14 May 2013
EMA/HMPC/304360/2012
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Plantago ovata* Forskk., semen

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Plantago ovata* Forssk. (*Plantago. ispaghula* Roxb.), semen
Herbal preparation(s)	Powdered herbal substance
Pharmaceutical forms	Herbal substance for oral use Herbal preparation in solid dosage forms for oral use
Rapporteur	Dr J. Wiesner
Assessor(s)	Dr B. Merz

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

Ispaghula seed consists of the whole dried ripe seeds of *Plantago ovata* Forssk. (*Plantago ispaghula* Roxb.). The herbal substance has to comply with the monograph "Ispaghula Seed" of the European Pharmacopoeia.

Ispaghula seeds contain 20 – 30% mucilages, which are a highly branched acidic arabinoxylan (Blaschek *et al.* 2003).

- Herbal preparation(s)

Powdered herbal substance.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

The active ingredients, the mucilages, are identical in ispaghula husk and ispaghula seed.
Ispaghula seed consists of the whole seeds and not only of the episperm and collapsed adjacent layers removed from the seeds as is the case for ispaghula husk. The seeds contain 20 – 30% mucilages, which are located in the epidermis of the husks (Blaschek et al. 2003). The seeds also contain proteins, fixed oil, sterols and the trisaccharide planteose (Sharma & Koul 1986, Heckers *et al.* 1984, Wichtl 1999).

1.2. Information about products on the market in the Member States

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	only combination products
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	only combination products
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	only a combination product (*Sennes angustifoliae* fructus, *Plantaginis ovatae* semen, *Plantaginis ovatae* testa)
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	3 combination products
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	only combination products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	only a combination product (*Sennes angustifoliae* fructus, *Plantaginis ovatae* semen, *Plantaginis ovatae* testa)
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	combination products as food supplements
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

Member State	Regulatory Status				Comments
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

The assessment report of the initial evaluation (EMEA/HMPC/166377/20060reviewed the scientific data available for ispaghula seed (*Plantago ovata* Forssk., semen), primarily the clinical data. When specific clinical data are lacking, results of investigations in animals are given. This report was prepared on the basis of the assessment report on ispaghula husk. Scientific publications do not always differentiate precisely the investigated preparations i.e. whether the investigated herbal substance was ispaghula husk or ispaghula seed or psyllium seed. They often refer to "psyllium" as the investigated herbal substance. If a differentiation was not possible, the term "psyllium" is used in this report. In the more recent investigations, ispaghula husk was used predominantly.

For the first revision of the monograph on ispaghula seed as well as on ispaghula husk a literature research was carried out in the data base Medline with the following keywords: "plantago ovata or psyllium or ispaghula; ispaghula husk; human"; publication year 2006 to 2012, language English or German. In summary 105 publications were listed.

The references mentioned were identified to have a possible impact on the revision of the monograph.

Additionally the outcome of the CHMP Pharmacovigilance Working Party (PhVWP) concerning powder formulations of *Plantago ovata* seeds and allergic reactions after prolonged occupational exposure in October 2011 (CMDh/PhVWP/035/2011) were included.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community and on traditional/current indications and specified substances/preparations

Please refer to the corresponding chapter of the assessment report on ispaghula husk.

The use of ispaghula husk and seed and other kinds of Plantago in traditional medicine is similar to the use of linseed, but such traditional use is not described as well and as consistently as for linseed. Furthermore, no precise posology is mentioned. None of the uses can therefore be accepted for inclusion in the 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products'**.**

Currently no traditional herbal medicinal product containing ispaghula is registered in the European Union.

Well-established use

France
Available since 1934
Pharmaceutical form: no information
Indication: symptomatic treatment of constipation
Posology for oral use: adult: daily 2 x 1 tablespoon, children 5 – 15 years: daily 2 x 2 teaspoon, children 2 to 7 years: daily 2 x 1 teaspoon; daily 3 x 1 – 3 teaspoon; daily 2 x 3.014 g drug.

2.2. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

See section 2.1 and section 4. Clinical Data.

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Primary pharmacodynamics

Laxative effect
The German Pharmacopoeia indicates that ispaghula seed has to be capable of absorbing at least 9 times its own weight in water. The British Pharmacopoeia indicates at least 12 times. The European Pharmacopoeia requests a swelling index of minimum 9. High-quality seeds are capable of absorbing 14 to 19 times their own weight of water (Blaschek *et al.* 2003).

Leng-Peschlow 1991 compared in rats the effects of a 4-week supplementation of a fibre-free elemental diet with 100 or 200 g Plantago ovata seeds/kg with that of the husks and wheat bran. The seeds increased faecal fresh weight up to 100%, faecal dry weight up to 50% and faecal water content up to 50%. The husks, at the high concentration only, were more effective than the seeds and wheat bran less effective. Faecal bacterial mass as estimated from the 2,6-diaminopimelic acid output was increased to the greatest extent by the seed-containing diet and by the high concentration of husks, but to a lesser extent by the wheat bran. Faecal and caecal protein content was enhanced by the seeds and wheat bran, but to a lesser extent by the husks. Total acetate in caecal contents or faeces was highest on the seeds and husks diet and not elevated by wheat bran. Total faecal bile acid excretion was stimulated and beta-glucuronidase activity reduced by both Plantago ovata preparations, but not by wheat bran. Mucosal digestive enzyme activities were inhibited to different degrees by all dietary fibres in jejunum, and sometimes activated in the ileum. The author concluded that these results suggest that Plantago ovata seed is a partly-fermentable dietary supplement, which increases stool bulk; metabolic and mucosa-protective effects are also probable.

Progress of action: Ispaghula seed usually acts within 12 to 24 hours after single administration. Sometimes the maximum effect is not reached before 2 or 3 days.

Conclusion
As for ispaghula husk, gut motility and transit rate can be modified by ispaghula seed through mechanical stimulation of the gut wall as a result of the increase in intestinal bulk by water and a decrease in viscosity of the luminal contents. When taken with a sufficient amount of liquid (at least 30 ml per 1 g of herbal substance) ispaghula seed produces an increased volume of intestinal contents due to their highly bulking properties and hence a stretch stimulus that triggers defecation; at the same time the swollen mass of mucilage forms a lubricating layer, which eases the transit of intestinal contents (Blaschek et al. 2003).

Secondary pharmacodynamics

Effect on diarrhoea

There are no specific data available for ispaghula seed.

Effect on blood lipids level

Kritchevsky *et al.* (1995) investigated the influence of psyllium preparations on plasma and liver lipids of cholesterol-fed rats. Rats were fed a semi purified diet containing 0.5% cholesterol and 10% fibre (cellulose, pectin, psyllium seed or defatted psyllium husk). One additional group of rats was fed cholesterol (0.5%) as part of a fibre-free diet; the sixth group was fed a fibre free diet without cholesterol. Cellulose had virtually no effect on serum or liver lipids. Pectin had a lipid lowering effect. Psyllium seed exerted an effect on total serum cholesterol equal to that of pectin but gave higher levels of high-density-lipoprotein (HDL) cholesterol. The effects of psyllium seed on liver lipids were more pronounced than those of pectin. Defatted psyllium husk feeding virtually normalised liver size and serum triglyceride levels and produced lower serum total cholesterol levels and higher HDL cholesterol than observed in normal controls. Feeding with defatted psyllium husk also yielded liver lipid values, which were in the normal range. Faecal wet and dry weights were significantly higher in rats fed either psyllium preparation.

Effect on blood glucose levels

Due to delayed intestinal absorption of carbohydrates, ispaghula seed may influence the glucose metabolism by reducing peak levels of blood glucose.

Mahapatra *et al.* (1988) investigated the effect of cellulose and ispaghula on the intestinal function of hamsters. Everted intestinal sacs were prepared from three groups of developing hamsters, which had been maintained on diets of varying fibre content. Irrespective of the dietary background of the animals, presence of fibre in the mucosal solution reduced the rate of transfer of monosaccharides from the mucosal to the serosal side in proximal and distal intestinal segments, but generally not in the middle segments. The transfer in the absence of any fibre in the mucosal solution, which can be considered to reflect the maximum absorptive capacity of the segment, was at a maximum in the proximal segments and at a minimum in the distal segments in the group of fibre-free diet. On the other hand, in fibre-fed groups, the transfer was maximum in the distal segment and minimum in the proximal segment.

Safety pharmacology

No data available.

Pharmacodynamic interactions

Effect on gastrointestinal enzymes

Leng-Peschlow (1989) incubated dietary fibres (*Plantago ovata* seed, *Plantago ovata* husk, wheat bran, alfalfa, pectin, xylan) *in vitro* with gastrointestinal enzymes (pepsin, trypsin, chymoptrypsin, lipase, alpha-amylase, maltase, lactase) in buffer solutions at concentrations of 1 – 5% for 10 – 30 min at 37°C. All fibres sometimes induced pronounced changes in enzyme activity, but the effect of the different fibres on the various enzymes varied individually and was not predictable. Both *Plantago ovata* preparations had either no actions (pepsin, trypsin, alpha-amylase) or only stimulating (chymotrypsin, lipase, lactase) actions whereas all other fibres showed inhibiting as well as stimulating influences. Wheat bran induced the most pronounced alterations increasing lipase, maltase and lactase activity and inhibiting alpha-amylase activity. Pectin and xylan were comparable in decreasing lipase and pepsin activity and in increasing chymotrypsin activity bud had opposite effects on maltase activity. Alfalfa was able to stimulate lactase and lipase activity but depressed trypsin and alpha-amylase

activity. The inactivation of enzymes by dietary fibres can, at least partly, be explained by adsorption to the fibre or by the presence of enzyme inhibitors especially in natural compounds.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No information available.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Please refer to the corresponding chapter of the assessment report on ispaghula husk. No specific data on the safety of ispaghula seed are available.

3.4. Overall conclusions on non-clinical data

Non-clinical data are limited. The data available for ispaghula seed and husk support the use as a laxative.

The non-clinical data on toxicology of ispaghula husk preparations are incomplete, but available data indicate no signals of toxicological concern. Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been published.

4. Clinical Data

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Laxative effect

Results of some studies of the effects of psyllium in healthy and constipated individuals did not detect a significant increase in transit rate or a decrease in transit time; however the majority indicate that it relieves constipation via the mechanism shown in preclinical investigations.

Psyllium has been shown to increase stool bulk (3.7 g for each gram consumed) (Spiller 1986). The increased volume of soft digesta may increase bowel wall tension, inducing additional propagating contractions, leading to more mass movements and an increased rate of transit for luminal contents. Furthermore intraluminal pressure is inversely related to radius and directly related to wall tension. Increasing stool bulk would increase intraluminal diameter, lower the wall tension needed to generate propulsive events and improve the efficiency of colonic motor events. A number of studies suggest that psyllium relieves constipation by increasing faecal bulk.

Effect on blood lipids level

Gelissen *et al.* (1994) investigated the effect of *Plantago ovata* (psyllium) husk and seed on sterol metabolism in normal and ileostomy subjects. The diet of 6 normal and 5 ileostomy subjects was supplemented with 10 g/d *Plantago ovata* (psyllium) husk for 3 weeks (experiment 1) while 6 normal and 4 ileostomy subjects received 10 g/d psyllium seed (experiment 2). A control period of 1 week preceded the treatment period. Faecal output and ileostomy output, sterol excretion, serum cholesterol, and triglycerides were measured before and after supplementation. The husk had no effect on cholesterol or triglyceride concentrations in either normal or ileostomy subjects. Total and HDL cholesterol concentrations were reduced on average by 6.4% and 9.3%, respectively, in the normal

group after seed supplementation. The average estimated low-density-lipoprotein (LDL) cholesterol value was reduced by 10.1% but this reduction was not statistically significant. The HDL-LDL ratio remained unchanged. No effect on faecal bile acid excretion in the normal subjects was found after both regimes. Ileostomy bile acids were increased (on average 25%) after seed supplementation, whereas no effect on cholesterol concentrations was found. The authors concluded that these results suggest that psyllium seed might be more effective than the husk in reducing serum cholesterol, and that this cholesterol-lowering effect is not mediated by increased faecal bile acid losses.

Segawa *et al.* (1998) examined the association of urea and lipid metabolism in 28 mild hypercholesterolemic male and female adults treated with psyllium seed for 3 months. The total serum cholesterol, LDL cholesterol and atherogenic index significantly decreased, but levels of HDL cholesterol, triglyceride and urea nitrogen did not. To determine the parameters associated with the cholesterol-lowering effect in the subjects' backgrounds, both biochemical and haematological parameters, the authors statistically examined the correlation between pre-treatment parameters and the absolute change of total cholesterol level. The absolute change of total cholesterol level showed a direct correlation with the triglyceride level at pre-treatment ($r=0.41$, $p=0.03$) and had an inverse correlation with urea nitrogen level ($r= -0.46$, $p=0.01$) but not with the total cholesterol level ($r= -0.18$). The change in urea nitrogen level had an inverse correlation with the urea nitrogen level itself at pre-treatment ($r= -0.82$, $p= 7x\ 10^{-8}$) and had a direct correlation with the triglyceride level ($r=0.43$, $p=0.02$). The change in triglyceride level had an inverse correlation with urea nitrogen level ($r= -0.48$, $p=0.008$). Furthermore the change in total cholesterol level had direct correlations with changes in the triglyceride level ($r=0.56$, $p=0.002$) and the urea nitrogen level ($r=0.51$, $p=0.006$), but these changes in triglyceride and urea nitrogen levels did not correlate significantly. The authors concluded that these findings suggest the close association of urea nitrogen and lipid metabolism in hyperlipidemia and psyllium seed treatment.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

For data concerning absorption, metabolism and excretion, see corresponding chapters of the assessment report on Plantago ovata Forssk., seminis tegumentum (ispaghula husk).

The pharmacokinetics of psyllium are essentially those of an inert unabsorbed substance; only small amounts of monosaccharides become available for systemic absorption through limited digestion of the few available α-linkages and fermentation by colonic bacteria. No pharmacokinetic data are available concerning the oil.

4.2. Clinical Efficacy

4.2.1. Dose response studies

There are no dose-finding studies available.

As a laxative for adults, elderly and children over 12 years of age, experts (Blaschek *et al.* 2003, Commission E 1990) recommend 12–40 g in 1 – 3 doses daily.

Even if ispaghula seed has about nearly 25% to 45% of the water-binding capacity of ispaghula husk (see above), which implies that the daily dose of ispaghula seed should be higher than the daily dose of ispaghula husk, the clinical data presented below justify a minimal daily dose of 8 g. A range of 8–40 g herbal substance or corresponding amount of herbal preparation daily is recommended by the Committee on Herbal Medicinal Products because there are different qualities of seeds available and the Ph. Eur. only recommends a swelling index of minimum 9.

The amount of 8–40 g herbal substance or corresponding amount of herbal preparation (daily dose) should be taken in 2–3 single doses daily because the amount of the fluid, which has to be taken with the single dose, is otherwise too high.

4.2.2. Clinical studies (case studies and clinical trials)

Laxative effect

Numerous clinical practice summaries, dating back to as early as 1935, recommended the use of fibre supplementation for the management and treatment of chronic constipation. Since 1976 numerous studies involving over 900 patients have been published. They evaluated the effects of psyllium intake on symptoms of constipation in a population specifically identified as “chronically constipated” meeting the definition of less than three bowel movements per week for more than 3 months. These studies were predominantly carried out with ispaghula husk; in other cases the investigated herbal substance was not exactly defined. These studies are described in the assessment report on ispaghula husk.

There are however some studies available with a combination of ispaghula husk and seed; 100 g of this preparation contains 65 g ispaghula semen and 2.2 g ispaghula husk.

Sölter & Lorenz (1983) conducted short-term trials of 7 days and long-term trials of up to 12 weeks. At 15 trial centres 669 patients (266 males and 403 females) ranging in age from 13 to 90 years were treated with a product containing psyllium “mucilloid” for 7 days. Twenty-eight patients were excluded because of uncertainty of diagnosis, administration of other laxatives and inadequately completed protocols. At three centres 139 patients (59 males and 80 females, ranging in age from 9 to 80 years) were treated over periods up to 12 weeks. Most of these patients were suffering from constipation, some from haemorrhoids, fistula in ano, anal fissures and abscesses. Very few patients were suffering from colonic diverticulosis, irritable bowel syndrome (IBS) and others. The most dominant symptoms were gaseous distension and abdominal pain. The standard dosage was 2 teaspoonfuls taken before the evening meal. If necessary, an extra teaspoonful could be taken before breakfast. Individual increases or decreases in dosage were permitted, if needed. In the short-term trials a response to treatment in the form of at least one daily bowel evacuation was achieved in nearly 56.8% on the first day, in 89.7% on the third day, in 93.3% of the fourth day and in 92.4% of the end of the study. Furthermore the faecal consistency was measured (1=liquid; 2=semi-liquid; 3=soft but formed; 4=hard, 5=no evacuation). As described in the publication the effect of treatment was significant in 7 trials ($p<0.01$). A change in consistency of a least 0.69 scale units was achieved. The aim for the long-term trials was a daily bowel evacuation with a soft but formed stool. 123 patients (88.4%) were successfully treated, 9 patients were treated without success, 2 patients were excluded because of lack of compliance, 1 dropped out due to a change of physician and 4 patients with dentures had difficulties in taking the product.

A post-evaluation of these studies concerning the dosage applied was done by Madaus (2005). The product containing psyllium “mucilloid” seems to be identical to the combination product of ispaghula husk and seed. According to Madaus, one teaspoonful corresponds to 5 g of the combination product, which contains 3.25 g ispaghula seeds and 0.11 g ispaghula husk. The data of each single patient included in the short-term studies (641 patients) were evaluated. The 85 patients with a negative outcome had received 2.6 teaspoonful with 8.4 g ispaghula seeds and 0.29 g ispaghula husks as mean daily dose. The 556 patients with a positive outcome had received 2.4 teaspoonful with 7.8 g ispaghula seeds and 0.26 g ispaghula husks as mean daily dose. No case report forms of the 3 long-term studies were available, only summarising reports without any information about the individual dosage.

Three reviews have been published that evaluate the existing clinical trials with laxatives in general (Tramonte *et al.* 1997, Petticrew *et al.* 1999, Singh 2007).

Tramonte *et al.* (1997) evaluated in 36 randomised trials lasting more than 1 week whether laxatives and fibre therapies improve symptoms and bowel movement frequency in adults with chronic

constipation. They concluded that both fibre and laxatives modestly improved bowel movement frequency. There was inadequate evidence to establish whether fibre was superior to laxatives or one laxative class was superior to another. No severe side effects for any of the therapies were reported.

Petticrew *et al.* (1999) reports the results of a systematic review of randomised controlled trials of the efficacy of laxatives in general in the treatment of constipation in the elderly. The authors concluded that the results of the review suggest that laxatives can improve bowel movement frequency, stool consistency, and symptoms of constipation, with a few exceptions, but that the relevant trials have serious methodological shortcomings. The review found little evidence of marked differences in effectiveness between laxatives. Comparisons between 2 bulk laxatives and between 2 stimulant formulations showed no major differences in frequency or consistency. The authors remarked that there appears to be no evidence to prescribe the more expensive stimulant laxatives.

The review of Singh (2007) discussed the therapeutic value of psyllium for the treatment of constipation among others: 'There is a scientific basis for psyllium working as a mild laxative. This evidence, combined with the available research in humans, suggests that psyllium decreases the time necessary to pass bowel movements, increases the number of bowel movements per day and increases the amount of stool passes.' However, no differentiation is made between ispaghula husk, ispaghula seed and psyllium seed.

Conclusion

The use of ispaghula seed as a laxative is based on experts' testimony and is scientifically substantiated by pharmacological data (see above). The clinical investigations of Sölter & Lorenz (1983) support the efficacy of ispaghula seeds, although these investigations were uncontrolled and unblinded, a combination preparation was used, and the information given in the publication is poor. The amount of ispaghula husk was very small, approximately 4% of the recommended minimal daily dose (7 g). It can therefore be concluded that the main efficacy was due to the amount of ispaghula seeds and that already 8 g ispaghula seeds are effective. The active ingredients in ispaghula seeds are the same as in ispaghula husk. In conclusion, the clinical data on ispaghula husk support the use of ispaghula seed as laxative and in conditions in which easy defecation with soft stool is desirable.

Antidiarrhoeal effect

Sölter & Lorenz (1983) also conducted a study in 84 hospital inpatients (48 psychiatric patients and 36 residents of a nursing home) with diarrhoea. They were treated for up to 3 days with a dose of 2 teaspoonfuls psyllium "mucilloid" 3 times daily, if necessary. Twenty-eight of the psychiatric patients were suffering from chronic diarrhoea. During treatment, a good response was noted in 16 cases and an adequate response in 8 others. The average daily frequency of bowel movements diminished from 3.4 before treatment to 1.5 after one week of treatment. The stool consistency changed from liquid or semi-liquid to soft but formed, or solid. When treatment was discontinued, increased frequency of bowel evaluations recurred in 7 out of the 28 patients within 7 days. In the 20 patients with acute diarrhoea, stool frequency decreased from an average of 4.7 daily pre-treatment to 2.3 on the third day of treatment, and to 1.6 on the seventh day. The nursing home patients were all suffering from acute diarrhoea. The stool frequency decreased from an average of 6.94 daily pre-treatment to 3.28 on the first day, 1.67 on the 2nd day, and 0.81 on the 3rd day. Liquid stools ceased on the 2nd and on the 3rd treatment day. The post-evaluation of Madaus (2005) stated that no other information than the publication was available. A further individual analysis of the daily dosage was not possible.

In an open pilot study Hamouz (1984) investigated the effect of a combination product (5 g of granula i.e. 1 teaspoon) containing ispaghula seed 3.25 g and ispaghula husk 0.11 g) on acute or chronic diarrhoea of 50 hospitalised patients of a psychiatric department. The patients received the combination product for 7 days (2 teaspoonful 3 times daily for 3 days following an individual dosage). The median number of stools decreased from 4.7 to 1.6 in the 22 patients with acute diarrhoea and

from 3.4 to 1.5 in the 28 patients with chronic diarrhoea. Stool consistency changed from loose to soft formed after one week treatment in all patients. All 28 patients with chronic diarrhoea had already been treated with other antidiarrhoeal agents before. Only moderate success or no success at all could be achieved with this prior treatment. The switch to treatment with the combination product brought success in 24 of the 28 cases. This publication seems to deal with the same study, which was reported by Sölter & Lorenz (1983).

Conclusion

Although these investigations suggest that ispaghula seed might exert an antidiarrhoeal effect, these data are not sufficient to prove the efficacy in this indication. There are only uncontrolled studies with a combination of ispaghula husk and seed; in addition acute diarrhoea is often a self-limited disease and a placebo-controlled study is therefore necessary. There is no detailed information available on the effective dosage.

Effect on irritable bowel syndrome (IBS)

Ligny (1988) tested the efficacy of a combination product (5 g of granula i.e. 1 teaspoon) containing ispaghula seed 3.25 g and ispaghula husk 0.11 g) in the three types of IBS in a randomised placebo-controlled study. Thirty out of 60 patients were administered 5 g of the combination product 4 times daily for 30 days. The daily dose contains 13 g ispaghula seeds and 0.44 g ispaghula husks. No special diet was required. In the verum group, only 3 patients were suffering from diarrhoea predominant IBS (Type I), 8 patients were suffering from constipation predominant IBS (Type II) and 19 patients from IBS with alternate occurrence of diarrhoea and constipation (Type III). In the placebo group, 4 patients were suffering from IBS Type I, 9 patients from IBS Type II, and 17 from IBS Type III. During the study patients were permitted to take an antispasmodic (methyl sulphate). The number of tablets was recorded. The severity of the condition was assessed on a scale from 0 to 4 scores for seven symptoms (intensity of pain, abdominal pain, flatulence, cardiac palpitation, asthenia, number of evacuation, severity of constipation). Baseline was the severity of the symptoms and the use of antispasmodics during the last 15 days before treatment. After 15 days treatment, there was a symptomatic improvement in both groups. After 30 days treatment, 27 out of 30 patients in the verum group reported symptomatic improvement and their need for antispasmodic medication dropped by more than 50%. In the placebo group, 10 out of 30 patients showed a symptomatic improvement, but their antispasmodic intake remained just as high as before the trial.

In a placebo controlled trial (Bijkerk *et al.* 2009) 275 patients with irritable bowel syndrome were randomised. Eighty-five subjects received 10 g psyllium, 97 subjects 10 g bran and 93 subjects placebo in two daily doses for 12 weeks. Irritable bowel syndrome had been diagnosed within the preceding two years in 25% of the patients, and 39% fulfilled the Rome II criteria for irritable bowel syndrome. 56% of the patients had constipation predominant irritable bowel syndrome. Rates of response (more than two weeks' adequate relief per month) were significantly higher with psyllium than with placebo during the first month of treatment (number to treat was four) and during the second month, but not during the third month. Only in the third month of treatment was bran more effective than placebo. Analysis restricted to patients who fulfilled the Rome II criteria showed larger responder rates for psyllium compared to placebo (relative risk during the first month 1.81 (1.12 to 2.94) compared with 1.60 (1.13 to 2.26) for all patients with irritable bowel syndrome). A subgroup analysis of patients with constipation dominated irritable bowel syndrome showed comparable results (relative risk during the first month 1.65 (1.05 to 2.62)).

Successful blinding of dietary interventions is difficult. In retrospect, approximately three quarters of patients correctly guessed which treatment they were given. Forty percent of the patients stopped participation before final visit, mainly because they felt worse when taking the fibre supplement. The dropout rate was highest in the bran group and the first month of treatment. The number of patients

stopping treatment because of intolerance was twice as high in the bran group as in the psyllium or placebo group. Psyllium is not exactly specified.

In contrast one recent review (Chouinard 2011) concluded that the data available indicate limited and conflicting evidence to support the recommendation of psyllium supplementation for symptomatic irritable bowel syndrome treatment. According to the authors psyllium supplementation does not appear to be effective for abdominal pain, flatulence, or patient-reported quality-of-life measures. However the authors concluded that psyllium fibre supplementation may be effective for patient-reported global symptom relief and constipation-related symptoms.

Conclusion

The data available are not sufficient to prove the efficacy of ispaghula seed for the indication irritable bowel syndrome in general or a special subgroup. The clinical data available for ispaghula husk and mentioned in the assessment report on ispaghula husk cannot be extrapolated to ispaghula seed because the pathomechanism of irritable bowel syndrome is still unclear. Therefore the exact mechanism of action and the involved active ingredient are still unknown.

Constipation in connection with irritable bowel syndrome is covered by the first indication.

Protection against colorectal cancer / diseases

Tan & Seow-Choen (2007) concluded that the role of fibre in the prevention of colorectal diseases remains controversial.

Lopéz *et al.* (2009) conducted a comparative ecological study of Spain provinces, with colorectal cancer mortality as the dependent variable and per capita consumption of *Plantago ovata* by province and year as the independent variable. The results show an inverse trend between the consumption of *Plantago ovata* and colorectal mortality. The authors recommend additional observational studies of individuals, in order to better control confounding factors.

Effect on blood lipids levels

In a randomised, crossover, controlled, single-blind study in 28 men with cardiovascular disease (myocardial infarction or stable angina and LDL-concentration ≤3.35 mmol/l) Solà *et al*. (2007) compared the effects of *Plantago ovata* husk (10.5 g/d) with those of *Plantago ovata* seeds (10.5 g/d) on plasma lipid, lipoprotein, and apolipoprotein concentrations during 8 weeks. Plasma triacylglycerol decreased (6.2%, $p<0.02$), the ratio of apo B 100 to apo A-I decreased (4.7%; $p<0.02$), and apo A-I increased (4.3%; $p<0.01$) in the husk consumers. Compared to the seed the intake of husk increased HDL-cholesterol concentrations by 6.7% ($p=0.006$) and decreased the ratio of total to HDL-cholesterol and of LDL to HDL cholesterol by 10.6% ($p=0.002$) and 14.2% ($p=0.003$), respectively.

4.2.3. Clinical studies in special populations (e.g. elderly and children)

Effect on blood lipids levels in patients with diabetes mellitus

Sartore *et al*. (2009) examined the effects of 2 months of ispaghula treatment (probably seeds according to internet research) in optimising metabolic control and lipoprotein profile, and its postprandial effects on lipids in type II diabetes. Forty type II diabetic patients who were on sulfonylureas and a controlled diet, were sequentially assigned to ispaghula treatment (3.5 g t.i.d.) or to a control group. After 2 months of treatment, body mass index, waist circumference, HbA1c and fasting plasma glucose levels had significantly decreased in both groups. There were no postprandial differences in the lipoprotein profile between the two groups. Triglycerides were significantly lower in the ispaghula group, but not in the control group.

Laxative effect in children

There are numerous publications, which indicate that the potential health benefits of increased dietary fibre in childhood outweigh the potential risks, especially in highly industrialised countries (Williams *et al.* 1995). A review of the scientific literature by Williams *et* Bollela (1995) suggested that a small loss of energy, protein, and fat may occur with a high intake of dietary fibre but that a moderate increase in dietary fibre is more likely to be healthy than harmful, especially in children with constipation. McClung *et al.* (1995) confirmed that only half of the children received the recommended amounts of dietary fibre intake. According to the recommendations from a conference on dietary fibre in childhood, children older than 2 years of age should increase their daily intake of dietary fibre (increased consumption of a variety of fruits, vegetables, cereal and other grain product) to an amount equal or greater than their age plus 5 g (e.g. 8 g/day at age 3) (Williams *et al.* 1995).

Conclusion

Considering these remarks, laxative bulk producers should be used before using other purgatives in children, if change of nutrition is not successful. As a general precaution and because clinical data are lacking, the use is not recommended in children below the age of 6 years.

Children from 6 to 12 years of age should take 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 according to general recommendations of posology for children of this age derived from the adult dose (Kooperation Phytopharmaka 2002).

Use during pregnancy and lactation

There are no data available for the use of ispaghula seed during pregnancy and lactation.

Bishop (1978) concluded that bulk-forming laxatives appear to be safe and effective in pregnancy. The author referred to 2 studies, which compared bulk-forming laxatives to irritant laxatives in antenatal patients (see below).

Greenhalf *et al.* (1973) stated that constipation was corrected in a higher percent of pregnant and breast-feeding women using irritant laxatives but normalisation of bowel habit was similar (statistically) in all groups (an irritant, an emollient/irritant combination, a bulk forming/mild irritant combination, and a bulk forming agent). The side effects were higher in the irritant group than in the bulk forming group.

Fianu *et al.* (1975) compared psyllium hydrophilic mucilloid with irritant laxatives in 199 pregnant women (plus control patients) and observed no significant differences between irritant laxatives and psyllium. The authors concluded that due to its more physiological way of normalising and promoting defecation psyllium hydrophilic mucilloid granules, mixed in food, should be used as first choice. Psyllium when given to the mothers appeared to have had no effect on the defecation of their new-born infants.

Conclusion

Based on the known well-established use of ispaghula seed and husk and the known pharmacokinetics, that only small amounts of monosaccharides become available for systemic absorption (see above 4.1.2) the HMPC concluded during the first assessment that there is no restriction in pregnancy and lactation. However first measure should be change of nutrition and in case of failure laxative bulk producers like ispaghula seed should be used before using other purgatives.

Since publication of the HMPC-monograph no new safety or efficacy data concerning pregnancy and lactation have been published. No specific toxicological data concerning ispaghula seed are available. The animal studies with ispaghula husk are insufficient with respect to reproductive toxicity.

Assessment during revision 1 according to the Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203297/2005) would now lead

to the wording "is not recommended", because non-clinical data are insufficient and less than 300 prospective exposed pregnancies are documented.

On the other hand no reports on safety concerns in pregnancy and lactation have been published during the last five to six years of use according to the HMPC monograph. Within the Guideline a case-by-case wording is recommended, reflecting also to pharmacokinetics and the effects detected (e.g. growth retarding effects are estimated to be less concerning than morphological effects). Also other aspects such as therapeutic benefit compared with options available or therapeutic alternatives should be considered. Limited amount of data (less than 300 pregnancy outcomes) from the use of ispaghula husk in pregnant women are available. Taken together, the following wording is supported:

"There are no data from the use of ispaghula seed, but limited data (less than 300 pregnancy outcomes) from the use of ispaghula husk in pregnant women. Animal studies are insufficient with respect to reproductive toxicity.

The use of ispaghula seed may be considered during pregnancy and lactation, if necessary and if change of nutrition is not successful. Laxative bulk producers should be used before using other purgatives.

No fertility data are available"

Use in post-menopausal women

Ganji & Kuo (2008) showed in a small study population of 8 pre- and 11 post-menopausal women, that mean HDL-cholesterol and total cholesterol were significantly lower in post-menopausal women with psyllium fibre intake compared to baseline. In contrast no significant change was observed in pre-menopausal women with psyllium.

Conclusion

This study was an uncontrolled one with a very small population. The used psyllium fibre was not specified exactly. Therefore no conclusion can be drawn.

4.3. Overall conclusions on clinical pharmacology and efficacy

Indication 1: For the treatment of habitual constipation

The use of ispaghula seed as a laxative is mainly based on experts' testimony and is scientifically substantiated by pharmacological data. The clinical investigations of Sölter & Lorenz (1983) support the efficacy of ispaghula seeds. The active ingredients are the same as in ispaghula husk; the clinical data on ispaghula husk support therefore the use of ispaghula seed as laxative. It can be concluded that the use as a laxative is a well-established use. Taking into account the investigations of Sölter and Lorenz, the current level of evidence[1] can be identified as level III to IV.

Indication 2: In conditions in which easy defecation with soft stools is desirable, e.g. in case of painful defecation after rectal or anal surgery, anal fissures and haemorrhoids

The use in condition in which easy defecation with soft stool is desirable is scientifically substantiated by the well-known laxative effects but there are no specific data available. The level of evidence in this indication is therefore level IV.

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.

The use of ispaghula seed may be considered during pregnancy and lactation, if necessary and if change of nutrition is not successful. Laxative bulk producers should be used before using other purgatives.

[1] As referred to in the HMPC 'Guideline on the assessment of clinical safety and efficacy in the preparation of Community herbal monographs for well-established and of Community herbal monographs/entries to the Community list for traditional herbal products/substances/preparations' (EMEA/HMPC/104613/2005)

The data available are not sufficient to prove the efficacy of ispaghula seed for the indication irritable bowel syndrome in general or a special subgroup. The clinical data available for ispaghula husk and mentioned in the assessment report on ispaghula husk cannot be extrapolated to ispaghula seed because the pathomechanism of irritable bowel syndrome is still unclear. The exact mechanism of action and the involved active ingredient are still unknown. Constipation in connection with irritable bowel syndrome is covered by the first indication.

Some investigations suggest that ispaghula seed might exert an antidiarrhoeal effect; however these data are not sufficient to prove the efficacy in this indication. There are only uncontrolled studies with a combination of ispaghula husk and seed; in addition acute diarrhoea is often a self-limited disease and a placebo-controlled study is therefore necessary.

Pharmacological data as mentioned in chapter 3.1 Mode of action suggest that ispaghula seed has a positive effect on blood lipid levels but the clinical data are insufficient. The clinical data available for ispaghula husk and mentioned in the assessment report on ispaghula husk cannot be extrapolated to ispaghula seed because the exact mechanism of action and the involved active ingredient are still unknown. This is supported by the investigations of Solà *et al*. (2007). As the clinical data are insufficient, it is not possible to recommend a specific indication.

Efficacy data and pharmacological data concerning further indications are insufficient.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

No adequate data are available. We refer to the assessment report on ispaghula husk.

5.2. Patient exposure

No adequate data available.

5.3. Adverse events and serious adverse events and deaths

Gastrointestinal adverse events

Flatulence, occurring with the use of ispaghula seed, is common like for other bulk forming agents.

Bliss *et al.* (2011) compared the severity of adverse gastrointestinal symptoms during supplementation with dietary fibre or placebo over time in 189 adults with faecal incontinence in a randomised study. Subjects were given either placebo or a supplement of 16 g total dietary fibre per day from 1 of 3 sources: gum arabicum, psyllium, or carboxymethylcellulose. Severity of symptoms in all groups was minimal. A greater feeling of fullness in the psyllium group was the only symptom that differed from symptoms in the placebo group. Psyllium fibre was described as follows: primarily an arabinoxylane form of hemicellulose with limited solubility extracted from *Plantago ovata* seed husks.

Oesophageal obstruction

Because of possible oesophageal obstruction associated with the use of psyllium laxatives in granular dosage form when taken without sufficient liquid, the FDA meanwhile prohibits the use of psyllium granules as “OTC”-product (Federal Register 03/29/2007) and requires an approved application for marketing. Concerning this matter adequate warnings are already included in the monograph.

Allergic adverse reactions

Ispaghula seed contains potent allergens. Exposure to these allergens is possible through the oral route or through contact. Ispaghula seed should be considered as a possible cause of anaphylaxis from laxatives. Reactions of hypersensitivity including anaphylaxis-like reactions may occur very rarely.

Ispaghula seed is not to be used by patients with known hypersensitivity to ispaghula (Rubira *et al.* 2000, Aleman *et al.* 2001, Khalili *et al.* 2003).

In July and October 2011 the Pharmacovigilance Working Party (PhVWP) concluded that the product information of *Plantago ovata* seed-containing medicinal products as powder formulations should be updated to include the risk of allergic reactions after prolonged occupational exposure and the warning to stop current exposure and avoid future exposure to these products in the case of proven allergic sensitisation (EMA/CHMP/PhVWP/569591/2011, 28 July 2011 and EMA/CHMP/PhVWP/851373/2011/Final, 14 November 2011).

The following wording was agreed (CMDh/PhVWP/035/2011, October 2011):

Summary of product characteristics

4.2 Posology and method of administration
(…)
When preparing the product for administration, it is important to try to avoid inhaling any of the powder in order to minimise the risk of sensitisation to the active ingredient.

4.3 Contraindications
- addition of a cross reference to section 4.4 "/see 4.4 Special warnings and precautions for use)", following the current statement on the contraindication in patients with known hypersensitivity to the product.

4.4 Special warnings and precautions for use
(…)

"Warning on hypersensitivity reactions
In individuals with continued occupational contact to powder of *Plantago ovata seeds* (i.e. healthcare workers, caregivers) allergic sensitisation may occur due to inhalation, this is more frequent in atopic individuals. This sensitisation usually leads to hypersensitivity reactions which could be serious (see 4.8 Undesirable effects).

It is recommended to assess clinically the possible sensitisation of individuals risk and, if justified, to perform specific diagnostic tests.

In case of proven sensitisation leading to hypersensitivity reactions, exposure to the product should be stopped immediately and avoided in the future (see 4.3 Contraindications)."

4.8 Undesirable effects
(…)
"Ispaghula/psyllium husk contains potent allergens. The exposure to these allergens is possible through oral administration, contact with the skin and, in the of powder formulations, also by inhalation.

As a consequence to this allergic potential, individuals exposed to the product can develop hypersensitivity reactions such as rhinitis, conjunctivitis, bronchospasm and in some cases, anaphylaxia. Cutaneous symptoms as exanthema and/or pruritus have also been reported. Special attention should be given to individuals manipulating the powder formulations routinely (see 4.4 Special warnings and precautions for use)."

6.6
See 4.2

Package Leaflet

2. What you need to know before you use <X>
Do not use <Herbal medicinal product>:
if you allergic to *Plantago ovata* seeds or any of the other ingredients of this medicine (see in this section "Warnings and precautions" below)
(...)

Warning and precautions:
Talk to your doctor or pharmacist before taking <Herbal medicinal product>:
If you are a healthcare worker or care giver who has preparing for administration products with powder of *Plantago ovata* seeds to patients for a long time you might have become allergic to these products due to continued inhalation of the powder. In case of symptoms (listed in section 4) are confirmed as allergic, do not use the product (see in this section, "Do not use")

3. How to use <Herbal medicinal product>
(...)
(At the end of the paragraph describing the method of administration)
When preparing the product for administration it is important to try to avoid inhaling the powder.

4. Possible side effects
(...)
(At the end of the paragraph describing the possibility of allergic reactions)
Plantago ovata seeds contain substances which may lead to allergic reactions after use of the product by the oral route, contact with the skin or, in case of powder formulations, also by inhalation.
The allergic symptoms may include running nose, redness of the eye, difficulty in breathing, skin reactions, itching, and in some cases anaphylaxis (a sudden, generalised allergic reaction that may lead to life-threatening shock). Individuals manipulating the powder formulations routinely are more prone to these reactions (see section 2).

"Summary Assessment Report of the PhVWP July 2011"

Association of allergic reactions with the inhalation of Plantago ovata seeds (ispaghula seeds) during prolonged occupational exposure

Reason for current safety review

Spain has informed the Pharmacovigilance Working Party of 31 cases of allergic reactions associated with the use of powder formulations of Plantago ovata seeds (ispaghula seeds), an herbal medicinal product used as laxative. Most of them (25) were reported recently in persons who inadvertently inhaled the powder when preparing it for administration.

Safety concern

Most of the cases reported involved healthcare workers who had been handling these powder formulations for years, while preparing them for administration to patients. Subjects predominantly presented respiratory symptoms (rhinitis, asthma), which could be severe, shortly after inhalation of the product.

According to the results of a study performed in Spain (Bernedo et al. 2008) in a sample of healthcare workers in geriatric care homes repeatedly exposed to Plantago ovata seed products, about 9% suffered allergic reactions confirmed by allergy tests.

Other studies published in the past in different countries show similar results

In addition, similar cases have also been reported in pharmaceutical industry workers manipulating the seeds during their preparation.

Although these products are available in most European countries, only a limited number of cases of allergic reactions associated to the individual use of Plantago ovata have been reported, and most of them were non-serious.

Clinical setting

Chronic constipation is very common in the elderly and Plantago ovata seeds have been widely used as bulk laxatives for many years in this population. In care homes for the elderly in Spain, powder formulations are commonly used and caregivers may be exposed to them on a daily basis when preparing these formulations for administration.

Important aspects of the substance/product

Plantago ovata seeds are also known as ispaghula. The active ingredients are the mucilages located in the husk of the seed. Other species from this plant family, Plantago psyllium (scientific names: Plantago afra or Plantago indica), have the same properties and mode of action. As available scientific data do not always differentiate precisely the investigated herbal substance, it is assumed that all these products have the same risk of allergic reactions. The term "psyllium" has been commonly used in the past for Plantago ovata.

Plantago ovata-containing products are available as powder or as granules for oral use. The safety concern is related to the inhalation of the product in powder formulation, since the particles, before dissolution in water, are sufficiently small to become airborne, reaching the airways.

Information on the data assessed

A number of well documented case reports and some studies performed in different settings and countries provide sufficient evidence for a risk of allergic reactions after long term occupational exposure to Plantago ovata seeds due to unintended inhalation. However, the limited available evidence does not indicate that there is a relevant risk in the general population.

Outcome of the assessment

Based on the review, the PhVWP concluded that allergic symptoms, confirmed by allergic tests, are present in a proportion (around 9%) of subjects with prolonged occupational exposure to Plantago ovata seed powder. Cases may be serious (asthma, anaphylactic reactions with hypotension). People with atopy are considered to be at increased risk. As with other allergic reactions, avoiding exposure to the causal agent (by inhalation or ingestion) is the best way to prevent the adverse events in the sensitised population.

The PhVWP considered relevant to increase the awareness of this risk in healthcare professionals (healthcare workers, caregivers) and workers in the pharmaceutical industry. The PhVWP recommended that Summaries of products characteristics and package leaflets of medicinal products containing powder formulations of Plantago ovata seeds should be updated to include this information."

The following references were also taken into account: Machado et al. (1979), Shoenwetter (1985), Bardy et al. (1987), Malo et al. (1990), McConnochie et al. (1990), Marks et al. (1991), Khalili et al. (2003).

5.4. Interactions

Because of their pharmacodynamic properties, all bulk forming laxatives may delay the enteral absorption of concomitantly administered medications. Ispaghula seed should therefore be taken at least ½ to 1 hour before or after intake of other medicinal products.

There are no specific data on interactions between ispaghula seed and medicinal products. Because seeds and husks have the same origin and comparable ingredients, it is assumed that ispaghula seed interacts with the same medicinal products as ispaghula husk. Resulting from the assessment of data

on interactions available for ispaghula husk, the following information should be included in the product information of ispaghula seed containing medicinal products:

- 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.
- Diabetic patients should take ispaghula seeds only under medical supervision because adjustment of anti-diabetic therapy may be necessary.
- Use of ispaghula seed concomitantly with thyroid hormones requires medical supervision because the dose of the thyroid hormones may have to be adjusted.

Pharmacological data suggest that ispaghula seed lowers peak blood glucose levels due to delayed intestinal absorption of carbohydrates, like ispaghula husk and that there might be a positive influence of the diabetic metabolism.

Bajorek & Morello (2010) reviewed the data available on the effects of dietary fibre and a low glycaemic index diet on glycaemic risk factors in people with type 2 diabetes mellitus with or without dyslipidaemia. The assessment was based on randomised controlled studies or meta-analysis. The authors showed that a daily dosage of psyllium 10.2 significantly decreased all-day postprandial plasma glucose concentrations, although the decrease was perhaps due to a significantly decreased post lunch plasma glucose level. Psyllium's effect on glycaemic risk factors (haemoglobin A_{1C}) is inconsistent between studies.

Karhunen *et al.* (2010) also concluded that solid meals enriched with psyllium fibre strongly modified postprandial signals arising from the gastrointestinal tract. In a single-blind, randomised, cross-over study in 16 healthy young adults the effects of dietary fibre and/or protein enrichments on satiety-related metabolic and hormonal responses were investigated. Addition of psyllium fibre (23 g) to the test meals decreased the postprandial plasma glucose and serum insulin responses compared with the lower-fibre meals. No postprandial decrease in ghrelin was found.

Considering this, the contraindication "cases of diabetic mellitus where insulin adjustment is difficult" is deleted. However, because of the observed influence of diabetic metabolism the advice mentioned above is given in the monograph under "Interactions with other medicinal products and other forms of interaction".

5.5. Laboratory findings

No adequate data available.

5.6. Safety in special populations and situations

Contraindications

Ispaghula seed is a bulk forming agent and several other contraindications for this kind of agents must be respected:

Ispaghula seed should not be used by patients with a sudden change in bowel habit that persists for more than 2 weeks, undiagnosed rectal bleeding and failure to defecate following the use of a laxative. Ispaghula seed should also not 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), or megacolon.

Ispaghula seed preparations should not be taken by patients who have difficulty in swallowing or who have any throat problems.

Warnings and precautions

There are several warnings to include in the product information of ispaghula seed containing medicinal products.

In order to decrease the risk of gastrointestinal obstruction (ileus) ispaghula seed should be used together with medicinal products known to inhibit peristaltic movement (e.g. opioids) only under medical supervision.

Ispaghula seed should not be used by patients with faecal impaction and symptoms such as abdominal pain, nausea and vomiting unless advised by a doctor because these symptoms can be signs of potential or existing intestinal blockage (ileus).

Furthermore the following advice should be given:

If the constipation does not resolve within 3 days or if abdominal pain occurs or in cases of any irregularity of faeces, the use of ispaghula seed should be discontinued and medical advice must be sought.

Special warnings for bulk forming agents must be included, too.

Use in pregnancy and lactation

There are no data from the use of ispaghula seed, but limited data (less than 300 pregnancy outcomes) from the use of ispaghula husk in pregnant women. Animal studies are insufficient with respect to reproductive toxicity.

The use of ispaghula seed may be considered during pregnancy and lactation, if necessary and if change of nutrition is not successful. Laxative bulk producers should be used before using other purgatives.

5.7. Overall conclusions on clinical safety

The long-term medicinal use of ispaghula seed has confirmed an adequate safety profile.

During the use of ispaghula seed in particular mild gastrointestinal adverse reactions like flatulence can occur. When using ispaghula seed without adequate fluid intake, oesophageal and intestinal obstruction can occur like with all bulk producers. Theoretically this can be promoted when the medicinal product is taken immediately prior to bed-time. Therefore adequate warnings have to be included in the package leaflet.

Hypersensitivity reactions are possible. This includes the risk of allergic reactions after prolonged occupational exposure in healthcare workers or caregivers. The final SmPC and PL wording as agreed by PhVWP in October 2011 has to be included in the monograph.

The wording concerning fertility, pregnancy and lactation has to be adapted like proposed above.

No revision of the monograph is necessary concerning other safety aspects.

The use of ispaghula seed can be considered as safe when administered according to the recommendation in the revised monograph.

6. Overall conclusions

Ispaghula seed is an herbal medicinal product with well-established use

1) for the treatment of habitual constipation;

2) in conditions in which easy defecation with soft stool is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures and haemorrhoids.

The use of ispaghula seed as a laxative is mainly based on experts' testimony and is scientifically substantiated by pharmacological data.

The active ingredients are the same as in ispaghula husk; the clinical data on ispaghula husk support therefore the use of ispaghula seed as laxative.

The use in conditions in which easy defecation with soft stool is desirable is scientifically substantiated by the well-known laxative effects but there are no specific data available.

The 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.

There are no data from the use of ispaghula seed, but limited data (less than 300 pregnancy outcomes) from the use of ispaghula husk in pregnant women. Animal studies are insufficient with respect to reproductive toxicity.

The use of ispaghula seed may be considered during pregnancy and lactation, if necessary and if change of nutrition is not successful. Laxative bulk producers should be used before using other purgatives.

Known risks or adverse events are predominantly mild and adequately addressed in the monograph.

Animal studies are insufficient with respect to toxicity. Tests on genotoxicity are lacking and have to be performed according to the “guideline on the assessment of genotoxicity of herbal substances/preparations” (EMEA/HMPC/107079/2007). Provided the results are negative and taking into account the long-term medicinal use of ispaghula seed, an adequate safety profile can be confirmed.

The benefit-risk assessment for the claimed well-established use is positive.

The available clinical data mentioned in section 4 ‘Clinical data’ are insufficient to recommend further specific indications, neither for well-established nor for traditional use.

Some investigations suggest that ispaghula seed might exert an antidiarrheal effect; however these data are not sufficient to prove the efficacy in this indication. There are only uncontrolled studies with a combination of ispaghula husk and seed; in addition acute diarrhoea is often a self-limited disease and a placebo-controlled study is therefore necessary.

Concerning traditional use there are no detailed information available on the effective dosage.

Annex

List of references