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Evaluation of Medicines for Human Use

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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

COMMUNITY HERBAL MONOGRAPH ON PLANTAGO OVATA FORSSK., SEMEN

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COMMUNITY HERBAL MONOGRAPH ON PLANTAGO OVATA FORSSK., SEMEN

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished product.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1]

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10a of Directive 2001/83/EC as amended *Plantago ovata* Forssk. (*P. ispaghula* Roxb.), semen [2] (ispaghula seed) - dried ripe seeds (herbal substance) - powdered herbal substance	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended

3. PHARMACEUTICAL FORM

Well-established use	Traditional use
Herbal substance or herbal preparation in solid oral dosage forms such as granules or powders. The pharmaceutical form should be described according to the standard terms published by the European Pharmacopeia.	

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Well-established use	Traditional use
Herbal medicinal product a) for the treatment of habitual constipation; b) in conditions in which easy defaecation with soft stools is desirable, e.g. in cases of painful defaecation after rectal or anal surgery, anal fissures or haemorrhoids.	None

[1] The declaration of all active substances should be done in accordance with the 'Guideline on quality of herbal medicinal products / traditional herbal medicinal products' (CPMP/QWP/2819/00 Rev.1, EMEA/CVMP/814/00 Rev.1).

[2] The herbal substance complies with the European Pharmacopoeia (monograph reference 01/2005:1333)

4.2. Posology and method of administration

Well-established use	Traditional use
Posology Oral use *Adolescents over 12 years of age, adults, elderly* 8 - 40 g herbal substance or corresponding amount of herbal preparation (daily dose) in –2 - 3 single doses *Children from 6 to 12 years of age* Half to two-thirds of the adult dose (4 - 25 g herbal substance or corresponding amount of herbal preparation, daily dose) in 2 – 3 single doses. **Method of administration** Mix approximately x g of the [pharmaceutical form] (amount corresponding to 1 g herbal substance) with at least 30 ml of water, milk, fruit juice or similar aqueous liquid; stir briskly and swallow as quickly as possible. Alternatively the herbal substance can be taken and swallowed with sufficient quantity (at least 30 ml per g of herbal substance) of water, milk, fruit juice or other liquid; then maintain adequate fluid intake. The product should be taken during the day at least ½ to 1 hour before or after intake of other medicines. Warning: not to be taken immediately prior to bed-time. **Duration of use** See section 4.4 Special warnings and precautions for use.	

4.3. Contraindications

Well-established use	Traditional use
Ispaghula seed is not to be used by patients with a sudden change in bowel habit that persists for more than 2 weeks, undiagnosed rectal bleeding and failure to defaecate following the use of a laxative. Ispaghula seed is also not to be used by patients suffering from abnormal constrictions in the gastro-intestinal tract, with diseases of the oesophagus and cardia, potential or existing intestinal blockage (ileus), paralysis of the intestine, or megacolon, diabetes mellitus, which is difficult to regulate. Patients with known hypersensitivity to Ispaghula seed should not use Ispaghula seed preparations.	

4.4. Special warnings and precautions for use

Well-established use	Traditional use
As there is no sufficient experience available, use is not recommended in children below the age of 6 years. Laxative bulk producers should be used before using other purgatives if change of nutrition is not successful. Ispaghula seed is not to be used by patients with faecal impaction and undiagnosed abdominal symptoms, abdominal pain, nausea and vomiting unless advised by a doctor because these symptoms can be signs of a potential or existing intestinal blockage (ileus). If the constipation does not resolve within 3 days or if abdominal pain occurs or in case of any irregularity of faeces, the use of Ispaghula seed should be discontinued and medical advice must be sought. A sufficient amount of liquid should always be taken e.g. 30 ml of water per 1 g of herbal substance. In the package leaflet, the patient is informed about the following warning: **Warning:** 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. Taking this product without adequate fluid may cause it to swell and block your throat or oesophagus and may cause choking. Intestinal obstruction may occur should an adequate fluid intake not be maintained. Do not take this product if you have ever had difficulty in swallowing or have any throat problems. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention. The treatment of the debilitated patient requires medical supervision. The treatment of elderly patients should be supervised.	

4.5. Interactions with other medicinal products and other forms of interaction

Well-established use	Traditional use
Enteral absorption of concomitantly administered medicines such as minerals (e.g. lithium), vitamins (B 12), cardiac glycosides, coumarin derivatives,	

and carbamazepine may be delayed. For this reason the product should not be taken ½ to 1 hour before or after intake of other medicinal products. If the product is taken together with meals in the case of insulin dependent diabetics it may be necessary to reduce the insulin dose. Ispaghula seed should be used concomitantly with thyroid hormones only under medical supervision because the dose of the thyroid hormones may have to be adjusted. In order to decrease the risk of gastrointestinal obstruction (ileus) Ispaghula seed should only be used under medical supervision together with medicinal products known to inhibit the peristaltic movement (e.g. morphinomimetics, loperamide).	

4.6. Pregnancy and lactation

Well-established use	Traditional use
No restriction. Laxative bulk producers should be used before using other purgatives if change of nutrition is not successful.	

4.7. Effects on ability to drive and use machines

Well-established use	Traditional use
Not relevant.	

4.8. Undesirable effects

Well-established use	Traditional use
Flatulence may occur with the use of the product, which generally disappears in the course of the treatment. Abdominal distension and risk of intestinal or oesophageal obstruction and faecal impaction, particularly if swallowed with insufficient fluid. Due to the allergic potential of Ispaghula, patients must be aware of reactions of hypersensitivity including anaphylaxis-like reactions very rarely. If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.	

4.9. Overdose

Well-established use	Traditional use
Overdose with Ispaghula seed may cause abdominal discomfort and flatulence and even intestinal obstruction. An adequate fluid intake should be maintained and management should be symptomatic.	

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Well-established use	Traditional use
Pharmacotherapeutic group: Laxatives – Bulk Producers ATC-Code: A 06 AC The active ingredient Ispaghula seed consists of the dried, ripe seeds of *Plantago ovata* Forssk. Ispaghula seed is particularly rich in alimentary fibres and mucilages. Ispaghula seed is capable of absorbing up to 10 times its own weight in water. Ispaghula seed consists of 20 – 30 % mucilages which are located in the episperms. It is partly fermentable (in vitro 72 % unfermentable residue) and act by hydration in the bowel. The pharmacological effects, gut motility and transit rate can be modified by Ispaghula through mechanical stimulation of the gut wall depending on the increase in intestinal bulk by water and the decrease in viscosity of the luminal contents or by contact with rough fiber particles. When taken with a sufficient amount of liquid (at least 30 ml per 1 g of herbal substance) Ispaghula produces an increased volume of intestinal content due to its highly bulking properties and hence a stretch stimulus, which triggers defaecation; at the same time the swollen mass of mucilage forms a lubricating layer which makes the transit of intestinal content easier. *Progress of action*: Ispaghula seed usually acts within 12 to 24 hours after single administration. Sometimes the maximum effect is not reached for 2 or 3 days.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended

5.2. Pharmacokinetic properties

Well-established use	Traditional use
The material hydrates and swells to form a mucilage because it is only partially solubilised. Polysaccharides, such as those which comprise dietary fibre, 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 was 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.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended

5.3. Preclinical safety data

Well-established use	Traditional use
There are only data 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 3360 mg/kg ispaghula husk administered by gavage of an aqueous suspension. The LD50 in mice was greater than the highest dose tested corresponding to 2940 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 3876 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-	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended

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 rats fed psyllium may give evidence that there are no adverse effect of psyllium on protein meatbolism **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 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. **Mutagenicity and carcinogenicity:** No data are available. The available non-clinical data reveal no special hazard for humans supported by extensive human experience.	

6. PHARMACEUTICAL PARTICULARS

Well-established use	Traditional use

7. DATE OF COMPILATION

30 June 2006