Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Agiolax 52%w/w, 2.2%w/w and 6.74-13.2%w/w Granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

5g of granules contain:

Ispaghula Seed	2.60g	(52% w/w)
Ispaghula Husk	110mg	(2.2% w/w)
Tinnevelly Senna Pods	340-660mg	(6.74-13.2% w/w)
(corresponding to 15 mg (0.3% w/w) of sennosides calculated as sennoside B)		

Exipients with known effect: includes sucrose 17.604 - 24.014% w/w
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules.

Small-grained, medium brown granules, with an aromatic odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Herbal medicinal product for short-term use in cases of occasional constipation.

4.2 Posology and method of administration

Posology:

Adolescents over 12 years, adults and elderly:
One or two 5 g measuring spoons once daily.
The maximum daily dose is equivalent to 30 mg hydroxyanthracene glycosides (calculated as sennoside B). This is equivalent to two 5 g measuring spoons of Agiolax.
The correct individual dose is the smallest required to produce a comfortable soft-formed motion.

Children:
Use in children below the age of 12 years is contraindicated (see section 4.3).

Duration of use:
Not to be used for more than 1 week (see section 4.4). Usually it is sufficient to take this medicinal product up to two to three times per week.

If the symptoms persist during the use of Agiolax, a doctor or a pharmacist should be consulted.

Method of administration:
For oral use.

Agiolax should be placed dry on the tongue and, without chewing or crushing, swallowed whole with an abundant amount of liquid (at least 150 ml for each 5g measuring spoon), i.e. water, milk, fruit juice or similar aqueous liquid; then maintain adequate fluid intake. A daily fluid intake of 1-2 litres is recommended.
Preferably taken in the evening but not immediately prior to bedtime.

An interval of half an hour to one hour should be kept after taking another medicinal product.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- pregnancy and lactation (see section 4.6 and 5.3)
- possible or existing bowel obstruction (ileus)
- abnormal narrowing (stenosis) of the gastroinstestinal tract, especially of the oesophagus and cardia
- intestinal atony
- megacolon
- acute inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis, appendicitis)
- abdominal pain of unknown origin,
- severe dehydration (with loss of fluid and electrolytes)
- difficult-to-control diabetes mellitus
- patients who have difficulty in swallowing or any throat problems
- children below 12 years of age

4.4 Special warnings and precautions for use

Like all laxatives, Agiolax should not be used by patients suffering from faecal impaction and undiagnosed acute or persistent gastro-intestinal complaints e.g. abdominal pain, nausea and vomiting, unless advised by a doctor, because these symptoms can be signs of potential or existing intestinal blockage (ileus).

Patients with hiatus hernia should take this medicine with caution.
If abdominal pain occurs or in cases of any irregularity of faeces, the use of Agiolax should be discontinued and medical advice must be sought.

Agiolax should always be taken with liquid. Take each 5g measuring spoon of Agiolax with at least 150 ml of water or similar aqueous fluid. Taking Agiolax without adequate liquid, the product may swell and obstruct the pharynx or oesophagus, creating the risk of suffocation. Intestinal obstruction may occur if adequate fluid intake is not maintained. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking Agiolax, seek immediate medical attention.

The treatment of debilitated patients requires medical supervision. The treatment of elderly patients should be supervised.

Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, should consult a doctor before taking Agiolax concomitantly.

If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of laxatives (more than 1 week) should be avoided.

If stimulant laxatives are taken for longer than a brief period of treatment, this may lead to impaired function of the intestine and dependence on laxatives.

Like all laxatives, Agiolax should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.

When Agiolax is administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces.

Patients with kidney disorders should be aware of possible electrolyte imbalance.

Excipients with known effect
Sucrose
Each 5 g measuring spoon of Agiolax contains approximately 1.04g of sucrose.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Agiolax should be taken at least ½ to 1 hour before or after taking other medicinal products as enteral absorption of concomitantly taken medicines such as minerals, vitamins (B12), cardiac glycosides, coumarin derivatives, carbamazepine and lithium may be delayed.

Diabetic patients should take Agiolax only under medical supervision because adjustment of anti-diabetic therapy may be necessary.

Use of Agiolax concomitantly with thyroid hormones requires medical supervision because the dose of the thyroid hormones may have to be adjusted.

Hypokalaemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides and interacts with antiarrhythmic medicinal products, with medicinal products which induce reversion to sinus rhythm (e.g. quinidine) and with medicinal products inducing QT-prolongation. Concomitant use with other medicinal products inducing hypokalaemia (e.g. diuretics, adrenocorticosteroids and liquorice root) may enhance electrolyte imbalance.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited data from the use of Agiolax in pregnant women. Studies in animals have shown a genotoxic risk of several anthranoids, e.g. emodin and aloe-emodin (see section 5.3). As a precautionary measure, Agiolax is contraindicated during pregnancy (see section 4.3).

Lactation
Metabolites, such as rhein, are excreted in breast milk in small amounts. A risk to the suckling child cannot be excluded. Agiolax is contraindicated during breast-feeding (see section 4.3).

Fertility
Studies on fertility have not been performed.

4.7 Effects on ability to drive and use machines

Agiolax does not affect the ability to drive or operate machinery.

4.8 Undesirable effects

Very rare (< 1/10000 patients affected), Agiolax may produce abdominal pain and spasm and passage of liquid stools, in particular in patients with irritable colon. However, these symptoms may also occur generally as a consequence of individual overdosage. In such cases dose reduction is necessary.
Very rare, abdominal distension and risk of intestinal or oesophageal obstruction and faecal impaction may occur, particularly if swallowed with insufficient fluid.
Very rare, hypersensitivity reactions (pruritus, urticaria, local or generalised exanthema) may occur.

Not known (cannot be estimated from the available data), flatulence may occur with the use of Agiolax, this generally disappears in the course of the treatment. Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.
Chronic use may lead to disorders in water equilibrium and electrolyte metabolism and may result in albuminuria and haematuria.
Furthermore, chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdose/abuse with Agiolax may cause abdominal discomfort, abdominal pain, flatulence, intestinal obstruction and severe diarrhoea with consequent losses of fluid and electrolytes. Diarrhoea may especially cause potassium depletion, which may lead to cardiac disorders and muscular asthenia, particularly where cardiac glycosides, diuretics, adrenocorticosteroids or liquorice root are being taken at the same time.

Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored and replaced, if necessary. This is especially important in the elderly.

Chronic ingested overdoses of anthranoid-containing medicinal products may lead to toxic hepatitis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Laxatives
ATC-code: A 06 AB 56

The active substance ispaghula seed/husk is capable of absorbing up to 10 times its own weight in water and acts by hydration in the bowel. Gut motility and transit rate can be modified by ispaghula through mechanical stimulation of the gut wall as a result of the increase in intestinal bulk by water and the decrease in viscosity of the luminal contents or by contact with rough fibre particles. When taken with a sufficient amount of liquid (at least 30 ml per 1 g Agiolax) ispaghula produces an increased volume of intestinal contents due to its highly bulking properties and hence a stretch stimulus, which triggers defaecation; at the same time the swollen mass of mucilage forms a lubricating layer, which makes the transit of intestinal contents easier.
The other active substance, senna pods contain 1,8-dihydroxyanthracene derivatives which possess a laxative effect. The β-O-linked glycosides (sennosides) are not absorbed in the upper gut; they are converted by bacteria of the large intestine into the active metabolite (rhein anthrone).

There are two different mechanisms of action:
1. stimulation of the motility of the large intestine resulting in accelerated colonic transit.
2. influence on secretion processes by two concomitant mechanisms viz. inhibition of absorption of water and electrolytes (Na^+, Cl^-) into the colonic epithelial cells (antiabsorptive effect) and increase of the leakiness of the tight junctions and stimulation of secretion of water and electrolytes into the lumen of the colon (secretagogue effect) resulting in enhanced concentrations of fluid and electrolytes in the lumen of the colon.
Defaecation takes place after a delay of 8 - 12 hours due to the time taken for transport to the colon and metabolisation into the active compound.

5.2 Pharmacokinetic properties

The active substance ispaghula seed / husk hydrates and swells to form a mucilage because it is only partially solubilised. Polysaccharides, such as those which dietary fibres are made of, 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 ß-linkages, which cannot be broken by human digestive enzymes.

Less than 10 % of the mucilage gets hydrolysed in the stomach, with formation of free arabinose. Intestinal absorption of the free arabinose is approximately 85 % to 93 %.

To varying degrees, dietary fibre is fermented by bacteria in the colon, resulting in production of carbon dioxide, hydrogen, methane, water, and short-chain fatty acids, which are absorbed and brought into the hepatic circulation. In humans, psyllium reaches the large bowel in a highly polymerised form that is fermented to a limited extent, resulting in increased faecal concentration and excretion of short-chain fatty acids.

The β-O-linked glycosides (sennosides) of the active substance senna pods are neither absorbed in the upper gut nor split by human digestive enzymes. They are converted by the bacteria of the large intestine into the active metabolite (rhein anthrone). Aglyca are absorbed in the upper gut. Animal experiments with radio-labeled rhein anthrone administered directly into the caecum demonstrated absorption < 10%. In contact with oxygen, rhein anthrone is oxidised into rhein and sennidins, which can be found in the blood, mainly in the form of glucuronides and sulphates.

After oral administration of sennosides, 3 - 6% of the metabolites are excreted in urine; some are excreted in bile. Most of the sennosides (ca. 90%) are excreted in faeces as polymers (polyquinones) together with 2 - 6% of unchanged sennosides, sennidins, rhein anthrone and rhein. In human pharmacokinetic studies with senna pods powder (20 mg sennosides), administered orally for 7 days, a maximum concentration of 100 ng rhein/ml was found in the blood. An accumulation of rhein was not observed. Active metabolites, e.g. rhein, pass in small amounts into breast milk. Animal experiments demonstrated that placental passage of rhein is low.

5.3 Preclinical safety data

There are only data available for ispaghula husk and psyllium without defining the exact test preparation.

Single dose toxicity
The acute toxicity of senna pods, specified extracts thereof, as well as of isolated sennosides, was low after oral administration in rats and in mice.

Subchronic toxicity
Psyllium was fed to rats at levels high as 10 % of the diet for periods up to 13 weeks (three 28-day studies, one 13-week study). Psyllium consumption ranged from 3,876 to 11,809 mg/kg/day. Because the absorption of psyllium is very limited, histopathological evaluations were limited to the gastrointestinal tract, liver, kidneys and gross lesions without observing any treatment-related effect. Effects considered to be biologically significant and related to psyllium supplementation were lower serum total protein, albumin, globulin, total iron-binding capacity, calcium, potassium, and cholesterol; and 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 psyllium fed rats may give evidence that there are no adverse effect of psyllium on protein metabolism.

Genotoxicity and carcinogenicity
Tests on genotoxicity and carcinogenicity have not been performed with Agiolax.

Most data refer to senna pod extracts containing 1.4 to 3.5% of anthranoids, corresponding to 0.9 to 2.3% of potential rhein, 0.05 to 0.15% of potential aloe-emodin and 0.001 to 0.006% of potential emodin or isolated active constituents, e.g. rhein or sennosides A and B. As a result of investigations with parenteral application in mice, extracts are supposed to possess a higher toxicity than purified glycosides, possibly due to the content of aglyca. In a 90-day rat study, senna pods were administered at dose levels from 100 mg/kg of up to 1,500 mg/kg. The tested drug contained 1.83 % sennosides A-D, 1.6 % potential rhein, 0.11 % potential aloe-emodin and 0.014 % potential emodin. In all groups epithelial hyperplasia of the large intestine of minor degree was found and was reversible within the 8-week recovery period. The hyperplastic lesions of the forestomach epithelium were reversible as well. Dose-dependent tubular basophilia and epithelial hypertrophy of the kidneys were seen at a dose of, or greater than 300 mg/kg per day without functional affection. These changes were also reversible. Storage of a brown tubular pigment led to a dark discoloration of the renal surface and still remained to a lesser degree after the recovery period. No alterations were seen in the colonic nervous plexus. A no-observable-effect-level (NOEL) could not be obtained in this study.

A 104-week study on rats of both genders did not reveal any carcinogenic effects with the same senna pods preparation at oral dosages of up to 300 mg/kg.

In long term carcinogenicity studies with senna pods effects on kidneys and colon/caecum were reported. In addition a specified senna extract given orally for 2 years was not carcinogenic in male or female rats. The extract investigated contained approximately 40.8% of anthranoids from which 35% were sennosides, corresponding to about 25.2% of potential rhein, 2.3% of potential aloe-emodin and 0.007% of potential emodin and 142 ppm free aloe-emodin and 9 ppm free emodin.

Further 2-year studies on male and female rats and mice with emodin gave no evidence of carcinogenic activity for male rats and female mice, and equivocal evidence for female rats and male mice.

Sennosides displayed no specific toxicity when tested at doses up to 500 mg/kg in dogs for 4 weeks and up to 100 mg/kg in rats for 6 months.
There was no effect on male or female fertility in rats. Data for herbal preparations are not available.

Senna pods, extracts thereof and several hydroxyl anthracene derivatives (except sennosides, rhein and sennidins) were mutagenic and genotoxic in several in vitro test systems. However, for senna and aloeemodin this was not proven in in vivo systems.
In long term carcinogenicity studies with senna pods effects on kidneys and colon/caecum were reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Caraway Oil
Sage Oil
Peppermint Oil
Acacia
Talc
Iron Oxide, red (E172)
Iron Oxide, yellow (E172)
Iron Oxide, black (E172)
Hard Paraffin
Liquid Paraffin
Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
Once opened, shelf-life is 6 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

The 250g size is a composite container, cylindrical in shape with an inner lid and a screw cap both made of PP. The container consists of paper, aluminium foil and inner lacquer of PVDC/PVCA with a base consisting of a tin plate.

The 400g size is comprised of a rectangular container with rounded edges. The container body consists of three layers of chip paper with an internal protective lacquer laminate – the pack is preserved with a sealed aluminium membrane. The push-in lid is made of HDPE and the base consists of an electrolytically tin-coated tin plate 0.19mm in thickness. The container measures 121mm in height × 100mm in width ×64mm in depth.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Madaus GmbH
51101 Cologne
Germany

8 MARKETING AUTHORISATION NUMBER

PA1288/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 January 1996

Date of last renewal: 03 January 2011

10 DATE OF REVISION OF THE TEXT

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