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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Linum usitatissimum* L., semen

Final

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Linum usitatissimum* L., semen
Herbal preparation(s)	Not applicable
Pharmaceutical form(s)	Herbal substance for oral use
Rapporteur(s)	J. Wiesner
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Table of contents

1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

This assessment report reviews the scientific data available for linseed (*Linum usitatissimum* L., semen).

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 (Tarpila *et al.* 2004). The most commonly used laxatives are either stimulant laxatives (containing e.g. anthracene derivates from senna, frangula or cascara) or lubricant laxatives (e.g. mineral oils) or bulk forming agents such as linseed.

- Herbal substance(s)

Linseed is a herbal 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.

Linseed consists of the dried, ripe seeds of *Linum usitatissimum* L. The herbal substance has to comply with the monograph “Linseed” of the European Pharmacopoeia (ref. 04/2011:0095).

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, 0.1 - 1.5% cyanogenic glycosides, vitamins, lignan precursors, linustatin, neolinustatin and linamarin, enzymes. The content of water is 5 - 14% (Blaschek e*t al.* 2011; Benedum *et al.* 2000; Oomah *et al.* 1992).

- Herbal preparation(s)

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 (Evans 1989; Standardzulassungen 1996; Kommission E 1984; Steinegger and Hänsel 1988; Weiss and Fintelmann 1999; Willuhn in Wichtl 1989). There are however insufficient data that can clarify the main pharmacological properties. Therefore the use as a poultice cannot be regarded as plausible for the traditional use.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

1.2. Information about products on the market in the EU/EEA Member States

In 4 of 6 MS answering the market request (2011) the herbal substance and the comminuted herbal substance are on the market. In BE the comminuted herbal substance is prepared as tea. Linseed oil is used in soft gel capsules as food supplement there. In Germany linseed oil is used as nutrition.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not available as herbal medicinal product
Belgium	☒ MA	☐ TRAD	☒ Other TRAD	☒ Other Specify:	Herbal teas (other trad.) and oil in soft gel capsules (food suppl.)
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Available in combination products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not available as herbal medicinal product

Member State	Regulatory Status				Comments
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

The literature search was performed in Pubmed and Scifinderwith the terms linseed and *Linum usitatissimum*, flaxseed, alpha-linoleic acid, starting from the adoption date of the monograph. The results were evaluated, whether new data are available.

2. Data on medicinal use

2.1. Information on period of medicinal use in the European Union

Linseed has a long history of medicinal use (Benedum *et al.* 2000; Madaus 1938), 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.

Medicinal use of linseed has been reported for a set of member states amongst them Germany, Denmark, France, Lithuania, Poland, Austria and Hungary. Based on products in Germany and reference to a standard authorisation scheme a long history of medicinal usage for more than 30 years is fulfilled.

2.2. Information on traditional/current indications and specified substances/preparations

Dioskurides already mentioned linseed in his materia medica 50-70 A.D. (Benedum *et al.* 2000; Berendes 1902; Madaus 1938). These accounts related to the properties of linseed to dispel and soften every internal and external tumour or swelling when taken after cooking with honey, oil and little water. It was also noted, that taken with honey linseeds could clean the breast and relieve cough anda decoction as klysma was useful for injuries of the bowels and uterus. It was reported, that linseed was beneficialfor defaecation or as hip-bath for uterine inflammations.

These applications were approved by Tabernaemontanus in 1625 (Theodorus 1625). Matthiolus in 1626 also indicated the use as a klysma and like Tabernaemontanus, he referred as well to its internal use for consumptive patients, external use (mixed with vinegar) to stop epistaxis and the inhalation of linseed smoke for common cold (Benedum *et al.* 2000; Theodorus 1625; Madaus 1938). In 1679, Lonicerus indicated the use of linseed for internal and external tumours and for intestinal affections. In 1800, Vietz recommended the internal use of linseed for intestinal inflammations and for constipation (Benedum *et al.* 2000).

Culbreth (1927) recommended the use of linseed as an infusion 5% or tea for inflammation of mucous membranes of respiratory, digestive, and urinary organs, renal and vesical irritation, catarrh, dysentery, calculi and strangury. According to the author, the decoction (5%), owing to the oil it contains, is less tolerable to the mouth, but acceptable for enema. It was also reported, that a poultice of ground seeds (for swollen glands, swellings, boils, pneumonia, etc.) was made by adding boiling

water to meal for proper consistency, then it was bringing to boil. Before applying, skin should be coated with glycerine, olive or other oil. The poultice was placed as near to the affected spot as possible and might be covered with oiled silk to retain heat and moisture. Olive oil, lard, laudanum or any anodyne, stimulating, or adstringent solution might be added to the poultice.

Stahl (1962) and Fischer (1966) described the internal use for acute respiratory and urinary catarrh and the external use as a poultice, especially for suppurating skin inflammations. Stahl recommended linseed as a mild laxative.

Dragendorff (1967) indicated the internal application of the seeds for catarrh, diarrhoea, gonorrhoea, dysmenorrhoea and the external use of linseed cakes as a cataplasm.

Madaus (1938) indicated that linseed was also used to remove foreign substance from the eye. This was approved by Lewis, professor of biology of the Washington University (Lewis and Elvin-Lewis 1977). Linseeds were used in domestic medicine to remove foreign material from the eye; a seed was moistened and placed under the eyelid, the eye was closed for a few moments, and the material in the eye stuck to the seed and could be removed with it.

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

The Kommission E monograph on Lini semen (Leinsamen) BAnz Nr. 228 from 05.12.1984 indicated the internal use of linseed for habitual constipation, irritable bowel syndrome (IBS), diverticulitis (as demulcent preparation), gastroenteritis and the external use as a poultice for local inflammations.

The ESCOP Monograph described the laxative effect and the beneficial effects on gastrointestinal complaints of linseed (ESCOP 2003).

Leclerc (1983) indicated the use of linseed as a cataplasm for wounds, and internally for constipation and for urinary inflammations, in his “Essais de thérapeutique par les plantes françaises”.

Penso (1989) described the use of linseed as cataplasm, infusion (tea) and enema in Italy.

Madaus (1938) also described 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 cataplasm;
Austria: as a poultice for colds;
Hungary: for cough and nausea.

In Pakistan as per Unani-medicine practice (Usmanghani *et al.* 1997) linseed has been used on all kinds of local inflammations, sores and ulcers. Mucilage of linseed has been applied to the affected areas to resolve or to suppurate hard swellings; to relieve pain and to subside the affected inflamed areas. According to the author, linseed helps suppuration and bursts the blind ulcers and assists in driving off the putrid matter. Internal inflammations, for example pleurisy, pneumonia, inflammation in bronchioles, peritonitis as well as inflammatory swellings in rheumatism were reported to be treated successfully if the prepared paste or ointment with linseed as a major component (in combination with other herbal substances), was applied under bandage to increase warmness.
With *Glycyrrhiza glabra* L. infusion of the seeds has been experienced as a useful demulcent expectorant in colds, cough, urinary irritations, gonorrhoea, spermatorrhoea, diarrhoea etc. Oral administration of linseed was generally considered to be antispasmodic. Seeds mucilage has also been reported to be an effective treatment of eye irritation as eye drops.

A Chinese materia medica (Pharmacopoeia Commission China 1995) indicated the use in cases of constipation, dryness and itching of the skin, withering and loss of hair.

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

Martindale (1967) gave 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) recommended 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 was usually applied enclosed in muslin; the poultice was suggested to be smeared with oil to prevent its adhering to the skin.

Madaus (1938) recommended mixing 125 g powdered linseed with a cup of hot water, to apply it in muslin and to cover it with wool, flannel or cotton.

For cystitis 2 teaspoons of linseed were boiled up with 2 glasses of water, left to settle for 10 minutes and drunk during the day (Dragendorff 1967).

Leclerc (1983) reported the preparation of an infusion with 20 g seeds to 1 litre of water, macerating for 5 hours. In 1989 Penso recommended 50 g linseed to 500 ml water to prepare a cataplasm and 30 g linseed to 1000 ml water to prepare an infusion by boiling it up, macerating for 12 hours, filtrating, sweetening ad libitum and drinking 200 ml three times a day.

An enema was prepared with 30 g linseed to 1000 ml water.

Well-established use

The recommended dosage as a laxative for adults, elderly and adolescents (10 - 15 g, 2 - 3 times daily) is supported by general evidence from monographs and literature (Kommission E 1984; Schilcher 1990; Schilcher *et al*. 1986; Steinegger and Hänsel 1988; Willuhn in Wichtl 1989) and by clinical investigations referred to in chapter 4.2.2. Clinical studies.

Traditional use

Single dose for adults, elderly and adolescents: For a mucilaginous preparation, soak 5 - 10 g whole or broken seeds in 250 ml water until swelling is completed and take this half an hour before eating up to three times during the day. The mucilaginous preparations may be consumed with or without the seeds.

Assessor´s comment

The use of linseed for intestinal affections was referred to by Lonicerus in 1679 (Wilcox et al. 1990). Madaus (1938) also described the use of linseed for intestinal affections in other European countries like Denmark, Lithuania and Hungary. There is one non-controlled pilot study with 70 patients available (see chapter 4.2.2 Clinical studies). This use is plausible, attributed to the protective effect on the mucosa by the coating action of the mucilage.

Therefore the indication as a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort can 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 under the age of 12 years.

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 was described by Culbreth (1927), Komission E (1984), Madaus (1938), Martindale (1967) and Martindale (1972). 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.

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 respiratory 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.

These uses are not supported by long-standing evidence nor by clinical evidence.

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

3.1.1. Mode of action

Laxative effect

Animal experimental studies concerning the effectiveness of linseed in the indications approved for humans are scarce.

The laxative effects of linseed have long been recognised empirically then shown in animal and clinical investigations (Blaschek e*t al.* 2011; Kurth 1976; Wirths *et al.* 1985*;* Meier *et al.* 1990). 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. According to the Ph. Eur. Monograph “Linseed” (Lini semen - 0095) the minimum swelling index is 4. Hence, 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 (Blaschek e*t al.* 2011; Schilcher *et al.* 1986*;* Weiss and Fintelmann 1999).

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 (Lewis and Weingold 1985; Schilcher *et al.* 1986).

In an animal study with rats the excremental moist weight under a linseed containing diet (10%, 20%, 40% crushed linseed for 90 days) in comparison to a control group increased to 84%, the dry weight of the excrements to 20%; the water content of the faeces increased dose-dependently from 39% up to 58% (Ratnayake *et al.* 1992).

Effect on blood lipids levels

In vitro antioxidant and *in vivo* antidiabetic and antihyperlipidemic activity in rats with streptozotocin induced diabetes were reported for linseed oil (Kaithwas and Majumdar 2012).

Experiments with rats indicated that dietary supplementation of linseed may result in a lowering of serum cholesterol levels. It was claimed that this effect is caused by the content of unsaturated fatty acids (Blaschek e*t al.* 2011). Data on other fibres indicate that this effect may be linked to the soluble fibres.

Lucas *et al*. (2011) designed the following *in vivo* study to investigate whether linseed oil exerts hypocholesterolemic effects similar to ground whole linseed and to gain insight into its hypocholesterolemic mechanism. Forty-eight 6-month-old female Golden Syrian hamsters were either sham-operated (Sham) or ovariectomised (Ovx) and randomly assigned to one of four treatment groups (n=12/group) for 90 days: Sham, Ovx, Ovx+whole linseed, or Ovx+linseed oil. Hamsters in the Sham and Ovx groups were fed a semipurified diet (control), whereas Ovx+whole linseed and Ovx+linseed oil received the same basic diet supplemented with either whole linseed (15% w/w) or linseed oil (amount equivalent to the oil contribution of whole linseed). Ovariectomy significantly ($p<0.05$) increased serum total concentrations by approximately 15%; whole linseed, but not linseed oil, prevented ($p<0.05$) the ovariectomy-induced increase in serum total cholesterol concentration (12% and 4% reduction by whole linseed and linseed oil, respectively). Hamsters fed with linseed oil or whole linseed had high-density lipoprotein (HDL)-cholesterol concentrations similar to those of the Ovx hamsters receiving the control diet. Non-HDL-cholesterol concentrations were lowest in the whole linseed group, albeit not statistically different from the other treatment groups. There were no significant differences among groups in serum triglyceride concentration and liver lipids. Both whole linseed and linseed oil more than doubled the hepatic protein levels of 7α-hydroxylase in comparison to the Ovx hamsters receiving the control diet ($p<0.05$) (Lucas *et al*. 2011).

Zanwar *et al*. (2012) investigated the *in vivo* effect of a linseed lignan concentrate on the hyperlipidaemia in Triton WR-1339 induced hyperlipidemic rats. The concentrate was gained after an *n*-hexane extraction of a double cold pressed Linseed cake. The defatted cake was hydrolysed with 1 M aqueous sodium hydroxide for 1 h with intermittent shaking followed by extraction with 50% ethanol (V/V or m/m not mentioned). The lignan content was 40 mg/g. The linseed lignan concentrate showed a dose dependent significant decrease in total cholesterol, triglyceride and very high density lipoprotein. It increased the HDL-cholesterol level.

In New Zealand rabbits the effect of ground linseed (24 g/day/animal, day 29-56) on total cholesterol (TC), HDL cholesterol, LDL-cholesterol (LDL-C) and triacylglycerole (TAG) under a hypercholesterolaemic diet (1% cholesterol extracted from lyophilised egg, day 1-56) was tested. Linseed consumption showed hypolipaemic action by reducing LDL-C and TC levels; however, this cholesterol-lowering effect did not reduce the atherosclerotic lesions induced by a hypercholesterolaemic diet (1% cholesterol) for a short period of time (Prim *et al*. 2012).

Assessor´s comment

The lacking effect of ground linseed on the atherosclerotic lesions in the study of Prim et al. (2012) is may be due to the too short period of linseed supplementation (26 day) during the study. Due to the different preparations and posologies used, data neither support the plausibility of traditional use nor justify pre-clinically a lipid lowering indication.

Oestrogenic effect

Linseed contains lignan-precursors (Axelson *et al*. 1982). *In vitro* studies demonstrated that bacteria present in the colon convert these precursors into mammalian lignans, which are resorbed subsequently. The lignans were reported to interfere with the metabolism and activity of oestrogens (Borriello *et al*. 1985; Blaschek e*t al.* 2011; Luyengi *et al*. 1993; Nesbitt *et al*. 1999). Experiments in pigs demonstrated the capacity of various fibres, including linseed, to bind oestrogens (Arts *et al*. 1991).

It has therefore been suggested that linseed may lower the risk of oestrogen dependent tumours, e.g. some colon and mammary carcinomas (Adlercreutz 1984; Adlercreutz *et al*. 1987; Axelson *et al*. 1982; Borriello *et al*. 1985).

Anti-tumour effect

Diverse experiments with rats and mice investigated a potential anti-tumour effect of linseed ingestion (ESCOP 2003).

Menéndez *et al.* (2006) investigated the *in vitro* effect of different concentrations of α-linolenic acid (ALA) supplementation (10 µM, 20 µM) on the expression of HER2 (human epidermal growth factor receptor 2) overexpressing human breast cancer cell lines (BT-474 and SKBr-3 breast cancer cells). HER2 plays a pivotal role in malignant transformation and tumourigenesis. HER2 is associated with more aggressive phenotypes of breast cancer and an increased potential for forming metastasis. Both cell lines showed a concentration dependent decrease in expression of HER2. Exogenous supplementation with ALA significantly reduced HER2 mRNA levels and HER2 gene promoter activity ($p<0.001$). Finally ALA co-exposure enhanced trastuzumab efficacy (concentration 5 µg/ml) in HER2 overexpressing human breast cancer cell lines in concentrations of 2.5 µM, 5 µM, 10 µM, 20 µM, 40 µM synergistically.

SHN mice (selected for high early mammary tumour incidence) were fed a high-linoleate diet, a high-alpha-linolenate diet or a control diet. Spontaneous mammary tumourigenesis was significantly inhibited in the high alpha-linolenate group compared to the other two groups, while little difference was observed among groups in the rates of lung metastasis. The dietary alpha-linolenate/linoleate balance affected the fatty acid patterns of tissue lipids. According to the authors the results suggested that the dietary alpha-linolenate/linoleate balance affects the fatty acid composition and, in turn, spontaneous mammary tumourigenesis in mice selected for high early mammary tumour incidence (Kamano *et al.* 1989*)*.

The following study determined the effect of linseed oil on the growth of oestrogen receptor-positive human breast tumours (MCF-7) in ovariectomised athymic mice at high premenopausal-like oestrogen (E2) levels *in vivo*. Mice with established MCF-7 tumours were fed basal diet (control) or basal diet supplemented with linseed oil (40 g/kg) for 8 weeks. Compared with control, linseed oil reduced tumour size (33%, $p<0.05$) and tumour cell proliferation (38%, $p<0.05$) and increased apoptosis (110%, $p<0.001$). Linseed oil also reduced human epidermal growth factor receptor-2 (79%, $p<0.05$) and epidermal growth factor receptor (57%, $p=0.057$) expression, which then may have led to a reduction in protein kinase Akt (54%, $p<0.05$) and phosphorylation of mitogen-activated protein kinase (MAPK) to phosphorylated MAPK (pMAPK, 28%, $p<0.05$). ALA (50 µM) reduced MCF-7 cell proliferation *in vitro* (33%, $p<0.001$). Thus the authors reported that linseed oil regressed oestrogen receptor-positive human breast tumourigenesis at high E2 levels via down regulation of the growth factor mediated pathway, likely through its ALA content, and may explain the anti-tumourigenicity of linseed (Truan *et al.* 2010).

The proinflammatory cytokines IL-1α and IL-1β were reported to promote tumor angiogenesis that might be counteracted by IL-1 receptor agonists (IL-1Ra). By using microdialysis in a model of human breast cancers in nude mice, Lindahl *et al*. (2011) could perform species-specific analyses of released proteins in the microenvironment. They showed that tumours treated with tamoxifen and linseed or enterolactone decreased *in vivo* release of IL-1β, derived from the murine stroma and decreased microvessel density whereas dietary genistein had no effects. Cancer cell-released IL-1Ra was approximately 5 times higher than stroma-derived IL-1Ra. Tamoxifen, linseed or enterolactone increased IL-1Ra levels significantly whereas genistein did not. The tumour stroma contained macrophages, which expressed the oestrogen receptor. *In vitro*, oestradiol decreased IL-1Ra released from breast cancer cells and from cultured macrophages. IL-1Ra decreased endothelial cell proliferation significantly *in vitro* whereas breast cancer cell proliferation was unaffected in presence of oestradiol. Finally, IL-1Ra therapy of tumour-bearing mice opposed oestrogen-dependent breast cancer growth and decreased angiogenesis.

The objective of an investigation by Bommareddy *et al.* (2006) was to study the effects of dietary linseed meal, a source of both omega-3 fatty acid and lignans, on colon tumour development and compare them with the effects of dietary corn meal. Male Fischer rats, two groups of 24 each, were assigned to the AIN-93M diet supplemented with either 15% corn meal or 15% linseed meal, respectively.

Carcinogenesis was initiated with subcutaneous injections of azoxymethane (15 mg/kg) once a week for 3 consecutive weeks. Thirty-five weeks after initiation, blood was collected by cardiac puncture, and rats were sacrificed. The gastrointestinal tract was isolated. The site, size, and number of tumours were recorded. The fatty acid analysis of the collected serum and colon samples was performed. Expression of cyclooxygenase (COX)-1 and COX-2 was performed by Western blot method. Lignan levels in serum and colon samples were assayed. In corn and linseed meal groups the colon tumour incidence, multiplicity and size were found to be 82.6% and 29.4%, 1.3 and 0.3, 44.4 and 5.3 mm, respectively. Colon and serum samples of the corn meal group showed higher levels of omega-6 fatty acid levels whereas the linseed meal group exhibited higher levels of omega-3 fatty acids. COX-1 and COX-2 expression in the linseed group was significantly lower ($p<0.05$) as compared to the corn group (Bommareddy *et al.* 2006).

The next *in vivo* study of this group was designed to investigate the chemo preventive effects of dietary linseed on the development of intestinal tumours in Apc (Min) mice (model for colorectal and intestinal cancer). Apc (Min) mice were divided into five different groups, fed with control (AIN-93M meal), corn meal, linseed meal (15% w/w), corn oil, and linseed oil (15% w/w) supplemented diets.

Results showed that dietary linseed significantly decreased ($p<0.05$) tumour multiplicity and size in the small intestine and colon as compared to control, corn-treated groups. Intestine, colon, and serum samples of corn-treated groups showed higher levels of omega-6 fatty acids, whereas the linseed treated groups exhibited higher levels of omega-3 fatty acids. Lignans were detected in the serum, intestine, and colon samples for linseed meal group. COX-1 and COX-2 expression in the colon samples from the linseed meal group were significantly lower ($p<0.05$) as compared to the corn meal group. The authors concluded, that dietary linseed might be chemopreventive by increasing omega-3 fatty acid levels, lignans and decreasing COX-1 and COX-2 levels in Apc (Min) mice (Bommareddy *et al.* 2009).

The aim of the following *in vivo* study was to determine if a linseed-enriched diet had a chemo preventive effect on ovarian cancer in the laying hen. White Leghorn hens were fed with 10% linseed-enriched or standard diet for 1 year. The incidence and severity of ovarian cancer were determined by gross pathology and histology in the two groups. General health markers were also measured. Eggs were collected and analysed by gas chromatography to determine omega-3 fatty acid levels. A significant reduction in late stage ovarian tumours was detected in the linseed-fed hens. Incidences of ovarian cancer were not significantly different between the two groups. The authors concluded that a linseed diet increased overall survival in the laying hen. Linseed-fed hens' eggs incorporated significantly more omega-3 fatty acids compared to control hens. According to the authors, 10% linseed supplementation for 1 year in the laying hen results in a significant reduction in the severity of ovarian cancer, but causes no change in the incidence of the disease (Ansenberger *et al.* 2010).

The aim of a subsequent study was to determine if long-term consumption of a linseed enriched diet decreased ovarian cancer severity and incidence in the laying hen and to investigate its potential correlation with the expression of COX enzymes and prostaglandins E_2 ($PGE_{2)}$ concentration. White Leghorn hens were fed 10% linseed-enriched or standard diet for 4 years. The severity and incidence of ovarian cancer were determined by gross pathology and histology. COX-1, COX-2 protein, mRNA expression and PGE_2 concentrations in ovaries were measured by Western blot, quantitative real-time PCR and ELISA, respectively. The authors reported that there was a reduction in ovarian cancer severity and incidence in hens fed linseed diet. In correlation with decreased ovarian cancer severity and incidence, concentration of PGE_2 and expression of COX-2 were diminished in ovaries of hens fed linseed (Eilati *et al.* 2013).

Assessor's comments

Pre-clinically it has been investigated whether linseed has in vitro and in vivo influence on mammary tumourigenesis, possibly due to its high ALA-rich oil content in animal species selected for their early tumour development. In these in vivo models linseed decreased HER2 expression and expression of the oestrogen receptor. Dietary linseed meal containing high levels of omega-3 fatty acids and lignans was reported to affect colon tumour development possibly by increasing omega-3 fatty acid levels and decreasing COX-1 and COX-2 levels. The validity of the laying hen model developing ovarian cancers is not generally accepted. The transferability to the clinical level is questionable due to the different preparations used in these experiments and the preconceived animal models in early tumour development.

Anti-inflammatory and anti-oxidative effects

Linseed is a rich source of natural antioxidants. Linseed is composed of high concentrations of omega-3 fatty acids and lignans. While omega-3 fatty acids are reported to reduce inflammation, lignans have antioxidant properties. Specifically, secoisolariciresinol diglucoside (SDG), isolated from Linseed was shown *in vitro* to have direct hydroxyl radical scavenging properties and to inhibit lipid peroxidation

(Prasad 1997; Prasad *et al.* 2012; Kitts *et al.* 1999). These findings were supported recently by and Kinniry *et al*. (2006) and Lee *et al*. (2008) in the context of oxidative lung injury experiments.

The study of Bhatia *et al.* (2007) investigated the radioprotective and antioxidative potential of linseed oil *in vivo*. Swiss albino mice were administered linseed oil orally once daily for 15 consecutive days, then exposed to a single dose of 5 Gy of gamma radiation. Lipid peroxide, reduced glutathione and total protein were estimated in the liver. Liver enzyme assays (AST, ALT, AP) were also performed. Radiation-induced increases in the levels of lipid peroxidation, AST, ALT and AP were significantly ameliorated by linseed oil pre-treatment, and radiation-induced depletion in the level of glutathione (GSH) and AP activities was significantly inhibited by linseed oil administration. The authors reported that the lifespan was increased in the linseed oil treated irradiated mice in comparison with their respective control mice, with survival data showing an $LD_{(50/30)}$ (lethal dose for 50% of animals after 30 days) of 7.1 and 10 Gy for control and linseed oil treated irradiated mice, respectively, and produced a dose reduction factor for linseed oil of 1.40. Radiation-induced deficits in body and organ weight were significantly reduced or prevented in linseed oil pretreated mice (Bhatia *et al.* 2007).

Linseed supplementation was evaluated given to mice before and post-XRT (X-ray radiation therapy). Linseed-derived lignans were evaluated in abrogating ROS (reactive oxygen species) generation in cultured endothelial cells following gamma radiation exposure. Mice were fed 10% linseed or isocaloric control diet for three weeks and given 13.5 Gy thoracic XRT. Lungs were evaluated at 24 hours for markers of radiation-induced injury, after three weeks for acute lung damage (lipid peroxidation, lung oedema and inflammation), and after four months for late lung damage (inflammation and fibrosis). Linseed-lignans blunted ROS generation *in vitro*, resulting from radiation in a dose-dependent manner. Linseed-fed mice had reduced expression of lung injury biomarkers (Bax, p21 and TGF-beta1) at 24 hours following XRT and reduced oxidative lung damage as measured by malondialdehyde (MDA) levels at 3 weeks following XRT. In addition, linseed-fed mice had decreased lung fibrosis as determined by hydroxyproline content and decreased inflammatory cell influx into lungs at 4 months post XRT. Importantly, when Lewis lung carcinoma cells were injected systemically in mice, linseed dietary supplementation did not appear to protect lung tumours from responding to thoracic XRT (Lee *et al.* 2009).

A mouse model of ischemia reperfusion injury (IRI) was used with 60 min of ischemia followed by 180 min of reperfusion and the anti-apoptotic and anti-inflammatory effects of 10% linseed dietary supplementation was evaluated. Mice fed 10% linseed undergoing lung IRI were reported to have significantly lower levels of caspases and decreased apoptotic activity compared with mice fed 0% linseed. Lung homogenates and bronchoalveolar lavage fluid analysis demonstrated significantly reduced inflammatory infiltrate in mice fed with 10% linseed diet. Additionally, 10% linseed supplemented mice showed significantly increased expression of antioxidant enzymes and decreased markers of lung injury (Razi *et al.* 2011).

Bleomycin, an antineoplastic agent, has been associated with severe pulmonary toxicity, primarily fibrosis. Previous work has shown a reduction in bleomycin-induced lung pathology by long-chain omega-3 fatty acids. Treatment by short-chain omega-3 fatty acids, α-linolenic acid, found in dietary linseed oil may also reduce lung fibrosis. To test this hypothesis, 72 rats were divided between diets receiving either 15% (w/w) flaxseed oil or 15% (w/w) corn oil (control). These groups were further divided to receive either bleomycin or vehicle (saline) via an oropharyngeal delivery, rather than the traditional intratracheal instillation. Lungs were harvested at 2, 7, and 21 days after bleomycin or saline treatment. Animals receiving flaxseed oil showed a delay in oedema formation ($p=0.025$) and a decrease in inflammatory cell infiltrate and vasculitis ($p=0.04$ and 0.007, respectively). At days 7 and 21, bleomycin produced a reduction in pulmonary arterial lumen patency

(p=0.01), but not in rats that were treated with linseed oil. Bleomycin-treated rats receiving linseed oil had reduced pulmonary septal thickness (p=0.01), signifying decreased fibrosis (Lawrenz *et al.* 2012).

In an *in vivo* study Naqshbandi *et al.* (2012) investigated the protective effect of linseed oil on cisplatin-induced damage in liver. Adult male Wistar rats (8/group) were pre-fed with normal diet and then fed with diet rich in linseed oil (15%) for 10 days and then a single dose of cisplatin (6 mg/kg body weight) was administered intraperitoneally while still on diet. Control groups received a normal diet and either a dose of cisplatin or none. Serum/urine parameters, enzymes of carbohydrate metabolism and oxidative stress were analysed. Cisplatin caused perturbation of the antioxidant defence as reflected by the decrease in the activities of catalase, superoxide dismutase and glutathione peroxidase. Further the activities of various enzymes involved in glycolysis, tricarboxylic acid cycle, gluconeogenesis and hexose monophosphate shunt pathways were determined and were found to be differentially altered by cisplatin treatment. However, these alterations were ameliorated in cisplatin-treated rats fed on linseed oil.

This study investigated the impact of varying ratios of dietary linoleic acid (LA, 18:2n-6) to ALA, 18:3n-3) on the inflammatory response in dextran sulphate sodium (DSS)-induced colitis. Weanling male Sprague-Dawley rats were divided into five groups: a non-colitic group with a LA:ALA ratio of 215 (CON-215), and colitic groups with LA:ALA ratios of 215 (DSS-215), 50 (DSS-50), 10 (DSS-10) and 2 (DSS-2). Blends of groundnut, palmolein and linseed oils were used to provide varying LA:ALA ratios. All the rats were fed the respective experimental iso-energetic diets containing 10% fat for 90 days and DSS was administered during the last 11 days. Colonic inflammation was evaluated by clinical, biochemical and histological parameters. The results showed attenuation of colitis in the DSS-2 group as evidenced by significant reductions in disease activity index, mucosal myeloperoxidase activity ($p<0.05$), alkaline phosphatase activity ($p<0.01$) and increase in colon length ($p<0.01$) compared to the groups fed with higher ratios (DSS-215). This was accompanied by significant reductions in mucosal pro-inflammatory cytokines TNF-α ($p<0.01$) and IL-1β ($p<0.01$) and improvement in the histological score. Further, ALA supplementation increased long-chain (LC) n-3 PUFA and decreased LC n-6 PUFA in colon structural lipids (Tyagi *et al*. 2012).

The *in vivo* efficacy of *Linum usitatissimum* fixed oil was evaluated in nine mastitis-affected cows divided into three groups (three in each group), following once-a-day intramammary infusion of cold macerate petroleum-ether extracted linseed oil, cefoperazone or an oil-cefoperazone combination for 7 days and by monitoring the California mastitis test score, somatic cell count and microbial count in milk samples. The *in vitro* antimicrobial activity of the oil against *Staphylococcus aureus*, *Streptococcus agalactiae* and *Escherichia coli* was comparable to that of cefoperazone while the antimicrobial activity against *Enterococcus faecalis*, *Micrococcus luteus* and *Candida albicans*, was greater than that of cefoperazone. In the *in vivo* study, the oil exhibited significant reduction in the California mastitis test score and somatic cell count in milk samples from infected udders following 7 days of intramammary administration suggesting its anti-inflammatory effect. The microbial count in milk samples was also reduced significantly following oil treatment. The effects were comparable to the treatment by cefoperazone alone or in combination with the linseed oil. The authors concluded that the anti-inflammatory and antimicrobial properties of the oil may contribute to its therapeutic efficacy in mastitis and the oil could be used as an alternative treatment for bovine mastitis (Kaithwas *et al.* 2011a).

An *in vivo* study assessed the activity/anti-inflammatory potential of *Linum usitatissimum* fixed oil against castor oil-induced diarrhoea, turpentine oil-induced joint oedema, formaldehyde and Complete Freund's Adjuvant (CFA)-induced arthritis in Wistar albino rats (6 animals/group). The cold macerate petroleum-ether extracted linseed oil applied intraperitoneally (1 ml/kg, 2 ml/kg, 3 ml/kg

i.p.) significantly inhibited the castor oil-induced diarrhoea and turpentine oil-induced exudative joint oedema in a dose-dependent manner. Significant inhibitory effect of *Linum usitatissimum* fixed oil was observed in formaldehyde-induced proliferative global oedematous arthritis when given intraperitoneally, with significant checking of the serum glutamic oxaloacetic acid transaminase and serum glutamic pyruvic acid transaminase. Further, *Linum usitatissimum* fixed oil showed a significant dose-dependent protective effect against CFA-induced arthritis as well. Secondary lesions produced by CFA due to a delayed hypersensitivity reaction were also reduced in a significant manner. The authors concluded, that the anti-inflammatory activity of *Linum usitatissimum* fixed oil could be attributed to the presence of alpha linolenic acid (57.38%, an omega-3 fatty acid, 18:3, n-3) having dual inhibitory effect on arachidonate metabolism resulting in suppressed production of pro-inflammatory n-6 eicosanoids (PGE(2), LTB(4)) and diminished vascular permeability. Based on these observations the authors suggested a possible therapeutic potential of *Linum usitatissimum* fixed oil in inflammatory disorders like rheumatoid arthritis (Kaithwas *et al.* 2011b).

Tülüce *et al.* (2012) tested the antioxidant and antiapoptotic effects of linseed oil in Sprague Dawley male albino rats (7/group) exposed to ultraviolet C. Malondialdehyde (MDA), protein carbonyl (PC) and reduced GSH levels as well as glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities were measured in lens, skin and serum. In addition, β-carotene, vitamin A, C and E contents were measured in serum, while apoptosis was determined in retina. Rats were divided into three groups as control, UVC and UVC + linseed oil (4 ml/kg bw). UVC and UVC + linseed oil groups were exposed to UVC light for 1 h twice a day for 4 weeks. Linseed oil (4 ml/kg bw) was given by gavage before each irradiation period to the UV + linseed oil group. While MDA and PC levels of the UVC group increased compared to the control group, their levels decreased in the UVC + linseed oil group compared with the UVC group in skin, lens and serum. Skin GSH level decreased significantly in the UVC and UVC + linseed oil groups. As GPx and SOD activities of the UVC group were lower, their activities were higher in the UVC + linseed oil group in skin, lens and serum. There was only marked elevation of vitamin A level in the UVC group compared to the control group.

Apoptosis increased in the UVC group and the UVC + linseed oil groups in retina. However, retinal apoptosis was lower in the UVC + linseed oil group compared with the UVC group.

In a study investigating wound healing properties of linseed oil (Farahpour *et al.* 2011) 32 male rats received two circle shaped 7 mm^2 wounds each on both sides of the backbone. In 4 groups they were treated with 1.5% linseed oil in eucerin-vaselin, 0.75% linseed oil in eucerin-vaselin, control and placebo. Tissue samples were obtained on day 3, 7, 14 and 21. In the group with the 1.5% linseed oil treatment epithelialisation was prior to the other groups, the number of inflammatory cells was reduced compared to the other groups. Neo-angiogenesis was good and an epithelial layer was about to form, collagen filaments started forming cross junctions on day 7. Group A was completely epithelialised on day 14, neo-angiogenesis was not yet finished. On day 21 wound healing was almost finished in the control group.

Assessor's comments

In different in vivo models predominantly linseed oil was shown to have anti-inflammatory and anti-oxidant properties.

Other effects

Twenty-four Boxers dogs with arrhythmogenic right ventricular dysplasia (ARVC) were included in a study reported by Smith *et al.* (2007). Asymptomatic Boxers not receiving antiarrhythmic medications were evaluated with echocardiogram and electrocardiogram. Dogs with at least 1 ventricular

premature contraction (VPC) received 24-hour ambulatory electrocardiography recordings. Dogs with > 95 VPCs in 24 hours were randomised to 1 of 3 treatments: (1) Fish oil, 2 g; (2) linseed oil, 2 g; or (3) sunflower oil, 2 g (Control group), for 6 weeks. Investigators and owners were blinded to the treatment groups. All baseline measurements were repeated after the 6-week supplementation. The authors concluded that ω-3 fatty acids from fish oil, but not linseed oil, supplementation for 6 weeks reduced arrhythmia in Boxers with ARVC and that it could be useful in treating this common disease.

Lorenc-Kubis *et al.* (2001) could isolate a serine-proteinase-type inhibitor from linseed by ethanol fractionation.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

One part of the bulk materials in linseed is defaecated, the other part is fermented in the colon by bacteria (Cummings 1981). This process of fermentation can produce gas and lead to flatulence (Petroski 2000). The predominant products of fermentation are short chain fatty acids (SCFA), which are mainly resorbed (Blaschek *et al.* 2011). These acids can serve as nutrients for those cells forming the colonic mucosa (Guillon and Champ 2000).

In general investigations with fibres it was shown 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.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Preclinical tests on single dose toxicity, repeat dose toxicity, genotoxicity, carcinogenicity, reproductive toxicity, developmental and local tolerance of linseed have not been performed.

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 (Blaschek e*t al.* 2011).

In their publication “Thioyanate catalyzes myeloperoxidase-initiated lipid oxidation in LDL” Exner (2004) concluded that the myeloperoxidase-hydrogen peroxide-pseudo-halide thiocyanate-system (MPO/H2O2/SCN-system) might 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 was concluded that available scientific data are not sufficient to substantiate such a risk associated to linseed consumption.

Theoretically, very high lignan production could lead to infertility, as in clover disease of sheep (Adlercreutz 1984).

3.4. Overall conclusions on non-clinical data

Preclinical data on the laxative effect of linseed are scarce. The mode of action is supported by the swelling index of linseed and the lubrication via the mucilage.

The preclinical data on effects regarding the levels of blood lipids are inconsistent. Due to the different preparations, posologies and different targets tested, data neither support the plausibility of traditional use (not possible due to necessary medical supervision) nor justify pre-clinically a lipid lowering indication in well-established-use.

The anti-tumour effects are pre-clinically investigated especially using animal models linked to tumour development. The relevance for clinical situation is questionable.

The anti-inflammatory and anti-oxidant effects of predominantly linseed oil add to the plausibility of the traditional use of the demulcent preparation in mild gastrointestinal discomfort and data on wound healing effects can support the plausibility of a traditional use as poultice for minor skin inflammations.

Preclinical data covering single-dose, repeated-dose toxicity, genotoxicity and carcinogenicity are not available.

4. Clinical Data

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

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.

Effect as a demulcent preparation (traditional indication)

The effect as a demulcent preparation is attributed to the protective effect on the mucosa by the coating action (Kurth 1976; Schilcher *et al.* 1986; Steineggerand Hänsel 1988). Only general evidence supports 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) and the anti-inflammatory effects of linseed. Data to clarify the main pharmacological effects in humans are however insufficient.

Effect on blood lipids levels

Consumption of 50 g/day ground, raw linseed by 9 healthy female volunteers for 4 weeks lowered serum total cholesterol by 9% and LDL-Cholesterol by 18% (Cunnane 1993).

Austria *et al.* (2008) published data on the bioavailability of ALA in 30 healthy volunteers after ingestion of three different forms of linseed. Each group (n=10/group) received either 30 g of whole or ground linseed or 6 g of ALA from linseed oil baked into muffins per day for three month. Due to gastrointestinal side effects as bloating, flatulence, stomach aches/cramps 3 probands quitted in the

whole linseed group and two in the linseed oil group. ALA values increased after 4 weeks of diet within the ground and the linseed oil group, but did not increase in the whole linseed group. Cholesterol and triglyceride levels were unchanged. To compare the effects of hempseed oil and linseed oil on the profile of serum lipids and fasting concentrations of serum total and lipoprotein lipids, plasma glucose and insulin in healthy humans was the aim of the following study. Fourteen healthy volunteers participated in the study. A randomised, double-blind crossover design was used. The volunteers consumed hempseed oil and linseed oil (30 ml/day) for 4 weeks each. The periods were separated by a 4-week washout period. The linseed oil period resulted in a higher proportion of ALA in both serum CE (cholesteryl esters) and TG as compared with the hempseed oil period ($p < 0.001$). The proportion of arachidonic acid in CE was lower after the linseed oil period than after the hempseed oil period ($p < 0.05$). No significant differences were found between the periods in measured values of fasting serum total or lipoprotein lipids, plasma glucose, insulin.

The effects of hempseed oil and linseed oil on the profile of serum lipids differed significantly, with only minor effects on concentrations of fasting serum total or lipoprotein lipids, and no significant changes in concentrations of plasma glucose or insulin (Schwab *et al.* 2006).

Oestrogenic effect

According to quantitative urine assays performed with urine samples from 64 women (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) (Adlercreutz *et al.* 1987).

The effect of the ingestion of linseed powder on the menstrual cycle was evaluated in 18 normally cycling women, using a balanced randomised cross-over design. Each subject consumed her usual omnivorous, low fibre (control) diet for 3 cycles and her usual diet supplemented with linseed (linseed supplement dose 10 g/day) for another 3 cycles. Each second and third cycle were compared. Three anovulatory cycles occurred 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 oestradiol or oestrone during the early follicular phase, midfollicular phase, or LP. Although linseed ingestion had no significant effect on LP progesterone concentrations, the LP progesterone/oestradiol 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-sulphate (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 (Phipps *et al.* 1993).

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 oestrogen deficiency (Wilcox *et al.* 1990). 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 (Blaschek e*t al.* 2011). (See also chapter Clinical safety.)

Antitumor effect

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 affects 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 the 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 were 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 (Demark-Wahnefried *et al.* 2004).

Interactions

Because of their pharmacodynamic properties all bulk forming laxatives may delay the enteral absorption of concomitantly administered medications (Hardt and Geisthövel 1986; Standardzulassungen 1993). Linseed should therefore be taken at least ½ to 1 hour before or after intake of other medicinal products (Standardzulassungen 1993).

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 EMA in June 2004 in an HMPWP Position statement1 (EMEA/HMPWP/60/04)[1].

Morphine also belongs to the category of medicinal products, which inhibits 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 former 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 in combination with medicinal products known to inhibit the peristaltic movement (e.g. opioids, loperamide) only under medical supervision. Similar considerations can be made for high-ceiling diuretics, which might prevent swelling due to a negative fluid balance. Diuretics are not included in the monograph because there are no specific case reports in literature.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

According to Petroski (2000) in man, the presumed site of fermentation must 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 microorganisms 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.

Linseed usually acts within 12 to 24 hours. Sometimes the maximum effect is not reached before 2 to 3 days (Weiss and Fintelmann 1999).

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

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 cross-over 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 (Lampe *et al*. 1994).

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 (Kurzer *et al*. 1995).

In another randomised cross-over 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 ($p\leq0.001$) by 9 hours after linseed ingestion. The total plasma area under the curve (AUC) was higher on the 8th than on the 1st day (Nesbitt *et al*. 1999).

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 ALA concentration (Tarpila *et al*. 2002). In this controlled, double-blind, cross-over study they also examined the effect of the linseed supplementation on plasma enterolactone in the 80 volunteers. Serum enterolactone concentration was doubled during linseed supplementation.

4.2. Clinical Efficacy

4.2.1. Dose response studies

There are no dose-finding studies available.

4.2.2. Clinical studies (case studies and clinical trials)

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 consistency 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. Sixty-six patients recognised a clear improvement of their symptoms. There was no differentiation of the improved symptoms (Kurth 1976).

The laxative effects of linseed were investigated in 19 geriatric patients. They received purgative medicines such as either 20 ml lactulose or paraffin oil with phenolphthalein for one month and then either 10 g bruised linseed or 7 g psyllii semen or 14 g wheat bran with karaya gum two times a day for two month (one month as adaption, one month as study phase). The frequency of defaecation was similar in both phases (Meier *et al.* 1990).

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%) (Wirths *et al.* 1985).

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/day 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 of regular use (Tarpila *et al.* 2004).

Irritable Bowel syndrome (IBS)

In an open randomised controlled trial, subjects with IBS (n=40) were allocated to one of three intervention groups: two tablespoons of whole linseeds per day (n=14), two tablespoons of ground linseeds per day (n=13) and no linseeds as controls (n=13) by Cockerell *et al*. (2012). Symptom severity (primary outcome) and bowel habit were assessed before and after a 4-week intervention and statistical differences between the groups were compared. Thirty-one subjects completed the present study. Between-group analysis comparing the improvement in symptom severity did not reach statistical significance for whole linseeds (n=11) versus ground linseeds (n=11; p=0.62), whole linseeds versus controls (n=9; p=0.12) and ground linseeds versus controls (p=0.10). There were no significant changes in stool frequency or stool consistency for any of the groups. The authors concluded, that linseeds might be useful in relief of IBS symptoms. Further research is needed to detect clear differences between the effects of whole and ground linseeds.

Assessor's comments

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".

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 (Schilcher 1986; Weiss and Fintelmann 1999; Willuhn in Wichtl 1989).

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, heartburn, loss of appetite. For evaluation of the efficacy of linseed the abdominal symptoms (pain, nausea, heartburn, gastrospasm, 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%) (Grutzner *et al.* 1997).

Effect on blood lipids level

In the above-mentioned investigation (Wirths *et al.* 1985) 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 were 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 (Tarpila *et al.* 2004) 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 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), respectively. 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.

The effects of a lignan complex, providing 500 mg/day of secoisolariciresinol diglucoside (SDG), on serum concentration and urinary excretion of enterolactone (ENL), plasma lipids, serum lipoprotein oxidation resistance, and markers of antioxidant capacity were investigated. Healthy postmenopausal women ($n=22$) completed a randomised, double-blind, placebo-controlled, crossover study. Women consumed daily a low-fat muffin, with or without a lignan complex, for 6 weeks, separated by a 6-week washout period. Serum ENL concentration, urinary ENL excretion, plasma concentrations of total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), triacylglycerol (TAG), serum lipoprotein oxidation lag time, plasma Trolox-equivalent antioxidant capacity (TEAC), and ferric reducing ability of plasma (FRAP) were measured at the beginning and end of each intervention period. ENL concentrations in serum ($p<0.001$) and ENL urinary excretion ($p<0.001$) were significantly higher after the lignan complex intervention period compared with placebo. Plasma concentrations of TC, LDL-C, HDL-C, TAG, lipoprotein oxidation lag time, TEAC and FRAP were not affected. Daily consumption for

6 weeks of a low-fat muffin had no effect on plasma lipid concentrations, serum lipoprotein oxidation resistance, or plasma antioxidant capacity (Hallund *et al.* 2006).

Assessor's comments

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.

The effects of linseed on markers of cardiovascular risk in hypercholesterolemic adults were studied by Bloedon *et al.* (2008). Sixty-two men and post-menopausal women (44-75 y) with pre-study LDL-C between 130 and 200 mg/dl were randomised to 40 g/day of ground linseed-containing baked products or matching wheat bran products for 10 weeks while following a low fat, low cholesterol diet. Fasting lipoproteins, measures of insulin resistance, inflammation, oxidative stress, and safety were assessed at 0, 5 and 10 weeks. Linseed was well-tolerated, and increased serum levels of ALA ($p<0.001$). Compared to wheat, linseed significantly reduced LDL-C at 5 weeks (-13%, $p<0.005$), but not at 10 weeks (-7%, $p=0.07$). Linseed reduced lipoprotein a (Lp[a]) by a net of 14% ($p=0.02$), and reduced the homeostatic model assessment of insulin resistance (HOMA-IR) index by 23.7% ($p=0.03$) compared to wheat at 10 weeks, but did not affect markers of inflammation (IL-6, Hs-CRP) or oxidative stress (ox LDL, urinary isoprostanes) at any time points. In men, linseed reduced HDL-C concentrations by a net of 16% ($p=0.03$) and 9% ($p=0.05$) at 5 and 10 weeks, respectively. The authors concluded that ground linseed had a modest but short term LDL-C lowering effect, yet reduced Lp(a) and improved insulin sensitivity in hyperlipidaemic adults. The HDL-C lowering effect of linseed in men should be further investigated.

Linseed reduced serum total (-0.20 ± 0.51 mmol/l; $p=0.012$) and HDL-C (-0.08 ± 0.24 mmol/l $p=0.031$) concentrations in 101 menopausal women compared with wheat germ placebo (see Dodin *et al*. 2005 under oestrogenic effects).

Health aspects of partially defatted linseed in relation to serum lipids, indicators of oxidative stress, and *ex vivo* sex hormone activities were evaluated in the following randomised, crossover trial. Twenty-nine hyperlipideamic subjects (22 men and 7 postmenopausal women) completed two 3-week treatment periods in a randomised, crossover trial. Subjects were given muffins that contributed approximately 20 g fibre/day from either linseed (approximately 50 g partially defatted linseed/day) or wheat bran (control) while they consumed self-selected National Cholesterol Education Program Step II diets. Both muffins had similar macronutrient profiles. Treatment phases were separated by > or=2 weeks. Partially defatted linseed reduced TC (4.6 ± 1.2%; $p=0.001$), LDL-C (7.6 ± 1.8%; $p<0.001$), apolipoprotein B (5.4 ± 1.4%; $p=0.001$), and apolipoprotein A-I (5.8 ± 1.9%; $p=0.005$), but had no effect on serum lipoprotein ratios at week 3 compared with the control. There were no significant effects on serum HDL-C, serum protein carbonyl content, or *ex vivo* androgen or progestin activity after either treatment. Unexpectedly, serum protein thiol groups were significantly lower (10.8 ± 3.6%; $p=0.007$) at week 3 after the linseed treatment than after the control, suggesting increased oxidation. The authors concluded that partially defatted linseed is effective in lowering LDL-C. No effects on lipoprotein ratios, *ex vivo* serum androgen or progestin activity, or protein carbonyl content were observed (Jenkins *et al.* 1999).

The objective of a study by Patade *et al.* (2008) was to investigate the extent to which the daily incorporation of approximately 30 g of linseed, a rich source of lignans, omega-3 fatty acids, and fibre, for a period of 3 months into the diet of Native American postmenopausal women positively affects

their lipid profiles. Fifty-five mild to moderately hypercholesterolemic (> or =5.1 to < or =9.8 mmol/l) Native American postmenopausal women were randomly assigned to control (A), linseed (B) or linseed + additional oat bran fibre (C) groups. Overnight fasting venous blood was collected at baseline and at the end of the treatment period to analyse lipid parameters. Dietary linseed supplementation lowered TC and LDL-C by approximately 7% and 10%, respectively. However, the levels of HDL and triglyceride remained unaltered. No changes were observed in other clinical and haematological parameters. According to the authors Native American postmenopausal women benefit from regular consumption of linseed by reducing their risk of cardiovascular disease as seen from lowered LDL-C and TC levels (Patade *et al.* 2008).

Leukocyte adhesion and transendothelial migration, the critical pathogenic components in the development of atherosclerotic lesions, are largely mediated by cellular adhesion molecules (CAMs). It was examined whether dietary supplementation with ALA, 18:3n-3 affects the levels of soluble forms of CAMs in dyslipidaemic patients. Ninety male dyslipidaemic patients (mean age=51 ± 8 years) following a typical Greek diet were recruited. They were randomly assigned either to 15 ml of linseed oil (rich in ALA) per day (n=60) or to 15 ml of safflower oil (rich in linoleic acid [LA, 18:2n-6]) per day (n=30). The ratio of n-6:n-3 in linseed oil supplemented group was 1.3:1 and in safflower oil supplemented group 13.2:1. Dietary intervention lasted for 12 weeks. Blood lipids, soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble E-selectin (sE-selectin) were measured. Dietary supplementation with ALA significantly decreased sVCAM-1 levels (median decrease 18.7% [577.5 ng/ml versus 487 ng/ml, p=0.0001]) compared to baseline values. In the LA supplemented group, sVCAM-1 was also significantly decreased but to a lesser extent (median decrease 10.6% [550.5 ng/ml versus 496 ng/ml, p=0.0001]). After controlling for smoking habits, no significant difference was observed in the reduction of sVCAM-1 levels between the two treatment arms (p=0.205). The decrease of sVCAM-1 was independent of lipid changes in both groups. Dietary supplementation with ALA for 12 weeks significantly decreased sVCAM-1 levels in dyslipidaemic patients. The authors considered a potential mechanism for the beneficial effect of plant n-3 polyunsaturated fatty acids in the prevention of coronary artery disease (Rallidis *et al.* 2004).

The hypothesis that dietary ALA can exert effects on markers of cardiovascular risk similar to that produced by its longer chain counterparts in fish-oil was investigated. A dietary intervention study was undertaken to examine the effects of an ALA-enriched diet in 57 men expressing an atherogenic lipoprotein phenotype (ALP). Subjects were randomly assigned to one of three diets enriched either with linseed oil (high ALA, n=21), sunflower oil (SO, high linoleic acid, n=17), or sunflower oil with fish-oil (SOF n=19) for 12 weeks, resulting in dietary intake ratios of n-6:n-3 PUFA of 0.5, 27.9 and 5.2, respectively. The relative abundance of ALA and eicosapentaenoic acid (EPA) in erythrocyte membranes increased on the linseed oil diet (p<0.001), whereas both EPA and docosahexaenoic acid (DHA) increased after fish-oil (p<0.001). There were significant decreases in total plasma cholesterol within (linseed oil -12.3%, p=0.001; SOF -7.6%, p=0.014; SO -7.3%, p=0.033) and between diets (p=0.019), and decreases within diets after 12 weeks for HDL-C on linseed oil (-10%, p=0.009), plasma TG (-23%, p<0.001) and small, dense LDL (-22% p=0.003) in fish-oil. Membrane DHA levels were inversely associated with the changes in plasma TG (p= 0.001) and small, dense LDL (p<0.05) after fish-oil. Fish-oil produced predictable changes in plasma lipids and small, dense LDL (sdLDL) that were not reproduced by the ALA-enriched diet. Membrane DHA levels appeared to be an important determinant of these fish-oil-induced effects (Wilkinson *et al.* 2005).

An 8-week, randomised, double-blind, placebo-controlled study was conducted in fifty-five hypercholesterolaemic subjects, using treatments of 0 (placebo), 300 or 600 mg/day of dietary SDG from linseed extract to determine the effect on plasma lipids and fasting glucose levels. Significant treatment effects were achieved (p<0.05 to <0.001) for the decrease of TC, LDL-C and glucose

concentrations, as well as their percentage decrease from baseline. At weeks 6 and 8 in the 600 mg SDG group, the decreases of TC and LDL-C concentrations were in the range from 22.0 to 24.38% respectively (all p<0.005 compared with placebo). For the 300 mg SDG group, only significant differences from baseline were observed for decreases of TC and LDL-C. A substantial effect on lowering concentrations of fasting plasma glucose was also noted in the 600 mg SDG group at weeks 6 and 8, especially in the subjects with baseline glucose concentrations > or=5.83 mmol/l (lowered 25.56 and 24.96%; p=0.015 and p=0.012 compared with placebo, respectively). Plasma concentrations of secoisolariciresinol (SECO), enterodiol (ED) and enterolactone were all significantly raised in the groups supplemented with linseed lignan. The observed cholesterol-lowering values were correlated with the concentrations of plasma SECO and ED (r 0.128-0.302; p<0.05 to < 0.001). According to the authors dietary linseed lignan extract decreased plasma cholesterol and glucose concentrations in a dose-dependent manner (Zhang *et al.* 2008b).

Assessor's comments

Although ALA supplementation may cause small decreases in fibrinogen concentrations and fasting plasma glucose, most cardiovascular risk markers do not appear to be affected. Further trials are needed, but dietary supplementation with ALA to reduce cardiovascular disease cannot be recommended. 300 or 600 mg/day of dietary secoisolariciresinol diglucoside (SDG) from linseed extract decreased plasma cholesterol and glucose concentrations in a dose-dependent manner.

Meta-analysis

The aim of the following systematic review and meta-analysis of randomised controlled trials was to determine whether dietary supplementation with ALA can modify established and emerging cardiovascular risk markers. The studies were identified by a search of Medline, Embase, Cochrane Controlled Trials Register (CENTRAL), and the metaRegister of Controlled Trials (mRCT). Changes in concentrations of TC, LDL-C, HDL cholesterol, very low density lipoprotein (VLDL) cholesterol, triglyceride, fibrinogen, and fasting plasma glucose, and changes in body mass index, weight, and systolic and diastolic blood pressure were analysed. Fourteen studies with minimum treatment duration of four weeks were reviewed. ALA had a significant effect on three of the 32 outcomes examined in these studies. Concentrations of fibrinogen (0.17 µmol/l, 95% confidence interval (CI) -0.30 to -0.04, p=0.01) and fasting plasma glucose (0.20 mmol/l, 95% CI -0.30 to -0.10, p<0.01) were reduced. There was a small but clinically unimportant decrease in HDL (0.01 mmol/l, 95% CI -0.02 to 0.00, p<0.01). Treatment with ALA did not significantly modify TC, triglycerides, weight, body mass index, LDL, diastolic blood pressure, systolic blood pressure, VLDL, and apolipoprotein B (Wendland *et al.* 2006).

In the following review a comprehensive literature search was performed on the basis of English reports of randomised controlled trials of linseed or its derivatives on lipid profiles in adults, which were published from January 1990 to October 2008. Attempts also were made to access unpublished data. Study quality was assessed by using the Jadad score, and a meta-analysis was conducted. Twenty-eight studies were included. Linseed interventions reduced total and LDL-C by 0.10 mmol/l (95% CI: -0.20, 0.00 mmol/l) and 0.08 mmol/l (95% CI: -0.16, 0.00 mmol/l), respectively; significant reductions were observed with whole linseed (-0.21 and -0.16 mmol/l, respectively) and lignan (-0.28 and -0.16 mmol/l, respectively) supplements but not with linseed oil. The cholesterol-lowering effects were more apparent in females (particularly postmenopausal women), individuals with high initial cholesterol concentrations, and studies with higher Jadad scores. No significant changes were found in the concentrations of HDL-cholesterol and triglycerides. Linseed significantly reduced circulating total

and LDL-C concentrations, but the changes were dependent on the type of intervention, sex, and initial lipid profiles of the subjects (Pan *et al.* 2009).

Assessor's comments

Several clinical trials have investigated the effects of linseed and linseed-derived products (linseed oil, lignans, SDG from linseed extract) on blood lipids; however, the findings have been inconsistent. The cholesterol-lowering effects were more apparent in females (particularly postmenopausal women), individuals with high initial cholesterol concentrations, and studies with higher quality. No significant changes were found in the concentrations of HDL-C and triglycerides.
Linseed significantly reduced circulating total and LDL-C concentrations, but the changes were dependent on the type of intervention, sex, and initial lipid profiles of the subjects. Further studies are needed to determine the efficiency of linseed on lipid profiles in men and premenopausal women and to explore its potential benefits on other cardiometabolic risk factors and prevention of cardiovascular disease.

Effect in metabolic syndrome, cardiovascular risk factors and Alzheimer's disease

Morbidly obese patients frequently display asymptomatic chronic activation of acute phase response, with potentially adverse metabolic and cardiovascular consequences. Nutritional preparations to improve this phenomenon have rarely been administered. Aiming to investigate the effect of the supplementation of linseed flour, a prospective randomised double-blind cross-over study was designed. Outpatient obese subjects (n=41) were clinically and biochemically screened, and results for 24 subjects were analysed. Age was 40.8 ± 11.6 years (83.3% females) and body mass index (BMI) was 47.1 ± 7.2 kg/m^2. Linseed flour in the amount of 30 g/day (5 g of alpha-linolenic acid - omega-3) and an equal mass of placebo (manioc flour) were administered for 2 weeks each. Variables included general biochemical investigation, white blood cell count (WBC), C-reactive protein (CRP), serum amyloid A (SAA) and fibronectin. No intolerance was registered. Body weight and general biochemical indices remained stable. Initial CRP and SAA were elevated (13.7 ± 9.9 and 17.4 ± 8.0). WBC (8100 ± 2100/mm^3) and fibronectin (463.2 ± 61.3 mg/dl) were acceptable but in the upper normal range. Corresponding findings after supplementation of linseed were 10.6 ± 6.2 mg/l, 14.3 ± 9.2 mg/l, 7300 ± 1800/mm^3 and 412.8 ± 38.6 respectively ($p<0.05$). No change during the control period regarding baseline occurred when placebo was randomised to be given first; however, when it was followed by omega-3 supplementation, CRP and SAA recovered, whereas WBC and fibronectin remained depressed during those 2 weeks (7500 ± 2100/mm^3 and 393.2 ± 75.8 mg/dl, $p<0.05$). Various inflammatory markers were elevated in the studied population, although not necessarily exceeding the normal range; significant reduction could be demonstrated; some persistent effects of linseed supplement 2 weeks after discontinuation were observed (Faintuch *et al*. 2007).

Aiming to focus an obese population, a prospective, randomised pilot study was designed. Morbidly obese candidates for bariatric surgery (n=29, age 46.3 ± 5.2 years), 82.8% females (24/29), BMI 44.9 ± 5.2 kg/m^2, with C-reactive protein/CRP > 5 mg/l were recruited. Twenty were randomised and after exclusions, 18 were available for analysis. Linseed powder (60 g/day, 10 g ALA, n=11) and isocaloric roasted cassava powder (60 g/day, fat-free, n=9) were administered in a double-blind routine for 12 weeks. During linseed consumption neutrophil count decreased and fibrinogen, complement C4, prothrombin time and carotid diameter remained stable, whereas placebo (cassava powder) was associated with further elevation of those measurements. Inflammatory and coagulatory markers tended to exhibit a better outlook in the linseed group. Also large-artery diameter stabilised whereas further increase was noticed in controls. The authors raised the question whether there will be

a less deleterious cardiovascular course in seriously obese subjects receiving a linseed supplement (Faintuch *et al.* 2011).

Obermann *et al.* (2013) analysed in a longitudinal observational cohort of Alzheimer patients (N=4414) from the National Alzheimer's Coordination Center Unifrom data set. The cognition parameters using 10 psycho-metric tests were observed regarding changes under the 100 most frequently medications. Medications associated with improved psychometric performance were naproxen, calcium-vitamin D, ferrous sulphate, potassium chloride, linum (n=175), and sertraline.

Assessor's comments

Very preliminary data addressed the anti-inflammatory effects of linum in pro-inflammatory profiles in metabolic syndromes and cognition parameters in Alzheimer's patients. They do not support any indication.

Effect on blood glucose level

Linseed is rich in omega-3 fatty acids and antioxidants and is low in carbohydrates. In exploratory studies, linseed was incorporated in recipes, which resulted in a reduction in the glycaemic index of the food items. These observations prompted us to investigate the efficacy of linseed supplementation in type 2 diabetics (n=29). Subjects were assigned to the experimental (n=18) or to the control group (n=11) on the basis of their desire to participate in the study. The diet of the experimental group was supplemented daily with 10 g of linseed powder for a period of 1 month. The control group received no supplementation or placebo. During the study, diet and drug intake of the subjects remained unaltered. The efficacy of supplementation with linseed was evaluated through a battery of clinico-biochemical parameters. Supplementation with linseed reduced fasting blood glucose by 19.7% and glycated haemoglobin HbA(1c) by 15.6%. A favourable reduction in TC (14.3%), triglycerides (17.5%), LDL-cholesterol (21.8%), and apolipoprotein B and an increase in HDL-cholesterol (11.9%) were also noticed (Mani *et al.* 2011).

The following study aimed to investigate the effect of a linseed-derived lignan supplement on glycaemic control, lipid profiles and insulin sensitivity in type 2 diabetic patients. This was a randomised, double-blind, placebo-controlled, cross-over trial and it was conducted between April and December 2006 in Shanghai, China. Seventy-three type 2 diabetic patients with mild hypercholesterolemia were enrolled into the study. Patients were randomised to supplementation with linseed-derived lignan capsules (360 mg lignan per day) or placebo for 12 weeks, separated by an 8-week wash-out period. HbA1c, lipid profiles, insulin resistance index and inflammatory factors were measured. Sixty-eight completed the study and were included in the analyses. The lignan supplement significantly improved glycaemic control as measured by HbA(1c) (-0.10 ± 0.65% vs. 0.09 ± 0.52%, p=0.001) compared to placebo; however, no significant changes were observed in fasting glucose and insulin concentrations, insulin resistance and blood lipid profiles. Urinary excretion of lignan metabolites (enterodiol and enterolactone) was significantly higher after the lignan supplement intervention was compared to baseline (14.2 ± 18.1 vs. 1.2 ± 2.4 µg/ml, p<0.001). According to the authors data also suggested minimal competition between lignan and isoflavones for bioavailability when measured by excretion concentrations (Pan *et al.* 2007).

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 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% (Cunnane *et al.*

1993). The authors concluded that linseed may be nutritionally beneficial by decreasing postprandial glucose responses in healthy people.

Assessor's comments

The preliminary results of the study of Mani et al. (2011) show a marginal effect in the treatment of diabetes mellitus type II. The posology was inefficient, the sample size too small and the baseline diet was not defined. Daily lignan supplementation resulted in modest, yet statistically significant improvements in glycaemic control in type 2 diabetic patients in China without apparently affecting fasting glucose, lipid profiles and insulin sensitivity. Further studies are needed to validate these findings and explore the efficacy of linum on type 2 diabetes The transferability of the results of the lignin-study to linum is questionable. Therefore these studies do not support a well-established use indication.

Oestrogenic and anti-tumour effects

The effects of daily intake of bread produced with partially defatted ground linseed on the climacteric symptoms and endometrial thickness of postmenopausal women were tested by Simbalista *et al.* (2010). A double-blind, placebo-controlled, randomised clinical trial was performed with 38 women who had been postmenopausal for 1-10 years and consumed 2 slices of bread containing 25 g of linseed (46 mg lignans) or wheat bran (<1 mg lignans; control) every day for 12 consecutive weeks. The outcome variables were the daily number of hot flashes, the Kupperman Menopausal Index (KMI), and endometrial thickness. The plasma lipid profile (TC and HDL, LDL, and VLDL-cholesterol fractions and triglycerides) and the hormones oestradiol, follicle-stimulating hormone, thyroid-stimulating hormone, and free thyroxine were also measured. Food intake was evaluated by means of two 24-h recalls, before and after the treatment. Twenty patients in the study group and 18 in the control group completed the study. The general characteristics did not differ between the 2 groups at the start of the study. Both had significant, but similar, reductions in hot flashes and KMI after 3 months of treatment. Moreover, endometrial thickness was not affected in either group. The study clearly shows that although linseed is safe, its consumption at this level (46 mg lignans/day) is no more effective than placebo for reducing hot flashes and KMI.

There are limited data on the efficacy of linseed on the consequences of oestrogen deficiency in menopausal women. The purpose of the following study was to assess the effects of linseed incorporation into the diet of healthy menopausal women. One hundred and ninety-nine menopausal women were randomly assigned to consume 40 g linseed/day (n=101) or wheat germ placebo (n=98) for 12 months. At baseline and at month 12, serum levels of lipids, bone mineral density (BMD), and menopausal symptoms were evaluated. Statistical analysis was performed under the intention to treat principle. Linseed reduced serum total (-0.20 ± 0.51 mmol/l; p=0.012) and high-density lipoprotein (-0.08 ± 0.24 mmol/l; p=0.031) cholesterol concentrations compared with wheat germ placebo. BMD did not differ significantly between the two arms. Both linseed and wheat germ reduced (p<0.0001) the severity scores of menopausal symptoms, but no statistical difference was found between the two arms. The authors concluded that 1-year incorporation of linseed into the diet produced a favourable, but not clinically significant effect on blood cholesterol and caused no significant change in BMD or symptoms in healthy menopausal women (Dodin *et al.* 2005).

A case-control study conducted in a homogeneous population from a central area in France was designed to explore the hypothesis that alpha-linolenic acid inhibits breast cancer, using fatty acid levels in adipose breast tissue as a biomarker of past qualitative dietary intake of fatty acids. Biopsies of adipose breast tissue at the time of diagnosis were obtained from 123 women with invasive non-

metastatic breast carcinoma. Fifty-nine women with benign breast disease served as controls. Individual fatty acids were analysed by capillary gas chromatography.

An unconditional logistic regression model was used to obtain odds ratio estimates whilst adjusting for age, menopausal status and BMI. No association was found between fatty acids (saturated, monounsaturated, long-chain polyunsaturated n-6 or n-3) and the disease, except for alpha-linolenic acid which showed an inverse association with the risk of breast cancer. The relative risk of breast cancer for women in the highest quartile of adipose breast tissue alpha-linolenic acid level was 0.36 (95% confidence interval=0.12-1.02) compared with those in the lowest quartile (p trend=0.026), suggesting, according to the authors, a protective effect of alpha-linolenic acid in the risk of breast cancer. The effects of dietary alpha-linolenic acid on the risk of breast cancer warrant further study (Klein *et al.* 2000).

A randomised double-blind placebo-controlled clinical trial examined the effects of dietary linseed on tumour biological markers and urinary lignan excretion in postmenopausal patients with newly diagnosed breast cancer. Patients were randomised to daily intake of either a 25 g linseed-containing muffin (n=19) or a control (placebo) muffin (n=13). At the time of diagnosis and again at definitive surgery, tumour tissue was analysed for the rate of tumour cell proliferation (Ki-67 labelling index, primary end point), apoptosis, c-erbB2 expression, and oestrogen and progesterone receptor levels. Twenty-four-hour urine samples were analysed for lignans, and 3-day diet records were evaluated for macronutrient and caloric intake. Mean treatment times were 39 and 32 days in the placebo and linseed groups, respectively. Reductions in Ki-67 labelling index (34.2%; p=0.001) and in c-erbB2 expression (71.0%; p=0.003) and an increase in apoptosis (30.7%; p=0.007) were observed in the linseed, but not in the placebo group. No significant differences in caloric and macronutrient intake were seen between groups and between pre- and post-treatment periods. A significant increase in mean urinary lignan excretion was observed in the linseed group (1,300%; p<0.01) compared with placebo controls. The total intake of linseed was correlated with changes in c-erbB2 score (r=-0.373; p=0.036) and apoptotic index (r=0.495; p<0.004) Side effects were abdominal fullness and increased bowel movements (Thompson *et al.* 2005).

Ninety menopausal women were randomly distributed (75 finished the study) into three study groups: group I (n=22) received 1 g per day of linseed extract containing at least 100 mg of SDG, group II (n=28)received 90 g per day of linseed meal containing at least 270 mg of SDG, and group III (n=25) received 1 g per day of collagen (placebo group). Subjects were assessed for menopausal symptoms by the Kupperman index at the beginning and at the end of the 6 months of treatment. Subjects were also assessed for endometrial thickness and vaginal cytology. The Kupperman index values at the beginning and end of the treatments were analysed using the paired t-test. Both the linseed extract (p=0.007) and the linseed meal (p=0.005) were effective in reducing the menopausal symptoms when compared with the placebo control (p=0.082). Alternatively, the changes in Kupperman index were also computed and submitted to analysis of variance. In this case, no significant differences were found (p=0.084) although the data indicate a decreasing tendency for the Kupperman index by both the linseed extract and the linseed meal groups. Neither the linseed extract nor the linseed meal exerted clinically important oestrogenic effects on the vaginal epithelium or endometrium as revealed by the absence of changes in the blood levels of follicle stimulating hormone and oestradiol, as well as in the endometrial thickness, and vaginal epithelial maturation value (Colli *et al.* 2012).

Another phase III, randomised, placebo, controlled trial was conducted to evaluate the efficacy of linseed in reducing hot flashes. Postmenopausal women with or without breast cancer were randomly assigned to a linseed bar (providing 410 mg of lignans) for 6 weeks versus a placebo bar. Participants completed daily, prospective, hot flash diaries during the baseline week, and then ate one study bar

per day for 6 weeks while recording their daily hot flashes. The intra-participant difference in hot flash activity between baseline and the last treatment week was the primary endpoint.

Adverse effects were evaluated through a self-report and the Common Terminology Criteria assessment. A total of 188 women were enrolled in this trial. The mean hot flash score was reduced 4.9 in the linseed group and 3.5 in the placebo group (p=0.29). In both groups, slightly more than a third of the women received a 50% reduction in their hot flash score. Only one adverse effect was significantly different between groups, grade 1 pruritus, which was more common in the placebo group (8% vs 1%). Both groups reported abdominal distension, flatulence, diarrhoea, and nausea. Adherence and ability to detect treatment assignment did not differ between groups. The results of this trial do not support the use of 410 mg of lignans for the reduction of hot flashes. The bars were fairly well tolerated, with both groups reporting gastrointestinal effects, probably due to the fibre content (Pruthi *et al.* 2012).

Assessor's comments

Very preliminary data mainly in postmenopausal women do not specify oestrogenic effects. But the base of data does not exclude oestrogenic effects as well.

The conclusion of the authors of the study (Thompson et al. 2005), that dietary linseed has the potential to reduce tumour growth in patients with breast cancer is preliminary. The sample size is too small and the duration of the trial too short to draw such a conclusion.

Psychiatric effects – Meta-Analysis:

Studies using augmentation of pharmacotherapies with omega-3 in bipolar disorder have been conducted. The significant findings from meta-analyses of omega-3 in the treatment of bipolar depression and bipolar mania are presented. The findings of 5 pooled datasets (n=291) on the outcome of bipolar depression revealed a significant effect in favour of omega-3 (p=0.029), with a moderate effect size of 0.34. On the outcome of mania, 5 pooled datasets (n=291) revealed a non-significant effect in favour of omega-3 (p=0.099), with an effect size of 0.20. Minor heterogeneity between studies on the outcome of bipolar depression was found (I^2=30%; p=0.213), which was not present on the outcome of bipolar mania (I^2=0%; p=0.98). Funnel plot symmetry suggested no significant likelihood of publication bias. Meta-regression analysis between sample size and effect size, however, revealed that studies with smaller sample sizes had larger effect sizes (p=0.05). According to the authors the meta-analytic findings provided strong evidence that bipolar depressive symptoms may be improved by adjunctive use of omega-3. The evidence, however, did not support its adjunctive use in attenuating mania (Sarris *et al.* 2012).

Assessor's comments

The results of the above mentioned meta-analysis regarding psychiatric effects of omega-3 essential fatty acids reducing the depressive symptoms of a bipolar disorder are preliminary and the used products might have been different (lacking information regarding the quality of the products) from Lini semen as described in the monograph. Therefore they are not transferable to Lini semen.

4.3. Clinical studies in special populations (e.g. elderly and children)

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 3.1.1. and chapter 5.1.4.). The clinical relevance yet cannot be evaluated, but as a precautionary measure the use of linseed during pregnancy, lactation and in children under 12 years of age is not recommended.

Use in women with hormonally dependent tumours also is not recommended.

Children and Adolescents

In a four-week placebo-controlled, blinded, randomised clinical trial 32 participants aged 8 to 18 years with LDL-cholesterol from 135 mg/dl (3.5 mmol/l) to less than 193 mg/dl (5.0 mmol/l) were included. The intervention group ate 2 muffins and 1 slice of bread daily containing ground linseed (30 g linseed total). The control group ate muffins and bread substituted with whole-wheat flour. The control group ate muffins and bread substituted with whole-wheat flour. Dietary linseed supplementation resulted in an attributable decrease of -7.35 mg/dl (-0.19 mmol/l) in HDL-cholesterol (95% CI, -3.09 to -11.60 mg/dl [-0.08 to -0.30 mmol/l]; relative: -15%, 95% CI, -24% to -6%; p=0.001), an increase of 29.23 mg/dl (+0.33 mmol/l) in triglycerides (95% CI, 4.43 to 53.14 mg/dl [+0.05 to +0.60 mmol/l]; relative: +26%, 95% CI, +4% to +48%; p=0.02), and an increase of +4.88 g/day in dietary polyunsaturated fat intake (95% CI, +0.22 to +9.53; relative: +76%, 95% CI, +3% to +148%; p=0.04). Linseed had no attributable effects on TC (-8.51 mg/dl [-0.22 mmol/l]; 95% CI, -21.66 to 4.25 mg/dl [-0.56 to +0.11 mmol/l]; relative: -4%, 95% CI, -10% to +2%; p=0.20), LDL-cholesterol (-6.96 mg/dl [-0.18 mmol/l]; 95% CI, -16.63 to 2.71 mg/dl [-0.43 to +0.07 mmol/l]; relative: -5%, 95% CI, -12% to +2%; p=0.15), body mass index z score (+0.002; 95% CI, -0.147 to +0.150; relative: +0%, 95% CI, -12% to +12%; p=0.30), or total caloric intake (+117 kcal; 95% CI, -243 to +479; relative: +8%, 95% CI, -17% to +33%; p=0.52). An attributable change in total and LDL-cholesterol failed to exclude a potential benefit of linseed supplementation based on a pre-specified minimum clinically important reduction of 10% (Wong *et al.* 2013)

Assessor's comments

The study has major shortcomings as lacking data regarding the small group of patients and the too short duration of the study and the increase in BMI. Therefore it can support safety data but is not sufficient for efficacy. Linseed supplementation therefore remains an unverified strategy for the clinical management of cardiovascular risk factors in youths with hyperlipidaemia.

Linseed oil

In a controlled clinical trial 30 children suffering from attention deficit hyperactivity disorder (ADHS) were supplemented with linseed oil corresponding to 200 mg ALA and 25 mg Vitamin C two times a day for three month. Total hyperactivity scores decreased significantly (Joshi *et al.* 2006).

Assessor's comments

The study is not relevant for this assessment. There is no information on the used linseed oil, the influence of vitamin C cannot be differentiated, the baseline diet is not comparable to European conditions, data on baseline content of ALA and LA are nor given. Therefore the data are not transferable.

To complete the data a randomised placebo controlled trial of linseed oil in paediatric bipolar disorder is mentioned. Gracious et al. supplemented 25 children with bipolar disorder with linseed oil capsules for 16 weeks without being able to demonstrate significant changes compared to virgin olive oil (Gracious et al. 2010).

This study is not relevant for this assessment, due to the lack of effect and because Linseed oil has no medical tradition in Europe when orally used.

4.4. Overall conclusions on clinical pharmacology and efficacy

The use of linseed for intestinal affections was referred to by Lonicerus in 1679. Madaus also described the use of linseed for intestinal affections in other European countries like Denmark, Lithuania and Hungary. There was one non-controlled pilot study with 70 patients available (see chapter 4.2 Clinical studies). The traditional use is plausible, attributed to the protective effect on the mucosa by the coating action of the mucilage. Therefore, the indication as a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort can be regarded as a traditional one.

There is very marginal experience available concerning the use in children. Therefore and because of the possible oestrogenic effects the use is not recommended in children under the age of 12 years.

For other safety concerns, see chapter 5 Clinical safety.

Since Dioskurides the use as a poultice in case of skin inflammations has been documented in many German, other European and non-European references. The procedure for the preparation of a poultice was described by Culbreth (1927), Madaus (1938), Martindale (1967, 1972). The use as a poultice has been mostly attributed to the water-binding capacity of mucilages. This action is a physical one. Some references reported 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. Furthermore it is difficult for patients to recognise the limit of self-medication concerning skin inflammations (from sunburn to erysipelas) or even furunculosis. The very preliminary clinical data regarding wound healing in external use are not sufficient to support a traditional use in minor skin inflammations.

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.

The available clinical data are inconclusive and therefore not sufficient to support a well-established indication with respect to levels of blood lipids in the monograph, a traditional indication is not possible, due to necessary medical supervision.

Concerning the treatment of inflammations of mucous membranes of respiratory 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 may act 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. These uses are neither supported by long-standing evidence nor by clinical evidence.

Table 1. Clinical trials performed with *Linum usitatissimum*

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
Human Pharmacology							
Cunnane *et al.* 1995	Open; 4 weeks	50 g Linseed/day orally	10 volunteers	Healthy	30% increase of bowel movement		Shows laxative effect
Lampe *et al.* 1994	Randomised cross-over study	10 g linseed/day	18 premeno-pausal women	Healthy	Enterodiol and enterolactone urine excretion increased Lignans unchanged in urine	CI 95%	Not relevant
Nesbitt *et al.* 1995	Randomised cross-over study; 7 days	5, 15, 25 g/day raw or processed linseed (muffin)	9 women	Healthy	Dose-dependent increase in urinary lignan excretion		Shows pharmaco-logical effect
Tarpila *et al.* 2002	Controlled, double-blind, cross-over study 4 weeks	Ground linseed of 1.3 g/100 g and linseed oil of 5 g/100 g	80 volunteers	Healthy	Increased significantly the serum alpha-linoleic acid concentration	CI 95%	Shows pharmaco-logical effect
Cunnane *et al.* 1993	Open	50 g carbohydrates as a piece of white bread or linseed bread; 25 g linseed mucilage	6 women volunteers	Healthy	The AUC for blood glucose 1 h postprandial decreased by 28%. decreased 2 h post-prandial hyperglycaemia after a glucose test meal by 27%		Shows pharmaco-logical effect
Blood lipid levels							
Austria *et al.* 2008	Randomised, double-blind design 3 months	30 g whole or ground linseed/day; 6 g ALA from linseed oil/day	30 volunteers n=10/group, Dropout: 3/0/2	Healthy	ALA increased after 4 weeks in group II and III; not in group I. Cholesterol and triglycerides Unaltered	Anova; SAS followed by Duncan Multiple range post	No effect on blood lipids

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
						hoc test; $p<0.05$	
Wirths *et al.* 1985	84 days	39 g ground linseed; 46 g fruit muesli; 34 g mixed raw fibres	32 elderly patients	Constipation	Increasing stool frequency in 69% of patients; ($p=0.001$) 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)	No information	Supports laxative effect
Tarpila *et al.* 2002	Controlled clinical trial	Ground linseed of 1.3 g/100 g and linseed oil of 5 g/100 g	80 volunteers	Healthy	Linseed reduced serum TC 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.	2/2 cross over trial; t-test; Wilcoxon rank sum test; CI 95%; SAS	Marginal cholesterol lowering effect
Schwab *et al.* 2006	Randomised, double-blind crossover design 3 months	Hempseed oil 30 ml/day linseed oil 30 ml/day 4 weeks each; 4 weeks wash-out	14 volunteers	Healthy	Minor effects on concentrations of fasting serum total or lipoprotein lipids	SPSS V 10.0 Wilcoxon matched pairs signed rank test $p<0.05$	No effect on blood lipids
Hallund *et al.* 2006	Randomised, double-blind,	Lignan complex rich in the plant; lignan	22 post-menopausal	Healthy	Daily consumption for 6 weeks of a low-fat muffin had no effect		Effect not clinically

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
	placebo-controlled, crossover study; 6 months	SDG was isolated from linseed	women		on plasma lipid concentrations, serum lipoprotein oxidation resistance, or plasma antioxidant capacity		relevant
Jenkins *et al.* 1999	Randomised, crossover trial; 3 weeks treatment phases were separated by > or =2 weeks	Muffins that contributed approximately 20 g fibre/day from either linseed (approximately 50 g partially defatted linseed/day) or wheat bran (control) while they consumed self-selected National Cholesterol Education Program Step II diets	29 (22 men, 7 postmenopausal women)	Hyperlipidaemia	Partially defatted linseed reduced TC (4.6 ± 1.2%; p=0.001), LDL-cholesterol (7.6 ± 1.8%; p<0.001), apolipoprotein B (5.4 ± 1.4%; p=0.001), and apolipoprotein A-I (5.8 ± 1.9%; p=0.005), but had no effect on serum lipoprotein ratios at week 3 compared with the control. Partially defatted linseed is effective in lowering LDL-C	CI 95%	Effect not clinically relevant
Patade *et al*. 2008	Randomised, double-blind, controlled, study; 3 months	Control (A), linseed (B) or linseed + additional oat bran fibre (C)	55 Native American post-menopausal women Group A/B/C: 17/20/18 Dropout: 8/3/2	Mild to moderately hypercholesterolemia	Linseed supplementation lowered TC and LDL-C by approximately 7% and 10%; the levels of HDL and triglyceride remained unaltered	CI 95%	Effect not clinically relevant
Rallidis *et al.* 2004	Randomised, double-blind,	Typical Greek diet 15 ml of linseed oil (rich	90 male Patients	Dyslipidaemia	Dietary supplementation with ALA for 12 weeks significantly		

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
	controlled, study; 3 months	in ALA) per day or to 15 ml of safflower oil (rich in linoleic acid [LA, 18:2n-6]) per day	(mean age=51 ± 8 years) Verum 60 Placebo 30 7 dropouts		decreased sVCAM-1 levels in dyslipidaemic patients; median decrease 18.7% [577.5 ng/ml versus 487 ng/ml, p=0.0001])		
Wilkinson *et al.* 2005	Randomised, double-blind, controlled, study; 3 months	Linseed oil (high ALA, n=21), sunflower oil (SO, high linoleic acid, n=17), or sunflower oil with fish-oil (SOF n=19) for 12 weeks	57 male	Atherogenic Lipoprotein Phenotype	Significant decreases in total plasma cholesterol within (linseed oil -12.3%, p=0.001; SOF -7.6%, p=0.014; SO -7.3%, p=0.033) and between diets (p=0.019), and decreases within diets after 12 weeks for HDL-cholesterol on linseed oil (-10%, p=0.009), plasma TG (-23%, p < 0.001) and small, dense LDL (-22% p=0.003) in fish-oil. Fish-oil produced predictable changes in plasma lipids and small, dense LDL that were not reproduced by the ALA-enriched diet	CI 95%	Effect not clinically relevant Not transferable to linseed
Zhang *et al.* 2008b	Randomised, double-blind, placebo-controlled study	Treatments of 0 (placebo), 300 or 600 mg/day of dietary SDG from linseed extract; Baseline diet open	55 17/18/20	Hypercholesterinaemia	Significant treatment effects (p<0.05 to <0.001) for the decrease of TC, LDL-C and glucose concentrations, as well as their percentage decrease from baseline. At weeks 6 and 8 in the 600 mg SDG group, the decreases of TC and LDL-C	SAS V 9.1; ITT yes Sample size calculation	Effect not clinically relevant Not transferable to linseed

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
					concentrations were in the range from 22.0 to 24.38% respectively (all $p<0.005$ compared with placebo)		
Laxative effect							
Kurth 1976	Multicentre non-controlled study		108 patients (81 female, 27 male, 19-81 y); 35 dropouts	Constipation, heartburn, eructation and diarrhoea	73 completed the study 66 clear improvement of symptoms		Supporting
Meier *et al.* 1990	Open	20 ml lactulose or paraffin oil with phenolphthalein for one month and then either 10 g bruised linseed or 7 g psyllii semen or 14 g wheat bran with karaya gum two times a day for two month (one month as adaption, one month as study phase).	19 geriatric patients	Constipation	Daily administration of a bulk-forming agent is, at the same level of effectiveness, less expensive (-35%) than therapy with lactulose alone		Supporting
Wirths *et al.* 1985	Open; 4 weeks; 2 months wash out	39 g linseed two times a day	32 geriatric patients	Constipation	Improvement of defaecation, particularly of the frequency in 52%		Supporting laxative effect
Tarpila *et al.* 2004	Randomised investigator-	6 - 24 g/day either linseed (roughly	55 patients	Constipation predominant	Bowel movement frequency, abdominal discomfort/bloating	CI 95%	Supporting laxative effect

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score e.g. Jadad score	Comments on clinical relevance of results
	blinded trial; 3 months	ground partly defatted) or psyllium		irritable bowel syndrome	and abdominal pain. Each symptom was scored 1 - 5 (1=worse, 2=unchanged, 3=somewhat relieved, 4=considerably relieved and 5=completely relieved) linseed decreased significantly (p=0.002)		
IBS							
Cockerell *et al.* 2012	Open randomised controlled trial	Two tablespoons of whole linseeds per day (n=14), two tablespoons of ground linseeds per day (n=13) and no linseeds as controls (n=13)	40	IBS	Between-group analysis comparing the improvement in symptom severity did not reach statistical significance for whole linseeds (n=11) versus ground linseeds (n=11; p=0.62), whole linseeds versus controls (n=9; p=0.12) and ground linseeds versus controls (p=0.10). There were no significant changes in stool frequency or stool consistency for any of the groups.		Groups too small to reach significance; dose too low
Functional upper abdominal complaints							
Grutzner *et al.* 1997	3 days	Linseed mucilage preparation	70	Functional upper abdominal complaints (pressure and pain in the	Abdominal symptoms (pain, nausea, heartburn, gastrospasm, feeling to have to vomit, loss of appetite, repletion, eructation, sensation of pressure) were		Supporting plausibility for tradition

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
				epigastrium, repletion, eructation, nausea, feeling to have to vomit, heartburn, loss of appetite.)	scored from 1 (no complain) to 5. The score decreased from 20.19 (± 6.03) to 13.20 (± 3.30) ($p < 0.01$).		
Effect in metabolic syndrome and cardiovascular risk factors							
Faintuch *et al*. 2007	Prospective randomised double-blind cross-over study	Linseed flour 30 g/day Manioc flour 30 g/day	24	Obesity	Initial CRP and SAA were elevated (13.7 ± 9.9 and 17.4 ± 8.0). WBC (8100 ± 2100/mm^3) & fibro-nectin (463.2 ± 61.3 mg/dl) were acceptable but in the upper normal range. Corresponding findings after supplementation of linseed were 10.6 ± 6.2 mg/l, 14.3 ± 9.2 mg/l, 7300 ± 1800/mm^3 & 412.8 ± 38.6 respectively ($p<0.05$). Significant reduction could be demonstrated.	SPSS 11.0; CI 95%	Effect not clinically relevant
Faintuch *et al.* 2011	Single phase, parallel arms, double-blind, placebo controlled study; 3	Linseed powder (60 g/day, 10 g ALA, n=10) and isocaloric roasted cassava powder (60 g/day, fat-free, n=8)	n=29, age 46.3 ± 5.2 years), 82.8% females (24/29), 20 random; 18 completed	BMI 44.9 ± 5.2 kg/m^2, with C-reactive protein/CRP > 5 mg/l were recruited.	Neutrophil count decreased & fibrinogen, complement C4, prothrombin time & carotid diameter remained stable, whereas placebo (cassava powder) was associated with further elevation of those measurements.	Sample size calculation: 5% reduction WBC Count; 80% power type 1 error	Effect not clinically relevant; too short; ill-defined baseline diet

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
	months					0.05	
Obermann *et al.* 2013	Longitudinal observational cohort	Linum	175	Alzheimer patients	5 out of 100 medications associated with improved psychometric performance, including linum n=175 out of n=4414		Interesting aspect; too preliminary
Blood glucose level							
Mani *et al.* 2011	Open 4 months	10 g of linseed powder/day vs. placebo	29 Verum: 18 Placebo: 11	Type 2 diabetes	Reduced fasting blood glucose by 19.7% and glycated haemoglobin by 15.6%. A favourable reduction in total cholesterol (14.3%), tri-glycerides (17.5%), low-density lipoprotein cholesterol (21.8%), & apo-lipoprotein B and an increase in HDL-cholesterol (11.9%).	SPSS 11.5 CI 95% Student´s t-test	Supporting, but not proving
Pan *et al.* 2007	Prospective randomised, double-blind, placebo-controlled, cross-over trial; 3 months 8 weeks wash-out	Linseed-derived lignan capsules (360 mg lignan per day; vs placebo)	73, 5 dropouts	Type 2 diabetic non-insulin dependent; 50-79 y; LDL-C Level ≥2,9 mmol/l; exclusion: oestrogen use last 6 months; phytoestrogen containing MP´s; antibiotics in last 3 m; severe	The lignan supplement significantly improved glycaemic control as measured by HbA(1c) (-0.10 ± 0.65% vs. 0.09 ± 0.52%, p=0.001) compared to placebo; however, no significant changes were observed in fasting glucose and insulin concentrations, insulin resistance and blood lipid profiles	CI 95% one-sided significance level 5%; sample size calc. 67 with 10% drop-out; 90% power	Effect not clinically relevant; too little information on the MP used

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
				renal, liver, heart, pituitary, thyroid or mental diseases; alimentary tract ulceration; absorption affecting diseases; history of cancer; drug, alcohol abuse			
Oestrogenic and anti-tumour effects							
Simbalista *et al.* 2010	Prospective double-blind, placebo-controlled, randomised clinical trial 3 months	Bread produced with partially defatted ground linseed Bread with wheat bran and toasted barley	38 women postmenopausal 1-10 y 20 verum; 18 control	Amenorrhoea <1y; oestradiol <73,4 pmol/l FSH> 39IU/l KMI 20-51, >2 flashes/day	Both groups had significant, but similar, reductions in hot flashes and KMI	SPSS 12.0 CI 95%	None
Dodin *et al.* 2005	Prospective double-blind, placebo-controlled, randomised clinical trial 1 year	40 g linseed/day vs. Wheat bran	199 post-menopausal women 101 verum/98		Reduced serum total (-0.20 ± 0.51 mmol/l; p=0.012) & high-density lipoprotein (-0.08 ± 0.24 mmol/l; p=0.031) cholesterol concentrations; KMI not influenced	ITT +	Effect not clinically relevant
Klein *et al.* 2000	Case control study	None	123 women	Invasive non-metastatic breast carcinoma	No association was found between fatty acids (saturates, mono-unsaturates, long-chain	Unconditional logistic re-gression	Effect not clinically relevant

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score e.g. Jadad score	Comments on clinical relevance of results
					polyunsaturates n-6 or n-3) and the disease, except for alpha-linolenic acid which showed an inverse association with the risk of breast cancer, suggesting a protective effect of alpha-linolenic acid in the risk of breast cancer	model was used to obtain odds ratio esti-mates whilst adjusting for age, meno-pausal status BMI	
Thompson *et al.* 2005	Randomised double-blind placebo-controlled clinical trial 39 days	25 g linseed-containing muffin (n=19) vs control (placebo) muffin (n=13)	32 women	Newly diagnosed breast cancer	Reductions in Ki-67 labelling index (34.2%; p=0.001) and in c-erbB2 expression (71.0%; p=0.003) and an increase in apoptosis (30.7%; p=0.007) were observed in the linseed, but not in the placebo group. Significant increase in mean urinary lignan excretion was observed in the linseed group (1,300%; p<0.01)	Sigma Stat; 30% difference between arms, 80% power; CI 95% two sided test	Effect not clinically relevant
Colli *et al.* 2012	Randomised double-blind placebo-controlled clinical trial 6 months	Group I received 1 g/ day of linseed extract containing at least 100 mg of SDG (n=28), group II received 90 g/day of linseed meal	75 postmeno-pausal women (group I 22, group II 28, group III 25)	FSH>40IU/ml oestradiol<30pg/ ml; amenorrhoea > 12 months; climacteric symptoms	Both the linseed extract (p=0.007) and the linseed meal (p=0.005) were effective in reducing the menopausal symptoms when compared with the placebo control (p=0.082) Neither the linseed extract nor	Graph Pad Prism 3.0 CI 95%	Supportive, groups too small to exclude oestrogenic effects

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
		containing at least 270 mg of SDG (n=22), and group III received 1 g/day of collagen (placebo group, n=25)	Age 46-68	Excl: history of thrombosis, -phlebitis; undiagnosed vaginal bleeding; family history of breast- or endometrium cancer, suspicious mammogram; hormones taken in past 6 months; signs of GI malabsorption	the linseed meal exerted clinically important oestrogenic effects on the vaginal epithelium or endometrium as revealed by the absence of changes in the blood levels of FSH and oestradiol, as well as in the endometrial thickness, and vaginal epithelial maturation value		
Pruthi *et al.* 2012	Phase III, randomised, placebo, controlled trial; 6 weeks	Linseed bar (providing 410 mg of lignans) vs Placebo bar	188 postmeno-pausal women (88 in verum, 90 in placebo) 10 dropout	With or without breast cancer	Slightly more than a third of the women received a 50% reduction in their hot flash score; adverse events abdominal distension, flatulence, diarrhoea, and nausea	CI 95%	Negative
Azrad *et.al.* 2012	Observation al study; 31 days	Samples from a previous randomised clinical trial	161 men; group 1 control n=41; group 2 linseed n=40; group 3 low fat diet	Prostate cancer pre prostatectomy	Despite consuming seven times more ALA per day, men in the flaxseed arm had similar amounts of prostatic ALA relative to men not consuming flaxseed. In unadjusted analysis, there were significant positive	Bonferroni correction for multiple testing; p=0.001	Preliminary data, not relevant for the monograph

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
			n=40; group 4 linseed and low fat diet n=40 Dropouts: 27		associations between prostatic ALA and PSA (ρ = 0.191, p = 0.028) and Ki67 (ρ = 0.186, p = 0.037). After adjusting for covariates (flaxseed, age, race, BMI and statin-use) the association between ALA and PSA remained (p = 0.004) but was slightly attenuated for Ki67 (p = 0.051).		
Special populations							
Wong *et al.* 2013	placebo-controlled, blinded, randomised clinical trial; 4 weeks	2 muffins and 1 slice of bread daily containing ground linseed (30 g linseed total) vs. muffins and bread whole wheat flour	32 (age 8-18 y)	LDL-cholesterol from 135 mg/dl (3.5 mmol/l) to less than 193 mg/dl (5.0 mmol/l)	An attributable change in total and LDL-cholesterol failed to exclude a potential benefit of linseed supplementation based on a pre-specified minimum clinically important reduction of 10%	ITT +; SAS 9.3; t-test	Inconclusive; groups too small; duration too short
Joshi *et al.* 2006	Controlled clinical trial three months	Linseed oil corresponding to 200 mg ALA and 25 mg Vitamin C two times a day	30 children	ADHS	Total hyperactivity scores decreased significantly	SPSS Students t-test CI 95%	Preliminary data not transferable to linseed
Billinsky *et al.* 2013	Placebo-controlled, double-blinded, randomised clinical trial	Linseed lignan (543 mg/day vs. Placebo	100 (49-87 y) 55 female, 40 male Verum: 49 Placebo: 46	Healthy	These data suggested the linseed lignan product does not pose a risk of hypoglycaemia or hypotension in healthy adults aged 49-87 years.	SAS 9.2; CI 95%; ITT +; LOCF	Negative

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
	6 months walking program		Dropouts: 5				
Safety							
Bentz *et al.* 2010	Double-blind cross-over study	None	40 patients	Crohn's disease	IgG antibodies against linseed in 70% of CD patients vs 10% of the healthy controls amongst other antibodies	SPSS, R and Sigma Stat; Kruskal Wallis; X^2; ANOVA	Pilot study
Fremont *et al.* 2010	patients attending the allergology department	None	1371 patients attending the allergology department		Prick-in-prick tests (PIP using the fresh seed; positive in 5.8% of the 1317 patients. 73 of 77 PIP-positive patients were atopic; cross-reactivity with five seeds: peanut, soybean, rapeseed, lupine and wheat, and with rape pollen; 0.15% of this population presented with food allergy to linseed and positive PIP to heated and extruded linseed. Sensitisation to processed linseed characterised only the allergic subjects. Positive prick tests to natural linseed were mainly due to cross-reactions.		Rare allergies to linseed are already labelled
Lemos *et al.* 2012	Randomised double-blind	1 g linseed oil two times daily (n=80) vs	160 patients Verum 75	Haemodialysis; chronic renal	Decrease of CRP and the absence of side effects.	80% power; CI	No adverse effects

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
	multicentre placebo-controlled clinical trial 120 days	placebo	Placebo 70 Dropouts before study 15	failure		95% 30% reduction of CRP	

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

5.1.1. Cyanide

Linseed contains about 20 - 50 mg cyanide/100 g in form of the cyanogenic diglycosids linustatin, neolinustatin and small amount of the monoglucoside linamarin.

Oomah analysed the seeds of 10 linseed 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 was also present in 8 of the 10 cultivars at low levels (< 32 mg/100 g) (Oomah *et al.* 1992).

In a study in 10 volunteers, neither a single dosage of 30 g and 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% (Schulz *et al.* 1983; Schulz *et al.* 1981).

Another investigation showed that 50 g ground, raw linseed consumed by 9 healthy female volunteers for 4 weeks raised the urinary thiocyanate excretion 2.2-fold (Cunnane *et al.* 1993). The reason appeared to be that cyanide was set free from diglycosides very slowly because of the acidity of gastric fluid. The detoxification process starts immediately and was not saturated because the cyanide was set free very slowly (Alonso *et al*. 1996; Anon 1983; Blaschek e*t al.* 2011; Schilcher 1979; Schilcher *et al.* 1986; Schilcher and Wilkens-Sauter 1986; Willuhn in Wichtl 1989).

In a randomised investigator-blinded trial, 55 patients suffering from constipation predominant irritable bowel syndrome received 6 - 24 g/day 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-month 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 treatment and 189 µmol/l after 3-month linseed treatment. After the open period this value decreased to 104 µmol/l (Tarpila *et al.* 2004). The reference value for thiocyanate is 250 µmol/l for smokers and 100 µmol/l for non-smokers (ACGIH 1995).

The enzyme rhodanase catalyses the change of cyanide into thiocyanate (rhodanide), which is 200 times less toxic than cyanide (Blaschek e*t al.* 2011). Regular consumption of linseed causes an accumulation of thiocyanate, which can be compared to the blood level of thiocyanate in heavy smokers. The accumulation 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 (Schulz *et al.* 1983).

5.1.2. Cadmium

The Ph. Eur. Monograph “Linseed” (Lini semen -0095) indicates a maximum content of 500 µg/1000 g (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 analysed more than 1500 samples of linseed. The content of cadmium in linseed cultivated for medical use was below 0.2 ppm (200 µg/1000 g) (Schilcher 2001).

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 (Tarpila *et al.* 2004) 55 patients suffering from constipation predominant irritable bowel syndrome received 6 - 24 g/day 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-month ingestion of an average linseed dose of 17.4 g/day. The mean blood cadmium concentration was normal at 3.4 nmol/l. The reference value is 10 nmol/l (ACGIH, 1995).

Other references indicate that linseed should not contain more than 0.3 mg/kg cadmium because toxic effects are not expected below this limit (Klein and Weigert 1987; Standardzulassungen Leinsamen 1996; Schilcher 2001).

The controlled, double-blind, cross-over study by Tarpila *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.

5.1.3. 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 (Adlercreutz 1984).

A standardised linseed [*Linum usitatissimum* L.], lignan enriched product with evidence of product quality and known quantity of the bioactive component, lignin was examined by Billinsky *et al.* (2013). It was determined whether linseed lignan causes clinical hypoglycaemia or hypotension in healthy older adults. Participants aged 49-87 years were randomised in a double-blind trial to receive linseed lignan (543 mg/day in product) or placebo while completing a 6-month walking program. The 94 participants who completed the study were stratified by age (<65 years versus ≥65 years) and treatment category to determine whether older adults were more susceptible to adverse effects. After 6 months of treatment, average plasma glucose level (5.4±0.6mmol/l), systolic blood pressure (127±14 mmHg), and diastolic blood pressure (80±9 mmHg) were within normal clinical range. Controlling for sex and body mass index covariates resulted in no observed differences between plasma glucose or blood pressure measurements between treatment or age groups ($p>0.05$). No incidents of hypoglycaemia or hypotension were observed during the treatment with the product, suggesting that 543 mg falls at or below the no observable adverse effect level (NOAEL). The authors concluded that the linseed lignan product does not pose a risk of hypoglycaemia or hypotension in healthy adults aged 49-87 years.

A linseed lignan extract containing 33% SDG was evaluated for its ability to alleviate lower urinary tract symptoms (LUTS) in 87 subjects with benign prostatic hyperplasia (BPH). A randomised, double-blind, placebo-controlled clinical trial with repeated measurements was conducted over a 4-month period using treatment dosages of 0 (placebo), 300, or 600 mg/day SDG. After 4 months of treatment, 78 of the 87 subjects completed the study. For the 0 (n=24), 300 (n=29), and 600 mg/day (n=25) SDG groups, respectively, the International Prostate Symptom Score (IPSS) decreased -3.67 ± 1.56, -7.33 ±1.18, and -6.88 ± 1.43 (mean ± SE, p=0.100, < 0.001, and < 0.001 compared to baseline), the Quality of Life score (QOL score) improved by -0.71 ± 0.23, -1.48 ± 0.24, and -1.75 ± 0.25 (mean ± SE, p=0.163 and 0.012 compared to placebo and p=0.103, < 0.001, and < 0.001 compared to baseline), and the number of subjects whose LUTS grade changed from "moderate/severe" to "mild" increased by three, six, and 10 (p=0.188, 0.032, and 0.012 compared to baseline). Maximum urinary flows insignificantly increased 0.43 ± 1.57, 1.86 ± 1.08, and 2.7 ± 1.93 ml/second (mean ± SE, no statistical significance reached), and post-voiding urine volume decreased insignificantly by -29.4 ± 20.46, -19.2 ± 16.91, and -55.62 ± 36.45 ml (mean ± SE, no statistical significance reached). Plasma concentrations of SECO, ED, and enterolactone (EL) were significantly raised after the supplementation. The observed decreases in IPSS and QOL score were correlated with the concentrations of plasma total lignans, SECO, ED, and EL. According to the authors dietary linseed lignan extract appreciably improved LUTS in BPH subjects, and the therapeutic efficacy appeared to be comparable to that of commonly used intervention agents of alpha1A-adrenoceptor blockers and 5alpha-reductase inhibitors (Zhang *et al.* 2008a).

Assessor's comments

The above mentioned two studies showed no specified safety risk. Due to the special preparations are not corresponding to the quality of linseed, these studies can be used as supporting evidence for the safety of higher lignan quantities.

5.1.4. Oestrogenic effect

The data mentioned under pharmacodynamics suggested that there might be an oestrogenic or anti-oestrogenic 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 considered that the oestrogenic effect might be a positive one e.g. to influence hormonally dependent tumours or to improve oestrogen deficiency.

In "Linseed in human nutrition" Hutchins and Slavin (2003) described in chapter 6 the effects of linseed 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."

Sprando *et al*. (2003) described the effect of linseed consumption on male and female reproductive function and foetal development. In their conclusion: "a review of the available literature has suggested that the consumption of linseed can affect various reproductive indices in both the male and female rat. The reviewed animal studies have suggested that the effect of linseed on various reproductive indices and sex hormone levels depends on the dose, timing, and duration of exposure.

In the female, effects included a lengthened oestrous 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 foetus. Neither testis structure, the process of spermatogenesis, sperm production, or sperm morphology were affected by linseed 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".

Assessor´s Comment:

Because of 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 to women with hormone-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 under 12 years of age.

These statements are also relevant for the traditional indication.

Prostatic alpha-linoleic acid (ALA)

Observational studies have reported associations between prostatic cancer and prostatic ALA content. In a pre-surgical model could be shown that linseed supplementation for 31 days in different dose groups prior to prostatectomy did not influence the amount of prostatic ALA found in gas chromatography of the resectate. Nevertheless, the authors concluded, that the study provided evidence, that prostatic ALA independent of the ALA amount consumed is positively associated with biomarkers of aggressive prostate cancer (Azrad *et al.* 2012).

Assessor's comments

The cited study is irrelevant for the labelling of linseed.

5.1.5. Crohn's Disease

Environmental factors are thought to play an important role in the development of Crohn's disease (CD). Immune responses against auto-antigens or food antigens may be a reason for the perpetuation of inflammation. In a pilot study, 79 CD patients and 20 healthy controls were examined for food immunoglobulin G (IgG). Thereafter, the clinical relevance of these food IgG antibodies was assessed in a double-blind cross-over study with 40 patients. Based on the IgG antibodies, a nutritional intervention was planned. The pilot study resulted in a significant difference of IgG antibodies in serum between CD patients and healthy controls. IgG antibodies against linseed in 70% of CD patients vs. 10% of the healthy controls amongst other antibodies against processed cheese, yeast and other foods were detected. The daily stool frequency significantly decreased by 11% during a specific diet compared with a sham diet. Abdominal pain was reduced and general well-being improved. According to the authors the mechanisms by which IgG antibodies might contribute to disease activity are remained to be elucidated (Bentz *et al.* 2010).

Assessor's comments

Patients suffering from Crohn´s Disease have a significantly higher rate of antibodies against linseed. Since this is the first publication and the data have to be reduplicated, a special labelling covering patients with Crohn´s disease in addition to the general allergenicity contraindication is not needed to be introduced.

5.1.6. Allergenicity

In a population of patients attending the allergology department, Fremont *et al.* (2010) evaluated the frequency of sensitisation to linseed, characterised allergens. Natural, heated and extruded linseeds were tested using prick-in-prick tests (PIP using the fresh seed), SDS PAGE, immunoblots, immunoblot inhibition and Fourier Transform Infrared (FTIR) spectroscopy. PIP tests to natural linseed were positive in 5.8% of the 1317 patients. Seventy-three of 77 PIP-positive patients were atopic. There was cross-reactivity with five seeds: peanut, soybean, rapeseed, lupine and wheat, and with rape pollen. Immunoblot inhibition by bromelain confirmed the presence of specific IgE to cross-reactive carbohydrate determinants (CCD). 0.15% of this population presented with food allergy to linseed and positive PIP to heated and extruded linseed. Sensitisation to processed linseed was characterised only the allergic subjects. Positive prick tests to natural linseed were mainly due to cross-reactions. Linseed allergy was rare and could be detected by PIP to heated extruded linseed.

Assessor's comments

The above cited trial is included in the contraindication due to allergenicity. An additional labelling is not necessary.

5.1.7. Linseed oil

Lemos *et al.* (2012) reported about a randomised double blind multicentre placebo controlled clinical trial with 160 haemodialysis patients suffering from chronic renal failure in Brazil, of whom 80 received 1 g linseed oil two times daily for 120 days resulting in a statistically significant decrease of C-reactive protein and the absence of side effects.

Assessor's comments

The above cited trial documents reported no adverse effects.

5.2. Patient exposure

Publication	n=adult probands	Disease n= adult patients	Children (age group)
Efficacy			
Healthy probands			
Lampe *et al.* 1994	18 premenopausal women		
Cunnane *et al.* 1993	6+9		
Phipps *et al.* 1993	18 women		
Wilcox *et al.* 1990	25 postmenopausal women		
Nesbitt *et al.* 1995	9 women		
Cunnane *et al.* 1995	10		
Dodin *et al.* 2005	101 women PMS		
Hallund *et al.* 2006	22 postmenopausal women		
Schwab *et al.* 2006	14		
Colli *et al.* 2012	22/28 (Linseed extract/ Linseed meal) women PMS		
Pruthi *et al.* 2012	88 women PMS		
Simbalista *et al.* 2010	20 women, hot flashes		
Austria *et al.* 2008	10 whole; 10 ground; 10 oil		
Constipation			
Kurth 1976		108 Constipation	
Meier *et al.* 1990		19 Constipation	
Wirths *et al.* 1985		32 Constipation	
Tarpila *et al.* 2004		55 Constipation	
Hyperlipidaemia and cardiovascular risks			
Rallidis *et al.* 2004		55 Dyslipidaemia (linseed oil)	
Jenkins *et al.* 1999		29 Hyperlipidaemia	
Bloedon *et al*. 2008		30 Hypercholesterinaemia	
Wilkinson *et al.* 2005		21 Hyperlipidaemia linseed oil	
Patade *et al.* 2008		33 native American postmenopausal women Hyperlipidaemia	
Zhang *et al.* 2008b		38 Hypercholesterinaemia	
Faintuch *et al.* 2011		11 Obesity	
Faintuch *et al.* 2007		24 Obesity	
Pan *et al.* 2007		37 Type II Diabetes; Hypercholesterinaemia; SDG	
Mani *et al.* 2011		18 Diabetes mellitus II	

Mixed			
Thompson *et al.* 2005		19 Breast Cancer	
Cockerell *et al.* 2012		27 IBS	
Obermann *et al.* 2013		175 Alzheimer	
Azrad *et al.* 2012		67 pre-surgical prostate	
Demark-Wahnefried *et al.* 2004		15 men with high-grade dysplasia and/or atypical small glands in prostate tissue	
Grutzner *et al.* 1997		70 functional upper abdominal complaints (linseed mucilage)	
Children			
Gracious *et al.* 2010			25 Linseed Oil BPD
Joshi *et al.* 2006			30 Linseed Oil ADHD
Sum efficacy	n=420	n=883	n=55
Safety			
Tarpila *et al*. 2002	80		
Billinsky *et al*. 2013	49		
Simbalista *et al.* 2010	20 female, PMS		
Wong *et al.* 2013			16 Hypercholesterolemia (8-18 y)
Azrad *et al.* 2012		67 Prostate cancer	
Bentz *et al.* 2010	20	79 Crohn Disease	
Zhang *et al.* 2008a		54 BPH	
Fremont *et al.* 2010		1317 Atopics	
Lemos *et al.* 2012		75 HD Linseed oil	
Sum safety	n=169	n=1592	n=16

5.3. Adverse events and serious adverse events and deaths

Meteorism, occurring with the use of linseed is common (Hardt and Geisthövel 1986; Schilcher *et al.* 1986) as already described under chapter 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 (Alonso *et al.* 1996).

Case Report

Prasad *et al.* (2012) reported a rare case of rhabdomyolysis (CK=61818 U/l) in a 35 year old man suffering from diabetes mellitus and hypertriglyceridemia since 2 years. There was no premorbid illness, chest pain, or abdominal pain and there was no relevant history which was suggestive of a muscle injury. He was a non-alcoholic and a non-smoker and he had no history of kidney disorders. There was no family history of a muscle disease or kidney disorders. Since three months, he had stopped all the drugs which had been prescribed by his physician and at that time, his triglyceride level was 473 mg/dl. Since then he had controlled his diet and had started taking linseeds (*Linum usitatissimum*), approximately 6-10 g daily once in the morning after breakfast to control his triglyceride levels. After 75 days, his triglyceride levels had come down to 148 mg/dl. On admission Creatine Kinase (CK) was 61818 U/l and Creatine Kinase-MB (CK-MB) - 71 U/l); liver enzymes were elevated. The patient's sample was negative for leptospirosis, hepatitis B and hepatitis C. Alkaline diuresis was started and his renal function, liver enzymes and creatine kinase were monitored during the hospital stay. At the time of his discharge, his renal function was normal; his creatine kinase was 6.244 U/l.

Assessor's comments

The patient suffered from rhabdomyolysis, but in the presence of elevated liver enzymes it is questionable, whether he stopped all medication, since for lipid lowering drugs as well hepatotoxicity and rhabdomyolysis are reported. Consequences for the labelling of the monograph have not to be drawn.

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

5.4. Laboratory findings

No specific data available.

5.5. Safety in special populations and situations

5.5.1. Use in children, adolescents

The use of the herbal substance for the treatment of habitual constipation or in conditions in which easy defaecation with soft stool is desirable (indication 1) is not recommended in children under 12 years due to insufficient data on safety and efficacy.

The use as a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort (indication 2) in children under 12 years of age has not been established due to lack of adequate data. No clinical studies have been reported in children.

5.5.2. Contraindications

Linseed in indication 1 WEU:

- 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.
- should 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) (Kommission E 1984), paralysis of the intestine or megacolon.

Linseed in indication 1 and 2 WEU+TU:

- should not be taken by patients with who have difficulties in swallowing or any throat problems (Taylor 1993).
- patients with known hypersensitivity to linseed should not use linseed preparations.

5.5.3. Special warnings and precautions for use

Linseed in indication 1 WEU:

- 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 (Taylor 1993).

Linseed in indication 1 and 2 WEU+TU:

- Treatment of debilitated patients and elderly requires medical supervision (Hardt and Geisthövel 1986).
- Investigations in healthy women suggest that long term use of linseed may have an oestrogenic effect, and its use is therefore not recommended in women with hormonally dependent tumours.

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.

5.5.4. Drug interactions and other forms of interaction

Linseed in indication 1 and 2 TU and WEU:

- Because of their pharmacodynamic properties all bulk forming laxatives may delay the enteral absorption of concomitantly administered medications (Hardt and Geisthövel 1986; Standardzulassungen 1996).
- Linseed should therefore be taken at least ½ to 1 hour before or after intake of other medicinal products.

Linseed in indication 1-WEU:

- 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 (EMEA/HMPWP/60/04).
- 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 former 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) under medical supervision. Similar considerations are possible for high-ceiling diuretics, which can provoke a negative fluid balance. Diuretics are not mentioned in the monograph because no specific cases have been reported.

5.5.5. Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

5.5.6. Overdose

Overdose with linseed, in indication 1 may cause abdominal discomfort, flatulence and possibly intestinal obstruction. Adequate fluid intake should be maintained and management should be symptomatic.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

Not relevant.

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

For well-established-use an appropriate labelling includes

Contraindications

- Hypersensitivity
- Abnormal gastrointestinal passage due to obstacles in passage or paralysis of the intestine
- Swallowing problems
- Sudden change in bowel habit (more than 2 weeks)
- Undiagnosed rectal bleeding
- Failure to defaecate following the use of laxative

Special warnings

- Not recommended for children under 12 years
- Discontinuation in irregularities of faeces, abdominal pain
- Intake of enough fluid

- Women with hormonally dependent tumours
- In case of chest pain, vomiting, or difficulty in swallowing or breathing, immediate medical attention should be sought
- Supervision of elderly and debilitated patients

Interactions

- Delayed enteral absorption of concomitantly administered medicinal products; cave time frame
- No concomitant medication with medicinal products known to inhibit peristaltic movement (e.g. opioids and loperamide)

Undesirable effects

- Bloating, flatulence , and stomach aches/cramps are common
- Reactions of hypersensitivity including anaphylaxis-like reactions may occur very rarely.

Overdose

- Abdominal discomfort, flatulence and possibly intestinal obstruction.
- Adequate fluid intake should be maintained and management should be symptomatic.

Under traditional use the labelling texts regarding the risks associated with ongoing swelling of the mucilaginous preparation can be omitted, if under method of administration the time frame is specified until the swelling is accomplished. Based on the considerations in section 5 the following labelling is adequate:

Contraindications

- Hypersensitivity
- Swallowing problems

Special warnings

- Not recommended for children under 12 years
- Supervision of elderly and debilitated patients
- Women with hormonally dependent tumours

Interactions

- Delayed enteral absorption of concomitantly administered medicinal products; cave time frame

Undesirable effects

- Bloating, flatulence , and stomach aches/cramps are common
- Reactions of hypersensitivity including anaphylaxis-like reactions may occur very rarely.

Considering these limitations the use of linseed and the traditional use of the mucilage can be regarded as safe.

Warnings can be concluded from the above mentioned considerations. In order to improve the safe use the method of administration should ensure an appropriate preparation, which is taking into account the finalisation of the swelling:

A minimum 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 formers (i.e. contraindications, special warnings, interactions, undesirable effects) can be omitted.

6. Overall conclusions

The medicinal use of *Linum usitatissimum* L., semen (linseed); dried ripe seed is documented within the European Union since centuries. The requirements laid down in Article 10a of Directive 2001/83/EC that the active substance has a recognised efficacy and an acceptable level of safety and that the period of well-established medicinal use (10 years) has elapsed are fulfilled for Lini semen for the treatment of habitual constipation or in conditions in which easy defaecation with soft stool is desirable.

The traditional use of Lini semen fulfils the requirement for at least 30 years of medicinal use as a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort, according to Directive 2001/83/EC as amended.

The *well-established* use of the seeds is to be predicated on general evidence and three open clinical trials as well as one randomised investigator-blinded trial documenting the laxative efficacy for the treatment of habitual constipation or in conditions in which easy defaecation with soft stool is desirable. There were no safety problems other than meteorism documented and from literature hypersensitivity is known. Both adverse are addressed by adequate labelling.

WHO-ATC A06AC05 linseed.

The traditional use as a demulcent preparation is supported by general evidence for far more than 30 years in Europe and the plausibility is supported by an open clinical trial, which documents the decrease of the relevant symptoms in patients with mild gastrointestinal discomfort. There were no safety problems documented and from literature hypersensitivity is known. It can be addressed by adequate labelling. The labelling texts regarding the swelling risks can be omitted, if the time frame is specified in which the swelling is accomplished, because these risks are not associated with the use of the demulcent preparation.

WHO Therapeutic area A02X.

The benefit risk assessment in both indications is positive, provided that an adequate labelling is used (see above).

Annex

List of references