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**COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)**

**ASSESSMENT REPORT ON
*PLANTAGO AFRA L., ET PLANTAGO INDICA L., SEMEN***

Herbal substance	<i>Plantago afra</i> L. (<i>Plantago psyllium</i> L.) or <i>Plantago indica</i> L. (<i>Plantago arenaria</i> Waldstein and Kitaibel), semen
Herbal preparation	Powdered herbal substance
Pharmaceutical forms	- Herbal substance for oral preparation - Herbal preparation in solid oral dosage forms such as granules and powders
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I. Introduction

This assessment report reviews the scientific data available for 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, use was made of the term “psyllium”. 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*.

The literature presented by the European Scientific Cooperative on Phytotherapy (ESCOP) and supporting the monograph “*Psyllii Semen*” (Psyllium seed) (ESCOP Monographs, second edition 2003) was also taken into account.

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

Psyllium seed is a natural substance and belongs to the bulk forming agents. It is used:

- a) for the treatment of habitual constipation,
- b) in conditions in which easy defaecation with soft stool is desirable, e.g. in cases of painful defaecation after rectal or anal surgery, anal fissures and haemorrhoids.

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

II. Clinical Pharmacology

II.1 Pharmacokinetics

Please refer to the assessment report on ispaghula husk.

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 (ref. 01/2005:0858).

Psyllium seed only contains approximately 10 – 12 % mucilage polysaccharides (2, 3) in the epidermis, consisting of xylose, galacturonic acid, arabinose and rhamnose residues (4). These ingredients suggest that the mucilage polysaccharides are similarly structured as in *Plantago ovata*. But the fraction of galacturonic acid and rhamnose is twice as high as in ispaghula husk. Psyllium seed does not contain starch as ispaghula seed does.

Conclusion

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.

II.2 Pharmacodynamics

II.2.1 Mode of action

- 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 (2, 3).

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.

- Effect on diarrhoea

There are no specific data available for psyllium seed.

- Effect on blood lipids levels

There are no specific pharmacological 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.

Fрати-Munari AC et al. 1985 (5) 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 not modify basal nor subsequent glucose values.

Fрати-Munari AC et al. 1989 (6) 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 ± 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 20g and 18 ± 15.4 mg/dl lower at 30 minutes and 15 ± 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 of hyperglycaemia.

Fрати-Munari AC et al. 1998 (7) evaluated the effect of acarbose and "Plantago psyllium mucilage" on 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, and 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 x 100) and insulin index (AUC insulin with bread plus treatment / AUC insulin with bread alone x 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) ($p < 0.01$). GI of bread plus acarbose was 26 +/- 13, and of bread with Plantago psyllium, 59 +/- 10 ($p < 0.05$). AUC insulin and insulin index behave similarly. In healthy individuals, AUC glucose and GI did not significantly change with the treatments; however, insulin 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 (8) **Frati-Munari AC** investigated Metamucil®, which he also defined as Plantago psyllium mucilage.

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

II.2.2 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.
- If the product is taken together with meals in the case of insulin dependent diabetics it may be necessary to reduce the insulin dose.
- Use of psyllium seed concomitantly with thyroid hormones requires medical supervision because the dose of the thyroid hormones may have to be adjusted.
- In order to decrease the risk of gastrointestinal obstruction (ileus) psyllium seed should only be used together with medicinal products known to inhibit the peristaltic movement (e.g. opioids, loperamide) under medical supervision.

III. Clinical Efficacy

III.1 Dosage

There are no dose-finding studies available.

As a laxative for adults, elderly and children over 12 years of age, experts (9) recommend 10 – 30 g daily in 1 – 3 single doses.

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.

III.2 Clinical studies

III.2.1 Laxative effect

Numerous clinical practice summaries, dating back to as early as 1935, recommended the use of fibre supplementation for the management and treatment of chronic constipation. Between 1976 and the present, numerous studies involving over 900 patients have been published; they evaluated the effects of psyllium intake on symptoms of constipation in a population specifically identified as “chronically constipated” and meeting the definition of less than three bowel movements per week for more than 3 months.

These studies were predominantly carried out with ispaghula husk; in other cases the investigated herbal substance was not exactly defined.

These studies are described in the assessment report on ispaghula husk.

Weis M 1996 (10) administered a preparation made from “Plantago psyllium” 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 defaecation 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.

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. 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.

III.2.2 Effect on blood lipids levels

As already mentioned above, **Weis M 1996** (10) detected a statistically significant decline of serum cholesterol in his uncontrolled investigation.

Conclusion

The clinical data are insufficient to mention a specific indication.

The clinical data available for ispaghula husk and mentioned in the assessment report on ispaghula husk cannot be extrapolated to psyllium seed because the exact mechanism of action and the involved active ingredient are still unknown.

III.3 Clinical studies in special populations

III.3.1 Use in children

There are numerous publications, which indicate that the potential health benefits of increased dietary fibre in childhood outweigh the potential risks, especially in highly industrialised countries (11). A review of the scientific literature by **Williams CL et al. 1995** (12) 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 (13). 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) (11).

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, use is not recommended in children below the age of 6 years.

In “Kinderdosierungen von Phytopharmaka” (14), 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 (9). 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 to 23.3 g. This is in line with general recommendations that posology for children from 6 to 12 years of age corresponds to half to two-thirds of the adult dose.

Given that the recommended dosage for adults has to be marked up (see chapter III.1 Dosage) because of the swelling index of psyllium seed in comparison to that of ispaghula husk, the recommended dosage for children is increased as well 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.

III.3.2 Use during pregnancy and lactation

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

Bishop C 1978 (15) concluded that bulk-forming laxatives appear to be safe and effective in pregnancy. The author referred to 2 studies which compared bulk-forming laxatives to irritant laxatives in antenatal women (see below).

Greenhalf JO et al. 1973 (16) stated that constipation was corrected in a higher percentage of patients using irritant laxatives but normalisation of bowel habit was similiar (statistically) in all groups (an

irritant, an emollient/irritant combination, a bulk forming/mild irritant combination, and a bulk forming agent). The side effects were higher in the irritant group than the bulk forming group.

Fianu S et al. 1975 (100) compared psyllium hydrophilic mucilloid (ViSiblin®) with irritant laxatives in 199 pregnant women (plus control patients) and observed no significant differences between irritant laxatives and psyllium. Psyllium when given to the mothers appeared to have had no effect on the defaecation of their new-born infants.

Conclusion

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

III.4 Traditional use

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

The use of *Plantago psyllium*, *Plantago ovata* and other kinds of *Plantago* in traditional medicine is similiar to the use of linseed, but such traditional use is not described as well and so consistently. Furthermore, no precise posology is mentioned.

None of the uses can therefore be accepted for inclusion in the ‘Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products’.

IV. Safety

IV.1. Preclinical Safety

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

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

IV.2 Clinical Safety

MacKay EM at al. 1933 (17) 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. Similiar effects have not been observed in humans (18). 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 (17).

In addition, please refer to the assessment report of ispaghula husk.

IV.2.1 Undesirable effects

Flatulence may occur with the use of psyllium seed.

Because *Plantago psyllium* and *Plantago ovata* belong to the same plant family, it is assumed that *Plantago psyllium* also contains 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.

IV.2.2 Contraindications

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

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

Furthermore it may be necessary to reduce the insulin dose, as mentioned under II.2. Interactions, if the product is taken together with meals by insulin dependent diabetic patients.

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 defaecate 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 esophagus and cardia, potential or existing intestinal blockage (ileus), paralysis of the intestine, or megacolon.

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

Psyllium seed should finally not be used by patients with known hypersensitivity to psyllium.

IV.2.3 Special warnings and precautions for use

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

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 72 hours or if abdominal pain occurs or in case 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.

IV.2.4 Interactions with other medicinal products and other forms of interactions

See chapter II.2.2.

V. Overall conclusions

Indication a): For the treatment of habitual constipation

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. As well-designed clinical studies are lacking, the current level of evidence¹ can be identified as level IV.

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

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

Superseded

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)