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

London, 28 February 2007
Doc. Ref. EMEA/HMPC/65063/2006

OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON PLANTAGO AFRA L. ET PLANTAGO INDICA L., SEMEN' (EMEA/HMPC/340865/2005)

Table 1: Organisations that commented on the draft 'Community herbal monograph on Psyllium seed (Plantago afra et Plantago indica, 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)
4.	The Medicines Evaluation Board of the Netherlands (MEB NL)
5.	Pharmacovigilance Division UK

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 in the indications given.	
Title	We would suggest adding the following and alternative way of expressing the plant name and part used: "***Psyllii semen***". We suggest to use the correct Latin expression in brackets: Psyllii semen.	The title was changed into `*Plantago afra* L. et *Plantago indica* L., 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 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'* all throughout the text.	We agree to change the wording in section 4.4 and 4.6.

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
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 psyllium 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 psyllium seed the efficacy also appears plausible in this indication. The data presented would qualify products containing psyllium seed for registration as traditional herbal medicinal products. The future classification of psyllium seed, well-established or traditional, will heavily depend on the scientific interpretation of criteria for recognised clinical efficacy.	The use of psyllium seed as a laxative is based on experts' opinions and is scientifically substantiated by the pharmacological data on ispaghula. The structure of mucilages of ispaghula may be similar to the structure of the mucilages of psyllium seed. Weis M conducted one uncontrolled investigation in 63 patients with "Plantago psyllium" (Plantago psyllium – natural plant laxative and its effect on cholesterol and triacylglycerol levels. Ceska a Slovenska Gastroenterologie 1996; 50: 45 – 47) but the publication does not give extensive information. However, the clinical data on ispaghula husk support the well-established use of psyllium seed as laxative and in conditions in which easy defecation with soft stool is desirable.
4.3. Contra-indications	For clarity purpose, we suggest to shorten and reword this section as follows: "***-Known hypersensitivity (allergy) to Psyllium seed*** ***-Unless advised by a physician, patients suffering from the following conditions should not use Psyllium seed preparations:*** • ***Acute abdominal pain of any origin*** • ***Existing intestinal obstructions (ileus) or conditions likely to lead to intestinal obstruction"*** 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)".	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.

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
4.4. Special warnings and precautions for use, under section "warnings"	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**."*	See below
	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 psyllium 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 psyllium seed may be suitable or not.
	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 prefer to recommend a defined 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.
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 psyllium seed does not reveal any relevance of the herbal substance in the context of the ability to drive and use machines.

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
4.8. Undesirable effects	6 reported ADRs: liver function test abnormal, aggression, choking sensation, urticaria, swelling face, erythemas, rash	No further information is given and the causality cannot be assessed. Reactions of hypersensitivity are already mentioned in the monograph.
5.1. Pharmaco-dynamic properties	The interested party has the opinion that inclusion of different kinds of data under 5. Pharmacological properties should be restricted to data, which are clearly based on results of sound pharmacological experiments.	Special data dealing with psyllium are not available. The data mentioned describe the mode of laxative action, which is similar for all laxative bulk producers and therefore also for psyllium. We agree to add: "Specific data on psyllium are not available but the mode of action seems to be similar for all laxative bulk producers."
5.2. Pharmacokinetik 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."

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
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 increase 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 is no adverse effect of psyllium on protein metabolism

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
5.3. Preclinical safety data continuation		**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. 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.