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., SEMINIS TEGUMENTUM' (EMEA/HMPC/340857/2005)

Table 1: Organisations that commented on the draft 'Community herbal monograph on Ispaghula husk (Plantago ovata, tegumentum)' 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)
4.	The Medicines Evaluation Board of the Netherlands (MEB NL)

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Table 2: Discussion of comments

General comment	Comment and rationale	Rapporteur's comments
	Compared to the former HMPWP core data, we appreciate the extension of therapeutic indications as well as the inclusion of children from 6-12 years of age for the indications a) and b).	
Title	We would suggest adding the following and alternative way of expressing the plant name and part used: "***Plantaginis ovatae testa***".	The title was changed into `Plantago ovata Forssk., seminis tegumentum´, 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) and in line with the Eur.Ph. monographs.
	For the title the draft, however, we suggest to use the correct Latin expression in brackets: Plantaginis ovatae testa.	
	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	In accordance with the ESCOP monograph, we suggest to add: "Adjuvant symptomatic therapy in cases of diarrhoea from various causes." We appreciate the extension of therapeutic indications as compared to the former HMPWP core data as well as the inclusion of children from 6-12 years of age.	No further data are submitted. The available data were evaluated and discussed in the Committee plenary meeting. The study **Hamouz W 1984** and the study **Frank HA et al. 1979** are uncontrolled and investigate a small and special population. The study of **Qvitzau S et al. 1988** and the study of **Lodge N et al. 1995** are randomised crossover studies, but the first one is an open one and the design of the second one is not exactly defined. The first one investigates ispaghula husk combined with calcium in only 25 patients and the second one only investigates 10 patients of a very special population. **Smalley JR et al. 1982** evaluated the use of psyllium in the management of only chronic non specific diarrhoea of childhood (CNDC) and only in 23 children between 6 and 36 months in a uncontrolled investigation.
	The interested party does not support part c) of the indication, because clinical evidence for IBS has to be in line with the Note for Guidance on IBS. Moreover, Ispaghula husk is not used in the country as an adjuvant to diet in hypercholesterolemia. Subsequently, the interested party is not supporting a special warning (4.4, for indication c,) with respect to the requirement of medical supervision.	IBS is only mentioned as an example and ispaghula husk is used only as an adjuvant in constipation predominant IBS. Furthermore only "Points to consider on the evaluation for medicinal products for the treatment of irritable bowel syndrome" (CPMP/EWP/785/97) of 19 March 2003 exist. Because ispaghula husk is not used for IBS in general the demand of the interested party goes too far. There is evidence even from meta-analysis that administration of ispaghula husk shows a reduction of total cholesterol by nearly 4-5% and of LDL cholesterol by nearly 7% but has no effect on HDL cholesterol. A treatment with statins is more potent but has to be carefully weighed because of possible adverse reactions. However, we take into account that patients with hypercholesterolemia are generally told to change their dietary management and to increase their daily fibre intake as a first step before starting a treatment with medicinal products. Therefore we conclude that these investigations support the indication c): „ in patients to whom an increased daily fibre intake may be advisable e.g. as an adjuvant to diet in hypercholesterolemia"

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4.2. Posology	We propose a daily dosage range of 4-20 g. This is in accordance with the ESCOP monograph as well as recent literature. Reference: Martindale. The complete drug reference. 33rd ed. Pharmaceutical Press. London-Chicago 2002:1129.	The daily dose of 7 – 11 g for indications a) and b) recommended in the HMPC monograph on ispaghula husk is supported by clinical data. **Dettmar DW et al. 1998** administered 7.0 g daily, **Fenn et al. 1986** 10.8 g or less, **Marlett et al. 1987** 7.2 g, **McRorie et al. 1998a** 10.2 g, **Wang HJ et al. 2004** 7 g, **Borgia et al. 1983** administered 10.5 g of an ispaghula husk preparation and **Moesgard et al. 1982** 12.2 g ispaghula husk. Indication c) **Kumara et al. 1987** stated that daily doses of 20 g or 30 g were significantly superior to 10 g for the treatment of IBS. **Prior A et al. 1987** administered 10.8 g, **Tarpila S et al.** 6 – 24 g daily. Effects on blood lipid levels were studied with 10.2 g (**Anderson JW et al. 1988, Bell LP et al. 1989, Anderson et al. 2000**). **Davidson MH et al. 1998** administered foods containing 0, 3.4, 6.8 or 10.2 g ispaghula husk. In the 10.2 g group LDL cholesterol remained below baseline during treatment. **MacMahon M et al, 1998** administered 7 g or 10.5 g. A meta-analysis by **Olson BH et al. 1987** showed a daily dose of 9.4 – 12 g in 9 studies and a lower dose (3.0, 6.7 and 7.6 g) in 3 studies. In the 8 studies of the meta-analysis by **Anderson JW et al. 2000** 10.2 g were daily administered.
	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 ESCOP monograph** 7-11 g in 1-3 doses (as a laxative) 4-20 g in 2-3 doses (as a laxative),	For clarification, we propose to reword as follows: Indication a) and b): *Adolescents over 12 years of age, adults, elderly*: 7 – 11 g herbal substance or corresponding amount of herbal preparation (**daily dose**) in 1 – 3 **single** doses *Children from 6 to 12 years of age:* Half to two-thirds of the adult dose (3 - 8 g herbal substance or corresponding amount of herbal preparation, **daily dose**) in 1 – 3 **single** doses Indication c): *Adolescents over 12 years of age, adults, elderly*: 7 – 20 g herbal substance or corresponding amount of herbal preparation (**daily dose**) in 1 – 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 7 g is too high. ESCOP has proposed a lower dose level of 4 g which is supported by Martindale 2002: "3.5 g one to three times daily". For this reason we propose a daily dose of 4 - 20 g.	
4.3. Contra-indications	For clarity purpose, we suggest to shorten and reword this section as follows: ***"-Known hypersensitivity (allergy) to Ispaghula Husk*** ***-Unless advised by a physician, patients suffering from the following conditions should not use Ispaghula husk 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 shortening 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)".	

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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 husk 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***."	
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 husk does not reveal any relevance in the context of the ability to drive and use machines.

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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."
5.3. Preclinical safety data Continuation	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.	There are only unpublished data available for ispaghula husk and psyllium without defining the exact test preparation. **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.

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5.3. Preclinical safety data	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.	**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% (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. 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.