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Evaluation of Medicines for Human Use

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ASSESSMENT REPORT ON *LINUM USITATISSIMUM* L., SEMEN

Herbal substance	*Linum usitatissimum* L., semen
Herbal preparation	Mucilaginous preparation of the dried ripe seeds
Pharmaceutical forms	- Herbal substance for oral preparation - Mucilaginous preparation of the herbal substance for oral preparation
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TABLE OF CONTENTS

I. INTRODUCTION

This assessment report reviews the scientific data available for linseed (*Linum usitatissimum* L., semen), primarily the clinical data.
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 (62). The most commonly used laxatives are either stimulant laxatives (containing e.g. anthracenic derivates from senna, frangula or cascara), lubricant laxatives (e.g. mineral oils) or bulk forming agents such as linseed.

Linseed is a natural substance and belongs to the bulk forming agents. It is used for the treatment of habitual constipation or in conditions in which easy defaecation with soft stool is desirable. These indications are medically substantiated by the pharmacological effects of linseed. Linseed preparations have to be regarded as herbal medicinal products with a "well-established medicinal use" in these indications 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.

The use as a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort is regarded as a traditional use. This use is plausible, attributed to the protective effect on the mucosa by the coating action of the mucilage.

The traditional use as a poultice for the symptomatic treatment of minor skin inflammations is also described in the literature (12, 24, 29, 42, 46, 47). There are however insufficient data that can clarify the main pharmacological properties. Therefore the use as a poultice cannot be regarded as plausible.

II. CLINICAL PHARMACOLOGY

II.1 Pharmacokinetics

Linseed consists of the dried, ripe seeds of *Linum usitatissimus* L. (26). The herbal substance has to comply with the monograph "Linseed" of the European Pharmacopoeia (ref. 04/2005:0095).

The seeds contain nearly 25 % of bulk materials (3 – 6 % of mucilage, 4 – 7 % of alimentary fibres), 30 – 45% fatty oil, 20 – 27 % proteins, 3 – 5 % minerals, vitamins, lignan percursors, linustatin, neolinustatin and linamarin, enzymes. The content of water is 5 – 14 % (16, 22, 80).

One part of the bulk materials in linseed is defaecated, the other part is fermentated in the colon by bacteria (9). This process of fermentation can produce gas and lead to flatulence (32). The predominant products of fermentation are short-chain fatty acids (SCFA), which are mainly resorbed (16). These acids can serve as nutrients for those cells forming the colonic mucosa (14).
In general investigations with fibres show that a key marker of fermentation is an increase in the concentration of short-chain fatty acids. In monogastric species such as horse, pig and rat, there is evidence to support the view that the main site of fermentation of non-cellulose polysaccharides is the caecum and large intestine based mainly on the finding of high concentrations of volatile fatty acids. In man the presumed site of fermentation must also be the large bowel, since food residues take 18 – 68 hours to pass through, thus allowing time for digestion. In addition, high concentrations of volatile fatty acids are found in human faeces, and the colon contains a luxuriant mixed culture of anaerobic micro-organisms that are able to break down certain polysaccharides. While it is likely that the colon will prove to be the main site of fermentation, it is uncertain to what extent other parts of the gut, notably the stomach and the terminal ileum, contribute to this process (32).

Linseed usually acts within 12 to 24 hours. Sometimes the maximum effect is not reached before 2 to 3 days (45).
Since lignans and isoflavonoid phyto-oestrogens, produced from plant precursors by colonic bacteria, may be associated with protection against certain cancers, the effects of linseed ingestion on urinary lignans and isoflavonoids were investigated.

In a randomised crossover study with 18 premenopausal women, urinary excretion of the two major mammalian lignans, enterodiol and enterolactone, increased with linseed supplementation (10 g/day for 3 cycles) from 1.09 +/- 1.08 and 3.16 +/- 1.47 to 19.48 +/- 1.10 and 27.79 +/- 1.5 µmol/day respectively ($p<0.0002$). Enterodiol and enterolactone excretion in response to linseed varied among the subjects (3- to 285-fold). Excretion of isoflavonoids or the lignan matairesinol did not change. Excretion was not altered by phase of the menstrual cycle or duration of linseed consumption (55). In 13 of these women the excretion in faeces was investigated, too. The excretion of lignans increased significantly, from 80.0 +/- 80.0 to 2560 +/- 3100 for enterodiol ($p<0.01$), from 640 +/- 480 to 10,300 +/- 7580 for enterolactone ($p<0.01$), and from 7.33 +/- 10.0 to 11.9 +/- 8.06 nmol/day for matairesinol ($p<0.05$). There were no differences in faecal excretion of isoflavonoids (54).
In another randomised crossover study, 9 healthy young women supplemented their diets with 5, 15 or 25 g of raw or 25 g of processed (as muffins or bread) linseed for 7 days during the follicular phase of their menstrual cycles. A dose-dependent increase in urinary lignan excretion in response to linseed was observed and processing did not affect the quantity of lignan excretion. Plasma lignan concentrations were significantly greater than baseline ($p\leq 0.001$) by 9 hours after linseed ingestion. The total plasma AUC was higher on the 8th than on the 1st day (58).

The linseed oil is exceptionally rich in alphalinolenic acid that may be associated with a preventive effect against cancer and cardiovascular diseases. The daily food supplementation with ground linseed of 1.3 g/100 g and linseed oil of 5 g/100 g for 4 weeks increased significantly the serum alphalinolenic acid concentration (61). In this controlled, double-blind, crossover study Tarpila S *et al*. 2002 also examined the effect of linseed supplementation on plasma enterolactone in 80 volunteers. Serum enterolactone concentration was doubled during linseed supplementation.

II.2 Pharmacodynamics

II.2.1 Mode of action

- Laxative effect

The laxative effects of linseed have long been recognised empirically, then shown in animal and clinical investigations (16, 23, 28, 48). 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 (16, 38, 45).
Broken seeds do not always cause a stretch stimulus because the increase of the volume may already start in the stomach. Whole or "bruised seeds" have a delayed increase of the volume (25, 38).

Cunnane *et al.* 1995 published a study with 10 healthy volunteers. The objective was to determine the influence of consuming 50 g linseed per day for 4 weeks on several indexes of nutrition of young healthy adults. Bowel movement per week increased by 30 % while linseed was consumed ($p<0.05$). The authors concluded that linseed has modest beneficial effect on bowel function (51).

- Effect as a demulcent preparation (traditional indication, see III.4)

The effect as a demulcent preparation is attributed to the protective effect on the mucosa by the coating action (22, 38, 42). Only general evidence support this indication (symptomatic relief of mild gastrointestinal discomfort).

- Effect as a poultice

The use as a poultice (symptomatic treatment of minor skin inflammations) can be attributed to the water-binding capacity of mucilages (physical action). Data to clarify the main pharmacological effects are however insufficient and the use as a poultice cannot therefore be regarded as plausible.

- Effect on blood glucose level

The lowering effect on glucose level in the blood was investigated in 6 healthy volunteers. They received 50 g carbohydrates as either a piece of white bread or linseed bread. The postprandial increase of blood glucose level was clearly higher after eating white bread than after eating linseed bread. The area under the curve (AUC) for blood glucose 1 h postprandial decreased by 28 %.
An addition of 25 g linseed mucilage decreased 2 h postprandial hyperglycaemia after a glucose test meal by 27% (16, 52). These findings point out to the fact that linseed may delay glucose absorption in healthy people.

- Effect on blood lipids levels

Experiments with rats indicate that dietary supplementation of linseed results in a lowering of serum cholesterol levels. It is claimed that this effect is caused by the content of unsaturated fatty acids (16). Data on other fibres indicate that this effect may be linked to the soluble fibres.

Consumption of 50 g/d ground, raw linseed by healthy female volunteers for 4 weeks lowered serum total cholesterol by 9 % and low-density-lipoprotein (LDL) cholesterol by 18 % (52).

- Oestrogenic effect

Linseed contains lignan-precursors (6) (see also chapter II.1 Pharmacokinetics). *In vitro* studies demonstrated that bacteria present in the colon convert these precursors into mammalian-lignans, which are resorbed subsequently. The lignans interfere with the metabolism and activity of oestrogens (7, 16, 27, 31). Experiments in pigs demonstrated the capacity of various fibres, including linseed, to bind oestrogens (5).
It has therefore been suggested that linseed may lower the risk of oestrogen dependent tumours, e.g. some colon and mammary carcinomas (1, 2, 6, 7).

In quantitative urine assays in 64 women studied 4 times during one year, a significant positive correlation could be shown between the intake of fibre (amounts not mentioned), lignan and phytoestrogen excretion and the concentration of plasma sex hormone-binding globulin (SHBG) (2).

The effect of the ingestion of linseed powder on the menstrual cycle was evaluated in 18 normally cycling women, using a balanced randomised crossover design. Each subject consumed her usual omnivorous, low fibre (control) diet for 3 cycles and her usual diet supplemented with linseed (flax seed supplement dose 10 g/day) for another 3 cycles. Each second and third cycle were compared. Three anovulatory cycles occured during the 36 control cycles, compared to none during the 36 linseed cycles. Compared to the ovulatory control cycles, the ovulatory linseed cycles were consistently associated with longer luteal phase (LP) lengths. There were no significant differences between linseed and control cycles for concentrations of either estradiol or estrone during the early follicular phase, midfollicular phase, or LP. Although linseed ingestion had no significant effect on LP progesterone concentrations, the LP progesterone/estradiol ratios were significantly higher during the linseed cycles. Midfollicular phase testosterone concentrations were slightly higher during linseed cycles. Linseed ingestion had no effect on early follicular phase concentrations of dehydroepiandrosterone-sulfate (DHEA-S), prolactin (PRL) or SHBG. The authors concluded that these data suggest a significant specific role for lignans in the relationship between diet and sex steroid action, and possibly between diet and the risk of breast and other hormonally dependent cancers (59).

In 25 postmenopausal women, who consumed 25 g linseed daily, the stage of vaginal cells' maturation was stimulated. This finding was taken as an improvement of menopausal oestrogene deficiency (63).

In another clinical study 6 men received 13.5 g linseeds daily for 6 weeks. The urine concentration of lignans increased ten times. The concentration of testosterone did not change (16).

See also chapter IV Clinical safety.

- Anti-tumour effect

Diverse experiments with rats and mice suggest an anti-tumour effect of linseed ingestion (57). This could be related to the oestrogenic effect (see paragraph above).

A pilot study with 15 men, who were scheduled to undergo repeat prostate biopsy, explored whether a linseed-supplemented (30 g/day), fat-restricted diet over 6 months affected the proliferation rates in benign prostatic epithelium, the circulating levels of prostate-specific antigen (PSA), total testosterone and cholesterol. Statistically significant decreases in PSA and cholesterol (241.1 to 213.3 mg/dL) were observed. No statistically significant change was seen in total testosterone. Although 6-month repeat biopsies were not performed in 2 cases because of PSA normalisation, of the 13 men, who underwent repeat biopsy, the proliferation rates in the benign epithelium decreased significantly. The authors concluded that further investigations are needed to determine whether linseed supplementation, a low-fat diet, or a combination of the two regimes may affect the biology of the prostate and associated biomarkers and may be of use in controlling overall prostatic growth (53).

II.2.2 Interactions

Because of their pharmacodynamic properties, all bulk forming laxatives may delay the enteral absorption of concomitantly administered medications (15, 24). Linseed should therefore be taken at least ½ to 1 hour before or after intake of other medicinal products (24).

Attention is to be paid to interactions between laxative bulk agents and medicinal products that inhibit gastrointestinal propulsive motility given the risk of ileus development following concomitant use. Recommendation on the concomitant use of laxative bulk producers and medicinal products against diarrhoea was released by the EMEA in June 2004 in an HMPWP Position statement[1].
Morphine also belongs to the category of medicinal products, which inhibit peristaltic movement. Morphine is often used in patients for pain therapy in the final stage of a terminal illness and can cause spastic constipation. A bulk forming agent is often given concomitantly to prevent constipation. These patients are under medical supervision. There was no result to a search in the database XMEDALL concerning interactions between linseed and morphine.
In conclusion, in order to decrease the risk of gastrointestinal obstruction (ileus), linseed should be used with caution with medicinal products known to inhibit the peristaltic movement (e.g. opioids, loperamide) and only under medical supervision.

Enzyme inhibitor

Lorenc-Kubis I *et al*. could isolate a serine-proteinase-type inhibitor from linseed by ethanol fractionation. LUTI (Linum usitatissmum trypsin inhibitor) is the first serine-proteinase-type inhibitor isolated from a plant of the Linaceae family (56).

[1] Position paper of the Working Party on Herbal Medicinal Products (EMEA/HMPWP/60/04)

III. CLINICAL EFFICACY

III.1 Dosage

There are no dose-finding studies available.

Well-established use
The recommended dosage as a laxative for adults, elderly and adolescents over 12 years of age (10 – 15 g, 2 – 3 times daily) is supported by general evidence (29, 34, 38, 42, 47) and by clinical investigations referred to in chapter III.2 Clinical studies.

Traditional use (see chapter III.4)
Single dose for adults, elderly and adolescents over 12 years of age:
For a mucilaginous preparation, soak 5 – 10 g whole or broken seeds in 250 ml water and take this half an hour before eating up to three times during the day. If possible soak the seeds the evening before. The mucilaginous preparations may be consumed with or without the seeds.

III.2 Clinical studies

III.2.1 Laxative effect

- Open clinical studies

In one multicentre non-controlled study 108 patients (81 female, 27 male, 19 – 81 years old) mainly suffering from constipation were treated with 10 g bruised linseed three times a day for 4 – 6 weeks. The main symptoms were constipation (30%), heartburn (22%), eructation (19%) and diarrhoea (15%). The concistency of faeces was hard in 77 % of the patients at the beginning of the study. Out of the 108 patients, 35 patients dropped out, and 73 patients finished the study. 66 patients recognized a clear improvement of their symptoms. There was no differentiation of the improved symptoms (23).

The laxative effects of linseed were investigated in 19 geriatric patients. They received purgative medicines such as either 20 ml lactulose (Duphalac®) or paraffin oil with phenolphthalein (Agarol®) for one month and then either 10 g bruised linseed or 7 g psyllii semen (Effersyllium®) or 14 g wheat bran with karaya gum (Crusca di Fior®) two times a day for two months (one month as adaption, one month as study phase). The frequency of defaecation was similar in both phases (16, 28).

In another investigation 32 geriatric patients in an elderly/nursing home were fed with special test meals beside the usual home diet for 84 days. They received 39 g linseed two times a day for 4 weeks, then 34 g dietary fibre mix of fruits two times a day for 4 weeks, then 46 g fruit muesli two times a day for 4 weeks. There was an interruption of two months after each treatment. The treatment with linseed caused an improvement of defaecation, particularly of the frequency in 52 % of patients (dietary fibre mix 50%, fruit muesli 23%) (16, 48).

- Controlled clinical studies

In a randomised investigator-blinded trial with two parallel treatment groups, 55 patients suffering from constipation predominant irritable bowel syndrome received 6 – 24 g/d either linseed (roughly ground partly defatted) or psyllium for 3 months. In the following open period of 3 months the patients were treated with linseed only. During the blinded treatment period, 26 patients received linseed and 29 received psyllium. The efficacy of the study treatments was measured with assessment of the gastrointestinal symptoms: bowel movement frequency, abdominal discomfort/bloating and abdominal pain. Each symptom was scored 1 - 5 (1=worse, 2=unchanged, 3=somewhat relieved, 4=considerably relieved and 5=completely relieved). The mean dose of linseed was 17 g/day. In the linseed group, constipation and abdominal symptoms were decreased significantly (p=0.002) whereas in the psyllium group the reduction was not statistically significant. After the blinded treatment period, the difference between groups was statistically significant in constipation (p=0.05) and in bloating and pain

(p=0.001). Forty patients continued to the open period, 18 from the linseed group and 22 from the psyllium group. After the open period of 3 months, constipation and abdominal symptoms were further significantly reduced (p=0.001). The response to linseed treatment was expressed slowly i.e. after 2 –3 months' regular use (62).
The data given in the publication are not sufficient to prove the efficacy for the indication "treatment of irritable bowel syndrome". Data, however, support the indication "treatment of habitual constipation".

III.2.2 Effect as a demulcent preparation

It has been reported that linseed as a mucilage has a palliative effect in patients with gastrointestinal discomfort and as poultice in skin inflammations (38, 45, 47).

In a pilot study, 70 patients with functional upper abdominal complaints received a linseed mucilage preparation for three days. The patients enrolled in this study suffered from two of the following symptoms without suspicion of a gastric ulcer: pressure and pain in the epigastrium, repletion, eructation, nausea, feeling to have to vomit, heartburn, loss of appetite. For evaluation of the efficacy of linseed, the abdominal symptoms (pain, nausea, heartburn, gastrospasm, feeling to have to vomit, loss of appetite, repletion, eructation, sensation of pressure) were scored from 1 (no complain) to 5. The score decreased from 20.19 (± 6.03) to 13.20 (± 3.30) ($p < 0.01$). Each individual symptom was reduced on average, the largest reductions being observed for the sensation of pressure (41.5%) and the sensation of repletion (36.8%) (13).

III.2.3 Effect on blood lipids levels

In the above-mentioned investigation (48) concerning 32 subjects of an elderly/nursing home (special test meals beside usual diet for 84 days), the effect of fibre-rich test meals on blood lipids was studied. The identified reductions are insignificant in regard to the effect on an increased serum triglyceride level. A highly significant (p=0.001) reduction of blood cholesterol level was achieved with muesli (from 266.1 to 250.2 mg/dl), and a significant (p=0.05) reduction with linseed (from 266.9 to 251.1 mg/dL). The reduction under dietary fibre mix was not significant (from 247.8 to 240.4 mg/dL).

In the controlled clinical trial mentioned above (62), lipid parameters were also measured. There was a slight decrease in serum total cholesterol and in LDL cholesterol during the 3-month treatment in both groups (in linseed group serum total cholesterol from 5.71 mmol/l (220 mg/dL) to 5.50 mmol/l (212 mg/dL) and serum LDL cholesterol from 3.51 mmol/l (135 mg/dL) to 3.29 mmol/l (127 mg/dL) and in psyllium group respectively from 5.45 mmol/l (210 mg/dL) to 5.35 mmol/l (206 mg/dL) and from 3.16 mmol/l (122 mg/dL) to 3.15 mmol/l (121 mg/dL). Linseed reduced serum total cholesterol by 10 % (values from baseline 5.71 mmol/l (220 mg/dL) to 5.10 mmol/l (196 mg/dL), p=0.003) and LDL cholesterol by 12 % (values from baseline 3.51 mmol/l (135 mg/dL) to 3.10 mmol/l (119 mg/dL), p=0.006) after the additional 3-month open treatment. The decrease of total and LDL cholesterol in psyllium group was not significant.
Dietary calorie or fat intake of the patients was not recorded, so that there are no objective information as to whether the decrease of the lipids is a result of linseed treatment or of a change in diet especially concerning fat intake and lifestyle management under study conditions. Furthermore the increase of the lipids at the beginning is marginal and the necessity of a treatment depends on additional cardiovascular risks.

III.2.4 Effect on blood glucose level

There are no clinical data available.

III.2.5 Oestrogenic and anti-tumour effects

There are no clinical data available.

III.3 Clinical studies in special populations

Well-established use
There are insufficient systematic clinical data available concerning the use of linseed during pregnancy and lactation or in children. There are no reports of any harmful or deleterious effects during pregnancy and lactation and linseed preparations produce a gentle and safe laxation.
However the results of some investigations in human indicate an oestrogenic effect of linseed (see 'Oestrogenic effect' in chapter II.2.1 and chapter IV.5). The clinical relevance yet cannot be evaluated, but as a precautionary measure the use of linseed during pregnancy, lactation and in children below 12 years of age is not recommended.
Use in women with hormonally dependent tumours is also not recommended.

Traditional use
See chapter III.4.

III.4 Traditional use

III.4.1 Indications

Linseed has a long history of medicinal use (64, 73), its main effects being as a laxative and expectorant that soothes irritated tissues, controls coughing and relieves pain. The seeds or the oil from the seed were normally used.

Dioskurides already mentioned linseed in his materia medica 50-70 A.D. (64, 65, 73). Accounts relate to the properties of linseeds to dispel and soften every internal and external tumour or swelling when taken after cooking with honey, oil and little water. Taken with honey linseeds clean the breast and relieve cough. A decoction as klysma is useful for injuries of the bowels and uterus and for defaecation or as sitz-bath for uterine inflammations.
These applications were approved by Tabernaemontanus 1625 (66). Matthiolus 1626 also indicates the use as a klysma (64) and like Tabernaemontanus he refers as well to the internal use for consumptive patients and the external use mixed with vinegar to stop epistaxis and the inhalation of linseedsmoke for common cold (66, 73). Lonicerus 1679 (64) indicates the use for internal and external tumours and for intestinal affections. Vietz 1800 (64) recommends the internal use for intestinal inflammations and for constipation.

The manual of Culbreth 1927 (67) recommends the use as an infusion 5 p.c. or tea for inflammation of mucous membranes of respiratory, digestive, and urinary organs, renal and vesical irritation, catarrh, dysentery, calculi, strangury. The decoction (5 p.c.), owing to the oil it contains, is less tolerable to the mouth, but acceptable for enema. Poultice of ground meal to swollen glands, swellings, boils, pneumonia, etc. is made by adding boiling water to meal for proper consistency and bringing to boil. Before applying skin should be coated with glycerin, olive or other oil. The poultice is placed as near to affected spot as possible and may be covered with oiled silk to retain heat and moisture. Olive oil, lard, laudanum or any anodyne, stimulating, or adstringent solution may be added to the poultice.

Stahl 1962 (68) and Fischer 1966 (69) describe the internal use for the acute respiratory and urinary catarrh and the external use as a poultice, especially for suppurating skin inflammations. Stahl recommends linseed as a mild laxative.
Dragendorff 1967 (72) indicates the internal application of the seeds for catarrh, diarrhoea, gonorrhoea, dysmenorrhoea and the external use of linseed cakes as a cataplasma.

Madaus 1938 (73) indicates that linseed is also used to remove a foreign substance from the eye. This is approved by Lewis, professor of biology of the Washington university, 1977 (74). Linseeds were used in domestic medicine to remove foreign material from the eye, a seed is moistened and placed under the eyelid, the eye is closed for a few moments, and the material in the eye sticks to the seed and can be removed with it.

Weiss 1980 (75) describes the external use as a poultice for furunculosis, but without reporting any posology.

Leclerc 1983 (77) indicates the use as a cataplasma, for constipation and for urinary inflammations, in his “Essais de thérapeutique par les plantes françaises”.

Penso 1989 (76) describes the use of linseed as cataplasma, infusion (tea) and enema in Italy.

Madaus (73) also describes the use of linseed in other European countries:
Denmark: with honey for cough, as mucilage for stomach and abdominal pain;
Lithuania: as a decoction for cough, dyspepsia and urinary retention;
Poland: as a cataplasma;
Austria: as a poultice for colds;
Hungary: for cough and nausea.

In Pakistan as per Unani-medicine practice (78) linseed is used on all kinds of local inflammations, sores and ulcers. Mucilage of linseed is applied to the affected areas to resolve or to suppurate in case of hard swellings; pain is relieved along with subsiding the affected inflamed areas. Linseed helps suppuration and bursts the blind ulcers and assists in driving off the putrid matter. Internal inflammations, for example in pleurisy, pneumonia, inflammation in bronchioles, peritonitis as well as inflammatory swellings in rheumatism are treated successfully if the prepared paste or ointment with linseed as a major component is applied under bandage and in combination with other herbal substances to increase warmness. With *Glycyrrhiza glabra* L. infusion of the seeds is a useful demulcent expectorant in colds, cough, urinary irritations, gonorrhoea, spermatorrhoea, diarrhoea etc. Oral administration of linseed is generally considered to be antispasmodic. Seeds mucilage is also an effective treatment of eye irritation as eye drops.

A Chinese materia medica (79) indicates the use in cases of constipation, dryness and itching of the skin, withering and loss of hair.

III.4.2 Dosage

Martindale 1967 (70) gives more precise information of the posology of linseed:
- The seeds, one or two 5-ml spoonfuls in a tumbler of water, may be taken to increase the bulk of intestinal contents in the treatment of constipation.
- A mucilage (1 in 8), prepared by pouring boiling water over linseed and straining, has been used as a demulcent drink.
- The poultice mass may be prepared by gradually adding 100 g of broken linseed to 250 g of boiling water.

Martindale 1972 (71) recommends for the poultice mass preparation the gradual addition of 4 oz. (ca. 120 g) of broken linseed to 10 fl. oz. (ca. 300 ml) of boiling water. It is usually applied enclosed in muslin; the poultice may be smeared with oil to prevent its adhering to the skin.

Madaus 1938 (72) recommend mixing 125 g powdered linseed with a cup of hot water, to apply it in muslin and cover it with wool, flannel or cotton.
For cystitis 2 teaspoons of linseed are boiled up with 2 glasses of water, left to settle for 10 minutes and drunk during the day (72).

Leclerc 1983 (77) prepares an infusion with 20 g seeds to 1 litre of water and macerating for 5 hours.

Penso 1989 (76) takes 50 g linseed to 500 ml water to prepare a cataplasma and 30 g linseed to 1000 ml to prepare an infusion by boiling up, macerating for 12 hours, filtrating, sweetening *ad libitum* and drinking 200 ml three times a day.
An enema is prepared with 30 g linseed to 1000 ml water.

III.4.3 Discussion and conclusion

The use of linseed for intestinal affections was referred to by Lonicerus in 1679 (64). Madaus (73) also describes the use of linseed for intestinal affections in other European countries like Denmark, Lithuania and Hungary. There is one uncontrolled pilot study with 70 patients available (see chapter III.2 Clinical studies). This use is plausible, attributed to the protective effect on the mucosa by the coating action of the mucilage.
The indication as a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort can therefore be regarded as a traditional one.
There is no experience available concerning the use in children. Therefore and because of the possible oestrogenic effects, the use is not recommended in children below the age of 12 years.
For other safety concerns, see chapter IV Clinical safety.

Since Dioskurides, the use as a poultice in case of skin inflammations is documented in many German, other European and non-European references. The procedure is described by Culbreth 1927 (67), Madaus 1938 (72), Martindale 1967 (70) and Martindale 1972 (71). The use as a poultice is mostly attributed to the water-binding capacity of mucilages. This action is a physical one. Some references report that the heat of such a poultice let a furuncle to maturate. This might be plausible for furuncles but not for other skin inflammations. In conclusion there are insufficient data, which can clarify the main pharmacological pattern for the use as a poultice and this use therefore cannot be regarded as plausible. Furthermore it is difficult for patients to recognise the limit of self-medication concerning skin inflammations (from sunburn to erysipelas) or even furunculosis.

There is no valid traditional evidence that a demulcent preparation was used for habitual constipation. No data of an effective laxative dose of such a preparation are available.

Concerning the treatment of inflammations of mucous membranes of respitory and urinary organs, references are not consistent as to whether the application is only an internal or external one or both. Sometimes the combination with other herbal substances is mentioned. Furthermore it is questioned how linseed can works without a direct contact to the affected mucous membranes. In case of inflammations of the throat like pharyngitis or in case of a dry cough, patients normally have difficulties in swallowing. Difficulties in swallowing are classified as contraindications for bulk forming agents like linseed and can cause a choking fit. Because of associated potential risks these indications cannot be accepted as traditional ones.

Symptoms of rheumatism are sometimes mentioned but not consistently. The term “rheumatism” changed in meaning over the years. In former times, all unspecific pains of the joints or the links were described as rheumatic. Nowadays “rheumatism” refers to a well-defined diagnosis. The conditions in which linseed was traditionally used are not described exactly enough.

The use of a decoction or mucilage of linseed as an enema is not mentioned consistently.
Only a few references mentioned the use of linseed to remove a foreign substance from the eye.
<u>These uses are not supported by long-standing evidence nor by clinical evidence.</u>

IV. CLINICAL SAFETY

IV.1 Preclinical tests on reproductive toxicity, genotoxicity and carcinogenicity

None have been performed.

IV.2. Cyanide

Linseed contains about 20 – 50 mg cyanide/100 g in form of the cyanogenic diglycosids linustatin, neolinustatin and and small amount of the monoglucoside linamarin.
Oomah BD *et al*. 1992 analysed the seeds of 10 flax cultivars for content of cyanogenic glucosides by HPLC. The main cyanogenic compound was the diglucoside linustatin at 213 – 352 mg/100 g of seed, accounting for 54 – 76% of the total content of cyanogenic glucosides. The content of neolinustatin ranged from 91 to 203 mg/100 g of seed. Linamarin also was present in 8 of the 10 cultivars at low levels (< 32 mg/100 g) (80).
Inappropriate storage of linseed may lead to a higher content of cyanogenic glycosides.

In a study in 10 volunteers, neither a single dosage of 30 g respectively 100 g linseed nor a chronic dose of 30 – 45 g daily for 4 – 6 weeks caused a significant increase of serum cyanide or thiocyanate. The urinary excretion of thiocyanate however increased about 40 to 80 % (40, 60).

Another investigation showed that 50 g ground, raw linseed consumed by healthy female volunteers for 4 weeks raised the urinary thiocyanate excretion 2.2-fold (52). The reason appeared to be that diglycosides set the cyanide free very slowly because of the acidity of gastric fluid. The detoxification process starts immediately and is not saturated because the cyanide is set free very slowly (3, 4, 16, 36, 38, 39, 47).

In a randomised investigator-blinded trial, 55 patients suffering from constipation predominant irritable bowel syndrome received 6 – 24 g/d either linseed or psyllium for 3 months. In the following 3-month open period patients were treated with linseed only. The mean value of serum thiocyanate elevated from 40.9 to 153.7 µmol/l after 3 months linseed treatment with a mean dose of 17 g/day. These patients were all non-smokers. The mean value of serum thiocyanate in four smokers was 133 µmol/l before the treatment and 189 µmol/l after 3 months' linseed treatment. After the open period this value decreased to 104 µmol/l (62). The reference value for thiocyanate is 250 µmol/l for smokers and 100 µmol/l for non-smokers (49).

The enzyme rhodanase catalyzes the change of cyanide into thiocyanate (rhodanide), which is 200 times less toxic than cyanide (16). Regular consumption of linseed causes a cumulation of thiocyanate, which can be compared to the blood level of thiocyanate in heavy smokers. The cumulation reaches a steady state after 2 – 3 weeks. A higher rate of premature delivery is observed in the female smokers population; there is however at present no evidence that this could be related to a higher blood level of thiocyanate (40).

In an investigation conducted on sheep fed on a diet of linseed, oats and lucernes, 8 out 14 sheep gave birth to lambs with a struma. Rhodanide (thiocyanate), which is the product of cyanide catalysis with thiosulfate, inhibits the uptake of iodine. It has however to be taken into account that additional cyanide may be set free in the fore-stomach of ruminants out of linamarin because of the microflora and the pH (5 to 6), whereas the reaction is stopped in the human stomach because of its acidity (16).

In their publication "Thioyanate catalyzes myeloperoxidase-initiated lipid oxidation in LDL" Exner M *et al*. 2004 (83) conclude that the myeloperoxidase-hydrogen peroxide-pseudo-halide thiocyanate-system ($MPO/H_2O_2/SCN$-system) may have the potential to play a significant role in the oxidative modification of LDL – an observation further pointing to the link between the long-recognised risk factors of atherosclerosis: elevated levels of LDL and smoking.

It is concluded that available scientific data are not sufficient to substantiate such a risk associated to linseed consumption.

On the other side, daily food supplementation with ground linseed and linseed oil increased significantly the serum alphalinolenic acid concentration, which is supposed to have a preventive effect against cardiovascular diseases (61).

IV.3 Cadmium

The Ph. Eur.Monograph "Linseed" (Lini semen – 04/2005:0095) indicates a maximum content of 500 µg/1000g (0.5 ppm) cadmium in linseed. With a maximum daily intake of 45 g linseed the maximum daily uptake of cadmium adds up to 22.5 µg.
Concerning cadmium, the WHO recommends a PTWI (provisional tolerable weekly intake) of 7 µg/kg body weight weekly. In consideration of this PTWI the critical limit is 490 µg weekly for a person of 70 kg and 70 µg daily.
The daily intake of cadmium from food is 30 – 50 µg in average. Considering the additional ingestion of 45 g linseed per day, the critical limit of 70 µg daily is just achieved (worst-case calculation).

Schilcher *et al*. analysed more than 1,500 samples of linseed. The content of cadmium in linseed cultivated for medical use was below 0.2 ppm (200 µg/1000g) (37).

It is assumed that whole or "bruised" seeds do not set free cadmium in the same amount as broken seeds. Whole or "bruised" seeds should therefore be favoured. It is furthermore assumed that the swelling of linseed prevents the complete release of cadmium.

In the above-mentioned randomised investigator-blinded trial (62), 55 patients suffering from constipation predominant irritable bowel syndrome received 6 – 24 g/d either roughly grounded partly defatted linseed or psyllium for 3 months. In the following 3-month open period the patients were treated with linseed only. Blood cadmium was analysed from 11 non-smoking patients after 6 months'ingestion of an average linseed dose of 17.4 g/d. The mean blood cadmium concentration was normal at 3.4 nmol/l. The reference value was 10 nmol/l (49).
Other references indicate that linseed should not contain more than 0.3 mg/kg cadmium because toxic effects are not expected below this limit (21, 24, 37).

In the controlled, double-blind, crossover study (61), Tarpila S *et al.* 2002 also examined the effect of linseed supplementation (ground linseed of 1.3 g/100 g and linseed oil of 5 g/100 g for 4 weeks) on serum thiocyanate and blood cadmium in 80 volunteers. The serum thiocyanate and blood cadmium values did not exceed reference values and showed no differences between the diets.

IV.4. Lignans

It is not known whether high lignan excretion is associated to any adverse effects. Theoretically, very high lignan production could lead to infertility, as in clover disease of sheep (1).

IV.5 Oestrogenic effect

The data mentioned in chapter II.2 Pharmacodynamics suggest that there might be an oestrogenic or antioestrogenic effect of linseed. Some authors therefore call mammalian lignans modulators of endogenous sex steroid hormones. Whether this effect has any clinical relevance has yet to be studied in further investigations. Predominantly the authors of the above-mentioned publications consider that the oestrogenic effect might be a positive one e.g. to influence hormonally dependent tumours or to improve oestrogen deficiency.

In "Flaxseed in human nutrition" (2003) Hutchins AM and Slavin JL (81) described in chapter 6 the effects of flaxseed on sex hormone metabolism. They summarise as follows: "Since the identification of mammalian lignans in human urine in 1981, evidence supporting their role as modulators of endogenous sex steroid hormones has increased. However, the most convincing results have come from *in vitro*, animal and epidemiological studies. Results of the few intervention studies that have been conducted have been mixed; therefore, further research, in particular long-term intervention trials, is needed to provide clarification for this relationship."

In chapter 19 Sprando RL *et al*. (82) describe the effect of flaxseed consumption on male and female reproductive function and fetal development. In their conclusion, "a review of the available literature has suggested that the consumption of flaxseed can affect various reproductive indices in both the male and female rat. The reviewed animal studies have suggested that the effect of flaxseed on various reproductive indices and sex hormone levels depends on the dose, timing, and duration of exposure. In the female, effects included a lengthened estrous cycle, changes in the anogenital distance (AGD), extended or shortened onset of puberty, ovarian weight changes, and effects on the maturation of the mammary gland. In the male, effects included changes in serum hormone levels and secondary sex organ weight, especially of the prostate. Effects were not observed in the male fetus. Neither testis structure, the process of spermatogenesis, sperm production, or sperm morphology were affected by flaxseed exposure during gestation or postnatal development. Epididymal effects (i.e. extended sperm storage times) have been reported; however, further studies are required to corroborate or dispute this finding. At this time, the relevance of these findings with respect to the human population is unknown and further research is required".

Because of these literature reports on hormone-like actions the use during pregnancy and lactation cannot be recommended until reproductive toxicological investigations will be available.

Advice has to be given for women with hormonally dependent tumours as a precaution:
"Investigations in healthy women suggest that linseed may have an oestrogenic effect, use is therefore not recommended in women with hormonally dependent tumours."

The use in children is not recommended in children below 12 years of age.

These statements are also relevant for the traditional indication.

IV.6. Undesirable effects

Meteorism, occuring with the use of linseed is common (15, 39) as already described under chapter II.1 Pharmacokinetics.
Linseed contains potent allergens. Exposure to these allergens is possible through the oral route or through contact. Linseed should be considered as a possible cause of anaphylaxis from laxatives. Reactions of hypersensitivity including anaphylaxis-like reactions may occur very rarely. Linseed is not to be used by patients with known hypersensitivity to linseed (3).

Linseed is a bulk forming agent and special warnings and contraindications for this kind of agents must be followed.

IV.7 Contraindications

Linseed 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. Linseed should also not be used by patients suffering from abnormal constrictions of the gastrointestinal tract, diseases of the oesophagus and cardia, potential or existing intestinal blockage (ileus) (29), paralysis of the intestine or megacolon.
Linseed should not be taken by patients, who have difficulties in swallowing or any throat problems (43).

Patients with known hypersensitivity to linseed should not use linseed preparations.

IV.8 Warnings

Each single dose (10 – 15 g linseed) should be taken with at least 150 ml of water or similar aqueous fluid. Taking this product without adequate fluid may cause it to swell and block the throat or oesophagus and may cause choking. Intestinal obstruction may occur if adequate fluid intake is not maintained. If the patient experiences chest pain, vomiting, or has difficulties in swallowing or breathing after taking this product, medical attention should be sought immediately (43). Treatment of debilitated patients and elderly requires medical supervision (15).

Linseed 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) (46).

IV.9 Interactions

See chapter II.2.2 Interactions.

IV.10 Traditional use

As the demulcent preparation can be administered with or without the seeds, linseeds as a demulcent preparation should not be used by patients with potential or existing intestinal blockage (ileus), paralysis of the intestine or megacolon and by patients with a sudden change in bowel habit that persists for more than 2 weeks.
Linseed should not be used by patients with abnormal constrictions on the oesophagus, cardia or gastrointestinal tract.
Linseed should also not be used by patients, who have difficulty in swallowing.
If the symptoms persist for more than 1 week or worsen during the use of the medicinal product or if adverse effects not mentioned in the package leaflet occur, a doctor or a qualified health care practitioner should be consulted.

Linseed is not to be used by patients with faecal impaction and undiagnosed abdominal symptoms, abdominal pain, nausea and vomiting unless advised by a doctor because these symptoms can be signs of a potential or existing intestinal blockage.

Linseed is not to be used by patients with melanorrhoea because this is a sign of gastric bleeding.

Warnings:
See above.

Concerning the method of administration, a minimal definite period can be given in which the seeds have to be soaked. If it is proved for the specific preparation that the seeds do not swell more, the wordings concerning bulk forming agents (i.e. contraindications, special warnings, interactions, undesirable effects) can be omitted.

V. OVERALL CONCLUSIONS

<u>Indication for linseed containing herbal medicinal products with a well-established use: For the treatment of habitual constipation or in conditions in which easy defaecation with soft stool is desirable</u>

The use of linseed as a laxative has only been investigated in open uncontrolled studies with moderate scientific quality. The use of linseed as a laxative however relies also on a vast medicinal experience documented in the literature and on a positive benefit/risk ratio. The therapeutic action of linseed is substantiated by its pharmacological effects. The only available controlled clinical trial investigates patients with constipation predominant irritable bowel syndrome. This trial's results support the use as a laxative albeit in a special population. The recommended indication covers constipation caused by

another primary disease such as irritable bowel syndrome. The current level of evidence for the indication "treatment of habitual constipation" can be identified as level II to III[2].

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 special data available (level of evidence IV). In the absence of specific data, no reference is made to examples of conditions in which easy defaecation with soft stool is desirable (e.g. cases of painful defaecation after rectal or anal surgery, anal fissures and haemorrhoids).

Traditional use of linseed as a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort

The use as a demulcent preparation is only investigated in one pilot study (13) and is mainly supported by empirical data. The coating effect is plausible on the basis of limited data on pharmacology in animals (50) (level of evidence IV).
It should be acknowledged that diagnostic and therapeutic management of gastric complaints have evolved over time as have the guidelines to carry out such studies (ROME II criteria).
Therefore, only the traditional use in mild gastrointestinal discomfort is justified.

Concerning the use as a poultice for minor skin inflammations, insufficient data are available that can clarify the main pharmacological properties. The use as a poultice cannot therefore be regarded as plausible.

Available data on blood cholesterol and glucose lowering effects, anti-tumour and oestrogenic effects are not sufficient.

There are no reports of harmful or deleterious effects during pregnancy and lactation. However, the use during pregnancy and lactation cannot be recommended without further investigations because of literature reports on hormone-like actions and because of insufficient toxicological data. The use is not recommended in children below 12 years of age.

There is no evidence of harmful effect of thiocyanate in human beings in the amount generated by linseed consumption (40).

The major indication of linseed is constipation. From the most common laxative medicines – stimulant laxatives, lubricant laxatives and bulk forming laxatives, the latter should preferably be given.
Most of the patients suffering from constipation seek rapid return to normal intestinal transit and use stimulant laxatives; they often become addicted to the medication. As the desired effects are no longer attained, patients being accustomed to these medicines tend to increase the dosage. The frequent and prolonged use of these laxatives or an overdosage cause an increased loss of water and salts, particularly of potassium salts and this potassium depletion may, in particular, potentiate the action of cardiac glucosides.
Linseed preparations produce a gentle and safe laxation and have an acceptable level of safety when the special warnings for such bulk forming agents are followed (see chapter IV Clinical safety).

[2] 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)