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**OVERVIEW OF COMMENTS RECEIVED ON
'COMMUNITY HERBAL MONOGRAPH ON
LINUM USITATISSIMUM L., SEMEN'
EMEA/HMPC/340849/2005**

This document was valid from 13 July 2006 until 10 March 2015.

Table 1: Organisations that commented on the draft 'Community herbal monograph on Linseed (Linum, semen)' released for consultation in October 2005 until 31 January 2006

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)
2.	Bioforma BV
3.	European Herbal Practitioners Association (EHPA)
4.	Medical Products Agency (MPA), Sweden
5.	The European Scientific Cooperative on Phytotherapy (ESCOP)
6.	The Medicines Evaluation Board of the Netherlands (MEB NL)
7.	Agenzia Italiana del Farmaco (AIFA)
8.	Pharmacovigilance Division, UK

Table 2: Discussion of comments

General comment	Comment and rationale	Rapporteur's comments
Title	<p>We would suggest adding the following and alternative way of expressing the plant name and part used: "<i>Lini semen</i>".</p> <p>We suggest to use the correct Latin expression in brackets: Lini semen.</p>	<p>The title was changed into 'Linum usitatissimum L., semen', which is in line with guidance on the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMA/HMPC/182352/2005 Rev.1) and 'Procedure for the preparation of Community monographs for traditional herbal medicinal products' (EMA/HMPC/182320/2005 Rev.1).</p>
	<p>We would suggest correcting the reference to "Article 10(1)(a)(ii)" into Article "10a" of Directive 2001/83/EC as amended.</p>	<p>Agreed, see 'Template for a Community herbal monograph' (EMA/HMPC/107436/2005 Rev.2).</p>

Supersedes

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
4.1. Therapeutic indications	<p>Well-established use We suggest adding "irritable bowel syndrome" as well as "diverticular disease". These indications are supported by the following literature references: Kay et al. 1978, Brunton LL. 1990</p>	<p>The literature mentioned reflects no special investigations concerning these indications, but experts' opinions. This problem was already discussed by the Committee, which concluded that if at all use of linseed was helpful in constipation predominant irritable bowel syndrome. This indication is covered by the accepted indication „habitual constipation or conditions in which easy defecation with soft stool is desirable“. This indication also covers „diverticular disease“. The data available are too poor to claim these indications. The recommended indication also covers constipation caused by other primary diseases.</p>
	<p>We suggest moving "gastrointestinal discomfort" to the area of well-established use, because the following clinical study provides data on the efficacy of Linseed in gastrointestinal complaints: Grützner et al. 1997 In this study 70 patients suffering from various gastrointestinal complaints such as sensation of pressure and repletion, loss of appetite, nausea, vomiting and heartburn were treated with an aqueous linseed mucilage preparation (1:10) at a dose of 8 x 25 g (including excipients) per day. After 3 days the total symptom score was significantly reduced (p<0.01). Each individual symptom was reduced, the largest reductions being observed for the sensation of pressure (41.5%) and the sensation of repletion (36.8%) The global assessment of efficacy (by patients and by physicians) was estimated good or very good in most cases.</p> <p>Traditional use We propose to add the following indication for external use: "Painful skin inflammations". This indication is supported by the following references: Franz G, Alban S. 1999, Weiß RF, Fintelmann V. 1997, Evans WC. 1996, Fassina-Ragazzi 1995, Repertorio fitoterapico 1996, Capasso et al. 2000, Trease and Evans 2002</p>	<p>The pilot study mentioned was already discussed in the Committee plenary meeting with the decision that the data only justify a traditional use. It also has to be taken into account that the diagnostic and therapeutics possibilities of gastric complaints have developed and also the guidelines to carry out such studies (ROME II criteria). Therefore, only the traditional use in gastrointestinal discomfort is justified.</p> <p>This indication was not accepted as a traditional one by the Committee because of insufficient data to clarify the main pharmacological background. The references mentioned (Franz and Alban 1999, Weiss and Fintelmann 1997, Evans 1996, Trease and Evans 2002) do not help. Weiss and Fintelmann report that the heat of such a poultice lets a furuncle to mature. That might be plausible but not for other "painful skin inflammations". Special data are missing concerning the dose, the duration and mode of application. Furthermore it is difficult for the patient to recognise the limit of the self-medication concerning skin inflammations (from sunburn to erysipelas) or even furunculosis. Evans 1996 refers to oil and leaves, which are applied to burns or as poultice for rheumatism and gout. The references Fassina-Ragazzi 1995, Repertorio fitoterapico 1996 and Capasso et al. 2000 are not presented. The references presented do not cover a period of 30 years.</p>

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<p>4.1. Therapeutic indications</p> <p>Continuation</p>	<p>Well-established use We suggest to add "irritable bowel syndrome" as well as "diverticular disease". These indications are supported by the references Kay and Strasberg [1] as well as Brunton [2]. We propose to move "gastrointestinal discomfort" to the area of well-established use, because a clinical study published by Grützner et al. [3] provides data on the efficacy of Linseed in gastrointestinal complaints. In this study 70 patients suffering from various gastrointestinal complaints such as sensation of pressure and repletion, loss of appetite, nausea, vomiting and heartburn were treated with an aqueous linseed mucilage preparation (1:10) at a dose of 8 x 25 g (including excipients) per day. After 3 days the total symptom score was significantly reduced (p<0.01). Each individual symptom was reduced, the largest reductions being observed for the sensation of pressure (41.5%) and the sensation of repletion (36.8%) The global assessment of efficacy (by patients and by physicians) was estimated good or very good in most cases.</p> <p>Traditional use We propose to add an indication for the external use "Painful skin inflammations". This indication is supported by the references Franz and Alban [4], Weiss and Fintelmann [5] as well as Evans [6].</p>	<p>See above.</p> <p>See above.</p>

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<p>4.1. Therapeutic indications</p> <p>Continuation</p>	<p>The interested party seriously questions whether the data on clinical efficacy in the claimed indication do fulfil the criteria of “well-established medicinal use with recognised efficacy” according to Directive 2001/83/EC.</p> <p>However, the interested party recognises that linseed has a well-documented traditional use as a mild laxative for treatment of constipation. Based on the content of bulk material (indigestible polysaccharides) in linseed the efficacy also appears plausible in this indication. The data presented would qualify products containing linseed for registration as traditional herbal medicinal products in this indication. The future classification of linseed, well-established or traditional, will heavily depend on the scientific interpretation of criteria for recognised clinical efficacy.</p> <p><i>We note that the indications for traditional use are given as “Traditional herbal medicinal product for use as a demulcent preparation for the symptomatic treatment of gastrointestinal discomfort.” We make the following comments:</i></p> <p>We would like to see the words “<i>and for habitual constipation</i>” added to this traditional herbal indication as this herbal medicine has for centuries been traditionally used to treat chronic constipation.</p> <p>The meaning of the phrase “<i>exclusively based on long-standing use</i>” is unclear. We believe that the word “<i>exclusively</i>” will probably not be understood as meant here - i.e. “<i>entirely based on</i>”.</p> <p>Moreover “<i>exclusively based on long-standing use</i>” could easily be misinterpreted as a direction to the patient to take the medicine over a long period of time to achieve any effect. We suggest some other phrase is used such as “<i>the basis of this medicine is traditional use</i>”. <i>Please note that this last point applies to all draft proposed traditional use indications.</i></p>	<p>3 open clinical investigations (Kurth W: Therapeutische Wirksamkeit, Verträglichkeit und Akzeptabilität von Linusit in der Praxis. Der Kassenarzt 1976, 16: 3546; Meier P., Seiler WO., Stahelin HB: Bulk-forming agents as laxatives in geriatric patients. Schweiz Med Wochenschr 1990 Mar 3; 120 (9): 314-7; Wirths W., Berglar T., Dieckhues A., Bauer G: Ballaststoffreiche Zwischenmahlzeit in ihrer Wirkung auf Verdauungstätigkeit und Blutlipide älterer Probanden. Z. Gerontol 1985 Mar – Apr; 18 (2): 107-10) and one randomised controlled investigator-blinded trial (Tarpila S et al: Efficacy of ground flaxseed on constipation in patients with irritable bowel syndrome. Current Topics in Nutraceutical Research 2004; 2: 119-25) are available. The last one was conducted in patients suffering from constipation predominant irritable bowel syndrome. In the linseed group, constipation and abdominal symptoms were decreased significantly. Therefore this study supports the efficacy in constipation. The level of evidence for the indication “habitual constipation” was identified as level II to III, which supports a well-established use.</p> <p>See above.</p> <p>In addition, there exists no traditional evidence that a demulcent preparation like the one described in the section Traditional Use of the monograph was used for habitual constipation. No evidence of an effective dose is available. Furthermore, the laxative effect of such a demulcent preparation is not plausible because the bulk material already swells and forms a demulcent gel before administration. Therefore, no further swelling causing an increase of content and a stretch stimulus in the intestine is to be expected.</p> <p>This is a general comment, see ‘Template for a Community herbal monograph’ (EMA/HMPC/107436/2005).</p>

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<p>4.1. Therapeutic indications</p> <p>Continuation</p>	<p>Traditional use One of the well known traditional used of linseed is constipation therefore we like to included "relives of constipation" after "gastrointestinal discomfort". Beside the mentioned indication linseed is traditional used for skin inflammations. This is mentioned for instance in the ESCOP monograph Lini semen. We like to propose to include this too. Our proposal for the indication is: <i>Traditional herbal medicinal product for the use as a demulcent for the symptomatic treatment of gastrointestinal discomfort relieves of constipation and painful skin inflammations exclusively based on long-standing use.</i></p> <p>The interested party is of the opinion that the proposed indication for traditional use: <i>"Traditional herbal medicinal product as a demulcent preparation for the symptomatic treatment of gastrointestinal discomfort"</i> is rather vague and intended for a broad use, of which the safe use can be questioned.</p> <p>The interested party proposed to add "in case of obstipation" to the proposed indication: <i>"Traditional herbal medicinal product as a demulcent preparation for the symptomatic treatment of gastrointestinal discomfort, in case of obstipation"</i></p>	<p>See above</p> <p>This was discussed in the MLWP and HMPC with the result of the following wording "for the symptomatic relief of mild gastrointestinal discomfort".</p> <p>See above.</p>
<p>4.2. Posology</p>	<p>Traditional use For the external use a dosage recommendation as can be found in the ESCOP monograph, should be included: <i>External use: 30–50 g of crushed or powdered seed as a warm poultice or warm compress.</i></p> <p>Traditional use: We suggest to add the dosage for the external use which is in accordance with the ESCOP monograph: "30-50 g of crushed or powdered seed as a warm poultice or warm compress".</p>	<p>The external use is not accepted as a traditional one, see above.</p>

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<p>4.2. Posology</p> <p>Continuation</p>	<p>The dosage form for traditional use should also be on the daily dose basis as is recommended in the well-established use category and as merited in the treatment of chronic constipation. The use of this herb for habitual constipation is so well known in traditional medicine, so that it makes no sense to limit the dose to single use.</p> <p>The same method of administration as in traditional use could be given as an alternative under well-established use.</p>	<p>We have not limited the dose to single use because we recommend taking this half an hour before eating during the day. To make the recommendation more precise, we propose to add up to three times during the day.</p> <p>The laxative effect of such a demulcent preparation is not plausible because the bulk material already swells and forms a demulcent gel before administration. Therefore, no further swelling causing an increase of content and a stretch stimulus in the intestine, is to be expected. There are no clinical data available which confirm the use as a demulcent preparation for laxative purpose.</p>
<p>4.3. Contraindications</p>	<p>For clarity purpose, we suggest to shorten and reword this section as follows:</p> <p><i>“-Known hypersensitivity (allergy) to Linseed -Unless advised by a physician, patients suffering from the following conditions should not use Linseed preparations:</i></p> <ul style="list-style-type: none"> • <i>Acute abdominal pain of any origin</i> • <i>Existing intestinal obstructions (ileus) or conditions likely to lead to intestinal obstruction”</i> <p>The text is too long and therefore not understandable. We suggest to shorten this paragraph and a clearer wording could be:</p> <p><i>Atonic and obstructive ileus, subileus or conditions likely to lead to intestinal obstruction. Acute abdominal pain of any origin (e.g. appendicitis)”</i></p> <p>We suggest to shorten this paragraph in order to make it better understandable for the user of the medicinal product. A clearer wording could be:</p> <p><i>"Atonic and obstructive ileus, subileus or conditions likely to lead to intestinal obstruction. Acute abdominal pain of any origin (e.g. appendicitis)".</i></p>	<p>We maintain the recommended wording because first of all these contraindications are addressed to the patient and the patient cannot interpret the general term “conditions likely to lead to intestinal obstruction”.</p>

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4.4. Special warnings and precautions for use	We find that the wording given under "Warning" is too long and may deter patients from using the product. We therefore suggest the following text: <i>"Take this product with at least 10 times the amount of fluid in order to avoid swelling and obstruction."</i>	We prefer to recommend a definite amount of fluid per single dose to make sure that the amount is sufficient. We agree to omit the sentence "This product should not be taken by patients with difficulties in swallowing" because this is already mentioned as a contraindication. The other information is necessary for the understanding and the safety of the patient.
	The given wording is too long and would prevent the user from taking the product. We therefore suggest the following wording: <i>Linseed should be taken with at least 10 times the amount of fluid because otherwise bezoar formation and intestinal obstruction may occur."</i>	
	The wording given under "Warnings", 1st paragraph, is too long and would prevent the user from taking the product. We therefore suggest the following text: " Linseed should be taken with at least 10 times the amount of fluid because otherwise bezoar formation and intestinal obstruction may occur."	
	Warnings, second line: replace "other fluid" with "similar aqueous fluid" in order to avoid the use of unsuitable liquids.	
4.6. Pregnancy and lactation	Two interested parties suggest: We agree that there are no reports of any harmful or deleterious effects during pregnancy and lactation. This is in line with the paper of Lewis JH, Weingold AB., 1985. We therefore propose to delete the sentence " <i>As there are no sufficient data available, the use is not recommended ...</i> ", because this is a contradiction to the statement that there are no reports on any harmful or deleterious effects.	We propose to reword "As there are insufficient systematic data available, use is not recommended during pregnancy and lactation".

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4.6. Pregnancy and lactation Continuation	We agree that there are no reports of any harmful or deleterious effects during pregnancy and lactation. We therefore propose to delete the sentence " <i>As there are no sufficient data available, the use is not recommended ...</i> ", because this is a contradiction to the statement that there are no reports on any harmful or deleterious effects.	
4.8. Undesirable effects	We suggest deleting the statements related to meteorism and hypersensitivity reactions because to our knowledge there are no reports on these. If any recent data is available, we would like to ask for reference/copy.	The process of fermentation can produce gas and flatulence (Petroski D. Bulk Fiber Therapy – The impact of product selection on patient acceptance and compliance. Today's Therapeutic Trends 97-105). This causes meteorism.
	Two interested parties suggest to delete the statements related to meteorism and hypersensitivity reactions because to our knowledge no reports are available at all. If any recent data is available, we would like to ask for a copy.	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 (3: Alonso L. et al. Anaphylaxis caused by linseed (flaxseed) intake. J Allergy Clin Immunol Volume 98, Number 2).
	2 reported ADRs in UK: 1 x cholestasis and jaundice; 1 x bullous conditions	No further information is given and the causality cannot be assessed. Reactions of hypersensitivity are already mentioned in the monograph.
5.2. Pharmacokinetic properties	The text refers to pharmacodynamics and not to kinetics. The text on short chain fatty acids appears highly speculative. What is the evidence that these acids serve as nutrients for the cell forming the colonic mucosa? It is suggested to delete the whole first paragraph. The paragraph on progress of action should be moved to section 5.1. Pharmacodynamics.	Pharmacokinetic describes the process by which a drug is absorbed, distributed, metabolised and eliminated by the body or not and also the study of this process. We agree that the paragraph on progress of action is to be moved to section 5.1, but the other statement describes the pharmacokinetics properties of linseed as far as it is known. Fermentation is a kind of metabolism, which just makes a resorption possible. Concerning the short chain fatty acids we refer to Hänsel R., K. Keller, H. Rimpler. Hagers Handbuch 5/676 – 683; Guillon F., Champ M: Structural and physical properties of dietary fibres, and consequences of processing on human physiology. Food Research International 33 (2000) 233-245 and Petroski D: Bulk Fiber Therapy – The impact of product selection on patient acceptance and compliance. Today's Therapeutic Trends 2000; 18 (2): 97-105.

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<p>5.3. Preclinical safety data</p>	<p>If possible, it should be clarified whether thiocyanate is harmless or not. The increased thiocyanate levels in smokers have been associated with the development of atherosclerosis.</p>	<p>We have found one reference Exner M et al. Thiocyanate catalyzes myeloperoxidase-initiated lipid oxidation in LDL. <i>Free Radical Biology & Medicine</i> 2004; 37 (2): 146 – 155. The authors conclude that the myeloperoxidase-hydrogen peroxide-pseudo-halide thiocyanate-system (MPO/H₂O₂/SCN-system) may have the potential to play a significant role in the oxidative modification of LDL – an observation further pointing to the link between the long-recognised risk factors of atherosclerosis: elevated levels of LDL and smoking.</p> <p>Up to now in our view it is a hypothesis, which needs further investigations. The scientific data available are not sufficient to derive such a risk for linseed. On the other side daily food supplementation with ground linseed and linseed oil increased significantly the serum alpha-linolenic acid concentration, which is supposed to have a preventive effect against cardiovascular diseases (Tarpila S et al. The effect of flaxseed supplementation in processed foods on serum fatty acids and enterolactone. <i>European Journal of Clinical Nutrition</i> 2002; 56: 157-165).</p>
	<p>"Preclinical safety data - Well-established use": Linseed contains 20-50 mg cyanide/100 g in form of the cyanogenic diglycosides linustatin, neolinustatin and small amount of monoglycoside linamarin (see Br. J. Nutr.1993 Mar;69(2):443-53 and several others).</p> <p>The linamarin content in linseed is low, but increases with maturation, ageing and over all during the germination. It can even vary depending on the cultivar. Following the examination of linseed of ten cultivars of <i>Linum</i> the following results were reported: "The main cyanogenic compound was linustatin at 213-352 mg/100 g of seed, accounting for 54-76% of total cyanogenic glucosides. The content of neolinustatin was 91-203 mg/100 g of seed; linamarin was present at low levels (<32 mg/100 g of seed) in 8 of the 10 cultivars analyzed." (Oomah, B. Dave, Mazza Giuseppe, Edward O. in <i>Journal of Agricultural and Food Chemistry</i> (1992), 40 (8), 1346-8, "Cyanogenic compounds in flaxseed") As linamarin is toxic, its presence in old linseed might raise safety concerns and therefore this issue should be point out in the pharmaceutical section</p>	<p>We agree to add "small amount of the monoglycoside linamarin".</p>