EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 May 2013
EMA/HMPC/199775/2012
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Plantago ovata* Forssk., seminis tegumentum

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Plantago ovata Forssk. (*Plantago ispaghula* Roxb.), seminis tegumentum
Herbal preparation(s)	Powdered herbal substance
Pharmaceutical forms	Herbal substance for oral use Herbal preparation in solid dosage forms for oral use
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1. Introduction

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

- Herbal substance(s)

Ispaghula husk consists of the episperm and collapsed adjacent layers removed from the seeds of *Plantago ovata* Forssk. (*Plantago ispaghula* Roxb.). The herbal substance has to comply with the monograph "Ispaghula husk" of the European Pharmacopoeia.

Ispaghula husk consists of 85% water-soluble fibre. 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.

- Herbal preparation(s)

Powdered herbal substance.

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

Not applicable.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	only a combination product (*Sennes angustifoliae* fructus, *Plantaginis ovatae* semen, *Plantaginis ovatae* testa)
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	in addition: different combination products
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	in addition: different combination products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	in addition: different combination products
Ireland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	in addition: combination of *Plantago ovata* (husks) and *Plantago ovata* (seeds)
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Latvia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

Member State	Regulatory Status				Comments
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	in addition: different combination products

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

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

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

1.3. Search and assessment methodology

The assessment report of the initial evaluation (EMEA/HMPC/165838/2006) reviewed the scientific data available for ispaghula husk (*Plantago ovata* Forssk., seminis tegumentum), mainly the clinical data. The 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 reviewed 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, the term "psyllium" is used in this report , otherwise reference is made to "ispaghula husk".

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

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

2. Historical data on medicinal use

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

Ispaghula husk has a long history of medicinal use throughout the world, including in traditional medicine. Ispaghula husk is also known as Plantago ovata, ispagol 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 (Berendes 1902) already mentioned three species of Plantaginaceae family: *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" (Frerichs *et al.* 1927) describes the oral or topical use of the seeds of *Plantago psyllium* as mucilage for inflammations. Fischer (1966) 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 Todd (1967) only the well-known use for chronic constipation, dysentery and chronic diarrhoea is mentioned.

Lewis (1977) refers to the use of *Plantago ovata* and *Plantago psyllium* as purgatives.

The World Health Organization (WHO) published a monograph on Semen Plantaginis (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 (Usmanghani *et al.* 1997), 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.

Actually no traditional herbal medicinal product is registered in the European Union.

Well-established use

Austria
3 medicinal products (powder and granules) authorised. Indication and posology according to the HMPC monograph

Belgium
Pharmaceutical form: granules since 1963; powder since 1984
Indication: constipation
Posology: daily 2 times 5 g; daily 1 – 3 times 3.2 g

Finland
Pharmaceutical form: granules
Indications: Constipation: postoperatively to soften stool. Adjuvant therapy in colon irritable, anal fissures and haemorrhoids. Adjuvant therapy for diarrhoea in colon irritable syndrome.
Posology for oral use: 1) adults 3.660 g 2 -3 times daily; children over 6 years of age: 3.66 g twice daily; children of 2 to 6 years: ½ dose (ca. 1.8 g) twice daily. 2): adults ca. 3.5 – 4.0 g 1 – 3 times daily, children over 6 years of age: ca. 3.5 – 4.0 g twice daily; children of 2 to 6 years: ½ dose (ca. 1.8 g) twice daily

France
Pharmaceutical form: hard capsules since 1989, powder for oral suspension since 1956, granules or effervescent granules since 1955
Indication: symptomatic treatment of constipation
Posology for oral use: daily 2 to 4 hard capsules with 390 mg powder; daily 3 times 1 hard capsules with 430 mg powder; twice daily 2.143 – 7 g powder or granules, daily 1 to 2 sachets with 5 g powder.

Germany
Pharmaceutical form: granulate since 1990, powder since 1994

1) Indication: For the treatment of habitual constipation; in conditions in which easy defecation with soft stools is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures, haemorrhoids and in pregnancy; as an adjuvant to treat diarrhoea and irritable bowel syndrome.
   Posology: adults: daily 1 – 6 times 3.25 g herbal substance; daily 1 – 4 times 4.75 g herbal substance; daily 2 – 3 times 5.22 g herbal substance, children: daily 1 – 3 times 1.75 g herbal substance

2) Indication: For the treatment of habitual constipation; in conditions in which easy defecation with soft stools is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures, haemorrhoids and in pregnancy; as an adjuvant to treat diarrhoea, irritable bowel syndrome, diverticulosis and Morbus Crohn.
   Posology: daily 2 – 3 times 3.25 g herbal substance

3) Indication: For the treatment of habitual constipation; in conditions in which easy defecation with soft stools is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures, haemorrhoids and in pregnancy;
   Posology: daily 1 – 3 times 6.5 g herbal substance; daily 1 – 5 times 5 g granules; daily 2 – 3 times 2.5 g herbal substance

4) Indications: For the treatment of habitual constipation; in conditions in which easy defecation with soft stools is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures, haemorrhoids and in pregnancy; as an adjuvant to treat diarrhoea, in patients to whom an increased daily fibre intake may be advisable e.g. as an adjuvant in irritable bowel syndrome, as an adjuvant to diet in mild to moderate hypercholesterolemia;
   Posology: daily 2 – 3 times 3.25 g herbal substance or 2 – 6 times 3.25 g herbal substance, respectively.

5) Indications: For the treatment of habitual constipation; in conditions in which easy defecation with soft stools is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures, haemorrhoids; in patients to whom and increased daily fibre intake may be advisable e.g. as an adjuvant in irritable bowel syndrome.
   Posology: 3 times daily 3.25 g herbal substance or 3 times daily 3.25 – 6.5 g herbal substance, respectively.

Ireland
Pharmaceutical form: granules for effervescent suspension since 1975; powder for oral suspension since 1990
Indications: for the relief of constipation and for patients who need to increase their daily fibre intake.
Posology for oral use: adults and children over 12 years: daily 1 - 3 times 3.5 g herbal substance; children aged 6 to 12 years: daily 1 - 3 times 0.9 – 1.7 g herbal substance.

Latvia
Pharmaceutical form: granules for oral use since 2001
Indications: Chronic constipation; cases where soft faeces are desired, e.g., in anal fissures, haemorrhoids, after rectal surgery; supportive treatment after diarrhoea; irritable bowel syndrome.
Posology: adults and adolescents (over 12 years of age): daily 2 – 3 times 3.25 g herbal substance, supportive treatment daily 2 – 6 times 3.25 g herbal substance

United Kingdom
Pharmaceutical form: granules since 1995; powder since 1992
1) Indications: For the treatment of constipation, for use in patients with colostomy, ileostomy, haemorrhoids, anal fissures, chronic diarrhoea associated with diverticular disease, irritable bowel syndrome, and as adjunction in ulcerative colitis.
   Posology: adults: daily 3 times 3.5 g; children: half adult dose.

2) Indications: Herbal medicinal product for treatment of habitual constipation; conditions in which defecation with soft stools is desirable e.g. anal fissures, haemorrhoids, after rectal or anal surgery as well as pregnancy. Herbal medicinal product for symptomatic short-term treatment of non-specific diarrhoea. Herbal medicinal product for treatment of irritable bowel syndrome, when physician has excluded other reasons for the symptoms.
Posology: adults, elderly and children over 12 years: 2 – 3 spoons at 5 ml in the morning and evening.

3) Indications: Habitual constipation; conditions in which easy defecation with soft stools is desirable, e.g. anal fissures, haemorrhoids, after rectal or anal surgery as well as in pregnancy.
Posology: adults, elderly and children over 12 years: daily 4.75 – 9.5 g herbal substance, in special case up to 19 g herbal substance daily.

4) Indications: habitual constipation including cases due to spastic colon, dietary insufficiencies, diarrhoea, irritable bowel syndrome, management of patients with colostomy, in patients with haemorrhoids or diabetes, to normalise the bowel movement in patients with mucous or ulcerative colitis.
Posology: adults: 2 teaspoonful once or twice daily, children: 1 teaspoonful once or twice daily.

5) Indications: for the relief of constipation and for patients who need to increase their daily fibre intake.
Posology: daily 1 – 3 times 3.4 g

6) Indications: primary hypercholesterolaemia (mild and moderate), to be used in conjunction with dietary modification
Posology: adults: daily 2 times 5.25 g herbal substance for the initial 2 – 3 months, maintenance of lowered levels with 2 times 3.5 g.

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

See section 2.1 and section 4. Clinical data
No precise posology is given in the older literature mentioned in chapter 2.1.

3. Non-Clinical Data

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

Primary pharmacodynamics

Laxative effect
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 (Struthers 1986). Stool viscosity is highly affected by stool water content (McRorie *et al.* 1998b). 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 (McRorie *et al.* 1998c).

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 when administered in the diet in hamsters either with 7.5% or with variable levels (2, 4, 6, 8%) for 2.5 or 3.5 weeks, respectively (Turley et al. 1994), in the diet in hamsters either with 7.5% for 14, 17 or 21 days, respectively (Turley et al. 1991) or African green monkeys with 10% for 3.5 years (McCall et al. 1992), but apparently enhanced bile acid loss in rats when administered in diet (5%) for 4 weeks (Matheson et al. 1995), due to its gel-forming ability and its viscosity. For fibre in general Gallaher et al. (1993) show that in hamster greater viscosity of intestinal contents is strongly associated with cholesterol reduction, but that the contribution of fibre fermentation remains uncertain.

Ispaghula husk increased the activity of hepatic 7α-hydroxylase, the initial and rate-limiting enzyme in the conversion of cholesterol bile acids, when administered for 4 weeks in rats (5% of the diet) (Matheson et al. 1995), hamsters (7.5% of the diet) (Horton et al. 1994), guinea pigs (7.5% of the diet) (Fernandez et al. 1995).

Ispaghula husk as part of the diet (7.5%) also altered the hepatic cholesterol homeostasis in guinea pigs, when administered for 4 weeks (Fernandez et al. 1995).

Influence of fibre in general 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 based on studies in rats (Chen et al. 1984). The cholesterol-lowering effect can be attributed to the soluble fibre-fractions.

Secondary pharmacodynamics

No data available.

Safety pharmacology

No data available.

Pharmacodynamic interactions

No additional data available (see assessment report on ispaghula seed).

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

No information available.

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

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

Single dose toxicity

These studies (Study IT-0001, Study SA 2067, Study SA 2068,) 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 LD_{50} 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 LD_{50} 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.

Subchronic toxicity

There are 4 studies available which were conducted in accordance with GLP.

Rats were fed with ispaghula husk at levels high as 10% of the diet for periods up to 13 weeks (two 28-day studies in Sprague-Dawley rats (Study 6114-184, Study 6114-194), one 28-day study (Study 6114-187) and one 13-week study (Study 6114-188) in Fischer rats).

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% ispaghula husk 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 ispaghula husk 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 ispaghula husk 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 ispaghula husk may give evidence that there are no adverse effect 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 ispaghula husk-fed rats did not support this hypothesis.

Because the absorption of ispaghula husk is very limited, histopathological evaluations were limited to the gastrointestinal tract, liver, kidneys and gross lesions without observing any treatment-related effect.

Reproductive toxicity

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

During a rat multigeneration reproduction/teratology study (Study 6114-191) ispaghula husk as 0, 1.25, or 5% (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. In this 2-generation-study in rats changes in weight could be seen in the pups (middle and high dose group). This decreased body weight was only seen in male pups.

During a segment II study in rabbits (Study 6114-249) ispaghula husk 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. This rabbit embryo-foetal study was only conducted as preliminary dose range finding study, therefore the results are inconclusive.

Conclusion
Reassessing the available preclinical data it must be stated that the animal studies are insufficient with respect to reproductive toxicity.

Genotoxicity/Carcinogenicity
Tests on genotoxicity and carcinogenicity have not been performed.

3.4. Overall conclusions on non-clinical data

Non-clinical data are limited.

The data available support the use of ispaghula husk as laxative and as an adjuvant to diet in hypercholesterolemia, even if the mechanism is not fully understood.

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

4. Clinical Data

4.1. Clinical Pharmacology

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

Laxative effect

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

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

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 (Marlett *et al.* 2000). 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 (Brunton 1990, Kay *et al.* 1978).

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.

Effect on blood lipids levels

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) (Ganji *et al.* 1994).

In 16 healthy volunteer's 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 (Chaplin *et al.* 2000).

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 (Everson *et al.* 1992).

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 (Weingand *et al.* 1997).

In a randomised crossover study Khossousi *et al.* (2008) examined the effects of a dietary fibre supplement on post-prandial lipaemia, glycaemia and insulin response after a high- (12 g additional fibre in the form of psyllium husk supplement) (HFM) or low fibre standard meal (LFM) in 10 overweight/obese male subjects (BMI >25 kg/m^2 and waist circumference of ≥102 cm). Two isoenergetic breakfast meals with similar composition one with low (3 g) and one with high (15 g) amount of fibre were consumed at interval of one week. Analysis was carried out using *t* test and ANOVA. The serum triacylglycerol (TAG) incremental area under the curve during 6 h of the postprandial period was significantly lower after the consumption of HFM compared with LFM. At the first hour of the postprandial period, the plasma apo B48 concentration after consumption of HFM was significantly lower compared with LFM. The resting energy expenditure and diet-induced thermogenesis after both meals was similar during 6 h postprandial period. According to the authors, these findings suggest that a single acute dose of dietary fibre in the form of psyllium supplement can decrease arterial exposure to TAG and modify chylomicron responses in the postprandial period.

In a three-arm experiment Vuksan *et al.* (2011) compared the lipid-lowering effect of low-viscosity wheat bran (WB), medium-viscosity psyllium (PSY, no further specification) and a high-viscosity viscous fibre blend (VFB) in 23 health individuals. Final intake of the WB, PSY and VFB was 10.8, 9.0 and 5.1 g, respectively. Reduction in LDL cholesterol was greater with VFB compared with PSY (-12.6% (SEM 3.5), p=0.002) and WB (-14.6% (SEM 4.2), p=0.003). The magnitude of LDL cholesterol reduction showed a positive association with fibre apparent viscosity. Despite the smaller quantity consumed, the high-viscosity fibre lowered LDL cholesterol to a greater extent than lower-viscosity fibres.

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 (Capani *et al.* 1980, Abraham *et al.* 1988, Cummings 1978).

Brennan *et al.* (2012) evaluated the impact of dietary fibre-enriched ready-to-eat extruded snacks on the postprandial glycaemic response of 12 non-diabetic patients by using both an *in vitro* starch degradation methodology and conventional *in vivo* glycaemic response procedures. Psyllium (no further specification available) and oat bran were incorporated into a ready-to-eat snack at a 15% replacement concentration to flour. Comparisons were made between the response of individuals after consuming a standard 25 g glucose drink as well as a product control (recipe without added dietary fibre) against the different dietary fibre treatments. Psyllium snacks reduced the *in vivo* postprandial blood glucose concentrations compared to glucose drink (p≤0.005), and both oat bran or control

snacks (p≤0.05). The postprandial glucose value at 60 min was also lowered compared to the other treatments. Predictive glucose release using *in vitro* methodology showed that all snack products were significantly different to each other at each sample time (p≤0.05). The order of the *in vitro* glucose response of the snacks was control > oat bran> psyllium. The *in vivo* psyllium average incremental area under the curve (iAUC) response was lower than the control snack (p≤0.05), oat bran snack, and glucose drink (p≤0.05). According to the authors, these results indicate that there is a potential utilisation of psyllium fibre in reducing the glucose response of extruded products.

In a single-blind crossover study Dow *et al.* (2012) wanted to determine the effects of two water-soluble dietary fibres, ultrahigh-viscosity hydroxypropylmethylcellulose (UHV-HPMC, nonfermentable) and ispaghula husk (fermentable), on postprandial glucose and second meal effects in 12 healthy women. They were given standardised, premeasured breakfast and lunch meals with either 4 g of the fibre supplements or a placebo. Subjects consuming UHV-HPMC had significantly (p<0.05) lower blood glucose area under the curve (AUC) 2 hours after breakfast than those receiving a placebo. Subjects consuming ispaghula husk only tended to have lower glucose levels than placebo group. Peak glucose concentrations following breakfast was significantly (p<0.01) less with UHV-HPMC when compared with placebo. Subjects consuming ispaghula husk only tended to have lower peak glucose levels (p=0.07). No significant differences in AUC or peak glucose concentration between treatments following the second meal (lunch) were detected.

Effects on cardiovascular risk in general
As exploratory secondary analysis of data from a parent randomised controlled study to evaluate the effect of fibre supplementation on C-reactive protein King & DeLegge (2009) studied 86 overweight/obese adults whether 3 months of psyllium supplementation would affect asymmetric dimethylarginine (ADMA). This biomarker has been associated with oxidative metabolism and increased vascular risk. Forty-one people in the intervention group received 14 g/day of ispaghula husk in addition to their usual diet compared with 45 controls who followed their usual diet alone. Baseline ADMA levels were elevated in this overweight/obese population compared with published reference values in healthy individuals (0.75 vs 0.50 µmol/l). The change in ADMA levels over 3 months was not different in the ispaghula husk group compared to the control group (-0.03 vs -0.01 µmol/l, p=0.73).

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 (Brunton 1990, Bradshaw *et al.* 1983, Smalley *et al.* 1982). 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 (Eherer *et al.* 1993).

Protection against colorectal cancer/diseases
Several mechanisms have been suggested to explain the presumed preventive effect. Thus, reduction of toxin exposure to the colonic mucosa through dilution of luminal contents and/or faster transit time; bile acid absorption; and the capacity to increase the generation of short chain fatty acids (SCFA) in the gut have all been proposed as potential mechanisms. Sohn *et al.* (2012) studied the potentially pro-apoptotic effect of ispaghula husk in the implicated mechanisms in colorectal cancer cells with different molecular phenotypes after ispaghula husk anaerobic fermentation with colonic bacteria as it occurs in the human colon. The fermentation products (SCFA) of ispaghula husk induced apoptosis in all primary tumour and metastatic cell lines. Apoptosis was caspase-dependent and both intrinsic and

extrinsic pathways were implicated. The authors concluded that ispaghula husk could be a useful chemotherapy adjuvant.

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

Absorption

Ispaghula husk consists of 85% water-soluble fibre and is relatively resistant to fermentation by colonic bacteria (Marteau *et al.* 1990). The active polysaccharidic fraction comprises 65% D-xylose, 20% L-arabinose, 6% rhamnose and 9% D-galacturonic acid (Kennedy *et al.* 1979). 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 (Gray 1981, Southgate 1982). These β-linkages cannot be broken by human digestive enzymes. While psyllium may contain a small number of α-linkages, these are sterically hindered (Sandhu *et al.* 1981). As a result of this chemical structure, psyllium is not expected to be hydrolysed in the upper gastrointestinal tract. Although most studies confirm that psyllium is not digested in the upper gastrointestinal tract or absorbed from the small intestine (Life Sciences Research Office 1993), Andersen *et al.* (1988) 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.

Metabolism

To varying degrees, dietary fibre is fermented by bacteria in the colon, resulting in the production of carbon dioxide, hydrogen, methane, water, and SCFA. The main SCFA produced by fibre fermentation are acetate, propionate, and butyrate (Pomare *et al.* 1985, Mortensen *et al.* 1992). 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 (Storer *et al.* 1983). In humans, psyllium transits the upper gastrointestinal 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 (Marteau *et al.* 1994).

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 *et al.* 1990, Wolever *et al.* 1991, Wolever & Robb 1992, Wolever *et al.* 1992, Lewitt *et al.* 1996.

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 (Bianchi *et al.* 2002). 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 oro-cecal transit time.

Excretion

In the gastrointestinal 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 (McRorie *et al.* 1998a, McRorie *et al.* 1998b, Atal *et al.* 1963). Cummings 1993 reported an average increase in human faecal output of 3.7 g of stool per gram of psyllium consumed.

4.2. Clinical Efficacy

4.2.1. Dose response studies

Kumar *et al.* 1987 tried to determine the optimum daily dose of ispaghula husk (10, 20 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.

Flannery & Raulerson (2000) explored the effect of 16-week daily dose of 6 g of psyllium hydrophilic mucilloid (taken all at once) on serum total cholesterol, LDL, HDL, and triglyceride levels in men and women with hypercholesterolemia. With testing a lower dose than the average dose used in previously reported studies with significant reduction of cholesterol level, the authors wanted to examine the possibility that response is dose related. Twelve men and 16 women with serum total cholesterol levels over 200 mg/dl were randomly assigned to either the treatment or control group (methylcellulose). Twelve participants were excluded during the first eight weeks because they developed a specific medical condition or were prescribed a medication for which study participation was contraindicated. During the second eight weeks, 6 participants were excluded because they did not obtain their final lipoprotein analyses, so that 18 participants remained in the treatment group and 10 in the control group for data analyses. None of the changes in serum total cholesterol, HDL, LDL, and triglyceride levels within subjects were significant and there were no significant interactions between groups. The authors concluded that hypercholesterolemic action of psyllium at levels below 10.2 g per day cannot be predicted. Until further research can be performed, psyllium at doses less than 10.2 g per day cannot be considered effective for patients with hypercholesterolemia for cholesterol-lowering effects.

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.

4.2.2. Clinical studies (case studies and clinical trials)

Laxative effect

Numerous clinical practice summaries, dating back to as early as 1935, recommended the use of fibre supplementation for the 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 (Dettmar *et al.* 1998) 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 similar 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 *et al.* (1986) 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 defecation 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 defecation 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 *et al.* (1987) 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 (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/week during laxative ingestion and in the combination group from 2 to 6.8 stools/week. 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/week and the mean dry stool weight from 75.4 g to 126.5 g/week. The combination treatment increased the mean wet stool weight from 277.7 g to 982.1 g/week and the mean dry stool weight from 79.9 g to 190.8 g/week. 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 *et al.* (1998a) compared the stool softening and laxative efficacy of ispaghula husk (2 times 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 defecation". 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 *et al.* 2004) 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 defecation 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 defecation 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 defecation 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 defecation rate increases to 8.48 instead of 5.71.

Attaluri *et al.* (2011) assessed and compared the effects of dried plums and ispaghula husk in patients with chronic constipation in an 8-week, single-blind, randomised cross-over study. Forty patients (m/f=3/37, mean age=38 years) received either dried plums (50 g twice a day, fibre = 6 g/day) or ispaghula husk (11 g twice a day, fibre = 6 g/day) for 3 weeks each with a 1-week washout period. Subjects maintained a daily symptom and stool diary. Assessment included number of complete

spontaneous bowel movements per week (primary outcome measure), global relief of constipation, stool consistency, straining, tolerability and taste. The number of complete spontaneous bowel movements per week and stool consistency scores improved significantly (p<0.05) with dried plums compared to ispaghula husk. Straining and global constipation symptoms did not differ significantly between treatments. Both treatments were well tolerated. No adverse effects were reported during the study. Objective assessment concerning efficacy is not possible because a placebo group is missing, the study population is small and the composition of the study medication is not exactly described.

Reviews

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

Tramonte *et al.* (1997) evaluated in 36 randomised trials lasting more than 1 week whether laxatives and fibre therapies improve symptoms and bowel movement frequency in adults with chronic constipation. They concluded that both fibre and laxatives modestly improved bowel movement frequency. There was inadequate evidence to establish whether fibre was superior to laxatives or one laxative class was superior to another. No severe side effects for any of the therapies were reported.

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

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

Conclusion

The use of ispaghula 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.

Effect on conditions in which easy defecation with soft stool is desirable

Haemorrhoidal disease

Non-controlled clinical studies
Fichera *et al.* (1978) studied the effects of ispaghula husk on 20 patients suffering from organic pathologies (haemorrhoids, anal fissures, after anal surgery) accompanied by painful defecation. 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 defecation, loss of blood with faeces, lesions of the rectal mucosa evidenced by endoscopy, and frequency of defecation.

Borgia *et al.* (1983) 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 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. Ninety-four percent 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 *et al.* (1978) evaluated ispaghula husk at 3.5 g twice a day. 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 defecation (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 defecation (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 *et al.* (1982) studied 51 patients with first or second degree haemorrhoids. 6.7 g three times a day corresponding to 12.2 g ispaghula husk or placebo was administered for 6 weeks. A significant reduction in bleeding (p<0.01) and pain at defecation (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 defecation. 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 defecation 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 *et al.* (2000) assessed the role of micronized purified flavonidic fraction in the management of bleeding nonprolapsed haemorrhoids. One hundred and sixty two 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; micronized 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%); micronized purified flavonidic fraction plus ispaghula husk n=2 (5.1%);

p=0.075). No complications or side-effect were noted. The author concluded that micronized purified flavonidic fraction used with fibre supplements rapidly and safely relieved bleeding from nonprolapsed haemorrhoids.

Painful defecation after rectal or anal surgery

Kecmanovic *et al.* (2006) describes the results of a prospective, randomised clinical study which assesses the usefulness of *Plantago ovata* (psyllium husk) in reducing postoperative pain and tenesmus after open haemorrhoidectomy in 98 patients. One group received postoperatively two sachets daily of 3.26 g of *Plantago ovata* for 20 days. The control group was treated with glycerine oil. *Plantago ovata* reduces pain, tenesmus rate and shortens postoperative hospital stay compared to glycerine oil. This study confirms the well-established use in the mentioned indication.

Eogan *et al.* (2007) describes a randomised clinical trial of a laxative alone (lactulose) versus a laxative and a bulking agent (lactulose combined with ispaghula husk) after primary repair of obstetric anal sphincter injury. Pain scores were similar in the two treatment groups, but incontinence in the immediate postnatal period was more frequent with the two preparations compared with lactulose alone (32.86% versus 18.18%, p=0.03). A treatment group with ispaghula husk alone is missing. Therefore this study is not relevant for the use according to the HMPC-monograph.

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

Effect on diverticular disease

Non-controlled clinical studies

Thorburn *et al.* (1992) 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 sensitive 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 5 hours. In the right colon there was an increase in the median percentage activity 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 6 of the 9 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 *et al.* (1980) enrolled 9 patients with constipation symptoms, i.e. infrequent (3–4 day interval) and painful defecation, associated with diverticular disease in a double-blind crossover study. Patients were treated with placebo vs. 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 occurred.

In a randomised double-blind cross-over study by Ornstein *et al.* (1981) 58 patients with uncomplicated symptomatic diverticular disease received ispaghula husk (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 161 g, 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 the diverticular disease itself; if the symptoms arise from constipation, fibre supplementation may be a useful therapy.

Conclusion

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

Effect on irritable bowel syndrome

As mentioned in section 4.2.1 (Dose response studies), Kumar *et al.* (1987) tried to determine the optimum dose of ispaghula husk (10, 20 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 *et al.* (1987) 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 (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 occurred: 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 *et al.* (1982) 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 et al. 2004) 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 et al. (2000) 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 et al. (2004) 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 interval (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.

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

Successful blinding of dietary interventions is difficult. In retrospect, approximately three quarters of patients correctly guessed which treatment they were given. Forty percent of the patients stopped participation before final visit, mainly because they felt worse when taking the fibre supplement. The dropout rate was highest in the bran group and the first month of treatment. The number of patients stopping treatment because of intolerance was twice as high in the bran group as in the psyllium or placebo group. Psyllium is not exactly specified.

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

Conclusion
The data available are not sufficient to prove efficacy for the indication irritable bowel syndrome in general. There are seen some benefits for constipation predominant irritable bowel syndrome. Therefore ispaghula husk is recommended as an adjuvant in constipation predominant irritable bowel syndrome.

Antidiarrhoeal effect

In an open pilot study Hamouz (1984) investigated the effect of a combination product (5 g of granula i.e. 1 teaspoon) containing ispaghula seed 3.25 g and ispaghula husk 0.11 g) on acute or chronic diarrhoea of 50 hospitalised patients of a psychiatric department. The patients received the combination product for 7 days (2 teaspoonful 3 times daily for 3 days following an individual dosage). The median number of stools decreased from 4.7 to 1.6 in the 22 patients with acute diarrhoea and from 3.4 to 1.5 in the 28 patients with chronic diarrhoea. Stool consistency changed from loose to soft formed after one week treatment in all patients. All 28 patients with chronic diarrhoea had already been treated with other antidiarrheal agents before. Only moderate success or no success at all could be achieved with this prior treatment. The switch to treatment with the combination product brought success in 24 of the 28 cases.

Frank *et al.* (1979) administered a mucilagenous hydrophilic colloid bulk laxative (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 *et al.* (1988) 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 conventional 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 (1990) noticed that psyllium may be helpful, if diarrhoea occurs as a side effect of medicinal products.

In a randomised crossover study Lodge *et al.* (1995) 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.

Conclusion
These studies have several shortcomings. The first two studies (Hamouz 1984 and Frank et al. 1979) are uncontrolled and investigate a small and special population. The combination product mainly contains ispaghula seed. The studies of Qvitzau et al. (1988) and of Lodge 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. 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.

Effect on blood lipids levels

In the above-mentioned study by Borgia *et al.* (1983) 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 *et al.* (1988). Following a 2-week baseline period, subjects were treated for 8 weeks with 3.4 g psyllium hydrophilic mucilloid (ispaghula husk) 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 *et al.* (1989) 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).

Bell *et al.* (1990) examined the cholesterol-lowering ability of soluble-fibre breakfast cereals in 58 male patients with mild to moderate hypercholesterolemia in a randomised, double-blind, placebo-controlled study. Patients followed a step I diet for a minimum of 6 weeks, then were randomly assigned to groups incorporating either corn flakes or one of two soluble-fibre cereals (pectin enriched or psyllium enriched further description is missing). In the diet for an additional 6 weeks. During the diet-only phase, total cholesterol dropped 3.8%. During the cereal-plus-diet phase, total and LDL cholesterol values of the pectin-enriched cereal group dropped an additional 2.1% (p=0.243) and 3.9% (p=0.16), respectively, and they dropped 5.9% (p=0.005) and 5.7% (p=0.034), respectively, in the psyllium-enriched cereal group. During the cereal-plus-diet phase, no significant effects on HDL cholesterol, triglyceride, or body weight were found within or between any cereal groups. The cereal was well tolerated by patients.

Levin *et al.* (1990) compared the effects of administration of 5.1 g of psyllium husk or placebo (cellulose) twice daily for 16 weeks as adjuncts to a prudent diet in the management of moderate hypercholesterolemia in a parallel, double-blind study. Ninety- six male and female individuals with plasma cholesterol levels > 5.17 mmol/l (200 mg/l) were included. Thirty-four subjects were withdrawn or were excluded during the 8-week diet stabilisation period. Sixty-two subjects were randomised to 16 week treatment with 58 successfully completing the study. Three subjects (one on psyllium husk, two on placebo) withdrew from the study because of gastrointestinal complaints; one was excluded because of a change in medication. Psyllium husk decreased the total cholesterol level by 5.6% compared with a 0.1% increase in the placebo group (p=0.01). The LDL-cholesterol levels were 8.6% below postdiet levels in the psyllium husk group and 2.2% below the postdiet levels in the placebo group (p<0.05). The HDL-cholesterol level decreased during the diet stabilisation period in both groups and returned to near-baseline values by week 16. Plasma triglyceride levels did not change substantially in either group. Eight patients in the psyllium husk group and 11 in the placebo group had minor gastrointestinal problems, such as flatulence, constipation, and loose stools.

Neal & Balm (1990) investigated psyllium husk supplementation as a means of enhancing the cholesterol-lowering effect of the phase I American Heart Association diet. In this parallel, open-label,

controlled clinical trial 59 subjects with total serum cholesterol (TC) levels ranging from 5.56 to 10.24 mmol/l (215 to 396 mg/dl) were given a 2-month dietary lead-in followed by 3 months of diet only (29 subjects) or diet supplemented with 20.4 g of psyllium husk daily (30 subjects). Unlike women, men had a significant decrease in levels of both TC (-8%) and LDL cholesterol (-10.1%) during the dietary lead-in. Psyllium husk supplementation resulted in an additional 5.5% reduction in the TC levels as compared to diet alone. Psyllium husk supplementation combined with dietary lead-in resulted in an overall 17.3% decrease in the TC and a 20% decrease in LDL-cholesterol for men, with decreases of 7.7% and 11.6%, respectively, for women. The authors conclude that psyllium effectively enhances the cholesterol-lowering effect of the phase I diet.

Anderson *et al.* (1991) compared in a placebo-controlled, parallel study psyllium husk with methycellulose, calcium polycarbophil, and placebo as dietary adjuncts in treating mild to moderate hypercholesterolemia. Of 163 men and women recruited with serum cholesterol levels above 5.17 mmol/l (200 mg/dl), 105 completed 8 weeks of an American Heart Association step I diet and then augmented the diet with one of the fibre supplements for 8 additional weeks (three times daily 3.4 g psyllium husk, or 2.0 g methylcellulose, or 1.25 g calcium polycarbophil, or placebo). Incremental differences from placebo for LDL cholesterol were -8.8% for psyllium husk, -3.2% for methylcellulose (not significant), and +8.7% for calcium polycarbophil; and for total cholesterol the differences were -4.3% for psyllium husk (not significant), -1.4% for methylcellulose (not significant), and +5.9% for calcium polycarbophil. Only mild gastrointestinal effects were observed. The author concluded that psyllium significantly enhances the American Heart Association diet effects in managing mild to moderate hypercholesterolemia, while methylcellulose and calcium polycarbophil provide little or no additional benefit.

In a randomised, double-blind, parallel study Anderson *et al.* (1992) investigated the lipid-lowering effects of a ready-to-eat cereal enriched with psyllium in 44 hypercholesterolemic ambulatory individuals for 7 weeks. After 1-week baseline period, subjects were randomly assigned to consume 114 g/d of a psyllium-flake or wheat-bran flake cereal for 6 weeks adjunctive to an American Heart Association Step I diet. No exact description of "psyllium" is given. Serum HDL-cholesterol and triglycerides remained unchanged throughout the study. Changes of total cholesterol and LDL-cholesterol in the psyllium-cereal group significantly differed from change in wheat-bran group (p<0.01). Average serum total cholesterol concentrations of the psyllium group decreased from 6.51 mmol/l at baseline to 5.06 mmol/l after 6 weeks, an 8.4% reduction (p<0.001). Average serum LDL-cholesterol concentrations of the psyllium group decreased 12% (P<0.001) over the 6-week treatment phase. Both wheat-bran and psyllium-enriched cereals were well tolerated and were not associated with any side effects.

Sprecher *et al.* (1993) included men and women with primary hypercholesterolemia (total serum cholesterol ≥5.7 mmol/l [220 mg/dl]) in a double-blind, placebo-controlled, 16-week parallel trial to determine the efficacy of ispaghula husk in reducing serum cholesterol levels. Thirty-seven participants followed a high-fat diet, and 81 participants a low-fat diet. Participants were randomly assigned to either ispaghula husk, 5.1 g twice a day, or placebo. The ispaghula husk group showed significant decreases (p<0.05) in total cholesterol and LDL cholesterol. Total cholesterol and LDL cholesterol levels decreased 5.8% and 7.2%, respectively, in psyllium recipients on high-fat diets and 4.2% and 6.4%, respectively, in psyllium recipients on low-fat diet. No significant difference was seen in LDL cholesterol response when psyllium recipients on low- and high-fat diets were compared (p>0.2). No significant reductions in lipid levels were observed in the placebo group. Adverse events were predominantly gastrointestinal events. They were mild, transient, and self-limited.

In a double-blinded, placebo-controlled, crossover study Maciejko *et al.* (1994) investigated if psyllium husk reduces the gastrointestinal side effects and enhances the cholesterol-lowering efficacy of cholestyramine resin in patients with primary hypercholesterolemia. The study was conducted in four

phases: (1) dietary lead-in (weeks -8 to 0); (2) cholestyramine therapy (weeks 0 to 6); (3) choestyramine therapy with study medication (psyllium husk or placebo) (weeks 7 to 12); and (4) cholestyramine therapy with crossover to alternate study medication (weeks 13 to 18). 27 male and female patients (LDL-C ≥ 4.91 mmol/l (190 mg/dl) and triglyceride concentration < 2.26 mmol/l) were randomised. 18 patients completed the study. They demonstrated significant reductions in their plasma total cholesterol (7.27 vs 6.67 mmol/l [281 vs 258 mg/dl]) and LDL-C (5.38 vs 4.63 mmol/l [208 vs 179 mg(dl]) concentrations compared with baseline levels. The addition of psyllium husk to the cholestyramine regimen provided a tendency toward further reductions in total cholesterol and LDL-C levels (6.67 vs 6.46 mmol/l [258 vs 250 mg/dl] and 4.63 vs 4.29 mmol/l [179 vs 166 mg/dl]), respectively, although statistical significance was not achieved. Psyllium husk significantly reduced the frequency and severity of constipation, abdominal discomfort, and heartburn. No reports of new gastrointestinal tract symptoms or untoward effects were noted with the addition of psyllium husk.

In a double-blind crossover trial, Roberts *et al.* (1994) studied the cholesterol-lowering effect of ready-to-eat cereal containing soluble fibre as psyllium, oatmeal and barley in 81 otherwise healthy men with mild hypercholesterolemia (plasma total cholesterol concentrations of 5.8 – 8.8 mmol/l), who were already eating a diet reduced in total and saturated fats. The study lasted 12 weeks, six weeks eating each cereal, with no washout period. Block randomisation was used to assign subjects to test cereal (50 g psyllium/oat/barley bran cereal) or control cereal (60 g wheat/wheat bran cereal). With the test cereal, subjects ate 10 g more soluble fibre than with the wheat cereal, mostly from psyllium (86%) but with some from oat and barley bran. No further details are available. Total cholesterol and LDL cholesterol concentrations fell significantly on psyllium cereal, relative to wheat cereal, in both periods (mean -3.2% and -4.4%, respectively). There were no consistent changes in triglyceride or HDL cholesterol concentrations. Some subjects reported mild flatulence, feelings of fullness and increased frequency and bulkiness of bowel motions on either cereal. No subject had to stop eating either cereal because of side effects.

Summerbell *et al.* (1994) investigated whether psyllium (without exact definition) has an intrinsic hypocholesterolaemic action when used as part of a low-fat diet with subjects in mild to moderate hypercholesterolaemia. 46 subjects (total cholesterol levels 5.2 – 7.8 mmol/l) were recruited to participate in the two-phase randomised double-blind, placebo-controlled study. The study period was 3 weeks in phase I and 6 weeks in phase II. In the first 3 weeks subjects were instructed to consume a low-fat diet, at the beginning of phase II they were randomly assigned to get either 60 g of a high-fibre breakfast cereal daily, containing 9.6 g of soluble fibre from psyllium, or 60 g of a high-fibre breakfast cereal daily, containing negligible amounts of soluble fibre. Both groups maintained a low-fat diet. Four subjects dropped out within the first 2 weeks. Another 5 subjects had reduced their total serum cholesterol level to below 5.2 mmol/l by the end of phase I and were not to ask to continue the study. During phase I, total and LDL cholesterol levels were reduced in all subjects (p<0.001); randomisation resulted in similar phase I changes in both the psyllium (-8.9% and -11.1%, respectively) and control (-8.9% and -12.8%, respectively) groups. During phase II, total and LDL cholesterol levels were further reduced in the psyllium group (-7.3% and 10.6%, respectively; p<0.001), but not in controls (-2.7 and -6.0%, respectively). Changes in HDL cholesterol levels and body weights over the study period were not significant. Differences between the psyllium and control groups in total, LDL and HDL cholesterol levels were not significant at any stage. No serious adverse reactions with the breakfast cereals were reported. The authors concluded that psyllium-containing breakfast cereals have a total and LDL cholesterol lowering effect which may be additional to that achieved with a low-fat diet.

Wolever *et al.* (1994) assessed the lipid lowering effect of soluble fibre in 42 subjects (21 men, 21 women) with hyperlipidaemia who were on a low-fat diet (American Heart Association step 2 diet). The participants were studied over two 2-week periods separated by a 2-week washout in a randomised crossover trial. 14 participants had been stabilised on lipid-lowering drugs, of which the dosage was

not changed throughout the study. Three participants had non-insulin dependent diabetes, two being well controlled on glyburide and one on diet alone. The participants had to consume pre-weighed packages of breakfast cereal, one daily (with breakfast) for the first 3 days, then two daily (one with breakfast and one with dinner) for the last 11 days. There were two types of test cereals, each providing 6.7 g psyllium fibre (no further information) daily, and two types of wheat bran control cereals. Half the subjects tested each type of cereal, and the results were pooled because the psyllium cereals had similar effects on serum cholesterol levels. Comparing values at the end of 2 weeks, psyllium reduced serum total (6.33 ± 0.12 mmol/l versus 6.76 ± 0.12 mmol/l, p<0.001; 6.4%), LDL (4.36 ± 0.11 mmol/l versus 4.73 ± 0.12 mmol/l, p<0.001; 7.8%) and HDL cholesterol levels (1.10 ± 0.05 mmol/l versus 1.14 ± 0.05 mmol/l, p<0.05) and the LDL/HDL cholesterol ratio (4.27 ± 0.20 versus 4.48 ± 0.22, p<0.02) with no effect on triglycerides. There was no significant interaction between the effects of treatment and sex for any of the blood lipid variables. Women tended to have greater decreases in total, LDL, and HDL cholesterol levels than men, but the percent decrease in LDL/HDL ratio on psyllium was similar in men, 4.9%, and women, 4.7%.

Jenkins *et al.* (1997) performed two studies to determine whether the lipid-lowering effect of viscous soluble fibre was modified by monounsaturated fatty acid (MUFA). First, psyllium (1.4 g/MJ (megajoule), mean daily intake of 11.9 g psyllium) was compared with wheat bran (control) in 1-mo metabolic diets by using a randomised crossover design (n = 32 hyperlipidemic subjects). The background diet contained ≈ 6% of energy as MUFA (20% of total fat). The second study (n = 27 hyperlipidemic subjects) was similar to the first but the background diet contained ≈ 12% MUFA (29% of total fat) because of addition of canola oil. At both fat intakes, psyllium resulted in significant reductions in total, LDL, and HDL cholesterol compared with the wheat bran control. For the psyllium diet at 6% compared with 12% MUFA, the decreases in LDL cholesterol were 12.3 ± 1.5% (p<0.001) and 15.3 ± 2.4% (p<0.001), respectively. With the higher-MUFA diet triacylglycerol fell significantly over the control phase (16.6 ± 5.5%, p=0.006) and the LDL/HDL ratio fell significantly over the psyllium phase (7.3 ± 2.8%, p=0.015). The authors conclude that psyllium lowered LDL- and HDL-cholesterol concentrations similarly at both MUFA intakes. However, there may be some advantage in combining soluble fibre and MUFA to reduce the ratio of LDL to HDL cholesterol.

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 *et al.* (1998). Two-hundred and eighty-six 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 & Carless 1998) 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.

Romero *et al.* (1998) recruited 70 normal (cholesterol<200 mg/dl) and hypercholesterolemic (Cholesterol>220 mg/dl) men from Northern Mexico to participate in a 8-week study to evaluate the cholesterol-lowering effect of cookies enriches with psyllium husk. The participants were randomly

assigned to one of three fibre groups: control (1.9% total fibre and 0.6% soluble fibre), psyllium husk (13.1% total fibre and 1.7% soluble fibre), oat bran (9.6% total fibre and 2.8% soluble fibre). The daily cookies portion corresponded to 100g. A frequency questionnaire was developed to assess consumption of food items associated with hypercholesterolemia of hypertriglyceridemia. Individuals were advised to reduce the consumption of those items during the study. Four individuals did not complete the study. Reductions in total cholesterol were 33.5 to 45.5 mg/dl for subjects in the psyllium husk and oat bran groups while reductions in the control group were only 2.1 mg/dl (p<0.001). The psyllium husk and oat bran groups had 44 and 43 mg/dl reduction in LDL cholesterol which was significantly higher than the 6 mg/dl reduction in the control group. Similarly, reductions in the LDL/HDL ratio in the psyllium husk and the oat bran groups were significantly more pronounced than those observed for the control group (p<0.01). Psyllium husk and oat bran had similar reductions of plasma total and LDL cholesterol. Changes in HDL cholesterol and triglycerides were not different among the three groups. Psyllium husk and oat bran reduced plasma cholesterol in normal as well as in hypercholesterolemic population.

Tai *et al.* (1999) assessed the effect of dietary supplementation of soluble fibre on lipid levels in normal subjects with hypercholesterolaemia in a randomised, placebo-controlled, double-blind, parallel-group study. Each sachet contained 5.5 g consisting of ispaghula husk 62.3%, guar gum 16.2%, glucomannan 0.65%, citric acid 4.6%, beta carotene 1.3%, aspartame 0.65%, natural range flavour 1.3% and potato starch 13%. After a 4-week run-in period, 83 subjects were randomised to receive placebo or the test product (16.5 g/d). 7 subjects defaulted follow up (5 on placebo, 2 on test product). In addition, 9 subjects (5 on test product, 4 on placebo) had total cholesterol fall into optimal range during the run-in phase and were removed from the study. The test product produced a 3.24% (SD = 7.85%, p=0.020) decrease in total cholesterol and 5.45% decrease in LDL cholesterol (SD = 10.25%, p=0.0034) but no significant difference in serum triglyceride, weight, body mass index or blood pressure. This was not seen in the placebo group. However no detectable difference was seen final lipid profiles between the groups. HDL cholesterol was significantly increased in both groups (0.1 mmol/l with placebo, and 0.09 mmol/l with test product, p<0.01). It has to be noted that the test product was a combination product.

Anderson *et al.* (2000a) published the results of a multicentre, 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. Two-hundred and forty-eight 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).

Jenkins *et al.* 2002 assessed the efficacy of soluble fibre intake at a dose approved by the US Food and Drug Administration for a claim of health benefits in reducing serum lipid risk factors for cardiovascular disease. 68 hyperlipidemic adults consumed a test (high-fibre) and a control low-fat (25% of energy), low-cholesterol (<150 mg/d) diet for 1 month each in a randomised crossover study. The high-fibre diet included 4 servings/d of food containing β-glucan or psyllium (no further specification) that delivered 8 g/d more soluble fibre than did similar, unsupplemented foods in the control diet. Compared with the control diet, the high fibre diet reduced total cholesterol (2.1 ± 0.7%; p=0.003), total HDL cholesterol (2.9 ± 0.8%; p=0.001), LDL/HDL cholesterol (2.4 ± 1.0%; p=0.015), and apolipoprotein B:A-I (1.4 ± 0.8%; p=0.076). Small reductions in blood pressure were found after both diets. The subjects reported no significant differences in palatability or gastrointestinal symptoms between the diets.

Jayaram *et al.* (2007) compare the efficacy of the combination of ispaghula husk (3.5 g twice daily) and atorvastatin (10 mg once daily) versus atorvastatin (10 mg once daily) alone in reduction of low-density lipoprotein cholesterol (LDL-C), total-cholesterol levels in hypercholesterolaemic patients after

8 and 12 weeks of therapy in India. The study was multicentric, randomised and open labelled. One-hundred men and women (LDL-C level >130 mg/dl, total cholesterol >220 mg/dl) were included and 97 patients completed the study. At the end of the 8th week, both the groups had a significant reduction in mean LDL-C (20.5% in ispaghula husk and atorvastatin group and 16% in the atorvastatin alone group) as compared to baseline. The difference between the groups was not significant. At the end of 12th week the difference between the groups was significant (31.4% in ispaghula husk and atorvastatin group and 22.8% in the atorvastatin alone group, p<0.05). Serum total cholesterol, HDL-C and triglyceride were significantly lowered within the groups at 8th and 12th weeks but between the groups, the difference was not significant. Comparison of adverse events shows that more number of patients from the atorvastatin alone group (n=14, 28%) had adverse reactions than from the combination group (n=4, 8%, p> 0.05). Adverse events in the first group were related to gastro-intestinal and skeletal muscle disorders, and in the second group only to gastro-intestinal disorders. The authors conclude that combining lower or standard dose of statin with other lipid lowering agent like psyllium fibre poses useful and efficacious alternative to using higher dose of statin.

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

Solà *et al.* (2010) evaluated whether *Plantago ovata* husk improves cardiovascular disease risk biomarkers including LDL-cholesterol (LDL-C). The study was carried out multi-centred, double-blind, placebo-controlled, parallel and randomised in Western Europe. 126 mild-moderate hypercholesterolaemic patients received 14 g/d *Plantago ovata* husk, and 128 patients placebo in a low saturated fat diet for 8 weeks. Subsequently, if LDL-C remained ≥ 3.35 mmol/l [130 mg/dl], participants proceeded with the fibre plus simvastatin (20 mg/d) for further 8 weeks. Relative to placebo, *Plantago ovata* husk reduced LDL-C by -6% (p<0.0002). 24.6% more *Plantago ovata* husk consumers achieved the target 5% reduction compared to placebo. Relative to placebo, *Plantago ovata* husk reduced total cholesterol by -6%, triglycerides by -21.6%, apolipoprotein B-100 by -6.7%, oxidised LDL by a mean of -6.82 U/L (95%CI: 3.15-10.48), insulin by -4.68 pmol/l (95%CI: 0.68-8.67) and systolic blood pressure by -4.0 mmHg (95%CI: 1.2-6.7)(p<0.05). At 16 weeks, the intra-group action of simvastatin added to *Plantago ovata* husk or placebo was a similar LDL-C reduction. The prevalence of adverse events was similar to placebo. Specifically, gastrointestinal disorders were 13.6% (n=16) in placebo and 13.2% (n=15) in *Plantago ovata* husk.

Pal *et al.* (2011) assessed the effect of a fibre supplement compared to a healthy diet on body composition, lipids, glucose, insulin and other metabolic syndrome risk factors in overweight and obese individuals. In a randomised, single-blind, parallel-design study over 12 weeks, 94 overweight and obese individuals (BMI between 25 and 40 kg/m^2) were recruited, and 72 were randomised into one of four groups: (1) placebo with their usual diet, n= 18; (2) fibre supplement with their usual study, n= 18; (3) placebo with a healthy eating regime, n=18; (4) fibre supplement with a healthy eating regime, n= 18. The fibre supplement consisted of 12 g psyllium mixed with 250 ml water three times daily 5-10 min before breakfast, lunch and dinner. The placebo consisted of 12 g breadcrumbs with flavouring, which provided 1.5 g of soluble fibre. 15 participants withdrew from the study due to unrelated reasons: group (1) 3, group (2) 2, group (3) 6, group (4) 4. Weight, BMI and % total body fat were significantly reduced in group (2) und (4), with weight and BMI significantly reduced in group (3) compared with group (1) at 12 weeks. Group (3) and (4) had significant reductions in

triacylglyceride (TAG) and insulin compared with group (1) at 6 and 12 weeks, and in insulin compared with group (2) at 12 weeks. Group (2), (3) and (4) had significant reductions in total cholesterol (TC) and LDL-cholesterol compared with group (1) after 6 and 12 weeks. The TC levels decreased from baseline in group (3) (6.28 mmol/l, p=0.002) and group (4) (6.34 mmol/l, p=0.014) both by 17% (5.22 and 5.29 mmol/l, respectively) at week 6. TC serum levels also significantly reduced at week 12 in group (2) (5.01 mmol/l, p=0.001), group (3) (5.15 mmol/l, p=0.001) and group (4) (5.07 mmol/l, p=0.003) by 15, 18 and 20%, respectively, from baseline. Comparison of differences between groups revealed that TC levels in group (2), (3), and (4) were lower by 15% (p=0.003), 16% (p=0.001) and 15% (p=0.02) at week 6, respectively, and lower by 21% (p<0.001), 19% (p<0.001) and 20% (p<0.000), respectively, at week 12 compared with group (1). There were no significant differences in TC levels between Group (2), (3) and (4) at week 6 and week 12. Initially there were some reports of minor bloating. According to Pal *et al.* (2012) 12 g of the psyllium product contain 7 g ispaghula husk.

Meta-analysis

A meta-analysis of Olson *et al.* (1997) 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 (Bell *et al.* 1990, Anderson *et al.* 1992, Roberts *et al.* 1994, Stoy *et al.* 1993, Wolever *et al.* 1994, Summerbell *et al.* 1994, Jenkins *et al.* 1997) 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 *et al.* (2000b) included 8 studies, 5 published (Weingand *et al.* 1997, Bell *et al.* 1989, Levin *et al.* 1990, Anderson *et al.* 1991, Sprecher *et al.* 1993) 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 pre-treatment 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.

Wei *et al.* (2009) included 21 studies in a meta-analysis (Anderson *et al.* 1988, Bell *et al.* 1989, Bell *et al.* 1990, Neal & Balm 1990, Levin *et al.* 1990, Anderson *et al.* 1991, Anderson *et al.* 1992, Everson *et al.* 1992, Sprecher *et al.* 1993 I, Sprecher et al. 1993 II, Summerbell *et al.* 1994, Wolever *et al.* 1994, Roberts *et al.* 1994, Maciejko *et al.* 1994, Jenkins *et al.* 1997 I, Jenkins *et al.* 1997 II, Romero *et al.* 1998, Davidson *et al.* 1998, MacMahon & Carless 1998, Anderson *et al.* 2000a, Flannery & Raulerson 2000). These studies enrolled a total of 1030 and 687 subjects receiving psyllium or placebo, respectively. The studies were randomised placebo-controlled trials, double blinded or open label, on subjects with mild-to-moderate hypercholesterolemia. The dose of psyllium was between 3.0 and 20.4 g per day and intervention period was more than 2 weeks. Any type of diet background was permitted. Diet lead-in period was between 0 and 8 weeks. 10 studies were carried out with an ispaghula husk medicinal product (10.2 g/day), the other studies with psyllium-enriched foods. No

further detailed information of composition was given. Compared with placebo, consumption of psyllium/psyllium husk lowered serum total cholesterol by 0.375 mmol/l (95%CI: 0.257-0.494 mmol/l), and LDL cholesterol by 0.278 mmol/l (95%CI: 0.213-0.312 mmol/l). The effect sizes of the ispaghula husk medicinal product on total cholesterol and LDL cholesterol were 0.442 mmol/l (95%CI: 0.210-0.674 mmol/l) and 0.300 mmol/l (95%CI: 0.167-0.430 mmol/l), respectively, whereas that of psyllium enriched foods were 0.320 mmol/l (95%CI: 0.162-0.477 mmol/l) and 0.260 mmol/l (95%CI: 0.180-0.340 mmol/l), respectively. The form of psyllium seemed to have no significant influence on lipid-lowering effects (p=0.2367 for total cholesterol and p=0.5688 for LDL cholesterol). A dose- (random effect meta-regression) and time-dependent effect of psyllium intake were shown. There was little effect for triglycerides. Based on the result of this meta-analysis, the authors concluded that after consuming psyllium for 20 weeks, serum total cholesterol level could be reduced from baseline level (about 6.36 mmol/l) to 5.73 mmol/l (nearly. 10%) and LDL concentration could be dropped from 4.31 to 4.00 mmol/l (nearly 7%). After psyllium consumption for about 1 year and a half, the LDL cholesterol could get to 3.1 mmol/l (the upper limit of the reference range). According to the authors there was a publication bias in this meta-analysis, based on the results of funnel plots. The publication bias was mainly caused by 'large effect but small trial' phenomenon.

Reviews

Petchetti *et al.* (2007) conclude that psyllium is useful as an adjunct to dietary therapy (step 1 or step 2 American Heart Association diet) in the treatment of patients with mild-to-moderate hypercholesterolemia. In combination with other cholesterol-lowering drugs such as statins, psyllium provides an added benefit on cholesterol lowering, and is well tolerated and cost-effective.

Bazzano (2008) concludes that evidence from observational epidemiologic studies and randomised controlled trials supports the idea that soluble dietary fibre lowers cholesterol and reduces some risk factors for coronary heart disease. Further research into different types of soluble dietary fibres, combinations of soluble fibres and other beneficial nutrients, and the effects of dietary fibre on other coronary heart disease risk factors is warranted. Increasing dietary soluble fibre should be an important part of strategies aimed at the primary prevention of coronary heart disease and other cardiovascular diseases.

Theuwissen & Mensink (2008) state that many well-controlled intervention studies have shown that four major water-soluble fibre types – β-glucan, psyllium, pectin and guar gum – effectively lower serum LDL cholesterol concentrations, without affecting HDL cholesterol or triacylglycerol concentrations. Furthermore, epidemiological studies suggest that a diet high in water-soluble fibre protects against cardiovascular disease. These findings underlie current dietary recommendations to further increase water-soluble fibre intake. With regard to psyllium each gram of water-soluble fibre lowered total and LDL cholesterol levels by -0.028 mmol/l and 0.029 mmol/l, respectively. Based on the total body of evidence, the FDA has approved in 1998 a health claim for psyllium that "A food product containing water-soluble fibre from psyllium seed husk, consumed as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease". For this, 7 g of water-soluble psyllium fibre must be consumed daily.

Giacosa & Rondanelli (2010) summarise that experimental and clinical studies suggest that psyllium does lower serum and liver cholesterol concentrations and may increase HDL-cholesterol levels. Moreover, water soluble fibres, such as psyllium, moderate post prandial glucose and insulin concentrations in non-insulin dependent diabetic patients, if taken with meals and favour the reduction of body weight and hypertension. Therefore, the favourable effect of various fibres and particularly of psyllium, on body weight reduction and satiety, on cholesterol and triglycerides levels, on fasting glycaemia and on blood pressure suggests a potential role of these fibres in the treatment of the metabolic syndrome.

Conclusion

In one of the first studies (Anderson et al. 1988), 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. Further studies show minor reductions. The meta-analyses showed a reduction of total cholesterol by nearly 4–5% and 10%, respectively and of LDL cholesterol by nearly 7% but ispaghula husk had no effect on HDL cholesterol.

Several recent investigations (Jayaram et al. 2007, Solà et al. 2007, Cicero et al. 2007, Khossousi et al. 2008 (pharmacology), King & DeLegge 2009 (pharmacology), Solà et al. 2010, Pal et al. 2011), review articles and a meta-analysis (Petchetti et al. 2007, Bazzano 2008, Theuwissen & Mensink 2008, Wei et al. 2009, Giacosa & Rondanelli 2010) deal with the effect of ispaghula husk on plasma lipids, cardiovascular risk, and metabolic syndrome risk factors. Jayaram et al. (2007) combined lower or standard dose of statin with other lipid lowering agent like psyllium fibre with the result that this poses useful and efficacious alternative to using higher dose of statin. The quality is varying and sometimes the study population is small. However in summary these investigations confirm the use of ispaghula husk in patients to whom an increased daily fibre intake may be advisable e.g. as an adjuvant to diet in hypercholesterolemia.

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 infarctions, 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 "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.

Hypoglycaemic effect

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

In a placebo-controlled, crossover trial (Pastors *et al.* 1991) 18 non-insulin-dependent diabetic patients were randomly assigned to receive either ispaghula husk or placebo. Each patient took two doses ispaghula husk (6.8 g) or placebo during each crossover period, one dose before breakfast and the other before dinner. Median of the washout period was 7 days. For meals eaten immediately after ispaghula husk ingestion, maximum postprandial glucose elevation was reduced by 14% at breakfast and 20% at dinner relative to placebo. Postprandial serum insulin concentrations measured after breakfast were reduced by 12% relative to placebo. Second-meal effects after lunch showed a 31% reduction in postprandial glucose elevation relative to placebo. No significant differences in effects were noted between patients whose diabetes was controlled by diet alone and those whose diabetes was controlled by oral hypoglycaemic drugs.

In a randomised double-blind placebo-controlled study Rodríguez-Morán *et al.* (1998) wanted to determine the plasma-lowering effects of 3.95 g three times daily ispaghula husk, as an adjunct to dietary therapy, on lipid and glucose levels, in patients with type II diabetes. The study consisted of a 6-week pre-treatments period of diet following by 6-week treatment period. One-hundred and twenty-

five subjects were included, 62 and 63 in ispaghula husk and placebo group, respectively. There were 2 dropouts in the ispaghula husk group, one case of abdominal discomfort, flatus, and colic pain, and unspecified causes in the other. In the pre-treatment period, there were no significant changes in glucose levels between the groups, but by the end of the 6-week treatment, fasting plasma glucose levels showed a significant reduction in the ispaghula husk group (p<0.01). Addition of ispaghula husk to diet also resulted in improvement of lipid profile: total serum cholesterol levels and LDL fraction showed a significant decrease, whereas HDL increased significantly. Triglycerides levels also showed a significant reduction in the ispaghula husk group. There were no significant differences in the lipid and glucose lowering effect o ispaghula husk based on gender. The aim of one study (Sierra *et al.* 2002) 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.

Ziai *et al.* (2005) investigated the plasma-lowering effects of 5.1 g twice daily of ispaghula husk, as an adjunct to dietary and drug therapy for 8 weeks on lipid and glucose levels, in patients with type 2 diabetes. 49 patients were randomly included in the double-blind placebo-controlled study. Fasting plasma glucose, and HbA1c, showed a significant reduction (p<0.05), whereas HDL cholesterol increased significantly (p<0.05) following ispaghula husk treatment. The LDL/HDL ratio was significantly decreased (p<0.05). No serious adverse event related to treatment was reported. A better gastric tolerance to metformin was recorded in the ispaghula husk group.

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

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

Hall & Flinkman (2012) assessed available data to answer the question if fibre and psyllium fibre improve diabetic metabolism. Concerning psyllium fibre the studies of Pal *et al.* (2011), Anderson *et al.* (1999) and Pastors *et al.* 1991 were evaluated and it was concluded that these three small studies have shown that ispaghula husk in modest amounts of 10.2 g/d to 13.6 g/d is associated with lower mean daily glucose concentrations, fewer hypoglycaemic events, lower A_{1c} levels, lower postmeal glucose concentrations, and lower insulin concentrations in people with diabetes mellitus.

Conclusion
The clinical data are not sufficient to support a specific indication like an adjuvant in the treatment of diabetes mellitus. Often, the study population was small and the treatment was not specified in detail. On the other hand the data indicate that there might be a positive influence on the diabetic

metabolism. Considering this the contraindication "cases of diabetic mellitus where insulin adjustment is difficult" is deleted.

However, because of the observed influence of diabetic metabolism after food intake in the presence of ispaghula husk, diabetic patients should take ispaghula husk only under medical supervision, to adjust the antidiabetic treatment, if necessary. A recommendation that "Diabetic patients should take ispaghula husks only under medical supervision because adjustment of antidiabetic therapy may be necessary" should be part of the information provided for ispaghula husk containing medicinal products concerning 'interactions with other medicinal products and other forms of interaction'.

Effects on other cardiovascular and metabolic syndrome risk factors

Burke *et al.* 2001 sought to determine whether dietary protein and fibre had additive effects on blood pressure reduction in hypertensive patients. Treated hypertensive patients changed for 4 weeks to a diet low in protein (12.5% energy) and fibre (15 g /d). Patients (n=41) were then randomised to 1 of 4 groups in an 8-week factorial study of parallel design in which they continued the low-protein, low-fibre diet alone of had supplements of soy protein to increase protein intake to 25% energy, of psyllium husk to provide an additional 12 g soluble fibre/d, or both protein and fibre. In the 36 subjects who provided complete data, protein and fibre had significant additive effects of lower 24-hour and awake systolic blood pressure. Relative to control, the net reduction in 24-hour systolic blood pressure was 5.9 mmHg with fibre and with protein.

In a six-month, randomised, open-label clinical trial, Cicero *et al.* (2007) enrolled 141 hypertensive, overweight patients in Italy. During the first four weeks of the study, all patients received dietary advice (according to step I of the recommendations issued by the American Heart Association) and any nutritional supplement use was withdrawn. Then, the patients were randomised to the oral ingestion of psyllium husk powder (3.5 three times daily) or guar gum (3.5 three times daily) or to a standard diet. Psyllium husk powder and guar fibres were supplied as identical, opaque, coded boxes. Both fibres significantly improved body mass index, fasting plasma glucose, fasting plasma insulin, homeostasis model assessment index, HbA1c, LDL-cholesterol, and ApoB. After six months the psyllium husk group showed a mean significant decrease in LDL-C of 9 mg/dl (t=5.69, p<0.001) and in HbA1c of 0.7% (t=5.71, p<0.001), the guar group in LDL-C of 10 mg/dl (t=4.09, p=0.002) and in HbA1c of 0.7% (t=4.9, p<0.001). Psyllium husk powder significantly improved plasma triglyceride concentration (-21 mg/dl; t=5.35, p<0.001) and systolic (-5.2 ± 1.3 mmHg; t=6.51, p<0.001) and diastolic blood pressure (-2.2 ± 0.8 mm; t=6.51, p<0.001), too. Neither the psyllium husk group nor the guar group showed any significant change in plasma HDL-cholesterol. Three patients in the psyllium husk group and four in the guar group experienced transient intercurrent abdominal bloating and 1 patient of the psyllium husk group and 3 in the guar group were withdrawn from the study after 3 months for this reason. One patient in the psyllium husk group and three patients in the guar group also experienced intercurrent diarrhoea, but no one withdrew from the study for this reason.

Pal *et al.* (2012) conducted a randomised, single-blind, parallel-design study to compare the effects of fibre intake from a healthy diet versus fibre supplement diets on blood pressure and vascular function over 12 weeks. 72 overweight and obese adults were randomised to one of three groups: (1) the control group consumed placebo with their usual diet, (2) fibre supplement group consumed 7 g ispaghula husk three times a day with their usual diet, (3) a healthy eating with placebo. Fifteen participants withdrew from the study due to unrelated illness, work commitments, poor compliance and personal reasons. Fifty-seven participants completed the 12-week study (15 in group (1), 16 in group (2), 12 in group (3)). Systolic blood pressure was lower in group (2) compared with (1) at week 6, but not at week 12. However systolic blood pressure was lower in group (3) compared to group (1) at week 12. At week 6, group (2) presented lower diastolic blood pressure and augmentation index compared to control, but not at week 12. According to the authors, the present study did not show any improvements in blood pressure or vascular function with ispaghula husk supplementation.

Pal & Radavelli-Bagatini (2012) assessed the available scientific data (Anderson *et al.* 2000b, Anderson *et al.* 1988, Burke *et al.* 2001, Cicero *et al.* 2007, Jenkins *et al.* 2002, Karhunen *et al.* 2010, Khossousi *et al.* 2008, Olson *et al.* 1997, Pal *et al.* 2012, Pal *et al.* 2011, Rodríguez-Morán *et al.* 1998, Sierra *et al.* 2002, Tai *et al.* 1999, Vuksan *et al.* 2011, Ziai *et al.* 2005). They concluded that the review of the literature supports the notion that the consumption of psyllium provides benefits to many components of the metabolic syndrome. Psyllium supplementation improves glucose levels and insulin response, blood pressure, as well as lipid profile in both animals and humans, thereby reducing metabolic risk factors. Appetite has also been reported to decrease after the consumption of psyllium in most studies.

Conclusion
An indication concerning the reduction of cardiovascular risks and/or metabolic syndrome risk cannot be included in the monograph because well conducted studies with cardiovascular endpoints as main target parameter are missing.

Protection against colorectal cancer/diseases

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

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

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

Effect on glucose and lipids levels in patients with diabetes mellitus

Anderson *et al.* (1999) evaluated the safety and effectiveness of ispaghula husk supplement to a traditional diet for diabetes in the treatment of men with type 2 diabetes and mild-to-moderate hypercholesterolemia in a double-blind, placebo-controlled, and parallel study. 56 men were recruited. After a 2-week dietary stabilisation phase, 34 of these men were randomly assigned to receive either 5.1 g ispaghula husk or cellulose placebo twice daily for 8 weeks. All-day and postlunch postprandial glucose concentrations were 11% ($p < 0.05$) and 19.2% ($p < 0.01$) lower in the ispaghula husk than in the placebo group. Serum total and LDL-cholesterol concentrations were 8.9% ($p < 0.05$) and 13% ($p < 0.07$) lower, respectively, in the ispaghula husk group than in the placebo group. No serious adverse events were reported.

See also Rodríguez-Morán *et al.* (1998) on page 33.

Clark *et al.* (2006) tested the relative importance of a low-glycaemic (kJ 1515; carbohydrate 78 g and psyllium soluble fibre 6.6 g without further specification) response versus a high glycaemic (kJ 1833; carbohydrate 78 g and psyllium soluble fibre 0g) response breakfast meal on postprandial serum glucose, insulin and free fatty acid (FFA) responses after consumption of a standardised mid-day meal in 42 adults with type 2 diabetes mellitus. Following an overnight fast of 8-10 h, a randomised crossover intervention using control and test meals was conducted over a 3-week period. In post-breakfast analyses, the low glycaemic breakfast had significantly lower area under the curve (AUC) values for plasma glucose and insulin compared to high glycaemic breakfast ($p < 0.05$). The AUC values for FFA were higher for the low glycaemic breakfast than for the high glycaemic breakfast ($p < 0.05$). Post-lunch analyses indicated similar glucose responses and AUC values for FFA for the two breakfast types. Insulin AUC values were significantly lower for the low glycaemic breakfast than for the high glycaemic breakfast ($p < 0.05$).

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

Rudkowska (2012) summarised the available scientific data (Clark *et al.* 2006, Sartore *et al.* 2009, Anderson *et al.* 1999, Sierra *et al.* 2002, Bajorek & Morello 2010) concerning impact of psyllium on plasma lipids levels and glycaemic control, as well as other potential cardiovascular disease risk factors in patients with type 2 diabetes mellitus. According to the author the results generally demonstrate that psyllium supplements improve lipid profiles as well as glycaemic control beyond a traditional diet in patients with type 2 diabetes mellitus.

Children/adolescents

Laxative effect in children
There are numerous publications, which indicate that the potential health benefits of increased dietary fibre in childhood outweigh the potential risks, especially in highly industrialised countries (Williams *et al.* 1995). A review of the scientific literature by Williams & Bollela (1995) 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. McClung *et al.* (1995) confirmed that only half of the children received the recommended amounts of dietary fibre intake. According to the recommendations from a conference on dietary fibre in childhood, children older than 2 years of age should increase their daily intake of dietary fibre (increased consumption of a variety of fruits, vegetables, cereal and other grain product) to an amount equal or greater than their age plus 5 g (e.g. 8 g/day at age 3) (Williams *et al.* 1995).

However specific clinical data with ispaghula husk are lacking.

Antidiarrhoeal effect in children
Smalley *et al.* (1982) evaluated the use of ispaghula husk in the management of chronic non-specific diarrhoea of childhood (CNDC) in an uncontrolled investigation. 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 with 1 tablespoon ispaghula husk 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.

Effect on blood lipids levels in children
In a randomised, double-blind, placebo-controlled crossover study (Dennison *et al.* 1993) 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. Twenty 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 *et al.* (1996) 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 *et al.* (2003) 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.

The data concerning the effect of ispaghula husk on blood lipid levels in children are not consistent (Dennison *et al.* 1993, Davidson *et al.* 1996, see above). The review of Moreno *et al.* (2003) requires better controlled trials and further studies to clarify the effect and the mechanisms.

Effect on blood lipids levels in adolescents

De Bock *et al.* (2012) assessed the effects of *Plantago ovata* supplementation on lipid profiles, insulin sensitivity and other parameters of the metabolic syndrome in an at risk adolescent population. The study was a participant-blinded, randomised, placebo-controlled, crossover trial. Forty-seven healthy adolescents males aged 15-16 years were recruited from secondary schools in lower socio-economic areas with high rates of obesity in New Zealand. At baseline, 44% of subjects were overweight or obese. Twenty-eight percent had decreased insulin sensitivity, but none had impaired glucose tolerance. Participants received 6 g/day *Plantago ovata* or placebo (potato starch) for 6 weeks, with a two-week washout before crossing over. The plant part of *Plantago ovata* is not described, but according to further statements in the publication it seems likely that *Plantago ovata* husk was used. 45 subjects completed the study. *Plantago ovata* supplementation led to a 0.12 mmol/l (6%) reduction in LDL-cholesterol (p=0.042). There were no observed effects on insulin sensitivity, fasting plasma insulin, or glycaemic status (i.e. fasting plasma glucose). Ambulatory blood pressure parameters were similar with placebo and fibre intake, except night time systolic blood pressure that tended to be on average 3.1 mmHg lower with *Plantago ovata* supplementation (p=0.073). Although fibre supplementation did not lead to a reduction in weight, BMI SDS (BMI data were converted to standard deviation scores according to British 1990 standards), or body percentage, it lead to a 4% reduction in android fat to gynoid fat ratio (p=0.019).

Conclusion
In summary, the use is not recommended:

- *in children below the age of 6 years for indication "treatment of habitual constipation and indication "use in conditions in which easy defecation with soft stool is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures and haemorrhoids" and*

- *in children below the age of 12 years for indication "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".*

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 (Kooperation Phytopharmaka 2002).

Use during pregnancy and lactation

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

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

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

Conclusion

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

Since publication of the HMPC-monograph no new safety or efficacy data concerning pregnancy and lactation have been published. Reassessing the available preclinical data during revision 1 it must be stated that the animal studies are insufficient with respect to reproductive toxicity. Assessment according to the 'Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling' (EMEA/CHMP/203927/2005) would now lead to the wording "is not recommended", because non-clinical data are insufficient and less than 300 prospective exposed pregnancies are documented.

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

"There are limited amount of data (less than 300 pregnancy outcomes) from the use of ispaghula husk in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

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

purgatives. There is no evidence of an effect on the fertility in the rat following oral application (see section 5.3)".

Use in post-menopausal women

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

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

4.3. Overall conclusions on clinical pharmacology and efficacy

Indication 1: For the treatment of habitual constipation
The well-established use of ispaghula husk as a laxative has been investigated in randomised controlled studies, however sometimes only single-blinded. 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 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[1] for indication 1) can be identified as level I.

Indication 2: In conditions in which easy defecation with soft stools is desirable, e.g. in case of painful defecation after rectal or anal surgery, anal fissures and haemorrhoids
The use in 'conditions in which easy defecation with soft stool is desirable' is scientifically substantiated by the well-established laxative effects. Special clinical data are available concerning the anti-haemorrhoidal effect of ispaghula husk and the positive effect after rectal/anal surgery. These data are based on randomised controlled trial. The mention of examples of such 'conditions in which easy defecation with soft stool is desirable' is therefore justified.

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

Indication 3: 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 efficacy for the indication irritable bowel syndrome in general. There are seen some benefits for constipation predominant irritable bowel syndrome. Therefore ispaghula husk is recommended as an adjuvant in constipation predominant irritable bowel syndrome following the general recommendation to increase daily fibre intake. These data are available from 3 randomised double-blind controlled studies with some shortcomings (difficulties in successful blinding, no validated symptom scores, results of subgroups).

The level of evidence is to be identified as at least level II.

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[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)

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, only a minor claim as indication 3) is scientifically supported.

In summary the current level of evidence for indication 3) 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.

The clinical data are not sufficient to support a specific indication like an adjuvant in the treatment of diabetes mellitus. Often, study's population was small and study treatment was not specified in detail.

Several recent investigations deal with the effect of ispaghula husk on plasma lipids, cardiovascular risk, and metabolic syndrome risk factors. A general recommendation to reduce cardiovascular risk and/or metabolic syndrome risk cannot be included because well conducted studies with cardiovascular endpoints as main target parameter are missing. King & DeLegge (2009) showed no significant impact of fibre supplementation on ADMA levels in middle-aged overweight/obese adults. The biomarker ADMA has been associated with oxidative metabolism and increased cardiovascular risk.

Efficacy data concerning the antidiarrhoeal effect are insufficient.

Use is not recommended:

- in children below the age of 6 years for indication "treatment of habitual constipation and indication "use in conditions in which easy defecation with soft stool is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures and haemorrhoids" and

- in children below the age of 12 years for indication "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".

Laxative bulk producers should be used before using other purgatives if change of nutrition is not successful.

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

5. Clinical Safety/Pharmacovigilance

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

Bonithon-Kopp *et al.* (2000) 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 diseases, 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.

Conclusion
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.

5.2. Patient exposure

No adequate data available.

5.3. Adverse events and serious adverse events and deaths

Gastrointestinal adverse events
Flatulence, occurring with the use of ispaghula husk, is common as already described under 4.1.2 Pharmacokinetics.

Uehleke *et al.* (2008) conducted a prospective observational study for 3 weeks to investigate whether the use of Ispaghula husks (3.5 g three times daily) in hypercholesterolemia is limited due to adverse effects on the gastrointestinal system. Forty-five of 62 patients enrolled in the study completed the study protocol. Four patients discontinued the study due to adverse reactions associated with Ispaghula husk. In week 1 most of the patients reported gastrointestinal symptoms and also gastrointestinal adverse reactions, which however, showed a decrease from week 1 to weeks 2 and 3 in the diaries. Only 3 of 54 patients had no symptoms in the first week. The number of symptom free patients increased to 11 during week 3. Adverse events considered related to study medication included 12 cases of flatulence, 11 cases of stomach pain, 8 incidents of bloating, 4 changes in bowel function, 2 incidents of nausea, one case of heartburn and one case of burping.

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

Oesophageal obstruction
Because of possible oesophageal obstruction associated with the use of psyllium laxatives in granular dosage form when taken without sufficient liquid, the FDA meanwhile prohibits the use of psyllium granules as "OTC"-product (Federal register 03/29/2007) and requires an approved application for marketing.

Concerning this matter adequate warnings are already included in the monograph.

Allergic adverse reactions
Ispaghula 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 (Rubira *et al.* 2000, Aleman *et al.* 2001, Khalili *et al.* 2003).

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

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

Summary of product characteristics

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

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

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

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

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

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

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

6.6
See 4.2

Package Leaflet

2. What you need to know before you use <X>
Do not use <Herbal medicinal product>:

if you allergic to *Plantago ovata* seeds or any of the other ingredients of this medicine (see in this section "Warnings and precautions" below)

(...)

Warning and precautions:

Talk to your doctor or pharmacist before taking <Herbal medicinal product>:

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

3. How to use <Herbal medicinal product>

(...)

(At the end of the paragraph describing the method of administration)
When preparing the product for administration it is important to try to avoid inhaling the powder.

4. Possible side effects

(...)

(At the end of the paragraph describing the possibility of allergic reactions)
Plantago ovata seeds contain substances which may lead to allergic reactions after use of the product by the oral route, contact with the skin or, in case of powder formulations, also by inhalation.

The allergic symptoms may include running nose, redness of the eye, difficulty in breathing, skin reactions, itching, and in some cases anaphylaxis (a sudden, generalised allergic reaction that may lead to life-threatening shock). Individuals manipulating the powder formulations routinely are more prone to these reactions (see section 2).

"Summary Assessment Report of the PhVWP July 2011
Association of allergic reactions with the inhalation of Plantago ovata seeds (ispaghula seeds) during prolonged occupational exposure

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

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

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

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

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

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

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

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

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

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

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

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

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

5.4. Interactions

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

Literature (Brunton 1990, Kay *et al.* 1978, Cummings 1978) mentions that absorption of minerals (calcium, iron, zinc), vitamins (B12), cardiac glycosides and coumarin derivatives 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 (Anderson *et al.* 1988). There was no influence on serum levels of minerals and vitamins in other studies (Bell *et al.* 1989, Sierra *et al.* 2002). Oliver (2000) 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

mineral and vitamin levels, and in some haematological and biochemical parameters. None of these were 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 (Brown *et al.* 1979), and no statistical effect on its plasma levels (Walan *et al.* 1977).

In one case report on a subject receiving a phenytoin/warfarin combination, ispaghula husk may have affected the subject's prothrombin ratio (Levine *et al.* 1984).

Ispaghula husk was reported to decrease the absorption of co-administered carbamazepine (Etman 1995) and lithium (Perlman 1990, D'Arcy 1990). 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 (Toutoungi *et al.* 1990).

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 (Liel *et al.* 1996). Twelve patients consuming unspecified quantities 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 & Sherman (1998) 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. Using non-isotopic measurement of absorption, the 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 suggested 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 diabetic patients it may be necessary to adjust the anti-diabetic therapy (see chapters 4.1.1 Effect on blood glucose level and 4.2.2 Hypoglycaemic effect). Therefore diabetic patients should take ispaghula husk only under medical supervision.

In 2012 Fernandez *et al.* (2012) reviewed the literature concerning interactions between drugs and *Plantago ovata* husk. They confirmed the possibility of the interactions mentioned above and included in the HMPC monograph. In addition, they described potential interaction with levodopa and carbidopa based on experimental studies in rabbits. These studies hypothesise that *Plantago ovata* husk could be beneficial in patients with Parkinson's disease. It regulates stool transit in the intestine and improves

levodopa pharmacokinetics when gastrointestinal peristalsis is slowed as common in many patients with Parkinson's disease. Such a clinical interaction was not reported so far. Therefore no additional labelling is considered.

5.5. Laboratory findings

No adequate data available

5.6. Safety in special populations and situations

Contraindications
Ispaghula husk is a bulk forming agent and several 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 defecate 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.

Warnings and precautions

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

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. (EMEA/HMPWP/60/2004)

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) and only under medical supervision.

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 1):
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 3):
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.

Use in pregnancy and lactation
There are limited amount of data (less than 300 pregnancy outcomes) from the use of ispaghula husk in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
The use of ispaghula husk may be considered during pregnancy and lactation, if necessary and if change of nutrition is not successful. Laxative bulk producers should be used before using other purgatives.

5.7. Overall conclusions on clinical safety

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

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

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

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

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

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

6. Overall conclusions

Ispaghula husk is a herbal medicinal product with well-established use (see also 4.3)

1) for the treatment of habitual constipation;

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

3) 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.

Indication 1: 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. The use as a laxative is substantiated by the pharmacological effects of ispaghula husk. The laxative effect of ispaghula husk is a mild one without severe side effects compared to those associated with stimulant laxatives.

Indication 2: In conditions in which easy defecation with soft stools is desirable, e.g. in case of painful defecation after rectal or anal surgery, anal fissures and haemorrhoids
The use in 'conditions in which easy defecation with soft stool is desirable' is scientifically substantiated by the well-established laxative effects. Specific clinical data are available concerning the antihaemorrhoidal effect of ispaghula husk and the positive effect after rectal/anal surgery.

Indication 3: 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 efficacy for the indication irritable bowel syndrome in general. There are seen some benefits for constipation predominant irritable bowel syndrome.

As an adjuvant to diet in hypercholesterolemia

The treatment with ispaghula husk results in average in a reduction of total cholesterol by nearly 5-10% and of LDL cholesterol by nearly 7% but without an effect on HDL. 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, only a minor claim as indication 3) is only scientifically supported.

Several recent investigations deal with the effect of ispaghula husk on cardiovascular risk, and metabolic syndrome risk factors in general. A general recommendation to reduce cardiovascular risk and/or metabolic syndrome risk cannot be included because well conducted studies with cardiovascular endpoints as main target parameter are missing.

The use is not recommended:

- in children below the age of 6 years for indication "treatment of habitual constipation and indication "use in conditions in which easy defecation with soft stool is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures and haemorrhoids" and

- in children below the age of 12 years for indication "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".

Laxative bulk producers should be used before using other purgatives if change of nutrition is not successful.

There are limited amount of data (less than 300 pregnancy outcomes) from the use of ispaghula husk in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. The use of ispaghula husk may be considered during pregnancy and lactation, if necessary and if change of nutrition is not successful. Laxative bulk producers should be used before using other purgatives.

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

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

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

Based on the clinical data mentioned above, it is not possible to recommend the specific indication diverticular disease. The indication "treatment of habitual constipation" covers constipation symptoms associated with diverticular disease.

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

The indication as an adjuvant in the symptomatic treatment of diarrhoea from various causes is not regarded as a well-established one. The degree of scientific interest seems to be low. The studies available are insufficient to prove the efficacy as an antidiarrhoeal agent. The underlying pharmacological principle is not clear.

Psyllium seems to be used in case of chronic diarrhoea, mainly. However "diarrhoea from various causes" as well as "chronic diarrhoea" are inadequate indications for simplified registration because these indications need a differential diagnosis and a monitoring by a medical doctor.

A traditional use is described for several other indications like catarrh and urethritis. But these are not plausible based on pharmacological data and no precise posology is available.

Annex

List of references