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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

ASSESSMENT REPORT ON *PLANTAGO OVATA* FORSSK., SEMINIS TEGUMENTUM

Herbal substance	*Plantago ovata* Forssk. *(*P. *ispaghula* Roxb.*)*, seminis tegumentum
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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TABLE OF CONTENTS

I. Introduction

This assessment report reviews the scientific data available for ispaghula husk (*Plantago ovata* Forssk., seminis tegumentum), primarily the clinical data. This report was prepared on the basis of the expert-report presented in 2001 for a pharmaceutical preparation containing 49.2 g powdered ispaghula husk in 100 g powder.The report reviews in particular the literature presented by the European Scientific Cooperative on Phytotherapy (ESCOP) to support the monograph "Plantaginis ovatae testa (Ispaghula Husk, Blond Psyllium Husk)" (ESCOP Monographs, second edition 2003).

Scientific publications do not always differentiate precisely which preparations were investigated; 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", otherwise reference is made to "ispaghula husk".

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.

Ispaghula husk 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;
c) in patients to whom an increased daily fibre intake may be advisable e.g. as an adjuvant in constipation predominant irritable bowel syndrome, as an adjuvant to diet in hypercholesterolemia.

These indications are medically substantiated by the pharmacological effects of ispaghula husk. Ispaghula husk preparations 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.

The indication as an adjuvant in the symptomatic treatment of diarrhoea from various causes cannot be regarded as a well-established one after assessment of available clinical data.

Traditional uses of ispaghula husk are reviewed in this report, none of them are supported by data on long-standing use and experience sufficient to justify the creation of an entry in the 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products'.

II. Clinical Pharmacology

II.1 Pharmacokinetics

II.1.1 Absorption

Ispaghula husk consists of the episperm and collapsed adjacent layers removed from the seeds of *Plantago ovata* Forssk (*Plantago ispaghula* Roxb.). The herbal subtance has to comply with the monograph "Ispaghula husk" of the European Pharmacopoeia (ref. 01/2005:1335).
Ispaghula husk consists of 85% water-soluble fibre and is relatively resistant to fermentation by colonic bacteria (2). The active polysaccharidic fraction comprises 65% D-xylose, 20% L-arabinose, 6% rhamnose and 9% D-galacturonic acid (3). The polysaccharide is shown to be a highly branched acidic arabinoxylan, the xylan backbone having both 1→4 and 1→3 sugar linkages. The structure accounts for its non-absorption and resistance to digestion by colonic bacteria.

Polysaccharides, such as those found in dietary fibre, must be hydrolysed to monosaccharides before intestinal uptake can occur. The sugar residues of the xylan backbone and the side chains of psyllium are joined by β-linkages (4, 5). These β-linkages cannot be broken by human digestive enzymes. While psyllium may contain a small number of α-linkages, these are sterically hindered (6). As a result of this chemical structure, psyllium is not expected to be hydrolysed in the upper gastrointestinal (GI) tract. Although most studies confirm that psyllium is not digested in the upper GI tract or absorbed from the small intestine (7), **Andersen JR *et al.*** (8) found that 1% to 6% of psyllium was hydrolysed in the stomach of healthy male volunteers, with formation of free arabinose. Intestinal absorption of the free arabinose was 85% to 93%. As arabinose is a simple pentase monosaccharide with no known pharmacological properties, there is no clinical significance attached to this finding.

II.1.2 Metabolism

To varying degrees, dietary fibre is fermented by bacteria in the colon, resulting in the production of carbon dioxide, hydrogen, methane, water, and short-chain fatty acids (SCFA). The main SCFA produced by fibre fermentation are acetate, propionate, and butyrate (9, 10). Soluble fibres are in general more extensively degraded by the intestinal flora than insoluble fibres. SCFA are efficiently absorbed in the gut and brought into the hepatic circulation (11). In humans, psyllium transits the upper GI tract and reaches the large bowel in a highly polymerised form that is fermented to a limited extent, resulting in increased faecal concentrations and excretion of SCFA, but with no detectable increase in faecal bacterial mass, rectal expulsion of gas, or excretion of methane or hydrogen in breath (12).

Several studies conducted in healthy human volunteers investigated whether ingestion of psyllium increases gas formation or not (as measured by breath-gas analysis with excreted methane and hydrogen as an index of rapid colonic fermentation): **Marteau P. *et al.* 1990** (2), **Wolever TMS *et al.* 1991** (13), **Wolever and Robb 1992** (14), **Wolever TMS *et al.* 1992** (15), **Lewitt M. *et al.* 1996** (16).
The fermentation by colonic bacteria produces small amounts of methane and hydrogen gases as flatus but does not produce measurable increases in breath hydrogen or methane.

A more recent study in 10 healthy volunteers evaluated the effect on gas production of a standard meal supplementation of a single 5 g dose of microcrystalline cellulose, guar gum or ispaghula by collecting and analysing breath samples; the role of fermentation on the genesis of symptom was also evaluated (17). Subjects experienced more symptoms such as bloating, abdominal distension, flatulence, when meals were supplemented with guar gum ($p=0.009$ vs standard meal) and ispaghula ($p=0.048$ vs standard meal). There was a poor, but significant, correlation between gas production and symptoms ($r=0.38$, $p=0.01$). In this study, addition of different dietary fibres to a solid meal did not influence gastric emptying and orocaecal transit time.

II.1.3 Excretion

In the GI tract, psyllium becomes an integral component of the digesta and faecal mass. It increases faecal bulk by providing highly polymerised undigested residue, forming a gel-like hygroscopic matrix that resists dehydration in the large bowel and thereby increases stool water content (18, 19, 20). **Cummings JH 1993** (21) reported an average increase in human faecal output of 3.7 g of stool per gram of psyllium consumed.

<u>Conclusion</u>

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 α-linkages and fermentation by colonic bacteria.

II.2 Pharmacodynamics

II.2.1 Mode of action

- Laxative effect

Ispaghula husk is particularly rich in alimentary fibres and mucilages; its mucilage content is actually higher than that of other Plantago species. Ispaghula husk is capable of absorbing up to 40 times its own weight in water (22). Stool viscosity is highly affected by stool water content (19). Small increases in stool water content can markedly decrease stool viscosity. Viscosity is a measure of resistance to flow. As stool viscosity decreases, it correlates with less resistance to the propulsive forces of propagating contractions, resulting in faster transit rates and shorter transit times (23).
Whereas results of some studies of the effects of psyllium in healthy and constipated individuals did not detect a significant increase in transit rate nor a decrease in transit time, the majority indicate that it relieves constipation via this mechanism.

Psyllium has been shown to increase stool bulk (3.7 g for each gram consumed) (24). 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.

In a study, 15 healthy adults consumed controlled diets for two 7-day periods, one of which included 8.8 g dietary fibre provided by 15 g/d of an ispaghula husk preparation (25). All stools were collected and evaluated. Ispaghula husk significantly increased the apparent viscosity of an aqueous stool extract, stool moisture, and wet and dry stool weights. A very viscous fraction, not present in low-fibre stool and containing predominantly 2 sugars that are also found in abundance in ispaghula husk, was isolated from ispaghula husk stool. The authors concluded that, in contrast with other viscous fibres that are fermented completely in the colon, a component of ispaghula husk is not fermented. This gel provided lubrication that facilitated propulsion of colon contents and produced a stool that was bulkier and moister than were stools resulting from use of comparable amounts of other bowel-regulating fibre sources.

Degradation products of dietary fibre resulting from bacterial action in the colon may also contribute to the laxative effect (26, 27).

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

Conclusion

Gut motility and transit rate can be modified by ispaghula husk 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 husk produces an increased volume of intestinal contents due to its 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.

- Effect on diarrhoea

Ispaghula husk has the ability to absorb water, to convert fluid in the intestine into a more viscous mass and to prolong transit time of intestinal contents in this case (26, 28, 29). Antidiarrhoeal effects are therefore also attributed to ispaghula husk.

In a crossover study 9 volunteers with diarrhoea induced by phenolphthalein were consecutively treated in a random sequence with 18 g of ispaghula husk, 6 g of calcium polycarbophil, 42 g of unprocessed wheat bran or placebo daily for 4 days. Only ispaghula husk treatment made stools firmer ($p<0.01$) and increased faecal viscosity ($p<0.001$). In 6 subjects, doses of 9, 18, and 30 g of psyllium per day caused a near linear increase in faecal viscosity (30).

- Effect on blood lipids levels

Ispaghula husk reduces experimentally-induced hyperlipidaemia and atherosclerosis in animals. Different mechanisms are discussed in several investigations in animals.

Ispaghula husk had little or no effect on the faecal excretion of neutral steroids or on cholesterol absorption (31, 32, 33) but apparently enhanced bile acid loss, due to its gel-forming ability and its viscosity (34, 35).
Ispaghula husk increased the activity of hepatic 7α-hydroxylase, the initial and rate-limiting enzyme in the conversion of cholesterol bile acids (35, 36, 37).
Ispaghula husk also altered the hepatic cholesterol homeostasis (37).
Influence on lipoprotein metabolism, in particular modification of the proportions of low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and apolipoprotein fractions as well as the influence of short-chain fatty acids on cholesterol synthesis are also discussed (38). The cholesterol-lowering effect can be attributed to the soluble fibre-fractions.

Investigations in humans

In 10 healthy volunteers, 20 g of ispaghula husk per day significantly decreased fat digestibility and increased faecal fat excretion. It did not affect faecal steroid excretion (neutral steroids and bile acids) (39).

In 16 healthy volunteers faecal lithocholic and isolithocholic acids and the weighed ratio of lithocholic to deoxycholic acid were significantly lower after ingestion of 7 g ispaghula husk per day for 8 weeks (40).

In a randomised, double-blind, placebo-controlled, crossover study involving 20 men with moderate hypercholesterolemia who took 15 g of ispaghula husk daily for 40 days, a significant increase in bile acid synthesis was observed in those subjects whose LDL cholesterol was lowered by more than 10 % ($p<0.0002$), suggesting that ispaghula husk acts by stimulating bile acid synthesis (41).

In another double-blind, placebo-controlled, crossover study with 23 adult men and women suffering from primary hypercholesterolemia, significantly increased levels of the serum cholesterol precursors lathosterol and Δ8-cholestanol were observed after daily treatment with 10.2 g of ispaghula husk for 8 weeks ($p=0.02$ vs. placebo) besides significantly decreased serum LDL cholesterol levels ($p<0.05$ vs placebo; 6.5 % lower than baseline). No significant effects on serum levels of total or high-density lipoprotein cholesterol, triglycerides, apolipoproteins A-1 or B-100, or LDL clearance (fractional catabolic rate) could be observed. According to the authors, results suggest an increased endogenous cholesterol synthesis caused by elimination of bile acids. A trend towards decreased LDL production in response to ispaghula husk treatment was observed, suggesting that the reduction in serum LDL cholesterol level may be due to decreased LDL production (42).

- Effect on blood glucose level

Ispaghula husk influences glucose metabolism, in the sense that glucose tolerance is improved and postprandial peaks in serum level, due to delayed intestinal absorption of carbohydrates, is prevented (43, 45, 46).

II.2.2 Interactions

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

Literature (26, 27, 46) mentions that absorption of minerals (calcium, iron, zinc), vitamins (B12), cardiac glycosides and coumarin derivates may be delayed.
Measurements of serum levels of iron and zinc in 13 men showed no modification after an 8-week treatment with 10.2 g ispaghula husk daily (47). There was no influence on serum levels of minerals and vitamins in other studies (48, 49).

Oliver SD 2000 (50) assessed the safety and tolerability of ispaghula husk in 93 healthy subjects over a 52-week period. Over the study period there were small but statistically significant changes in some measurements of minerals and vitamin levels, and in some haematological and biochemical parameters. None of these were however of clinical significance, with the possible exception of changes in vitamin B12 levels. A daily dose of 10.5 g ispaghula husk was well-tolerated and the majority of adverse events recorded were minor, of short duration and either unrelated or possibly related to the study treatment.

Concerning interaction with digoxin, ispaghula husk had a minor effect on the urinary level of digoxin (51), and no statistical effect on its plasma levels (52).
In one case report on a subject receiving a phenytoin/warfarin combination, ispaghula husk may have affected the subject's prothrombin ratio (53).
Ispaghula husk was reported to decrease the absorption of co-administered carbamazepine (54) and lithium (55, 56). For lithium, co-administration of ispaghula husk was found to decrease urinary excretion of lithium by 28.6 % in the 24 hours following their concomitant administration (57).

The clinical expert report for an ispaghula husk preparation, submitted as part of the marketing authorisation application evaluated by a national competent authority, refers to 2 cases of interaction with levothyroxine.
- A patient required more than 40 % above her usual dose of levothyroxine to control her hypothyroidism after starting to take ispaghula husk concomitantly. An 8-hour interval between ispaghula husk and levothyroxine intakes allowed the patient to be easily controlled on former dose of levothyroxine.
- A doctor reported that his thyroid level remained low despite taking high doses of levothyroxine 2 hours apart from his psyllium dose.

Decreased enteral absorption of levothyroxine was described in patients, who consumed fibre-enriched diets, including one who was also consuming a psyllium-containing laxative (58). Twelve patients consuming unspecified quantitities of foods high in natural fibres had higher serum TSH levels than when they were not consuming such foods. An important shortcoming in that study was the lack of documented compliance with levothyroxine administration in most patients.

Chiu AC and Sherman SI measured levothyroxine absorption without and with simultaneous ingestion of either calcium polycarbophil or psyllium hydrophilic mucilloid in 8 healthy volunteers: 3.4 g psyllium for 4 consecutive days, on the fifth morning 3.4 g psyllium and 600 μg Levothyroxine (59). Using non-isotopic measurement of absorption hormone absorption appears to be normal following simultaneous administration of levothyroxine with either psyllium or polycarbophil. There were no significant differences among the baseline TSH concentrations for the three different regimes. There are several shortcomings in this study affecting the interpretation of the results: the study was conducted only in healthy volunteers; there was a unique ingestion of levothyroxine; there were several limitations of the methods used in the study etc. The authors actually required longitudinal follow up studies in hypothyroid patients. It should also be noted that the ingested dose of psyllium is not within the dose range referred to in the HMPC Community herbal monograph

It is concluded that concomitant use of ispaghula husk with thyroid hormones requires medical supervision because the thyroid hormones dose may have to be adjusted.

In the case of insulin-dependent diabetic patients it may be necessary to reduce the insulin dose (see chapters II.2.1 Effect on blood glucose level and III.2.7 Hypoglycaemic effect).

Attention is to be paid to interactions between laxative bulk agents and medicinal products that inhibit gastrointestinal propulsive motility given the risk of ileus development following concomitant use. Recommendation on the concomitant use of laxative bulk producers and medicinal products against diarrhoea was released by the EMEA in June 2004 in an HMPWP Position statement[1].
Morphine also belongs to the category of medicinal products, which inhibit peristaltic movement. Morphine is often used for pain therapy in patients in the final stage of a terminal illness and can cause spastic constipation. A bulk forming agent is often given concomitantly to prevent constipation. These patients are under medical supervision. There was no result to a search in the database XMEDALL concerning interactions between ispaghula husk and morphine.
In conclusion, in order to decrease the risk of gastrointestinal obstruction (ileus), ispaghula husk should be used with caution with medicinal products known to inhibit the peristaltic movement (e.g. opioids, loperamide) and only under medical supervision.

III. Clinical Efficacy

III.1 Dosage

Kumara *et al*. 1987 (60) tried to determine the optimum daily dose of ispaghula husk (10 g, 20 g or 30 g) in patients with irritable bowel syndrome (IBS). All three doses produced a significant improvement in the symptoms. The 20 g and 30 g doses were equally effective and both were significantly superior to the 10 g dose. It was concluded that the optimum dose of ispaghula husk in IBS is 20 g per day.

The recommended dosage as a laxative (indications a) and b)) for adults, elderly and adolescents over 12 years (7 – 11 g herbal substance or corresponding amount of herbal preparation (daily dose) in 1 – 3 single doses) and for indication c) (7 – 20 g herbal substance or corresponding amount of herbal preparation (daily dose) in 1 – 3 single doses) is further supported by clinical investigations as reported below.

[1] Position statement from the Working Party on Herbal Medicinal Products (EMEA/HMPWP/60/04)

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 treatment and management 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 3 bowel movements per week for more than 3 months.

Non-controlled clinical studies

An open multicentre study (61) involved 224 patients with constipation who received 7 g per day of flavoured ispaghula husk. Assessment by the patients' general practitioner at 2 and 4 weeks rated ispaghula husk as significantly more effective than lactulose or their previously prescribed laxative with regard to overall effectiveness and bowel function improvement. In patients assessments, ispaghula husk was considered to improve significantly stool formation. The stool frequency and ease of passage were similiar across all treatment groups. The authors concluded that ispaghula husk was associated with better stool consistency and is therefore an effective treatment of simple constipation.

Controlled clinical studies

In a single-blind, randomised, placebo-controlled, parallel study **Fenn GC *et al.* 1986** (62) studied 201 patients (17 to 70 years of age) with functional constipation (baseline median bowel movement frequency was 2 to 3 times per week) who received either placebo (97 patients) or 10.8 g ispaghula husk or less per day (104 patients) for 14 days. Eighty six patients of the placebo group and 97 patients of the ispaghula husk group completed the study. Subjective diary assessments and observations were made with respect to number and consistency of stools, severity of abdominal discomfort, and number of sachets of medication taken. Global assessment was made both by the patient and the investigators at the end of the study. After treatment, the ispaghula husk group showed significant increase in stool frequency, increased number of formed stools, and decreased number of hard stools ($p<0.001$). The median number of bowel actions per week before treatment was 2.3 in each group. The median total number of bowel actions in the treatment period was 14 in the ispaghula husk group and 9 in the placebo group ($p<0.001$). There were significant reductions both in the severity of abdominal pain and discomfort and in the severity of straining on defaecation in patients taking ispaghula husk ($p<0.05$). The severity of abdominal pain and/or discomfort in the ispaghula husk group at the end of the study was better in 44 and worse in 11 subjects. This compares with 27 better and 15 worse in the placebo group. A total of 70 ispaghula husk treated patients and 63 placebo treated patients experienced moderate or severe straining on defaecation on admission, compared with 11 and 27, respectively, at the end of the study. Global relief assessments showed that 89% of ispaghula husk treated patients versus 48% of the placebo treated patients reported relief of constipation ($p<0.001$). Ispaghula husk significantly relieved constipation regardless of aetiology. There was a higher incidence of loose or watery stools in the ispaghula husk group ($p<0.001$). Adverse effects like wind, nausea, abdominal distension and haemorrhoids occurred in 5 or more subjects. Four of the complaints in the ispaghula husk group were thought by the investigator to be probably treatment-related.

A study was conducted by **Marlett JA *et al.* 1987** (63) involving 42 adults with chronic constipation who remained constipated after a week of single-blind placebo treatment. Qualifying patients were then randomised to receive ispaghula husk (Metamucil ®, 7.2 g/day) or psyllium plus senna (6.5 g + 1.5 g/day) for 1 week. Because the psyllium and senna preparation is a granular formulation ingested with a cold liquid, and the ispaghula husk product is a powder that must be mixed with a liquid before ingestion, no attempt was made to blind the identity of the treatment. Both preparations significantly increased stool frequency ($p<0.001$). In the ispaghula husk group stool frequency increased from 2.3 ± 1 during placebo to 3.6 ± 0.3 stools/wk during laxative ingestion and in the combination group from 2 to 6.8 stools/wk.

Both treatments also significantly increased mean wet and dry stool weights, although the added effect of senna was clearly evident. Ispaghula husk treatment increased the mean wet stool weight from 254.2 g to 444.8 g/7 day and the mean dry stool weight from 75.4 g to 126.5 g/7 day. The combination treatment increased the mean wet stool weight from 277.7 g to 982.1 g/7 day and the mean dry stool weight from 79.9 g to 190.8 g/7 day. Overall relief of constipation was reported by 90 % of patients on the combination therapy and by 85 % of patients on ispaghula husk alone. Interestingly, the objective improvement in stool frequency in both groups did not attain the high level of subjective improvement; 63 % of the combination group and 48 % of the ispaghula husk group had more than three bowel movements during the week of treatment. Reports of gastrointestinal side effects (pain and cramping) were predominant in the combination group (32 % versus 14 % for ispaghula husk alone). Three of the 22 patients treated with ispaghula husk reported incidences of side effects of cramping and gas. Seven of the 22 patients treated with the combination experienced 11 side effects, which included mainly cramps, uncomfortable diarrhoea, as well as bloating, gas, and nausea. After completion of the protocol and evaluation of the data, two distinct responses to the combination therapy were evident. These two groups were designated as normal responders and high responders. The subpopulation of high responders was responsible for most of the increases in stool frequency and wet weight and all of the effect on dry stool weight. All seven high responders classified their bowel movements as too frequent. Despite significant positive results from the objective faecal parameters, including an increase to more than 3 bowel movements per week after treatment, and despite the fact that 85 % of patients reported relief of constipation, the authors concluded that a dose higher than 7 g psyllium per day or a period of treatment longer than 7 days might be necessary to produce an effect in chronically constipated individuals. In addition, the authors suggested that doses of psyllium plus senna be individualised, given the higher incidence of undesirable side effects with the combination therapy.

A randomised controlled, parallel study (**McRorie JW *et al.* 1998)** (18) compared the stool softening and laxative efficacy of isapaghula husk (2 x 5.1 g per day) to that of docusate sodium (200 mg per day) in 170 patients with chronic idiopathic constipation. This study evaluated both objective and subjective parameters of constipation. The study consisted of a 2-week baseline (placebo) phase followed by a 2-week treatment phase. Compared to docusate sodium, ispaghula husk significantly increased stool water content (ispaghula husk 2.33 % vs. docusate 0.01 %, p=0.007), stool water weight (ispaghula husk 84.0 g/ bowel movement (BM) vs. docusate 71.4 g/BM, p=0.04) and total stool output (ispaghula husk 359.9 g/week vs. docusate 271.9 g/week, p=0.005) by the end of the first treatment week. By the end of the second treatment week the BM frequency was also significantly greater for ispaghula husk compared to docusate (ispaghula husk 3.5 BM/week vs. docusate 2.9 BM/week, p=0.02). The subjective parameters of constipation showed no significant differences by the end of the first treatment week; by the end of the second treatment week a significant difference was only observed for the parameter “completeness of defaecation”. The results of the objective parameters do not correspond to the results of the subjective parameters.

In a randomised, controlled, open-label, parallel-group trial (**Wang HJ *et al.* 2004**) (64) the efficacy and safety of polyethylene glycol (PEG) 3350 plus electrolytes (PEG+E) (13.8 g/sachet dissolved in water twice daily) were compared with that of ispaghula husk (3.5 g/sachet dissolved in water twice daily) in the treatment of constipation. Sixty three patients were randomised to each treatment group. Assessments were at baseline and after 1 and 2 weeks’ therapy and by patient daily diary card. Treatment was highly effective in 50/63 patients in the PEG+E group compared with 26/63 in the ispaghula husk group, and the overall efficacy rates were 92 % and 73%, respectively (p=0.005). PEG+E increased the mean weekly defaecation rate from 1.18 (SD 0.77) at baseline to 7.95 (SD 3.49) after 1 week and 8.48 (SD 3.55) after 2 weeks. In the ispaghula husk group the mean weekly defaecation rate increased from 1.33 (SD 0.68) at baseline to 5.33 (SD 2.81) after 1 week and to 5.71 (SD 2.49) after 2 weeks. The treatment differences for defaecation rates were all statistically significant (p<0.001). Two weeks of treatment with PEG+E or ispaghula husk normalised stools in 55/63 (87.3%) and 42/63 (66.7%) of patients (p<0.001). The incidence of adverse effects did not differ between groups and none were serious or required any treatment. Laboratory evaluations found no adverse effect from either treatment. It was concluded that

low-dose PEG+E is more effective and more rapid in its onset of action than ispaghula husk, and is equally well tolerated.
However, it should be discussed if there is any advantage for the patient when the weekly defaecation rate increases to 8.48 instead of 5.71.

Reviews

Two reviews have been published which evaluate the existing clinical trials with laxatives in general (65, 66).

Tramonte SM *et al.* 1997 (66) 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 M *et al.* 1999 (65) 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.

Conclusion

The use of ispaghula husk as a bulk forming laxative is well-established and substantiated by its pharmacological effects. The treatment of habitual constipation is even supported by randomised clinical trials, however, the studies have some shortcomings. Some studies were carried out single-blinded only. No recent randomised double-blind placebo-controlled study could be found following a search in the database XMEDALL.

III.2.2 Effect on haemorrhoidal disease

Non-controlled clinical studies

Fichera G *et al.* 1978 (67) studied the effects of ispaghula husk on 20 patients suffering from organic pathologies (haemorrhoids, anal fissures, after anal surgery) accompanied by painful defaecation. Ispaghula husk was administered as a powder for 20 days at the dose of one 7 g package 3 times daily (the exact content of ispaghula husk is not mentioned). They reported that in 95 % of the patients treated, the administration of ispaghula husk preparations proved to be positive vis-à-vis the following symptoms: painful defaecation, loss of blood with faeces, lesions of the rectal mucosa evidenced by endoscopy, and frequency of defaecation.

Borgia M *et al.* 1983 (68) studied 75 patients affected by chronic constipation, most patients (85%) suffered from haemorrhoids additionally. They were treated with 10.5 g of an ispaghula husk preparation (Fibrolax) daily for 4 weeks. Frequency, stool consistency, abdominal pain and signs of venous stasis improved after treatment. 59 % of the patients after the second week and 74 % after the fourth week showed a normalisation of their bowel frequency. 94 % of the patients at the end of the study referred normal or soft stool. Abdominal pain was present in 50 patients at the beginning of the study: of these patients 82% did not complain of any symptom after the fourth week of treatment. Most patients (86%) previously complaining of haemorrhoids reported the disappearance of signs of venous stasis after bowel

normalisation. Five patients failed to finish the study: 2 because they did not obtain a normalisation of their bowel habit, one because he was complaining of diarrhoea and 2 because of abdominal discomfort. The authors regarded this as unrelated to the herbal medicinal product.

Controlled clinical studies

In a double-blind placebo-controlled crossover trial **Webster DJ *et al.* 1978** (69) evaluated ispaghula husk at 3.5 g b.i.d. in 53 patients with haemorrhoids (18 patients had first-degree, 17 second-degree and 18 third-degree haemorrhoids). Patients were randomly assigned to receive 6 weeks each of ispaghula husk and placebo. There was no washout period. After 6 weeks of ispaghula husk treatment, symptoms of haemorrhoids like pruritus, bleeding and prolapse (ispaghula husk: in 37 patients improved, placebo group in 22 patients improved, $p<0.025$), ease of defaecation (ispaghula husk: in 33 patients improved, placebo group in 12 patients improved, $p<0.001$), bowel habits (ispaghula husk: in 28 patients improved, placebo group in 8 patients improved, $p<0.001$), consistency of stool (ispaghula husk: in 15 patients improved, placebo group in 5 patients improved, $p<0.01$) and frequency of defaecation (ispaghula husk: in 15 patients improved, placebo group in 7 patients improved, $p<0.05$) were significantly improved. Concomitant laxative use was permitted, potentially confounding the results, but it was reported that laxative use was more frequent in the placebo group. Patient assessment of daily comfort according to severity of haemorrhoids was significantly better in the ispaghula husk for first- and second-degree haemorrhoids but not for third-degree haemorrhoids compared to placebo.

In a randomised, double-blind, placebo-controlled parallel study **Moesgaard F. *et al.* 1982** (70) studied 51 patients with first or second degree haemorrhoids. Vi-Siblin® (6.7 g t.i.d., correspond to 12.2 g ispaghula husk) or placebo was administered for 6 weeks. A significant reduction in bleeding ($p<0.01$) and pain at defaecation ($p<0.03$) was observed at 6 weeks. Before treatment 22 patients in the ispaghula husk group and 21 patients in the placebo group were suffering from bleeding and 15 patients of the ispaghula husk group and 16 of the placebo group from pain at defaecation. At the end of the six-week treatment bleeding was still present in 2 patients of the ispaghula group and 11 patients of the placebo group and pain at defaecation in 1 patient of the ispaghula husk group and 9 patients of the placebo group. The effect was still recognisable at 3 months' follow up. Prolapse was directionally improved at 6 weeks, as were symptoms of pruritus and anal secretion without significant differences between the groups. Physical examination included palpation, proctoscopy, and sigmoidoscopy.

Ho YH *et al.* 2000 (71) assessed the role of micronised purified flavonidic fraction in the management of bleeding nonprolapsed haemorrhoids. 162 patients were randomly assigned to receive ispaghula husk alone, rubber band ligation plus ispaghula husk, or micronised purified flavonidic fraction plus ispaghula husk. Haemorrhoidal bleeding was relieved most expediently in the last group (ispaghula husk alone n=66, mean (standard error of the mean) 10.6 (2.3) days; rubber band ligation plus ispaghula husk n=57, 5.6 (1.1) days; micronised purified flavonidic fraction plus ispaghula husk n=39, 3.9 (1.2) days; p=0.03). However, there were no significant differences in the recurrences at 6 months of follow-up (ispaghula husk alone n=8 (12%); rubber band ligation plus ispaghula husk n=12 (21%); micronised purified flavonidic fraction plus ispaghula husk n=2 (5.1%); p=0.075). No complications or side-effect were noted. The author concluded that micronised purified flavonidic fraction used with fibre supplements rapidly and safely relieved bleeding from nonprolapsed haemorrhoids.

Conclusion

These clinical data support the indication b) "in conditions in which easy defaecation with soft stools is desirable, e.g. in cases of painful defaecation after rectal or anal surgery, anal fissures and haemorrhoids". Although there are only data available concerning haemorrhoids, the use in the other identified conditions is substantiated on the basis of the well-established laxative and stool softening effects.

III.2.3 Effect on diverticular disease

Non-controlled clinical studies

Thorburn HA *et al.* 1992 (72) examined the effect of ispaghula husk on colonic motility of the right and left side in 10 patients with left sided diverticular disease using an untethered pressure sensitve radiotelemetry capsule. After treatment, ispaghula husk reduced mouth to rectum transit by a median of 8.8 hours and the time to midtransverse colon by five hours. In the right colon there was an increase in the median percentage acitivity of 7 % and the median number of pressure waves greater than 5 mm Hg/hour rose by 35.3. Motility changes in the left colon were less pronounces. Five of 7 patients with abdominal pain and six of the nine patients with altered bowel habit responded to treatment. These results suggest that it is ispaghula husk's action on the right unaffected colon which alleviates the symptoms of left sided diverticular disease.

Controlled clinical studies

Ewerth S *et al.* 1980 (73) enrolled 9 patients with constipation symptoms, i.e. infrequent (3 – 4 day intervall) and painful defaecation, associated with diverticular disease in a double-blind crossover study. Patients were treated with placebo vs. Vi-Siblin® (8 g ispaghula husk/day) for 8 weeks with a washout period of 4 weeks while on a normal diet. Transit time was with a normal range at baseline and did not change significantly during the treatment period vs. placebo. Subjective symptoms were significantly reduced with ispaghula husk treatment ($p<0.05$). Six of the 9 patients had hard faeces during the placebo period but only 1 of these retained this symptom during the ispaghula husk period. In the placebo period one patient complained of mild diarrhoea, 2 of mild abdominal pain, 2 of mild flatulence and 2 of mild dyspepsia. In the ispaghula husk period none of these symptoms occured.

In a randomised double-blind cross-over study by **Ornstein MH *et al.* 1981** (74) 58 patients with uncomplicated symptomatic diverticular disease received ispaghula husk (Fibrogel®, 9 g/day), bran (7 g/day) and placebo for 4 months each in random order. Both fibre products produced significant changes in daily stool weight (mean after ispaghula husk treatment 161g, after bran treatment 136.5 g and after placebo 118.8 g), stool consistency score (mean after ispaghula treatment 4.08, after bran treatment 3.79, after placebo 3.56) , and weekly stool frequency (mean after ispaghula husk treatment 11.19, after bran treatment 10.34 and after placebo 9.55); improvement was better during the ispaghula husk-treatment period than during the bran-treatment period. There were no significant changes reported for either ispaghula husk or bran versus placebo in subjective symptomatology. The authors concluded that fibre supplements relieved constipation but not diverticular disease itself; if the symptoms arise from constipation, fibre supplementation may be useful therapy.

Conclusion

Based on the clinical data mentioned above, it is not possible to recommend a specific indication.
Indication a) covers constipation symptoms associated with diverticular disease.

III.2.4 Effect on irritable bowel syndrome

As mentioned in chapter III.1, **Kumara *et al.* 1987** (60) tried to determine the optimum dose of ispaghula husk (10 g, 20 g or 30 g) in patients with IBS. All three doses produced a significant improvement in the symptoms. The 20 g and 30 g doses were equally effective and both were significantly superior to the 10 g dose.

Controlled clinical studies

Prior A *et al.* 1987 (75) reported a double-blind placebo-controlled trial of ispaghula husk in 80 patients with IBS over a 3-month period. A dose of 1 sachet of Regulan® (6.4 g rough ground powder containing 3.6 g refined active mucilloid – 56 % ispaghula husk) or placebo three times daily was initially recommended with an option to change the dose depending on response. Fifty seven patients completed the trial. Four of the 8 withdrawals from the ispaghula husk group and 10 of the 15 placebo withdrawals were because of treatment failure. Ispaghula husk and placebo were well tolerated by patients with only 1 withdrawal from each group related to possible side effects (verum: flatulence; placebo: nausea). In the global assessment of treatment success, 82 % receiving ispaghula husk improved compared with 53 % for the placebo group ($p<0.02$). Bowel habit was unchanged in the placebo group, while in patients taking ispaghula husk constipation significantly improved ($p=0.026$). The number of days with no bowel actions decreased in the ispaghula husk group from 1.7 to 1 and in the placebo group from 1.8 to 1.7 days. But only little change in the number of days with 3 or more bowel action occured: ispaghula husk from 0.7 to 0.9 day; placebo from 0.5 to 0.6 day. Abdominal pain and bloating improved in both groups with no significant differences between ispaghula and placebo. Transit time decreased significantly in those patients taking ispaghula husk from 36.1 hours to 21.9 hours compared with placebo ($p=0.001$) (an increase from 28.8 to 39.8 hours), especially in patients with initially high transit times. The authors concluded that ispaghula husk significantly improves overall well-being in patients with IBS, and in those with constipation favourably affects bowel habit and transit time.

Golechha AC *et al.* 1982 (76) conducted a randomised double-blind crossover 6-week trial of ispaghula husk versus placebo on 26 patients with IBS. During the first 3 weeks the patients were allocated by random either biscuits of wheat flour alone or with powdered ispaghula husk. After a washout period of one week, they were allocated the alternate treatment. Assessment of the value of treatment (before and after three weeks of each treatment) was based on the patients' awareness of symptomatic improvement (with improved or not improved). In the global assessment out of a total of 26 patients, 13 patients (50 %) improved in the treatment group and 6 patients (23 %) in the placebo group. Abdominal pain of mild severity relieved after trial in 9 from 15 patients (60 %) of the treatment group versus 4 from 18 patients (22 %) in the placebo group. Abnormal bowel habits (constipation or diarrhoea) normalised in 13 from 26 patients (50 %) in the treatment group versus 6 from 26 patients (23 %) in the placebo group. Out of 15 patients with spastic colitis, 9 patients (60 %) in the treatment group and 4 patients (27 %) in the placebo group improved, while out of 7 patients having alternating constipation and diarrhoea only 1 patient (14 %) in the placebo group and 3 patients (43 %) in the treatment group improved after trial. Out of 4 patients with mucous colitis, 1 patient (25 %) in each group improved, while the remaining patients had no change in their symptoms in all the groups after trial. In the discussion the authors mentioned that ispaghula preparations are not effective in IBS-related diarrhoea.

In a randomised investigator-blinded trial (**Tarpila S *et al.* 2004** (1)) with two parallel treatment groups 55 patients suffering from constipation predominant IBS received 6 – 24 g/d either linseed (roughly ground partly defatted) or ispaghula husk for 3 months. In the following open period of 3 months the patients were treated with linseed only. During the blinded treatment period 26 patients received linseed and 29 received ispaghula husk. The efficacy of the study treatment was measured with assessment of the gastrointestinal symptoms: bowel movement frequency, abdominal discomfort/bloating and abdominal pain. Each symptom was scored 1 – 5 (1=worse, 2=unchanged, 3=somewhat relieved, 4=considerably relieved and 5=completely relieved). The mean dose of linseed was 17 g/day, the mean dose of ispaghula husk is not mentioned in the publication. In the linseed group, constipation and abdominal symptoms were decreased significantly ($p=0.002$) whereas in the ispaghula husk group the reduction was not statistically significant. After the blinded treatment period, the difference between groups was statistically significant in constipation ($p=0.05$) and in bloating and pain ($p=0.001$). Forty patients continued to the open period, 18 from the linseed group and 22 from the ispaghula husk group. After the open period of 3 months constipation and abdominal symptoms were further significantly reduced ($p=0.001$). The response to linseed treatment was expressed slowly i.e. after 2 – 3 months' regular use.

Because little information is given particularly concerning the ispaghula husk group, a complete evaluation of its efficacy is not possible.

Reviews

Jailwala J *et al.* 2000 (77) evaluated the efficacy of pharmacologic agents for irritable bowel syndrome by an electronic literature search of MEDLINE (1966 – 1999), EMBASE (1980 – 1999), PsycINFO (1967 – 1999), and the Cochrane controlled trials registry and a manual search of references from bibliographies of identified articles. Seventy randomised, double-blind, placebo-controlled, parallel, or crossover trials of a pharmacologic intervention for adult patients that reported outcomes of improvement in global or irritable bowel-specific symptoms were selected. The most common medication classes were smooth-muscle relaxants (16 trials), bulking agents (13 trials), prokinetic agents (6 trials), psychotropic agents (7 trials), and loperamide (4 trials). The strongest evidence for efficacy was shown for smooth-muscle relaxants in patients with abdominal pain as the predominant symptom. Loperamide seemed to reduce diarrhoea but did not relieve abdominal pain. In contrast, the efficacy of bulking agents was not established. Evidence related to the use of psychotropic agents was inconclusive; more high-quality trials of longer duration are needed. Evidence for the efficacy of 5-HT-receptor antagonists seemed favourable, although more studies are needed.

Bijkerk CJ *et al.* 2004 (78) quantified the effect of different types of fibre on global and symptom relief from irritable bowel syndrome following a systematic review using a structured literature search in MEDLINE (1966-2002). They selected 17 randomised controlled trials involving irritable bowel syndrome patients treated with fibre. None investigated primary care IBS patients. Fibre, in general, was effective in the relief of global IBS symptoms (relative risk, 1.33; 95% confidence intervall (CI), 1.19-1.50). It was stated that IBS patients with constipation may receive benefit from fibre treatment (relative risk, 1.56; 95% CI, 1.21-2.02), but there was no evidence that fibre was effective in the relief of abdominal pain in IBS. Soluble and insoluble fibre, separately, had different effects on global IBS symptoms. Soluble fibre (psyllium, ispaghula, calcium polycarbophil) showed significant improvement (relative risk, 1.55; 95 % CI, 1.35 – 1.78), whereas insoluble fibre (corn, wheat bran), in some cases, worsened the clinical outcome, but there was no significant difference compared with placebo. The authors concluded that the benefits of fibre in the treatment of irritable bowel syndrome are marginal for global IBS symptom improvement and IBS-related constipation.

Conclusion

The data available are not sufficient to prove efficacy for the indication irritable bowel syndrome in general. If at all, there are only marginal benefits for constipation predominant irritable bowel syndrome. Therefore ispaghula husk is recommended as an adjuvant in *constipation predominant* irritable bowel syndrome.

III.2 5 Antidiarrhoeal effect

In an open pilot study **Hamouz W 1984** (79) investigated the effect of Agiocur® (5 g of granula i.e. 1 teaspoon containing ispaghula semen = 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 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.

Frank HA *et al.* 1979 (80) administered a mucilagenous hydrophilic colloid bulk laxative (Metamucil®, ispaghula husk) to severely burned patients on tube feeding formulae (5,000 to 6,000 calories per day). The dosage and frequency were adjusted to individual patient needs, but averaged 7 g per litre of liquid formula. Colonic transit time increased. The stools became formed but soft, cohesive but not adhesive. Perianal irritation did not occur. No rebound constipation or obstructive symptoms were encountered. Exact data were not mentioned in the publication. The authors attributed the observed response to the same water binding mechanism that allows these mucilagenous colloids to prevent chronic constipation.

Qvitzau S *et al.* 1988 (81) included 25 patients with chronic diarrhoea in an open, randomised crossover trial comparing the effect of loperamide with ispaghula and calcium. The dose of loperamide administered was 4 mg initially and 2 mg after each loose stool. Maximal dose was 16 mg/day. Ispaghula husk-calcium contained ispaghula husk, $CaCO_3$ and $CaHPO_4$ (weight ratio 4:1:1). The daily dose was 5 g twice a day. Nineteen patients completed both treatments. Before treatment the median number of daily stools was 7 (range: 4-13), stool consistency was loose in all, and urgency was present in 16 out of 19 patients. Both treatments halved stool frequency, but with regard to urgency and stool consistency the treatment with ispaghula husk and calcium was significantly better. Urgency was significantly related to order of treatment, indicating that the washout period was too short. A combination of ispaghula husk and calcium seemed to be an effective alternative to convential treatment of chronic diarrhoea. Moreover, a tendency towards a reduced frequency of side effects during treatment with ispaghula husk-calcium was found, although this difference did not reach statistical significance.

In a short letter to the Editor, **Bobrove AM 1990** (82) noticed that psyllium may be helpful, if diarrhoea occurs as a side effect of medicinal products.

In a randomised crossover study **Lodge N *et al.* 1995** (83) investigated the efficacy of codeine phosphate versus ispaghula husk in 10 female patients with gynaecological cancer experiencing diarrhoea during pelvic radiotherapy. Quantitative data were collected from patient diaries and treatment flow-sheets. All five patients in the codeine phosphate arm received adequate control, while the five patients allocated to the ispaghula husk arm were all crossed-over to codeine phosphate with resolution of their diarrhoea. The authors concluded that ispaghula husk, whilst not totally ineffective at controlling diarrhoea induced by pelvic radiotherapy, was significantly less effective than codeine phosphate.

<u>Antidiarrhoeal effect in children</u>

Smalley JR *et al.* 1982 (29) evaluated the use of ispaghula husk (Metamucil®) in the management of chronic non specific diarrhoea of childhood (CNDC). Specific reasons of diarrhoea were excluded. Twenty three children between 6 and 36 months of age with CNDC received unrestricted diet including milk for 1 week, then were treated during the following 2 weeks Metamucil® 1 tablespoon twice a day (exact amount not mentioned) if diarrhoea persisted. Ispaghula husk was discontinued for 1 week, and if diarrhoea returned ispaghula husk was used for another 2 weeks. Seven children (30 %) responded to an unrestricted diet alone. From the 16 remaining children, 13 (81 %) responded during the first 2 weeks of treatment with ispaghula husk. Eleven had total resolution of their diarrhoea, 2 were partial responders. After taking off ispaghula husk for one week, 6 children relapsed but 3 of them did not redevelop symptoms as severe as those they had had initially. All 6 patients responded after another 2-week course of ispaghula husk. Three patients did not respond to either an unrestricted diet or ispaghula husk.

Conclusion

These studies have several shortcomings.
The first two studies **Hamouz W 1984** and **Frank HA *et al.* 1979** are uncontrolled and investigate a small and special population. Agiocur® mainly contains ispaghula seed.
The studies of **Qvitzau S *et al.* 1988 and of Lodge N *et al.* 1995** are randomised crossover studies, but the first one is an open one and the design of the second one is not exactly defined. The first one investigates ispaghula husk combined with calcium in only 25 patients and the second one only investigates 10 patients of a very special population.
Smalley JR *et al.* 1982 evaluated the use of ispaghula husk in the management of chronic non specific diarrhoea of childhood (CNDC) and only in 23 children beween 6 and 36 months in an uncontrolled investigation.

The indication as an adjuvant in the symptomatic treatment of diarrhoea from various causes is not regarded as a well-established one. These studies are insufficient to prove the efficacy as an antidiarrhoeal agent.

III.2.6 Effect on blood lipids levels

In the above-mentioned study by **Borgia M *et al.* 1983** (68) cholesterol, serum HDL cholesterol and triglycerides did not show significant changes in the normolipemic patients. Only a slight increase of HDL cholesterol was observed.

Controlled clinical studies

In a double-blind, placebo-controlled parallel study the effect of ispaghula husk on serum total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides levels was investigated in 26 men with mild to moderate hypercholesterolemia (range of cholesterol level, 4.86 to 8.12 mmol/L (188 to 314 mg/dL)) by **Anderson JW *et al.* 1988** (47). Following a 2-week baseline period, subjects were treated for 8 weeks with 3.4 g psyllium hydrophilic mucilloid (Metamucil®) or a cellulose placebo at mealtimes (3 doses per day). All subjects maintained their usual diets, which provided less than 300 mg of cholesterol per day and approximately 20 % of energy from protein, 40 % from carbohydrate, and 40 % from fat. Eight weeks of treatment with ispaghula husk reduced serum total cholesterol level by 14.8 %, LDL cholesterol by 20.2 %, and the ratio of LDL cholesterol to HDL cholesterol by 14.8 % relative to baseline value. The reductions in total cholesterol and LDL cholesterol became progressively larger with time, and this trend appeared to be continuing at the eighth week. Ispaghula husk treatment did not affect body weight, blood pressure, or serum levels of HDL cholesterol, triglycerides, glucose, iron, or zinc. No significant changes in serum lipid levels, body weight, blood pressure, or other serum parameters were observed with placebo treatment. No adverse effects were observed.

In a randomised, double-blind, placebo-controlled parallel study **Bell LP *et al.* 1989** (48) examined a psyllium hydrophilic mucilloid for its ability to lower serum cholesterol levels in 75 patients with mild to moderate hypercholesterolemia. Patients were treated with a Step I diet for 12 weeks before receiving placebo or 3.4 g of ispaghula husk (equivalent to 1 teaspoon) 3 times per day for 8 weeks. Compared with placebo, ispaghula husk achieved an additional 4.8 % reduction in total cholesterol level, 8.2 % reduction in LDL cholesterol, and 8.8 % reduction in apolipoprotein B level. Ispaghula husk did not significantly affect blood pressure or levels of HDL cholesterol, triglycerides, serum glucose, or iron. Compliance was excellent in both treatment groups. Eleven patients reported mild gastrointestinal side effects (placebo: 1 x transient abdominal bloating and cramping; verum: 6 x transient abdominal bloating and cramping, 3 x bloating and increased flatulence, 1 x increased stool frequency, 1 x constipation).

The effects of consuming foods containing 0 (control), 3.4, 6.8, or 10.2 g ispaghula husk/d for 24 weeks on the serum lipid profile were assessed in a randomised, double-blind controlled study by **Davidson MH *et al.* 1998** (84). 286 patients with LDL cholesterol concentrations between 3.36 and 5.68 mmol/L (130 and 220 mg/dL) were randomly assigned to one of four treatment groups after following a low-fat diet for 8 or more weeks. At week 24, LDL cholesterol was 3 % above baseline in the control group. In the group consuming 10.2 g ispaghula husk/d, LDL cholesterol remained below baseline during treatment, with a value 5.3 % below that of the control group at week 24 ($p<0.05$ compared with the control group). No significant differences were observed in HDL cholesterol or triacylglycerol. Although modest, the effect of 10.2 g ispaghula husk/d on LDL cholesterol (relative to the control) persisted throughout the 24 week treatment period, indicating potential for long-term-benefit.

In a randomised, double-blind, placebo-controlled study with 340 subjects with mild to moderate hypercholesterolaemia (**MacMahon M *et al.* 1998** (85)) the subjects received either 7 g or 10.5 g ispaghula husk or placebo for 12 weeks following an initial 8-week diet-only period. The serum LDL cholesterol levels were reduced by 4.4% (7 g ispaghula husk; $p=0.009$) and by 5.4% (10.5 g ispaghula husk; $p<0.001$) relative to placebo. The serum total cholesterol levels were reduced by 2.8% (7 g ispaghula husk; $p=0.040$) and by 3.4% (10.5 g ispaghula husk; $p=0.010$) relative to placebo. This result has a questionable clinical relevance.

Anderson JW *et al.* 2000 (86) published the results of a multicenter, randomised, double-blind, placebo-controlled parallel study, which investigated the long-term cholesterol-lowering effects of ispaghula husk as an adjunct to diet therapy in the treatment of hypercholesterolaemia. 248 patients with primary hypercholesterolemia received either 5.1 g ispaghula husk twice daily or placebo for 26 weeks following an initial 8-week diet-only period. The serum LDL cholesterol levels were reduced by 6.7% and the serum total cholesterol by 4.7% relative to placebo after 24-26 week ($p<0.001$).

Meta-analysis

A meta-analysis of **Olson BH *et al.* 1997** (87) aimed at determining the effects of ispaghula husk-enriched cereal products on blood total cholesterol, and LDL and HDL cholesterol levels, in mild to moderate hypercholesterolemic adults who consumed a low fat diet. The 8 published studies (ESCOP monograph references 39, 40, 41, 42, 43, 44,45) and 4 unpublished studies included, involving a total of 404 patients, met the criteria of randomised, controlled studies using either a crossover design (7 studies) or a design with parallel arms (5 studies). Three studies had no dietary lead-in period whereas the others had a 3- to 6-weeks lead-in period with a low fat diet. The daily dose of ispaghula husk was 9.4 – 12 g in 9 studies, but lower (3, 6.7 and 7.6 g) in the other 3 studies. The control groups ate cereals providing 3 g or less soluble fibre per day. The conclusions from this meta-analysis were that treatment with ispaghula husk-enriched cereals significantly lowered total cholesterol (by 5%; $p<0.0002$) and LDL cholesterol (by 9%; $p<0.0001$) but had no effect on HDL cholesterol.

Another meta-analysis of **Anderson JW *et al.* 2000** (91) included 8 studies (5 published (42, 48, 88, 89, 90) and 3 unpublished) involving a total of 656 subjects with mild to moderate hypercholesterolemia. Seven studies used a randomised, double-blind, placebo-controlled design, while one study used a crossover design. All the studies met the following criteria: ispaghula husk was used as an adjunct to an American Heart Association (AHA) Step I diet with a pretreatment dietary lead-in period of 8 – 12 weeks; the subjects received either 10.2 g ispaghula husk daily or placebo in 2 or 3 doses for 8 weeks (4 studies), or 12 – 26 weeks (4 studies).This meta-analysis shows a significant reduction in serum total cholesterol levels by 4% and in serum LDL cholesterol levels by 6.7% relative to placebo. But a decrease of the serum total cholesterol concentration of 4% has a questionable clinical relevance, although the decrease is significant.

Effect on blood lipids levels in children

In a randomised, double-blind, placebo-controlled crossover study (**Dennison BA *et al.* 1993** (92)) 25 children aged 5 – 17 years with elevated serum LDL cholesterol, who had already been on a low total fat, low saturated fat, low cholesterol diet for at least 3 months, were enrolled. 20 children completed the study. Treatment with an ispaghula husk enriched cereal (6 g ispaghula husk/d) for 4 – 5 weeks had no additional lowering effect on total cholesterol or LDL cholesterol levels.

Davidson MH *et al.* 1996 (93) compared, in a double-blind, crossover fashion, the effects on an ispaghula husk-enriched cereal (6.4 g ispaghula husk/d) or a matched control cereal, administered during 6-week phases (separated by a 6-week wash-out period) after 8 weeks of diet stabilisation, in 25 hypercholesterolemic children aged 6 – 18 years. Reductions in serum total cholesterol and LDL cholesterol concentrations were highly significant in favour of the ispaghula husk enriched cereal (p=0.03 and 0.01 respectively); the reduction in LDL cholesterol was 7 % in the ispaghula husk group compared to nil in the control group.

The aim of a review by **Moreno LA *et al.* 2003** (94) was to assess the usefulness of psyllium in the management of obese children and adolescents with abnormalities of carbohydrate and lipid metabolism. After psyllium supplementation, the percentage change in postprandial glucose in type 2 diabetes patients, ranged from -12.2 to -20.2 %. In hypercholesterolemic children, the effect of psyllium in LDL cholesterol serum concentrations ranged from 2.78 to -22.8%; the effect in HDL cholesterol from -4.16 to 3.05%; and the effect on triglycerides from 8.49 to -19.54 %. The authors concluded that the evidence reviewed seems to show that psyllium improves glucose homeostasis and the lipid and lipoprotein profile; however, more well controlled trials and further studies are needed to clarify its effect and the mechanisms involved.

Conclusion

In the study by **Anderson JW *et al.* 1988** (47), 8 weeks of treatment with ispaghula husk reduced serum total cholesterol level by 14.8 %, LDL cholesterol level by 20.2 %, and the ratio of LDL cholesterol to HDL cholesterol by 14.8 % relative to baseline value. The meta-analysis showed a reduction of total cholesterol by nearly 4 – 5% and of LDL cholesterol by nearly 7% but ispaghula husk had no effect on HDL cholesterol.
A treatment with statins is able to reduce the low-density lipoprotein by more than 20% with the effect of a decrease in coronary heart disease and in total mortality, reductions in myocardial infarcations, revascularisation procedures, stroke, and peripheral vascular disease. Treatment with statins has demonstrated a positive benefit/risk ratio; the use of statins has to be carefully weighed because of possible adverse reactions. Certain groups of patients should avoid treatment with statins.
The findings must be considered in the context of recommended management of hypercholesterolemia. Patients with hypercholesterolemia are generally told to change their dietary management and to increase their daily fibre intake as a first step before starting a treatment with medicinal products containing statins.

It is concluded that the above-mentioned investigations support the indication c) “Medicinal product for use in patients to whom an increased daily fibre intake may be advisable e.g. […] as an adjuvant to diet in hypercholesterolemia.”
The product information to patients of ispaghula husk containing medicinal products shall refer to the advice that the use of ispaghula husk as an adjuvant to diet in hypercholesterolemia requires medical supervision.
No investigation studying the effect of ispaghula husk on the incidence of cardiovascular events and of total mortality is available.
The use in children is further evaluated in chapter III.3 (see below).

III.2.7 Hypoglycaemic effect

A number of studies have shown that ispaghula husk lowers peak blood glucose levels due to delayed intestinal absorption.

The aim of a more recent study (**Sierra M *et al.* 2002** (49) was to evaluate the effects of psyllium in type 2 diabetic patients (12 men and 8 women). The study included 3 phases: phase 1 (1 week), phase 2 (treatment, 14 g fibre/day, 6 weeks) and phase 3 (4 weeks). At the end of each phase a clinical evaluation was performed after the ingestion of a test breakfast of 1824.2 kJ (436 kcal). Several parameters related to diabetes were measured. Glucose absorption decreased significantly in the presence of psyllium (12.2%); this reduction is not associated with an important change in insulin levels (5%). Glycosylated haemoglobin (HbA1c), blood C-peptide and 24-h urinary glucose excretion decreased (3.8, 14.9 and 22.5%, respectively) during the treatment with fibre (no significant differences) as well as fructosamine (10.9%, significant difference) and uric acid (10%, significant difference). Minerals and vitamins did not show significant changes, except sodium that increased significantly after psyllium administration.

Conclusion

Because of the observed decrease in glycaemia after food intake in the presence of ispaghula husk, cases of diabetes mellitus, where insulin adjustment is difficult, constitute a contraindication to the use of ispaghula husk. For other cases of diabetes mellitus, a recommendation that "If the product is taken together with meals by insulin dependent diabetic patients, it may be necessary to reduce the insulin dose" should be part of the information provided for ispaghula husk containing medicinal products concerning 'interactions with other medicinal products and other forms of interaction'.

The clinical data are not sufficient to support a specific indication like an adjuvant in the treatment of diabetes mellitus.

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 (95). A review of the scientific literature by **Williams CL *et al.* 1995** (96) 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 helpful than harmful, especially in children with constipation (97). 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) (95).
However special clinical data with ispaghula husk are lacking.
The data concerning the effect of ispaghula husk on blood lipid levels in children are not consistent (**Dennison BA *et al.* 1993** (92), **Davidson MH *et al.* 1996** (93), see above). The review of **Moreno LA *et al.* 2003** (94) requires more well controlled trials and further studies to clarify the effect and the mechanisms.

Conclusion

Considering these remarks, use is not recommended:
- in children below the age of 6 years for indication a) "treatment of habitual constipation and indication b) "use 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" and
- in children below the age of 12 years for indication c) "use in patients to whom an increased daily fibre intake may be advisable e.g. as an adjuvant in constipation predominant irritable bowel syndrome, as an adjuvant to diet in hypercholesterolemia".

For indications a) and b), laxative bulk producers should be used before using other purgatives if change of nutrition is not successful.
Children from 6 to 12 years of age should take half to two-thirds of the adult dose (3 – 8 g herbal substance or corresponding amount of herbal preparation daily in 1 – 3 single doses) according to general recommendations of posology for children of this age derived from the adult dose.

III.3.2 Use during pregnancy and lactation

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

Bishop C 1978 (98) 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 JO *et al.* 1973 (99) stated that constipation was corrected in a higher percent 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 in 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 husk containing products. Medicinal products should be avoided if possible during pregnancy and lactation; caution is recommended when administered.

III.4 Traditional use

Ispaghula husk has a long history of medicinal use througout the world, including in traditional medicine. Ispaghula husk is also known as Plantago ovata, Isapgol and psyllium.

It has been used in traditional medicine in the USA, Europe, India, and China. Uses of psyllium in traditional medicine include use as emollient, demulcent, and diuretic.

Dioskurides (104) already mentioned three kinds of Plantaginaceae: Plantago asiatica, lagopodus; Plantago albicans and Plantago psyllium.
The seeds of Plantago asiatica were taken with wine for diarrhoea and haematemesis. The seeds of Plantago psyllium had a cooling effect and they were used as a compress together with attar of roses, vinegar and water for gout, tumours, oedemas, luxations and headache. Intestinal or umbilical hernia of children was treated by a cataplasma together with vinegar.

"Hagers Handbuch der Pharmazeutischen Praxis" 1927 (105) describes the oral or topical use of the seeds of Plantago psyllium as mucilage for inflammations.

Fischer 1966 (106) mentioned Semen Psyllii to treat cough, catarrh and pertussis, diarrhoea and urethritis. Like linseed, Semen Psyllii can soften tumours and is used for eye irritation.

In Martindale 1967 (107) only the well-known use for chronic constipation, dysentery and chronic diarrhoea is mentioned.

Lewis, professor of biology of the Washington university, 1977 (108) refers to the use of Plantago ovata and Plantago psyllium as purgatives.

The World Health Organization (WHO) published a monograph on Semen Plantaginis (110) covering *Plantago afra* L., *P. indica* L., *P. ovata* Forsk, and *P. asiatica* L. (WHO, 1999). The uses described in folk medicine include use of Semen Plantaginis as an expectorant and antitussive, an antibacterial agent, and a diuretic and in the treatment of rheumatic and gouty afflictions, glandular swelling, and bronchitis.

Psyllium is mentioned in ancient Indian Ayurvedic prescriptions.
In Pakistan as per Unani-medicine (109), apart from its well-known use, ispaghula husk is used in febrile conditions, catarrhal and renal affections. A decoction of seeds is prescribed in cough and cold and the crushed seeds made into poultice applied to rheumatic and glandular swellings. It is claimed that seeds in the form of infusion are of value in urethritis, relieving the burning sensation associated with the disease.

Conclusion

Older references do not mention *Plantago ovata* because this plant is native to Iran and India.
The use of ispaghula husk and of the other kinds of Plantago in traditional medicine is similiar to the use of linseed, but such traditional use is not described just as well and so consistently. Furthermore, no precise posology is mentioned.
None of the above-mentioned 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

IV.1. Preclinical Safety

There are only unpublished data available concerning ispaghula husk and psyllium without an exact definition of the test preparation.

IV.1.1. Single dose toxicity

These studies (112, 113, 114) were conducted prior to the establishment of good laboratory practices. Three studies were carried out in mice, and one study was carried out in Sprague-Dawley rats. There were no test substance-related death or other effects noted in any of these studies during the 7-day observation periods.

The LD50 in rats was greater than the highest dose tested corresponding to 3,360 mg/kg ispaghula husk administered by gavage of an aqueous suspension. The LD50 in mice was greater than the highest dose tested corresponding to 2,940 mg/kg ispaghula husk also administered by gavage of an aqueous suspension.

IV.1.2. Subchronic toxicity

There are 4 studies available which were conducted in accordance with GLP.
Rats were fed with psyllium at levels high as 10 % of the diet for periods up to 13 weeks (two 28-day studies in Sprague-Dawley rats (115, 116), one 28-day study (117) and one 13-week study (118) in Fischer rats).
Psyllium consumption ranged from 3,876 to 11,809 mg/kg/day. For 3 studies comparisons were made to the cellulose-supplement diet; for one study comparisons were made to the basal diet, since there was no control fibre used in that study.
Treatment-related findings in these studies included decreased body weights and lower body-weight gains in males. Body weights and weight gains among Fischer females consuming 10% psyllium were greater than those of rats consuming 10% cellulose in the 28-day study and over 2 or 3 different weeks of the 13-week study.

No inter-group differences in body weights or weight gains were seen in Sprague-Dawley females. The administration of psyllium resulted in a number of statistically-significant differences in haematology, serum chemistry and urine analysis values. Most of these were small differences and not considered to be biologically significant, and many showed no clear relationship to the treatment. Effects considered to be biologically significant and related to psyllium supplementation were lower serum total protein, albumin, globulin, total iron-binding capacity, calcium, potassium, and cholesterol as well as higher aspartate transaminase (AST) and alanine transaminase (ALT) activities relative to control. Several of these effects are considered to be secondary effects to others. The reasons for the lower serum total protein, albumin and globulin are not clear, but the absence of any increases in urinary protein, any evidence of gastrointestinal pathology, which could account for protein loss, and any differences in growth or feed efficiency in rats fed psyllium may give evidence that there are no adverse effect of psyllium on protein metabolism.
While serum ALT and AST are often used as indicators of liver damage, the lack of differences in liver weight as a percentage of body weight, and the absence of any histopathological changes in the liver of psyllium-fed rats did not support this hypothesis.
Because the absorption of psyllium is very limited, histopathological evaluations were limited to the gastrointestinal tract, liver, kidneys and gross lesions without observing any treatment-related effect.

IV.1.3. Reproductive toxicity

There are 2 studies available, which were conducted in accordance with GLP.

A rat multigeneration reproduction/teratology study (119) showed no evidence of any adverse effects of psyllium on reproduction or development. Psyllium as 0, 1.25, or 5.0% (w/w) of the diet was administered in a standard (NIH-07) rat and mouse meal diet *ad libitum* through gestation of the third generation.

A segment II study in rabbits (120) also showed no evidence of any adverse effect. Psyllium as 0, 2.5, 5 or 10% (w/w) of diet was administered in a purine certified rabbit chow diet for days 2 – 20 of gestation.

IV.1.4. Genotoxicity and carcinogenicity

Tests on genotoxicity and carcinogenicity have not been performed.

IV.2. Clinical Safety

IV.2.1 Clinical safety evidence

Bonithon-Kopp C *et al.* 2000 (111) published the result of a randomised interventional trial and concluded that supplementation with fibre such as ispaghula husk may have adverse effects on colorectal adenoma recurrence, especially in patients with high dietary calcium intake. However, because very few patients developed large adenomas, they could not exclude the possibility of a beneficial effect of ispaghula husk on later stages of carcinogenesis, such as adenoma growth and malignant transformation. Calcium supplementation was associated with a modest but not significant reduction in the risk of adenoma recurrence. The authors concluded, however, that these findings should not prevent recommendations for high consumption of vegetables, fruits, and cereals, because this approach has potentially beneficial effects on other chronic disease, especially coronary heart disease.
665 patients with a history of colorectal adenomas were randomly assigned to three treatment groups, in parallel design: calcium gluconolactate and carbonate (2 g elemental calcium daily), fibre (3 – 5 g ispaghula husk), or placebo. Participants had colonoscopy after 3 years of follow-up. The primary endpoint was adenoma recurrence.
The study had several shortcomings, e.g. the number of participants was lower than planned, contributing to a decrease in statistical power; the rate of drop outs was 13.75 %,; the compliance in the calcium group was lower than in the other groups; the sought information could not be collected from all patients (nutrition from 62%, medication from 70.5%, familiar recurrence of colon or rectum carcinoma from 79.4 %).

This study is not sufficient to postulate that additional intake of ispaghula husk is associated with a higher risk of rectum or colon carcinoma.

IV.2.2 Undesirable effects

Flatulence, occuring with the use of ispaghula husk, is common as already described under II.1 Pharmacokinetics.

Ispaghula husk contains potent allergens. Exposure to these allergens is possible through the oral route or through contact. Ispaghula husk should be considered as a possible cause of anaphylaxis from laxatives. Reactions of hypersensitivity including anaphylaxis-like reactions may occur very rarely. Ispaghula husk is not to be used by patients with known hypersensitivity to ispaghula (101, 102, 103).

IV.2.3 Contraindications

A number of studies have shown that ispaghula husk lowers peak blood glucose levels due to delayed intestinal absorption (see II.2.7 Hypoglycaemic effect). Cases of diabetes mellitus where insulin adjustment is difficult constitute therefore a contraindication to the administration of ispaghula husk preparations.

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

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

Ispaghula husk 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 husk 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), paralysis of the intestine or megacolon.

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

Ispaghula husk is finally not to be used by patients with known hypersensitivity to ispaghula.

IV.2.4 Special warnings and precautions for use

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

Ispaghula husk 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:
concerning indication a)

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 husk should be discontinued and medical advice must be sought.

concerning indication c)

The use of ispaghula husk as an adjuvant to diet in hypercholesterolemia requires medical supervision.

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

IV.2.5 Interactions with other medicinal products and other forms of interaction

See chapter II.2.2.

V. Overall conclusions

Indication a): For the treatment of habitual constipation

The well-established use of ispaghula husk as a laxative has been investigated in randomised controlled studies, however sometimes only single-blinded studies have been performed. No recent randomised double-blinded placebo-controlled study is available. The use as a laxative is substantiated by the pharmacological effects of ispaghula husk.
It is important to remark that the laxative effect of ispaghula husk is a mild one without severe side effects compared to those associated with stimulant laxatives. In fact, most of these stimulant laxatives have only a temporary efficacy on constipation: they can produce an acute diarrhoea followed, 2 or 3 days later, by a renewed interruption of the intestinal transit. Patients then tend to increase the dose.

The current level of evidence[2] for indication a) can be identified as level I.

[2] 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)

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

The use in 'conditions in which easy defaecation with soft stool is desirable' is scientifically substantiated by the well-established laxative effects. Compared to the scientific data available on linseed, special clinical data are available concerning the antihaemorrhoidal effect of ispaghula husk. These data are based on at least one randomised double-blinded controlled trial. The mention of examples of such 'conditions in which easy defaecation with soft stool is desirable' is therefore justified. The current level of evidence for indication b) can be identified as level I.

Indication c): In patients to whom an increased daily fibre intake may be advisable e.g. as an adjuvant in constipation predominant irritable bowel syndrome, as an adjuvant to diet in hypercholesterolemia

As *adjuvant in constipation predominant irritable bowel syndrome*
The data available are not sufficient to prove the efficacy for the indication irritable bowel syndrome in general. If at all, there are only marginal benefits for constipation predominant irritable bowel syndrome which support a minor claim as indication c). These data are available from 2 randomised double-blind controlled studies with only a small number of subjects (57 and 26 patients respectively finished the study; 83 in total) and from 1 investigator-blinded study. Because of other shortcomings (e.g. no validated symptom scores) the level of evidence is to be identified as at least level II.

As an adjuvant to diet in hypercholesterolemia
The treatment with ispaghula husk results in average in a reduction of total cholesterol by nearly 4 – 5% and of LDL cholesterol by nearly 7% but without an effect on HDL. These data are available from randomised controlled trials and from meta-analysis of randomised controlled trials (level I). In consideration of this small effect compared to statins and in consideration that hypercholesterolemic patients should increase their daily fibre intake as a first step before starting a treatment with medicinal products, a minor claim as indication c) is only scientifically supported.

In summary the current level of evidence for indication c) can be identified as level I to II:
- level II for an adjuvant in constipation predominant irritable bowel syndrome and
- level I for an adjuvant to diet in hypercholesterolemia.