Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Linoforce granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose [4.1 g] (one level measuring spoon) contains:
1.76 g of *Linum usitatissimum* L., semen (Linseeds, whole),
0.43 - 0.70 g of *Cassia senna* L. and/or *Cassia angustifolia* Vahl, folium (Senna leaves, comminuted)
36 - 58 mg of *Rhamnus frangula* L., cortex (Frangula bark, comminuted),

corresponding to 20.5 mg of hydroxyanthracene derivatives, calculated as sennoside B.

Excipient with known effect:
One dose (4.1g) contains 480 mg sucrose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules
Linoforce is a glossy granulate of dark brown colour with an odour of vanillin and a sweetish taste.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Traditional herbal medicinal product for the short term relief of occasional constipation exclusively based on long-standing use.

This product is indicated for use in adults and adolescents over 12 years.

4.2 Posology and method of administration

Posology
Adults, older people and adolescents over 12 years: One level measuring spoon (4.1g), administered in a single dose at night with a glass of water or other liquid.

The recommended dose is equivalent to 20.5 mg of hydroxyanthracene derivatives expressed as sennoside B. The use in children under 12 years of age is contraindicated (see section 4.3 Contraindications).

Duration of use
If condition worsens or symptoms persist during the use of Linoforce or for more than 1 week, a doctor should be consulted. Prolonged continuous use is not recommended.

Method of administration
For oral use only.

The maximum daily dose of hydroxyanthracene glycosides is 30 mg. This is equivalent to 6 g of Linoforce. The pharmaceutical form of Linoforce allows the administration of smaller doses. The correct individual dose is the smallest required to produce a comfortable soft-formed motion.

The laxative effect occurs about 6-12 hours after oral administration and therefore the best administration time is at night to obtain the desired effect in the morning. Normally it is sufficient to take this medicinal product up to two to three times a week.

4.3 Contraindications

Do not use in cases of known hypersensitivity to any of the active ingredients, to plants of the Rhamnaceae or Linaceae families or to any of the excipients.

Melanorrhoea, potential or existing intestinal blockage (ileus), paralysis of the intestine or megacolon.

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.

Abnormal constrictions in the gastro-intestinal tract, with diseases of the oesphagus and cardia.

Patients who have difficulty swallowing or have throat problems.

Linoforce is contraindicated in cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis), abdominal pain of unknown origin, severe dehydration state with water and electrolyte depletion.

Do not use during pregnancy or lactation.

Children under 12 years of age.

4.4 Special warnings and precautions for use

Chronic abuse may cause hypokalaemia leading to risk of potentiation of the action of cardiac glycosides and interactions with antiarrhythmic medicinal products and medicinal products inducing QT-prolongation. Concomitant use with other medicinal products inducing hypokalaemia e.g. diuretics, adrenocorticosteroids or liquorice root may further result in electrolyte imbalance.

Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, have to consult a doctor before taking this product concomitantly.

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

If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of laxatives 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. Linoforce should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.

When administering this product 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.

If abdominal pain occurs or in cases of any irregularity of faeces, the use of this product should be discontinued and medical advice sought.

If condition worsens or symptoms persist during the use of Linoforce or for more than 1 week, a doctor should be consulted.

Prolonged continuous use is not recommended.

Take Linoforce with at least 150 ml of water or similar aqueous fluid. Taking this product without adequate fluid, may cause it to swell and block your throat or oesophagus and may cause choking. 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 this product, seek medical attention immediately. The treatment of debilitated patients and elderly should be supervised.

Investigations in healthy women suggest that linseed may have an oestrogenic effect, use of this product is therefore not recommended in women with hormonally dependent tumours.

Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.

This medicinal product contains 480 mg of sucrose per measuring spoon (4.1 g). 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

Enteral absorption of concomitantly administered medicines may be delayed by bulk forming laxatives such as Linoforce granules. For this reason Linoforce granules should not be taken ½ to 1 hour before or after intake of other medicinal products.

In order to decrease the risk of gastrointestinal obstruction (ileus), this product should only be used together with medicinal products known to inhibit peristaltic movement (e.g. opiods, loperamide) under medical supervision.

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 in case of abuse enhance electrolyte imbalance.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no reports of undesirable or damaging effects during pregnancy and on the foetus when used at the recommended dosage.

However, as a consequence of experimental data concerning a genotoxic risk of several anthranoids, e.g. aloe-emodin, emodin, frangulin, chrysophanol and physcion, the use is to be avoided during the first trimester and is not recommended in other phases of pregnancy.

Lactation
Use during breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in breast milk.

After administration of other anthranoids, active metabolites (such as rhein) are excreted in breast milk in small amounts. A laxative effect in breast fed babies has not been reported.

Fertility
Studies on fertility have not been carried out.

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties Linoforce is likely to have no influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Hypersensitivity reactions (pruritus, urticaria, local or generalised exanthema) may occur. The frequency is not known.

Meteorism occurring with the use of this product is common.

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.

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.

Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.

If other adverse reactions not mentioned above occur, a qualified healthcare professional e.g. a doctor or pharmacist should be consulted.

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, Earlsfort Terrace, IRL - Dublin 2; Tel +353 1 6764971; Fax +353 1 6762517; Website: www.hpra.ie; email: medsafety@hpra.ie.

4.9 Overdose

The major symptoms of overdose / abuse are griping pain and severe diarrhoea with consequent losses of fluid and electrolytes, which should be replaced. 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.

Abdominal discomfort, flatulence and possibly intestinal obstruction may occur.

Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. 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: contact laxatives
ATC-code: A 06 AB

Sennae folium and Frangulae cortex
The action of the actives Sennae folium and Frangulae cortex is due to the content of 1,8-dihydroxyanthracene derivatives (mainly sennosides, frangulins, glucofrangulins), which possess a laxative effect.

Glucofrangulins (O-diglycosides), frangulins (O-monoglycosides) and sennosides (β-O-glycosides) are neither absorbed as such nor largely split by human digestive enzymes in the upper gut and therefore are not absorbed to a large extent. They are converted by the bacteria of the large intestine into the active aglyca (glucofrangulins / frangulins: emodin-9-anthrone, sennosides: rhein anthrone).

Defaecation takes place after a delay of 8 – 12 hours due to the time taken for transportation to the colon and metabolisation into the active compound.

There are two different mechanisms of action:
1. Stimulation of the motility of the large intestine resulting in accelerated colonic transit. The motility effects are mediated by direct stimulation of colonic neurons and possibly by prostaglandins.
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.

Lini semen

Lini semen contributes to the overall action via hydration, which increases faecal volume, and softens intestine content as well as via the content of mucilage, which may act as a lubricant.

The seeds contain nearly 25 % of bulk materials (3 – 6 % of mucilage, 4 – 7 % of alimentary fibres). The laxative effects of linseed have long been recognised empirically and shown in animal and clinical investigations. These effects are attributed to the bulk materials and in particular to the mucilage that binds with water and swells to form a demulcent gel in the intestine. Water is held back in the intestine due to the swelling of the mucilage. Faeces become softer. The volume of the intestinal content increases and causes a stretch stimulus, which results in a decrease in transit time. The swollen mass of mucilage forms a lubrication layer facilitating the transit of intestinal content.

In addition, under the action of intestinal bacterial flora, the mucilage may be converted to short-chain fatty acids (SCFA) and metabolites of lignans genuinely contained in the seed in enterolignans. Both classes of constituents can exert a protective effect on the large bowel wall.

The laxative effect of linseeds usually occurs within 12 to 24 hours.

The use of linseed as a laxative is made plausible by information from clinical studies and pharmacological data. The use in conditions, in which easy defaecation with soft stool is desirable, is scientifically substantiated on the basis of the laxative effects but there are no special data available.

5.2 Pharmacokinetic properties

Sennae folium and Frangulae cortex
The β-O-linked glycosides from *Senna* and *Frangula* are not split by human digestive enzymes and therefore are not absorbed in the upper gut to a large extent. They are converted by the bacteria of the large intestine into the active aglyca (glucofrangulins / frangulins: emodin-9-anthrone, sennosides: rhein anthrone). The 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 antron 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.

After oral administration of frangula bark extract, rhein, emodin and traces of chrysophanol are found in human urine.

After administration of anthranoids, active metabolites, such as rhein, pass in small amounts into breast milk. Animal experiments demonstrated that placental passage of rhein is low.

Lini semen
One part of the bulk materials in linseed is defaecated, the other part is fermented in the colon by bacteria. This process of fermentation can produce gas and flatulence. The predominant products of fermentation are short chain fatty acids (SCFA), which are mainly resorbed and can act as nutrients for cells of the colonic mucosa. Other constituents that are metabolised by the intestinal bacteria are lignans, such as secoisolariciresinol diglucoside, generating enterolignans such as enterodiol and enterolactone.

5.3 Preclinical safety data

Sennae folium
Since the spectrum of constituent of Senna leaf and fruit is comparable the data can be transferred to Senna leaves. Most data refer to extracts of Senna pods 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.

The acute toxicity of Senna pods, specified extracts thereof, as well as of sennosides in rats and mice was low after oral treatment.

As a result of investigations with parenteral applications 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 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.

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.

An extract and aloe-emodin were mutagenic in *in vitro* tests, sennoside A, B and rhein gave negative results. Comprehensive *in vivo* examinations of a defined extract of Senna pods were negative.

In vivo studies of Senna herbal substance in rat hepatocytes (chromosome aberration test, mouse spot test, *in vivo/in vitro* UDS (unscheduled DNA synthesis) showed no evidence of any genetic effects.

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.

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.

There is no evidence of any embryo lethal, teratogenic or foetotoxic actions in rats or rabbits after oral treatment with sennosides. Furthermore, there was no effect on the postnatal development of young rats, on rearing behaviour of dams or on male and female fertility in rats. Data for herbal preparations are not available.

Frangulae cortex
There are no studies on single dose toxicity, on repeated dose toxicity, on reproductive toxicity or on carcinogenicity.

Experimental data, mainly *in vitro* tests showed a genotoxic risk of several anthranoids in the Salmonella microsome assay, emodin, chrysophanol and physcion were weakly mutagenic. No mutagenic effects were observed in the V79-HGPRT mutation assay and in the unscheduled DNA synthesis (UDS) assay for chrysophanol and physcion. Emodin was highly mutagenic in the V79-HGPRT mutation assay. In the UDS assay emodin was a strong inducer of UDS in primary hepatocytes. Emodin was also tested with respect to its transforming activity in C3H/M2 mouse fibroblasts *in vitro*. In the *in vitro* salmonella/microsome mutagen test and the deoxyribonucleic acid (DAN) repair test of primary rat hepatocytes emodin and frangulin, an alcoholic extract of "Rhamnus frangula", and a commercial Frangula bark preparation showed a dose-dependent increase in the mutation rate or the induction of DNA repair.

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.

Hydroxyanthracene laxative use, as a risk factor in colorectal cancer (CRC), was investigated in some clinical trials. Some studies revealed a risk for CRC associated with the use of anthraquinone-containing laxatives, some studies did not. However, a risk was also revealed for constipation itself and underlying dietary habits. Further investigations are needed to assess the carcinogenic risk definitely.

Lini semen
Linseed contains 20-50 mg cyanide / 100 g in form of the cyanogenic diglycosides linustatin, neolinustatin and small amount of the monoglucoside linamarin. Neither a single dosage of 100 g linseed nor a chronic dose of 45 – 50 g daily for 4 –6 weeks cause intoxication signs in man.

The enzyme thiosulphate sulphur transferase (rhodanase) catalyzes the change of cyanide into thiocyanate (rhodanide), which is 200 times less toxic than cyanide. The chronic use of linseed causes accumulation of thiocyanate, which can be compared with the blood level of thiocyanate in heavy smokers.

Investigations in healthy women suggest that there might be an oestrogenic effect of linseed due to the lignan-precursors in linseed, which are converted to mammalian- lignans and might interfere with the metabolism and activity of oestrogens.

Linoforce
No mutagenic effects of Linoforce were detected in Ames' test (with or without metabolic activation).

Tests on reproductive toxicity and carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Talc
Sucrose
Calcium carbonate
Acacia, spray dried
Red iron oxide
Calcium lactate pentahydrate
Black iron oxide
Vanillin
Ginger oil
Beeswax, yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Cardboard can laminated inside with aluminium and sealed with a tear-off aluminium membrane and LDPE closure. The bottom is made of a tin plate coated with varnish.

Included in the packaging is a measuring spoon made of polystyrene for one dose of 4.1 g.

The package leaflet is inserted between the polyethylene lid and the upper aluminium seal.

Pack size: 70 g

6.6 Special precautions for disposal

No special requirements.

7 REGISTRATION HOLDER

A. Vogel Ireland Limited
48 Upper Drumcondra Road

Dublin 9
Ireland

8 REGISTRATION NUMBER(S)

TR2309/006/001

9 DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

Date of first registration: 9th May 2014
Date of last renewal: 8th May 2019

10 DATE OF REVISION OF THE TEXT

April 2019
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