PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

LINOFORCE

COMPLEMENTARY MEDICINE

Western Herbal Medicine

This unregistered medicine has not been evaluated by the South African Health Products Regulatory Authority for its quality, safety or intended use.

SCHEDULING STATUS

S0

1 NAME OF THE MEDICINE

A.VOGEL LINOFORCE (granules)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 Dose (4,1 g) contains:

Linum usitatissimum L. (Linseed) [Whole seeds]	..... 1,76 g
Cassia senna L. and/or *Cassia angustifolia* VAHL [Leaves, comminuted]	..... 0,43 – 0,70 g
Rhamnus frangula L. (Frangula) [Bark, comminuted]	..... 36 – 58 mg

Corresponding to 20,5 mg of hydroxyanthracene derivatives, calculated as sennoside B.

Contains sugar: Sucrose ..... 480 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dark brown, coated, glossy granules with an aromatic odour of vanillin and a slightly sweet taste.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

A.VOGEL LINOFORCE is a herbal medicine that supports healthy bowel motion in those with constipation. It contains ingredients that support digestion, prevent cramping and act as a laxative.

4.2 Posology and method of administration

Posology

Adults and children over 12 years:

1 Full teaspoon (approximately 4,1 g) in the evening.
(The recommended dose is equivalent to 20,5 mg of hydroxyanthracene derivatives expressed as sennoside B).

Special populations

Elderly population:

No dosage adjustment is required for this population.

Paediatric population:

This product is not indicated in children younger than 12 years.

Method of administration

For oral use only.
Take A.VOGEL LINOFORCE with at least 150 ml of water or similar aqueous fluid.

The maximum daily dose of hydroxyanthracene glycosides is 30 mg. This is equivalent to 6 g of A.VOGEL LINOFORCE. The pharmaceutical form of A.VOGEL 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

- A.VOGEL LINOFORCE should not be used in patients who have a hypersensitivity to the active substances, to plants of the *Rhamnaceae* or *Linaceae* families or to any of the excipients listed in section 6.1.
- 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.
- 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.
- A.VOGEL LINOFORCE should not be taken 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).
- 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. A.VOGEL LINOFORCE should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.
- Patients with kidney disorders should be aware of possible electrolyte imbalance.
- If the condition worsens or does not improve after 1 - 2 weeks, a doctor, pharmacist or other healthcare professional should be consulted.
- Take A.VOGEL 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 immediately medical attention. The treatment of debilitated patients and elderly should be supervised.
- Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.

Sucrose warning:
A.VOGEL LINOFORCE contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.
Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take A.VOGEL LINOFORCE.

4.5 Interaction with other medicines and other forms of interaction

- In case of abuse, stimulant laxatives may reduce intestinal transit time and can affect the absorption of other oral medicines administered simultaneously, i.e. when taken in dosages provoking diarrhoea.
- Hypokalaemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides, interacts with antiarrhythmic medicinal products and 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

Women of childbearing potential/Contraception in males and females

No information available.

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.
A.VOGEL LINOFORCE should only be used under medical supervision intermittently and if other actions such as behavioural modification, dietary changes and use of bulk forming agents failed.

Breastfeeding

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
Fertility studies have not been performed.

4.7 Effects on ability to drive and use machines
A.VOGEL LINOFORCE has no known effect on mental and/or physical ability to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects
Adverse reactions are grouped into the following frequency classifications: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be assessed from the available data)

Tabulated list of adverse reactions

Body System	**Undesirable effect** (Frequency not known)
Immune system disorders:	Hypersensitivity reactions (pruritus, urticaria, local or generalised exanthema) may occur.
Metabolism and nutrition disorders:	Chronic use may lead to disorders in water equilibrium and electrolyte metabolism and may result in albuminuria and haematuria.
Gastrointestinal disorders:	In patients with irritable colon, A.VOGEL LINOFORCE may produce meteorism, abdominal pain / spasm and passage of liquid stool. However, these symptoms may also occur generally as a consequence of individual overdosage. In such cases dose reduction is necessary. Chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when treatment is stopped.
Renal and urinary disorders:	Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
In overdosage, side effects can be precipitated and/or be of increased severity (see section 4.8).
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.
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
D33.6 Western Herbal Medicine
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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-labelled 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 glucoronides 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 fetotoxic 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 an 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) catalyses 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.

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

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

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

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months unopened.

6.4 Special precautions for storage
Store at or below 25 °C in a cool, dry place.
Store in the original package/container.

6.5 Nature and contents of container
Packed in a HDPE plastic container with a tamper evident seal and a plastic screw cap.

Pack sizes: 105 g and 250 g.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product
A.VOGEL LINOFORCE granules must be taken with at least 150 ml (a glass) of water, preferably before bedtime, for the described dose of one full teaspoon (approx. 4,1 g).

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION
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To be allocated.

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