EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Linum usitatissimum* L., semen

Rapporteur(s)	J. Wiesner
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HMPC decision on review of monograph *Linum usitatissimum* L., semen adopted on 10 March 2015	31 January 2024
Call for scientific data (start and end date)	From 1 March 2024 to 31 May 2024
Discussion in Committee on Herbal Medicinal Products (HMPC)	September 2024 November 2024
Adoption by HMPC	20 November 2024

Review of new data

Periodic review (from 2014 to 2024)

Sources checked for new information:

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

☒ Scientific/Medical/Toxicological databases

A search was performed in the EBSCO database. The period covered was January 2014 – July 2024. Filters used were Linum usitatissimun or flaxseed (SU) and clinical trial/toxicology/ lactation/pregnancy.

☒ Pharmacovigilance databases

☒ data from EudraVigilance:

01.01.2014-12.07.2024 from EU; active substance Linum, Linum Usitatissum, Linum Usitatissum L., Linum Usitatissum L. semen, Linseed, Linseed oil; suspect, interacting

☐ from other sources (e.g. data from VigiBase, national databases)

☐ Other

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Regulatory practice

☒ Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10 years of WEU on the market)

☒ New market overview (including pharmacovigilance actions taken in member states)

☒ PSUSA

☒ Feedback from experiences with the monograph during MRP/DCP procedures

☒ Ph. Eur. monograph

☐ Other

Consistency (e.g. scientific decisions taken by HMPC)

☒ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☐ Other

Availability of new information that could trigger a revision of the monograph

Scientific data	Yes	No
New non-clinical safety data that could trigger a revision of the monograph	☒	☐
New clinical safety data that could trigger a revision of the monograph	☒	☐
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation that could trigger a revision of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☒	☐
Other scientific data that could trigger a revision of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒
New recommendations from a finalised PSUSA	☐	☒
Feedback from experiences with the monograph during MRP/DCP procedures that could trigger a revision of the monograph	☐	☒
New/Updated Ph. Eur. monograph that could trigger a revision of the monograph	☐	☒
Other regulatory practices that could trigger a revision of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions that could trigger a revision of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that could trigger a revision of the monograph	☐	☒
Other relevant inconsistencies that could trigger a revision of the monograph	☐	☒

Summary of new references

During the review, 71 new references not yet available during the first/previous assessment were identified. Out of these new references, 3 references were considered to be relevant for the monograph and 1 references that could trigger revision of the monograph.

No references were provided by Interested Parties during the Call for data.

Assessment of new data

New scientific data that could trigger a revision of the monograph

New efficacy data from randomised, controlled, clinical trial in indication(s) where there is a medicinal product on the EU market for more than 10 years (laxative effect)

Sun *et al*. (2020) evaluated in a prospective, randomized, controlled study the effects of flaxseed supplementation on functional constipation and quality of life in adult men and women in China. Ninety subjects with functional constipation diagnosed by the Rome IV criteria were enrolled. Subjects were randomly assigned to receive either 50 g/day flaxseed flour with meals (n=60) or 15 ml/day of a lactulose solution on an empty stomach (n=30) every morning for four weeks. Eight variables were included in the scoring system: frequency of bowel movements, painful evacuation, incomplete evacuation, abdominal pain, length of time per attempt, assistance for defecation, unsuccessful attempts for evacuation per 24 hours, and duration of constipation. Wexner constipation scores, stool consistency according to the Bristol Stool Form Scale, and bowel habits (frequency of bowel movements/week, the time spent on defecation) were the primary outcomes. The change in Patient Assessment of Constipation Quality of Life score was the secondary outcome. After four weeks, the bowel habits in both groups were significantly improved. At baseline, >78% of subjects reported hard stools. However, after four weeks of treatment, the proportion of subjects reporting hard stools was 25% and 3.3%, respectively, for the lactulose and the flaxseed flour groups. The median Wexner constipation score decreased from 14 to 6.5 in the flaxseed group ($p<0.001$) and from 15 to 9 in the lactulose group ($p<0.001$). Subjects with normal stool type at four weeks increased to 53.6% in the lactulose group and to 86.7% in the flaxseed group. The median defecation frequency per week increased significantly (2 to 7 for flaxseed and 2 to 6 for lactulose, $p<0.001$ for both groups). The Patient Assessment of Constipation Quality of Life score decreased significantly (-1.34 and -0.66 for flaxseed and lactulose, respectively; $p<0.001$ for both groups). The authors concluded flaxseed flour is somewhat more effective at increasing defecation frequency than lactulose, improving bowel movements and promoting life quality of subjects with chronic functional constipation.

Suraki *et al*. (2024) compared in a parallel randomized controlled clinical trial the effects of flaxseed powder and magnesium hydroxide on bowel movements of 70 acute myocardial infarction patients hospitalized in ICU, who had no history of chronic constipation. The patients in the intervention group were given three sachets of flaxseed powder (each sachet was 3 g) twice a day for four days. The patients in the control group were given 20 cc of magnesium hydroxide syrup each morning. The mean and standard deviation of the number of bowel movements within five days after intervention are 1.86±1.08 and 1.6±0.65 in the intervention and the control groups, respectively. The frequency of normal stool consistency of the first bowel movement is 94.3% for the intervention group and 85.7% for the control group, which shows no significant differences between the two groups in terms of stool consistency and bowel movement frequency ($p=0.510$). The bowel movements started on average after 35.2±97.97 hours in the flaxseed group and 24.771±2.677 hours in the magnesium hydroxide group ($p=0.023$). The results showed that flaxseed powder increases bowel movement

frequency and improves the patients' stool consistency, but the differences between the two groups are insignificant.

Soltanian and Janghorbani (2019) compared constipation symptoms, weight, glycaemia, and lipids in constipated patients with type 2 diabetes (T2D) who received baked flaxseed or psyllium versus those who received a placebo in a single-blinded, randomized controlled trial. Seventy seven constipated patients with T2D were randomized into three groups. Patients received either 10 g flaxseed or psyllium pre-mixed in cookies or placebo cookies twice per day for a total of 12 weeks. The constipation symptoms, body mass index (BMI), fasting plasma glucose (FPG), glycosylated haemoglobin (HbA1c), and lipid profile were determined at the beginning and end of 4, 8, and 12-week period. Constipation was assessed with the ROME III criteria score. The flaxseed appears to be superior to psyllium for improving constipation symptoms, weight, glycaemic, and lipid control. The change from baseline of constipation symptoms ($p=0.002$), stool consistency ($p<0.001$), weight ($p<0.001$), BMI ($p<0.001$), FPG ($p=0.004$), cholesterol ($p=0.010$), LDLC ($p=0.031$), and cholesterol/HDLC ratio ($p=0.019$), was significantly improved in both flaxseed and psyllium groups than in the placebo group. The compliance was good and no adverse effects were observed.

Assessor´s comment
The existing monograph lists as WEU indication "Herbal medicinal product for the treatment of habitual constipation or in conditions in which easy defaecation with soft stool is desirable" with a posology of 10-15 g 2-3 times daily (20-45 g daily). The posologies in the quoted clinical trials were 50 g/day, 18 g/day and 20 g/day. The results of the clinical studies in context of constipation are not contradictory to the HMPC-monograph.

Adverse event(s) or other safety data

In Eudravigilance 9 cases are listed – 6 cases with linseed and 3 cases with linseed oil.
Except for one case, existing diseases and co-medication (such as naproxen, antadys, simvastatin, valsartan, nortase, abemaciclib) were also given so that causality cannot be drawn.

One spontaneous case report concerned a 59 years old female who experienced breast cancer following the use of linseed 1 g herbal tea in sachets. The woman has been taking from around 2014 or 2015 linseed for gastric problems regularly. She has been making regular check-ups for breast cancer diagnosis (interchangeably USG and mammography) for 10 years. She was diagnosed for hormone depending breast cancer in April 2018 and she has started treatment for cancer since this time. She suspected cancer might have been caused by Linseed. This case was assessed as serious (other medically important condition). Breast cancer is unexpected adverse reaction for linseed according to SmPC for linseed [NASIONA LNU]. Causality was assessed as 'possible', with the total score (+2 points).

Assessor´s comment
Except for one case, no adverse event or other safety data not included in the monograph from published case reports, clinical studies, or case reports from pharmacovigilance database assessed to be relevant were identified.
Concerning the case report connected to breast cancer, many of the studies concluded that linseed intake may be related to the decreased risk of breast cancer (and also reduce the tumour's growth and size). However, there are also studies (including premenopausal and postmenopausal women) that did not show the same results. The hint to possible oestrogenic activity is already included in the monograph (chapter 4.6) and AR.
For now, no changes to the monograph are suggested. The case report concerning possible influence on breast cancer should be added into the AR during next review.

Preclinical safety

Animal reproductive and developmental toxicity study (lactation)

Guarda *et al.* (2014) evaluated the effects of high maternal intake of linseed oil during lactation upon milk and body composition in male and female offspring. Lactating rats were divided into: (1) control (C, n=10), 7% soybean oil; (2) hyper 19% soybean oil (HS, n=10); and (3) hyper 17% linseed oil + 2% soybean oil (HF, n=10). HF male offspring presented lower body and subcutaneous fat masses. The higher intake of linseed oil during lactation reduced the body weight of mothers and offspring, decreases milk lipids and apparently increases insulin sensitivity in this critical period of life.

The authors concluded, the higher intake of linseed oil during lactation reduced the body weight of mothers during lactation and changes the milk composition. The reduction of cholesterol and triglycerides in milk in both periods of lactation can be responsible for the reduction of pup's body weight during lactation and changes in lipid profile in male and female at weaning. The lower offspring fat mass can contribute to the higher insulin sensitivity, without discard an indirect effect of n-3 fatty acids on leptin production that improves insulin sensitivity. The higher insulin sensitivity in critical periods of life may imprint the pup future metabolic, hormonal and neural changes and the use during lactation is not without risk.

Assessor´s comment
The animal study Guarda et al. (2014) hints to possible harm for the pups from the use of flaxseed oil during lactation. In this in vivo study, linseed oil was supplemented but not the whole seeds. The animals had free access to a diet containing 19% lipid (2% from soybean oil and 17% from flax seed oil).
A maximum intake of Lini semen according to the monograph (max. 45 g) with a maximum content of 45% fatty oil, would lead to approx. 20 g linseed oil for humans. Assuming a food intake of approx. 1300 g per day, this would be approx. 1.5% of the daily food intake. Therefore, the relevance of the findings for the human situation is not clear.
Since the use during pregnancy and lactation is not recommended, there is no need to change chapter 4.6 of the monograph.
In addition, also a change in chapter 5.3 is not suggested. This is based on the fact, that in Guarda et al. (2014) former studies with linseed were discussed. In those studies (Figueiredo et al., 2009, 2011, 2012) it could be shown that if diet was supplemented with 25% linseed, the dams presented no significant changes in body weight and food intake.

New regulatory practice that could trigger a revision of the monograph

New herbal substances/preparations with 30/15 years of TU or 10 years of WEU were not identified.

From 2014 to 2024, no preparations were licenced in the EU.

Inconsistency that could trigger a revision of the monograph

Not applicable.

Other issues that could trigger a revision of the monograph

Not applicable.

New information not considered to trigger a revision at present but that could be relevant for the next review

Several clinical studies were identified in indications, for which there is no medicinal product on the EU market for more than 10 years. They could be relevant for the next review, as they give new information on the clinical pharmacology and laboratory data.

Examples:

Irritable Bowel syndrome (IBS) and other gastrointestinal conditions

Morshedzadeh *et al*. (2019) evaluated in an open-labelled randomized controlled trial the possible effect of grounded flaxseed and flaxseed oil on serum levels of inflammatory markers, metabolic parameters, and the severity of disease in 90 patients with ulcerative colitis. A significant change in several parameters including faecal calprotectin, INF-γ, IL-6, waist circumference, diastolic and systolic blood pressure and inflammatory bowel disease questionnaire-short form were seen in both groups compared to the control. In a second open-labelled randomized controlled trial on 70 patients with ulcerative colitis for 12 weeks flaxseed supplementation led to a significant reduction in the resistin and visfatin concentration and a significant increase in the adiponectin levels (Morshedzadeh *et al*., 2023).

Effect as an anti-inflammatory preparation

Musazadeh *et al.* (2024b) assessed the impacts of flaxseed on inflammatory biomarkers in adults in a meta-analysis. The 54 RCTs were included in the final analysis, which involved 3000 individuals from 12 countries. Overall, the flaxseed supplementation significantly decreased serum concentrations of C-reactive protein and interleukin 6, but not tumour necrosis factor α. Meta-analysis of Sorin et al. (2018) on 17 selected RCTs with 1256 individuals did not suggest a significant change in plasma C-reactive protein concentrations following supplementation with flaxseed-containing products.

Effect on blood lipids levels

Ahmed and Fateh (2024) performed a meta-analysis on the impact of flaxseed supplementation on lipid profile and liver enzymes. Results indicates that the overall effect on triglycerides, combining different doses, revealed a significant reduction, while for high-density lipoprotein an increase could be shown. The liver enzymes AST and ALT displayed reductions in their levels.

Chao *et al.* (2021) performed a dose–response meta-analysis of randomized controlled trials in patients with dyslipidaemia. Thirty-one RCTs involving 1,698 participants were included. Flaxseed consumption had an overall beneficial effect on serum TC, LDL-C, TG, apo B and IL-6 in patients with dyslipidaemia related diseases, but not on apo A, HDL-C, hs-CRP, CRP and anthropometric indices. However, different flaxseed products showed obviously different effects.

Sahebkar *et al*. (2021) performed a meta-analysis on patients who are at risk of a high residual cardiovascular disease (CVD). Of the 48 RCTs, 6 were eligible for inclusion. Results suggested a significant decrease in plasma Lp(a) levels-standardized mean difference following supplementation with flaxseed-containing products.

Hadi *et al*. (2020) analysed the impact of flaxseed supplementation on plasma lipoprotein(a) concentrations in a meta-analysis of 7 selected RCTs with 629 individuals. Results showed significant lowering effect of flaxseed supplementation on Lp(a).

Effect on blood glucose level

Xi *et al*. (2023) included a total of 13 studies in a systematic review on type 2 diabetes patients. Results showed that flaxseed supplementation significantly reduced haemoglobin A1c (HbA1c) compared with the control group. In contrast, it had no effects on body weight, body mass index, blood pressure, fasting blood glucose (FBG), homeostatic model assessment for insulin resistance, quantitative insulin sensitivity check index, and lipid parameters.

Mohammadi-Sartang *et al*. (2018) included 25 randomized clinical trials (30 treatment arms) in the meta-analysis on the effect of flaxseed supplementation on glucose control and insulin sensitivity. Results suggested a significant association between flaxseed supplementation and a reduction in

blood glucose, insulin levels and HOMA-IR index and an increase in QUIKI index. No significant effect on HbA1c was found. In subgroup analysis, a significant reduction in blood glucose, insulin, and HOMA-IR and a significant increase in QUIKI were found only in studies using whole flaxseed but not flaxseed oil and lignan extract.

Effect in metabolic syndrome, cardiovascular risk factors, obesity, fatty liver disease

Musazadeh *et al.* (2024a) analysed in a meta-analysis on sixty-four trials comprising 72 treatment arms the effects of flaxseed (lignans, whole flaxseed, and flaxseed oil) on anthropometric indices. The meta-analysis revealed significant reductions in body weight, body mass index and waist circumference following flaxseed supplementation. Subgroup analyses indicated that interventions lasting 10-20 weeks, and studies involving subjects with higher BMI (>30 kg/m^2) showed more significant anti-obesity effects.

Sabet *et al*. (2024) evaluated in a meta-analysis the effects of flaxseed supplementation on weight loss, lipid profiles, high-sensitivity C-reactive protein (hs-CRP), and glucose levels in patients with coronary artery disease (CAD). Of the 428 citations, six RCTs were included. Flaxseed supplementation was associated with lowering FBS, hs-CRP, and TG levels but did not affect weight loss parameters and other lipid markers in CAD.

Oestrogenic and anti-tumour effects

Musazadeh *et al*. (2023) analysed the effect of flaxseed supplementation on sex hormone profile in adults in a systematic review and meta-analysis. Inconsistent data suggest that flaxseed supplementation may have a role in sex hormones. Finding from ten RCTs revealed that flaxseed supplementation had no significant alteration in follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG), total testosterone (TT) levels, free androgen index (FAI), and dehydroepiandrosterone sulfate (DHEAS). Flaxseed supplementation had no significant effect on sex hormones in adults.

Flower *et al*. (2014) conducted a systematic review of flax for efficacy in improving menopausal symptoms in women living with breast cancer and for potential impact on risk of breast cancer incidence or recurrence. 10 studies were included: 2 randomized controlled trials, 2 uncontrolled trials, 1 biomarker study, and 5 observational studies. No significant decreases in hot flash symptomatology were seen with flax ingestion (7.5 g/d). Flax (25 g/d) increased tumour apoptotic index and decreased HER2 expression and cell proliferation among newly diagnosed breast cancer patients when compared with placebo.

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Rapporteur's proposal on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☐ Revision likely to have an impact on the corresponding list entry (if applicable)

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

HMPC decision on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph