EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 May 2013
EMA/HMPC/599745/2012
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Plantago afra* L. et *Plantago indica* L., semen

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Plantago* afra L. (*Plantago psyllium* L.) or *Plantago indica* L. (*Plantago arenaria* Waldstein and Kitaibel), semen
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)

Psyllium seed consists of the ripe, whole, dry seeds of *Plantago afra* L. (*Plantago psyllium* L.) or *Plantago indica* L. (*Plantago arenaria* Waldstein and Kitaibel). The herbal substance has to comply with the monograph “Psyllium Seed” of the European Pharmacopoeia.

Psyllium seed only contains approximately 10 – 12% mucilage polysaccharides (Blaschek *et al.* 2003, Sharma & Koul 1986) in the epidermis, consisting of xylose, galacturonic acid, arabinose and rhamnose residues (Karawya *et al.* 1971).

- 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:	
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:	
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	only German Standard Marketing Authorisations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	few products; no detailed info. given
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
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:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'

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

1.3. Search and assessment methodology

The assessment report of the initial evaluation (EMEA/HMPC/167338/2006) reviewed the scientific data available for psyllium seed (*Plantago afra* L. et *Plantago indica* L., semen), primarily the clinical data. This report was prepared on the basis of the assessment report of ispaghula husk and ispaghula seed because available scientific data do not always differentiate precisely the investigated preparations i.e. whether the investigated herbal substance was ispaghula husk, ispaghula seed or psyllium seed and often indicate “psyllium” as the investigated herbal substance. If a differentiation was not possible the term “psyllium”: was used in the more recent investigations ispaghula husk was used predominantly. When ‘Plantago psyllium’ is mentioned, it is not sure whether the investigated herbal substance is *Plantago psyllium* or *Plantago ovata*.

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

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

2. Historical data on medicinal use

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

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

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

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

Well-established use

France

Pharmaceutical form:

- effervescent powder for oral suspension since 1988;
- powder for oral suspension since 1982;
- seeds since 1992

Indication: symptomatic treatment of constipation

Posology: daily 1 – 3 times one sachet with 7 g powder; daily 1 times 1 – 2 tablespoons of seeds

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

See section 2.1 and 4. Clinical Data.

3. Non-Clinical Data

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

Primary pharmacodynamics

Laxative effect

The active ingredients are the mucilages like in ispaghula husk and seed. The European Pharmacopoeia monograph requests that the swelling index should be 'not less than 10'. High-quality psyllium seeds are capable of absorbing 14 to 19 times their own weight of water (Blaschek *et al.* 2003, Sharma & Koul 1986).

The mode of action seems to be similar to that of ispaghula husk and seed. Psyllium seed increases the volume of intestinal contents by binding fluid, resulting in increased faecal weights and decreased viscosity of the luminal contents. This leads to a physical stimulation of the gut. The intraluminal pressure is decreased and colonic transit is accelerated. At the same time the swollen mass of mucilage forms a lubricating layer, which eases the transit of intestinal contents.

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

Secondary pharmacodynamics

Effect on blood lipids levels

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

Effect on blood glucose levels

There are no specific preclinical 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

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

MacKay *et al.* (1932) reported that, after 125 days on a diet containing 25% of psyllium seed, albino rats showed a dark pigmentation of the suprarenal gland, the kidney marrow and the liver. Dogs showed a grey colour of the kidneys after being fed a diet containing 25% of psyllium seed for 30 days. Similar effects have not been observed in humans (Block 1947). The pigment probably originates from the black pericarp of *Plantago afra*. When the seeds were extracted with hot water and then fed to the animals as whole seeds, no pigmentation was observed (MacKay *et al.* 1932).

3.4. Overall conclusions on non-clinical data

Non-clinical data are limited. The active ingredients are the mucilages like in ispaghula husk and seed. Therefore the mode of action seems to be similar to that of ispaghula husk and seed. The data available for ispaghula support the use as a laxative.

The non-clinical data on toxicology of psyllium seed preparations are insufficient, but up to now available data indicate no signals of toxicological concern. Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been published.

4. Clinical Data

4.1. Clinical Pharmacology

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

Laxative effect

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

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

Effect on blood lipids levels

There are no specific data available for psyllium seed.

Effect on blood glucose levels

Psyllium seed may influence the glucose metabolism in the same way as ispaghula husk and seed do. Due to delayed intestinal absorption of carbohydrates, the glucose metabolism is influenced by the reduction of peak levels of blood glucose.

Frati-Munari *et al.* (1985) performed three oral glucose tolerance tests in eight healthy volunteers as follows: I) glucose alone (control test), II) glucose mixed with 10 g of powder of "Plantago psyllium mucilage", and III) 10 g of mucilage were given 30 minutes before glucose. In the test with mucilage mixed with glucose, significant ($p<0.05$) lower peak of serum glucose and insulin were observed. Blood glucose was 20.5 +/- 22.1 mg/dl (1.13 +/- 1.22 mmol/l) lower at 60 minutes than control test, blood glucose was also lower 9.2 +/- 14.2 mg/dl (0.51 +/- 0.78 mmol/l) at 120 minutes in the same test, but did not reach statistical significance ($p>0.05$). Serum insulin values had a parallel course with glucose. Previous ingestion of the mucilage did neither modify basal nor subsequent glucose values.

Frati-Munari *et al.* (1989) assessed the effect of different doses of "Plantago psyllium mucilage" on glucose tolerance test. Four oral glucose tolerance tests were performed in eight healthy volunteers. Glucose load (75 g) was mixed with 0 (control test), 10, 20 and 30 g of mucilage. Serum glucose levels were measured at 0, 30, 60, 120 and 180 minutes. Maximum peak of glucose at 30 minutes, and the area under curve of glucose were significantly lower in the test with 20 and 30 g of mucilage than in the tests with 0 and 10 g. Blood glucose after additional ingestion of 20 g of mucilage was 11.8 +/- 14.3 mg/dl lower at 30 minutes than after ingestion of 10 g and 14.3 mg/dl +/- 16 mg/dl lower at 60 minutes ($p<0.05$). Blood glucose after additional ingestion of 30 g of mucilage was 6.1 +/- 5.3 mg/dl lower at 30 minutes than after ingestion of 20 g and 18 +/- 15.4 mg/dl lower at 30 minutes and 15 mg/dl +/- 17.1 mg/dl lower at 60 minutes than after ingestion of 10 g ($p<0.01$). There was a significant relationship ($r = 0.44$, $p<0.025$) between the dose of "Plantago psyllium mucilage" and its attenuating effect on hyperglycaemia.

Frati-Munari *et al.* (1998) evaluated the effect of acarbose and "Plantago psyllium mucilage" on the glycaemic index (GI) of bread. Twelve patients with non-insulin-dependent diabetes mellitus (NIDDM) and ten healthy volunteers were studied. Three meal tests with an intake of 90 g white bread (50 g of carbohydrates) were performed on each subject. In one test, 200 mg of acarbose was given, while 15 g of Plantago psyllium mucilage was given in another test, while only bread was ingested in the control test. Serum glucose and insulin concentrations were measured every 30 min from 0-180 min. Net area under curve (AUC) concentrations of glucose and insulin, GI (AUC glucose with bread plus treatment / AUC glucose with bread alone times 100) and insulin index (AUC insulin with bread plus treatment / AUC insulin with bread alone times 100) were calculated. In NIDDM patients, AUC glucose in the test with acarbose (1.9 +/- 0.7 mmol/l) and with Plantago psyllium (4.3 +/- 1.2 mmol/l) were significantly lower than in the control test (7.4 +/- 1.5 mmol/l) ($p<0.01$). The GI of bread plus acarbose was 26 +/- 13, and of bread with Plantago psyllium, 59 +/- 10 ($p<0.05$). AUC insulin and insulinic index behave similarly. In healthy individuals, AUC glucose and GI did not significantly change with the treatments; however, insulinic index with acarbose was 17 +/- 16 and with Plantago psyllium was 68 +/- 15 ($p<0.05$). The authors concluded that adding acarbose or Plantago psyllium to meals may reduce glycaemic index of carbohydrate foods and may help diabetic control.

In another publication Frati-Munari *et al.* (1983) investigated a *Plantago ovata* husk containing medicinal product, which they also defined as Plantago psyllium mucilage.

It is therefore not sure if the above-mentioned investigations are performed with ispaghula husk or psyllium seed.

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

The known ingredients of psyllium seed suggest that the mucilage polysaccharides are similarly structured as in *Plantago ovata*. Only the fraction of galacturonic acid and rhamnose is twice as high as in ispaghula husk. Psyllium seed does not contain starch contrary to ispaghula seed.

For data concerning absorption, metabolism and excretion, see corresponding chapters of the assessment report on *Plantago ovata* Forssk., seminis tegumentum (ispaghula husk). (EMA/HMPC/199775/2012)

The pharmacokinetics of psyllium are essentially those of an inert unabsorbed substance, with only small amounts of monosaccharides becoming available for systemic absorption through limited digestion of the few available α-linkages and fermentation by colonic bacteria.

4.2. Clinical Efficacy

4.2.1. Dose response studies

There are no dose-finding studies available.

As a laxative for adults, elderly and children over 12 years of age, experts (Commission E Monographs 1990) recommend 10 – 30 g daily in 1 – 3 single doses.

In France the recommended dosage for psyllium seed is daily 1 – 3 times 1 sachet with 7 g powder.

Considering that there are no clinical data indicating a definite daily dose, that psyllium seed has nearly 25% to 45% of the water-binding capacity of ispaghula husk (see above) and that the recommended dosage for ispaghula husk is 7 – 11 g in 1 – 3 single doses daily, this recommendation seems to be too low and has to be increased. The Committee on Herbal Medicinal Products (HMPC) therefore recommends a range of 25 – 40 g herbal substance or corresponding amount of herbal preparation as a daily dose and it should be taken in 3 single doses because the amount of the fluid administered with a single dose is otherwise too high.

4.2.2. Clinical studies (case studies and clinical trials)

Laxative effect

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

Weis (1996) administered a preparation made from “Plantago psyllium” (3 times 3.4 g daily) to 63 patients suffering from chronic functional constipation for a period of 20 days. The tolerance of the preparation was satisfactory in 55 patients (87%), including 49 (89%), who reported a favourable effect, i.e. problem-free defecation and regression or disappearance of meteorism. A statistically

significant decline of serum cholesterol occurred. In 14 patients (25%) a weight loss of more than 1 kg was observed. With regard to these facts, the author concluded that the preparation can be considered suitable for the treatment and probably also the prevention of chronic functional constipation and as an adjuvant in the treatment of hyperlipoproteinaemia type II, in particular when associated with obesity.

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) reported 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 psyllium seed as a laxative is mainly based on experts’ testimony and scientifically substantiated by the pharmacological data on ispaghula whose structure of mucilages may be similar to the structure of the mucilages of psyllium seed.

Effect on blood lipids levels

As already mentioned above, Weis (1996) detected a statistically significant decline of serum cholesterol in his uncontrolled study.

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

Laxative effect in children

There are numerous publications, which indicate that the potential health benefits of increased dietary fibre in childhood outweigh the potential risks, especially in highly industrialised countries (Williams *et al.* 1995). A review of the scientific literature by Williams *et* Bollela. (1995) suggested that a small loss of energy, protein, and fat may occur with a high intake of dietary fibre but that a moderate increase in dietary fibre is more likely to be healthy than harmful, especially in children with constipation. McClung *et al.* (1995) confirmed that only half of the children received the recommended amounts of dietary fibre intake. According to the recommendations from a conference on dietary fibre in childhood, children older than 2 years of age should increase their daily intake of dietary fibre (increased

consumption of a variety of fruits, vegetables, cereal and other grain product) to an amount equal or greater than their age plus 5 g (e.g. 8 g/day at age 3) (Williams *et al.* 1995).

Conclusion

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

In "Kinderdosierungen von Phytopharmaka" (Kooperation Phytopharmaka 2002), doses for children are calculated on the basis of the body weight, body height and the body surface and the daily dose for adults (10 to 30 g) indicated in the German monograph of the Commission E (Commission E Monographs 1990). The daily dose for children between 4 – 10 years of age ranges from 3.7 g to 15.2 g and for children between 10 – 16 years of age from 6.8 g to 23.3 g. This is in line with general recommendations that posology for children from 6 to 12 years of age correspond to half to two-thirds of the adult dose.

Given that the recommended dosage for adults has to be increased (see section 4.2.1.) because of the swelling index of psyllium seed in comparison to that of ispaghula husk, the recommended dosage for children is equally increased for the same reason.

The daily dose for children from 6 to 12 years of years recommended by the HMPC is therefore 12 – 25 g herbal substance or corresponding amount of herbal preparation, in 3 single doses.

Use during pregnancy and lactation

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

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

Greenhalf & Leonard (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 seed and husk as well as of psyllium seed and the known pharmacokinetics, that only small amounts of monosaccharides become available for systemic absorption (see section 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 psyllium seed should be used before using other purgatives.

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

Assessment during revision 1 according to the 'Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling' (EMEA/CHMP/203297/2005) would now lead to the wording "is not recommended", because non-clinical data are insufficient and no adequate data from the use of psyllium seed in pregnant women are available.

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

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

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

No fertility data are available".

Use in post-menopausal women

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

Conclusion

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

4.3. Overall conclusions on clinical pharmacology and efficacy

Indication 1: For the treatment of habitual constipation

The use of psyllium seed as a laxative is mainly based on experts' testimony and scientifically substantiated by the pharmacological data on ispaghula whose structure of mucilages may be similar to the structure of the mucilages of psyllium seed. The above-mentioned investigation is an uncontrolled study and the information provided is too limited to decide if the study was well-designed or not. Because of the different amount and swelling index, a higher dosage for psyllium seed than that of ispaghula is required as explained above.

It can be concluded that the use as a laxative is a well-established use. The clinical data on ispaghula support the use of psyllium seed as a laxative. As well-designed clinical studies are lacking, the current level of evidence[1] can be identified as level IV.

Indication 2: In conditions in which easy defecation with soft stools is desirable, e.g. in case of painful defecation after rectal or anal surgery, anal fissures and haemorrhoids
The use in conditions in which easy defecation with soft stool is desirable is scientifically substantiated by the well-known laxative effects but there are no specific data available. The level of evidence in this indication is therefore level IV.

The use is not recommended in children below the age of 6 years. Laxative bulk producers should be used before using other purgatives if change of nutrition is not successful.

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

When using the key word “psyllium” for literature search, a lot of publications concerning effect on different cardiovascular risk factors can be found. However, most of them assessed ispaghula husk. Therefore, these publications are included in the assessment report of ispaghula husk. (EMA/HMPC/199775/2012)

With regard to effects on blood lipids levels and blood glucose levels the clinical efficacy of psyllium seed is not proven. The clinical data available for ispaghula husk concerning lipids and mentioned in the assessment report on ispaghula husk cannot be extrapolated to ispaghula seed because the exact mechanism of action and the involved active ingredient are still unknown. As the clinical data are insufficient, it is not possible to recommend further specific indications.

5. Clinical Safety/Pharmacovigilance

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

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

5.2. Patient exposure

No adequate data available.

5.3. Adverse events and serious adverse events and deaths

Gastrointestinal adverse events

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

Bliss *et al.* (2011) compared the severity of adverse gastrointestinal symptoms during supplementation with dietary fibre or placebo over time in 189 adults with faecal incontinence in a randomised study. Subjects were given either placebo or a supplement of 16 g total dietary fibre per day from 1 of 3 sources: gum arabicum, psyllium, or carboxymethylcellulose. Severity of symptoms in all groups was minimal. A greater feeling of fullness in the 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.

[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)

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

Plantago ovata contains potent allergens. Because *Plantago afra* and *Plantago indica*belongs to the same plant family, it is assumed that they also contain allergens. Exposure to these allergens is possible through the oral route or through contact. Psyllium seed should be considered as a possible cause of anaphylaxis from laxatives. Reactions of hypersensitivity including anaphylaxis-like reactions may occur very rarely. Psyllium seed is not to be used by patients with known hypersensitivity to psyllium (Rubira *et al.* 2000, Alemán *et al.* 2001, Khalili *et al.* 2003).

In July and October 2011 the Pharmacovigilance Working Party (PhVWP) concluded that the product information of *Plantago ovata* seed- and also for *Plantago psyllium (scientific names: Plantago afra or Plantago indica)* 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).

Conclusion

The PhVWP describes that other species from this plant family, Plantago psyllium (scientific names: Plantago afra or Plantago indica), have the same properties and mode of action and that 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. Therefore the agreed wording is also included in the monograph on Plantago psyllium.

5.4. Interactions

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

There are no specific data on interactions between psyllium seed and other medicinal products. Because of the similar structure of the active ingredients of psyllium seed to that of ispaghula seed and husk, it is assumed that psyllium seed interacts with the same medicinal products as ispaghula husk. Resulting from the assessment of data on interactions available for ispaghula husk, the following information should be included in the product information of psyllium seed containing medicinal products:

- Enteral absorption of concomitantly administered medicines such as minerals (e.g. lithium), vitamins (B 12), cardiac glycosides, coumarin derivatives, and carbamazepine may be delayed. For this reason the product should not be taken ½ to 1 hour before or after intake of other medicinal products.
- Diabetic patients should take psyllium seeds only under medical supervision because adjustment of anti-diabetic therapy may be necessary.
- Use of psyllium seed concomitantly with thyroid hormones requires medical supervision because the dose of the thyroid hormones may have to be adjusted.

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

Bajorek & Morello (2010) reviewed the data available on the effects of dietary fibre and a low glycaemic index diet on glycaemic risk factors in people with type 2 diabetes mellitus with or without dyslipidaemia. The assessment was based on randomised controlled studies or meta-analysis. The authors showed that a daily dosage of psyllium 10.2 g significantly decreased all-day postprandial plasma glucose concentrations, although the decrease was perhaps due to a significantly decreased post lunch plasma glucose level. Psyllium's effect on the glycaemic risk factor glycosylated haemoglobin A1 ($A1_C$) is inconsistent between studies.

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

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

5.5. Laboratory findings

No adequate data available.

5.6. Safety in special populations and situations

Contraindications

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

Psyllium seed should not be used by patients with a sudden change in bowel habit that persists for more than 2 weeks, undiagnosed rectal bleeding and failure to defecate following the use of a laxative. Psyllium seed should also not be used by patients suffering from abnormal constrictions in the gastro-intestinal tract, with diseases of the oesophagus and cardia, potential or existing intestinal blockage (ileus), or megacolon.

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

Warnings and precautions

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

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

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

Furthermore the following advice should be given:

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

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

Use in pregnancy and lactation

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

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

5.7. Overall conclusions on clinical safety

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

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

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

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

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

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

6. Overall conclusions

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

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

The use of psyllium seed as a laxative is based on experts' testimony and scientifically substantiated by the pharmacological data available on the mucilages in ispaghula, which seem to have a similar structure to that of the mucilages in psyllium seed. It can be concluded that the use as a laxative is a well-established use. The clinical data on ispaghula support the use of psyllium seed as laxative.

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

The use is not recommended in children below the age of 6 years. Laxative bulk producers should be used before using other purgatives if change of nutrition is not successful.

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

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

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

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

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

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

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

Annex

List of references