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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

ASSESSMENT REPORT ON *PLANTAGO OVATA* FORSSK., SEMEN

Herbal substance	*Plantago ovata* Forssk., semen
Herbal preparation	Powdered herbal substance
Pharmaceutical forms	- Herbal substance for oral preparation - Herbal preparation in solid oral dosage forms such as granules and powders
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I. Introduction

This assessment report reviews the scientific data available for ispaghula seed (*Plantago ovata* Forssk., semen), primarily the clinical data. When special 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 use is made in this report of the term "psyllium". In the more recent investigations, ispaghula husk was used predominantly.
The literature presented by the European Scientific Cooperative on Phytotherapy (ESCOP) and supporting the monograph "Plantaginis ovatae semen" (Ispaghula Seed) (ESCOP Monographs, second edition 2003) was also taken into account.

Constipation is a common complaint in 1 – 6% of the middle-aged population and 20 – 80 % of the elderly people, and may be treated by laxatives. Functional constipation is the most common type, without any specific etiology (1). The most commonly used laxatives are either stimulant laxatives (containing anthracenic derivatives from senna, frangula or cascara), lubricant laxatives (e.g. mineral oils) or bulk forming agents such as ispaghula husk and ispaghula seed.

Ispaghula seed is a natural substance and belongs to the bulk forming agents. It is used:
a) for the treatment of habitual constipation,
b) in conditions in which easy defaecation with soft stool is desirable, e.g. in cases of painful defaecation after rectal or anal surgery, anal fissures and haemorrhoids.

These indications are scientifically substantiated by the pharmacological effects of ispaghula seed. Preparations of ispaghula seed have to be regarded as herbal medicinal products with a "well-established medicinal use" in these indications with respect to the application of Directive 2001/83/EC of the Parliament and of the Council on the Community code relating to medicinal products for human use as amended.

II. Clinical Pharmacology

II.1 Pharmacokinetics

Ispaghula seed consists of the whole dried ripe seeds of *Plantago ovata* Forsk (*Plantago ispaghula* Roxb). The herbal substance has to comply with the monograph "Ispaghula Seed" of the European Pharmacopoeia (ref. 01/2005:1333).
Ispaghula seeds contain 20 – 30 % mucilages, which are a highly branched acidic arabinoxylan (2) (see also chapter II.2.1 Mode of action).

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

Conclusion

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.

II.2 Pharmacodynamics

II.2.1 Mode of action

- Laxative effect

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 (2). The seeds also contain proteins, fixed oil, sterols and the trisaccharide planteose (3, 4, 5).
The German Pharmacopoiea indicates that ispaghula seed has to be capable of absorbing at least 9 times its own weight in water. The British Pharmacopoiea 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 (2).

Leng-Peschlow E 1991 (6) 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 motilility 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 defaecation; at the same time the swollen mass of mucilage forms a lubricating layer, which eases the transit of intestinal contents (2).

- Effect on diarrhoea

There are no specific data available for ispaghula seed.

- Effect on blood lipids levels

Kritchevsky D *et al.* 1995 (7) 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.

Gelissen IC *et al.* 1994 (8) 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.

- Effect on blood glucose levels

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

Mahapatra SC *et al.* 1988 (9) 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.

- Effect on gastrointestinal enzymes

Leng-Peschlow E 1989 (10) 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.

II.2.2 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 derivates, 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 by insulin dependent diabetic patients it may be necessary to reduce the insulin dose.

- Use of ispaghula seed concomitantly with thyroid hormones requires 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 be used together with medicinal products known to inhibit peristaltic movement (e.g. opioids, loperamide) only under medical supervision.

III. Clinical Efficacy

III.1 Dosage

There are no dose-finding studies available.

As a laxative for adults, elderly and children over 12 years of age, experts (2, 11) recommend 12 – 40 g in 1 –3 doses daily.
Even if ispaghula seed has only 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.

III.2 Clinical studies

III.2.1 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. Between 1976 and the present, 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" and 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 (Agiocur®); 100 g of this preparation contains 65 g ispaghula semen and 2.2 g ispaghula husk.

Sölter H and Lorenz D 1983 (22) conducted short-term trials of 7 days and long-term trials of up to 12 weeks. At 15 trial centers 669 patients (266 males and 403 females) ranging in age from 13 to 90 years were treated with Prodiem Plain® for 7 days. 28 patients were excluded because of uncertainty of diagnosis, administration of other laxatives and inadequately completed protocols. At three centers 139 patients (59 males and 80 females, ranging in age from 9 to 80 years) were treated with Prodiem Plain® 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 teaspoonsful 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. Prodiem Plain® is described as a product containing psyllium mucilloid as its active constituent. 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 (23). Prodiem Plain® seems to be identical to Agiocur®. According to Madaus 1 teaspoonful corresponds to 5 g Agiocur®, which contain 3.25 g ispaghula husks and 0.11 g ispaghula seeds. 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 teaspoonsful 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 teaspoonsful 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.

Conclusion

The use of ispaghula seed as a laxative is based on experts' testimony and scientifically substantiated by pharmacological data (see above). The clinical investigations of Sölter and Lorenz support the efficacy of ispaghula seeds, even if these investigations were uncontrolled and unblinded, a combination preparation was used, and the information given in the publication are 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 defaecation with soft stool is desirable.

III.2.2 Antidiarrhoeal effect

Sölter H and Lorenz D 1983 (22) 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 teaspoonsful Prodiem Plain® 3 times daily, if necessary. Twenty eight of the psychiatric patients were suffering from chronic diarrhoea. During Prodiem Plain® 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 Prodiem Plain® 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 (23) 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 W 1984** (12) investigated the effect of Agiocur® (5 g of granula i.e. 1 teaspoon) containing ispaghula seed = 3.25 and ispaghula husk = 0.11 g) on acute or chronic diarrhoea of 50 hospitalised patients of a psychiatric department. The patients received Agiocur® for 7 days (2 teaspoonsful 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 Agiocur® brought success in 24 of the 28 cases.
This publication seems to deal with the same study, which was reported by Sölter and Lorenz (22).

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 are no detailed information available on the effective dosage.

III.2.3 Effect on irritable bowel syndrome

Ligny G 1988 (24) tested the efficacy of Agiocur® in the three types of IBS in a randomised placebo-controlled study. 30 out of 60 patients were administered 5 g Agiocur® 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 Agiocur® 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 (Visceralgine® forte – 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 Agiocur® 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.

Conclusion

The data available are not sufficient to prove the efficacy of ispaghula seed for the indication irritable bowel syndrome. Only 30 patients suffering from IBS were treated with a combination of ispaghula seed and husk (even if the amount of ispaghula husk was clearly below the amount of ispaghula seed). The various types of IBS were not represented equally and were not assessed separately.

III.2.4 Effect on blood lipids levels

Segawa K *et al.* 1998 (13) 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 pretreatment 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 pretreatment (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 pretreatment (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 associated of urea nitrogen and lipid metabolism in hyperlipidemia and psyllium seed treatment.

Conclusion

Pharmacological data as mentioned in chapter II.2.1 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. As the clinical data are insufficient, it is not possible to recommend a specific indication.

III.3 Clinical studies in special populations

III.3.1 Use 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 (14). A review of the scientific literature by **Williams CL et al. 1995** (15) suggests 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 (16). 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) (14).

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.

III.2.2 Use during pregnancy and lactation

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

Bishop C 1978 (17) 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 women (see below).
Greenhalf JO *et al.* 1973 (18) stated that constipation was corrected in a higher percentage of patients using irritant laxatives but normalisation of bowel habit was similiar (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 the bulk forming group.
Fianu S *et al.* 1975 (100) compared psyllium hydrophilic mucilloid (ViSiblin®) with irritant laxatives in 199 pregnant women (plus control patients) and observed no significant differences between irritant laxatives and psyllium. Psyllium when given to the mothers appeared to have had no effect on the defaecation of their new-born infants.

Conclusion

The following advice that "Laxative bulk producers should be used before using other purgatives if change of nutrition is not successful" should appear in the section 'Pregnancy and lactation' of the product information of ispaghula seed containing products. Medicinal products should be avoided during pregnancy and lactation if possible; caution is recommended when administered.

III.4 Traditional use

Please refer to the corresponding chapter of the assessment report on ispaghula husk, which concludes as follows:

Older references do not mention *Plantago ovata* because this plant is native to Iran and India.
The use of ispaghula husk and other kinds of Plantago in traditional medicine is similiar to the use of linseed, but such traditional use is not described as well and so 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'**.**

IV. Safety

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

IV.1 Undesirable effects

Flatulence may occur with the use of ispaghula seed.

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 (19, 20, 21).

IV.2 Contraindications

Pharmacological data suggest that ispaghula seed lowers peak blood glucose levels due to delayed intestinal absorption of carbohydrates, like ispaghula husk (see chapter II.2.1 Mode of action). Cases of diabetes mellitus where insulin adjustment is difficult constitute therefore a contraindication to the administration of ispaghula seed preparations. The following should appear in the product information of such preparations:

Ispaghula seed should not be used by patients with diabetes mellitus, which is difficult to regulate.

Furthermore, the product information should contain a statement, as already pointed out in chapter II.2.2 Interactions, that it may be necessary to reduce the insulin dose if the product is taken together with meals by insulin dependent diabetic patients.

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 defaecate 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 esophagus 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.

Ispaghula seed should finally not be used by patients with known hypersensitivity to ispaghula.

IV.3 Special warnings and precautions for use

There are several warnings to be included in the product information of ispaghula seed containing medicinal products:

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 72 hours 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.

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

IV.4 Interactions with other medicinal products and other forms of interaction

See chapter II.2.2.

IV. Overall conclusions

Indication a): 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 and Lorenz 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 b): In conditions in which easy defaecation with soft stool is desirable, e.g. in cases of painful defaecation after rectal or anal surgery, anal fissures and haemorrhoids

The use in condition in which easy defaecation 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.

[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)