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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Glycine max* (L.) Merr., lecithinum

Final

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Glycine max</i> (L.) Merr., lecithinum
Herbal preparation(s)	Soya-bean lecithin (de-oiled phospholipids from soya bean)
Pharmaceutical form(s)	Herbal preparations in liquid or solid dosage forms for oral use.
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1. Introduction

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

- Herbal substance(s)

Not applicable

- Herbal preparation(s)

Soya lecithin is phospholipids obtained from seeds of *Glycine max* (L.) Merr. Soya bean is an annual herbaceous plant in the family Fabaceae (legume or bean family) that is cultivated. The fruit contains 1-4 ovoid to spherical seeds of variable colour (Bruneton, 1999). The main phospholipids are phosphatidylcholine (average 76% in lecithin), phosphatidylethanolamine and phosphatidylinositol (Blumenthal *et al.*, 2000).

The following herbal preparations have been reported as constituents of medicinal products on the market in the EU/EEA Member States (for further information see section 2 "Data on medicinal use"):

For oral use:

- De-oiled phospholipids from soya bean (soya lecithin)
- De-oiled phospholipids from soya bean (soya lecithin) (*Lecithinum ex soya*)
Soya lecithin contains (3-sn-phosphatidyl) choline, phosphatidylethanolamine and phosphatidylinositol. Pharmacopoeial grade soya lecithin must contain a minimum 20% and maximum 31.6% phosphatidylcholine calculated on the dried substance (Blumenthal *et al.*, 2000).
- De-oiled, enriched phospholipids from soya bean (soya lecithin) calculated as 73-79% (3-sn-phosphatidyl) choline (*Sojae Lecithinum*). Enriched extract with 73-79% (3-sn-phosphatidyl) choline. The extract also includes phosphatidylethanolamine (maximum 7%), phosphatidylinositolic acid (less than 0.5%), oil (2-6%), and vitamin E (0.2-0.5%). The range includes both production and analytical variances (Blumenthal *et al.*, 2000).

In addition to the herbal preparations reported as constituents of medicinal products, there is a broad range of dietary soya products on the market, including whole soya foods, soya flours, textured soya proteins, soya protein concentrates, soya protein isolates, isoflavone rich soya proteins, isoflavone extracts from the soya seed or soya germ, isolated isoflavone mixtures, pure genistein, lecithin products of varying purity and soya oils. The composition of the bioactive compounds differs markedly between products and is affected by processing methods. Only references where a medicinal use is described or indicated, and where the extracts have been properly described, are taken into account in the assessment report.

- 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. Search and assessment methodology

Scientific databases: PubMed, Embase, Cochrane Database of Systematic Reviews

A PubMed search on soybean found 38,193 articles in February 2015. Thus, to be able to find relevant articles among this high number of citations, additional database searches were performed combining the following search terms: lecithin, phosphatidylcholine, phospholipid, polyenylphosphatidylcholine, polyunsaturated phosphatidylcholine, Essentiale, Lipostabil, extract, soya, soybeans, glycine max, cholesterol, hypercholesterolemia, lipids, LDL, HDL, hyperlipidemia, liver, hepatic, hepatitis, hepatotoxic, exhaustion, stress, tension, anxiety, hypersensitivity, allergy, immunology, drug interactions, humans. The citations found were manually screened and all English articles deemed relevant were accessed and included in the assessment report. Further references found in lists of references were included, if deemed relevant. An additional search in PubMed was performed in May 2016 combining the following search terms: soy and lecithin; soya and lecithin; soybean and lecithin; soyabean and lecithin.

Books, acts of law and regulations (see list of references in Annex): PDR for Herbal Medicines (LaGow ed. 2004); Martindale The Extra Pharmacopoeia (Reynolds ed., 1989); Hager's Handbuch der Pharmazeutischen Praxis (Hänsel ed., 1993); Lehrbuch der Pharmakognosie und Phytopharmazie (Steinegger, Hänsel, 1972); Herbal Medicine (Barnes ed. 2007); Expanded Commission E Monographs (Blumenthal ed. 2000); The Review of Natural Products (der Marderosian ed. 2015).

Search engines used: Google

Medical databases: Micromedex, HerbMed, MedlinePlus, ESCOP, WHO

Toxicological databases: TOXLINE, HSDB, LactMed

Data from EU and non-EU regulatory authorities: EMA Scientific Guidelines; HMPC Public Statements; FDA Federal Register; EFSA Journal; British Pharmacopoeia 2015 (updated); U.S. Pharmacopoeia National Formulary (USP 38-NF 33, 2015); NIH National Centre for Complementary and Integrative Health; Health Canada monographs.

2. Data on medicinal use

2.1. Information about products on the market

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

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data on soya lecithin (de-oiled phospholipids) obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
1. De-oiled phospholipids from soya beans	a) To support performance in case of physical and mental stress. b) For supplementation of dietetic measures in case of hypercholesterolemia.	Oral solution, 90 mg/ml Adults: 15 ml 3 times daily Duration of use: should be used for 4 weeks minimum. Long term use possible.	Since 1966 (THMP since 2010), AT, TU
2. De-oiled, enriched phospholipids from soya beans	For the improvement of subjective symptoms such as loss of appetite, feeling of pressure in right upper epigastrium due to toxic-metabolic liver damage and in hepatitis.	Hard gelatine capsules, 300 mg/capsule 2 capsules 3 times daily	Since 1998, CZ, full MA
3. De-oiled, enriched phospholipids from soya beans	To improve subjective complaints e.g. loss of appetite, feeling of pressure in the right epigastrium due to hepatic damage caused by hepatotoxic substances and incorrect nutrition (toxic-nutritive hepatic damage) and due to chronic hepatitis.	Capsule, hard, 300 mg/capsule >12 years: 2 capsules 3 times daily. Long-term use possible.	At least since 1976, DE, WEU
4. De-oiled, enriched phospholipids from soya beans	Mild hypercholesterolemia if diet and other non-pharmacological actions (e.g. physical training, weight reduction) alone are insufficient.	Capsule, hard, 300 mg/capsule >12 years: 2 capsules, 3 times daily. Long-term use possible.	At least since 1976, DE, WEU

<p>5. De-oiled, enriched phospholipids from soya beans</p>	<p>a) Mild hypercholesterolemia if diet and other non-pharmacological actions (e.g. physical training, weight reduction) alone are insufficient. This therapy is only justified if an improvement of the cholesterol level is observable.</p> <p>b) To improve subjective complaints e.g. loss of appetite, feeling of pressure in the right epigastrium due to hepatic damage caused by hepatotoxic substances and incorrect nutrition (toxic-nutritive hepatic damage) and due to chronic hepatitis.</p> <p>This therapy does not replace the abstinence of the toxic substances (e.g. alcohol). In case of chronic hepatitis the adjuvant therapy of phospholipids from soya-beans is only justified if an improvement of the patient's condition is observable.</p>	<p>Capsule, soft, 300 mg/capsule</p> <p>>12 years: 2 capsules 3 times daily.</p> <p>Long-term use possible.</p>	<p>At least since 1990, DE, WEU</p>
<p>6-11. De-oiled, enriched phospholipids from soya beans</p>	<p>a) Mild hypercholesterolemia if diet and other non-pharmacological actions (e.g. physical training, weight reduction) alone are insufficient.</p> <p>b) To improve subjective complaints e.g. loss of appetite, feeling of pressure in the right epigastrium due to hepatic damage caused by hepatotoxic substances and incorrect nutrition (toxic-nutritive hepatic damage) and due to chronic hepatitis.</p> <p>This therapy does not replace the abstinence of the toxic substances (e.g. alcohol). In case of chronic hepatitis the adjuvant therapy of phospholipids from soya-beans is only justified if an improvement of the patient's condition is observable.</p>	<p>Capsule, soft, 350 mg/capsule</p> <p>>12 years: 2 capsules 3 times daily.</p> <p>Long-term use possible.</p>	<p>Since 2005, DE, WEU</p>

12. De-oiled phospholipids from soya beans	To improve subjective complaints e.g. loss of appetite, feeling of pressure in the right epigastrium due to hepatic damage caused by hepatotoxic substances and incorrect nutrition (toxic-nutritive hepatic damage) and due to chronic hepatitis.	Capsule, hard, 300 mg/capsule >12 years: 2 capsules 3 times daily. Long-term use possible.	Since 2013, DE, WEU
13. De-oiled, enriched phospholipids from soya beans. The phospholipids are quantified to 73–79% phosphatidylcholine, contain up to 7% phosphatidyl-ethanolamine and less than 0.5% phosphatidylinositol.	To improve subjective complaints e.g. loss of appetite, feeling of pressure in the right epigastrium due to hepatic damage caused by hepatotoxic substances and incorrect nutrition (toxic-nutritive hepatic damage) and due to chronic hepatitis.	Capsule, hard, 600 mg/capsule Adults: 1 capsule 3 times daily. Long-term use possible.	Since 2013, DE, WEU
14. De-oiled, enriched phospholipids from soya beans	To improve subjective complaints e.g. loss of appetite, feeling of pressure in the right epigastrium due to hepatic damage caused by hepatotoxic substances and incorrect nutrition (toxic-nutritive hepatic damage) and due to chronic hepatitis.	Capsule, hard, 300 mg/capsule >12 years: 2 capsules 3 times daily. Long-term use possible	Since 2013, DE, WEU
15. De-oiled phospholipids from soya beans	In addition to diet in mild hypercholesterolemia	Granules, 3 g/sachet >12 years: 1 sachet 3 times daily, long-term use possible	At least since 1976, DE, WEU
16. Phospholipids from soya beans	Traditional used to improve general condition in exhaustion and to strengthen the nerves	Oral solution, 500 mg/10 ml >12 years: 15 ml (750 mg) 2 times daily	At least since 1976, DE, TU
17. Phospholipids from soya beans	a) Traditional herbal medicinal product for enhancing	Oral emulsion, 90 mg/ml	Since 1993 (since

Active substance	Indication	Pharmaceutical form	Regulatory Status
	physical and mental performance of the body. b) Treatment of mild hypercholesterolemia as an adjuvant to dietary measures	Adults: 15 ml 3 times daily. The maximal dose is 3x30 ml. If the symptoms persist for more than 4 weeks or worsen during the treatment the patients should consult with their physicians.	2012 THMP), HU, TU
18. De-oiled enriched phospholipids from soya beans	To improve subjective symptoms, such as loss of appetite or a feeling of pressure in the upper right abdomen, in patients with liver damage caused by the toxic effects of certain foods or hepatitis.	Capsule, hard, 300 mg/capsule >12 years: 2 capsules 3 times daily. Long-term use possible.	Since 2013, HU, TU

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Not applicable

Information on other products marketed in the EU/EEA (where relevant)

Not applicable

2.1.2. Information on products on the market outside the EU/EEA

Not applicable

2.2. Information on documented medicinal use and historical data from literature

Soya lecithin is used in the food and pharmaceutical industry for technical purposes, because it represents an easily digestible emulsifier of natural origin (e.g. margarine production and pharmaceutical emulsions). In medicine, it has been used in general physical weakness and to strengthen the nerves. Lecithin has also been used in certain diseases of the liver and fat metabolism (Steinegger and Hänsel, 1972).

In Hagers Handbuch der Pharmazeutischen Praxis, soya lecithin is reported to have been used in mild dyslipidaemia, in particular mild hypercholesterolemia, if dietary measures alone are not sufficient. Average daily dosage is 3.5 g. Traditionally, it has been used for the relief of physical weakness, concentration difficulties and to strengthen the nerves (Hänsel, 1993).

According to the Commission E, soya lecithin has historically been used in case of poor nutrition, rickets, anaemia, diabetes and tuberculosis. Furthermore, soya lecithin has been used to treat hypercholesterolemia, neurologic disorders, and liver disorders, including fatty liver and toxic liver damage. The Commission E has published two positive monographs on soya lecithin (Blumenthal *et al.*, 2000).

1. Soy lecithin (*lecithinum ex soya*)

In 1988 the Commission E approved soya lecithin extracted from soya beans and its preparations in effective dosage for moderate disturbances of fat metabolism, especially hypercholesterolemia if dietary measures are not sufficient.

Available dosage recommendations are the following:

Preparations from soya beans for oral intake containing total phospholipids in their natural mixture composition corresponding to 3.5 g (3-sn-phosphatidyl) choline/day.

2. Soy phospholipid with 73-79% (3-sn-phosphatidyl) choline

In 1994 the Commission E approved the internal use of soya phospholipid with 73-79% (3-sn-phosphatidyl) choline (soy lecithin, enriched extract) for:

- less severe forms of hypercholesterolemia in which diet and other non-medical interventions (e.g. exercise, weight control) have not shown results, and
- improvement of subjective complaints, such as loss of appetite and feeling of pressure in the region of the liver in toxic nutritional liver disease and chronic hepatitis; prerequisite to the therapy of chronic liver disease is the recognition and avoidance of noxious agents – in the case of liver disease, alcohol abstinence. In chronic hepatitis adjuvant therapy with phospholipids of soya beans is only indicated when improvement of symptoms is discernible from other therapy.

Daily dosage is 1.5-2.7 g phospholipid from soya bean with 73-79% (3-sn-phosphatidyl) choline in a single dose.

It is summarised in the Review of Natural Products, that lecithin is used for its emulsifying properties in the food, pharmaceutical, and cosmetic industries. Proposed pharmacological use of lecithin includes treatment for hypercholesterolemia, neurologic disorders, manic disorders, and liver ailments (The Review of Natural Products, 2014).

2.3. Overall conclusions on medicinal use

Based on the information obtained from Member States and literature, medicinal use of soya lecithin has been reported in the EU/EEA at least since 1966. According to the market overview the soya bean preparation in Table 2 fulfils the criteria of medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA.

Table 2: Soya bean preparation that fulfil the criteria of medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA considered acceptable for the EU herbal monograph

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Soya lecithin (de-oiled phospholipids from soya bean) Herbal preparations in liquid and solid dosage forms for oral use.	Traditional herbal medicinal product for the relief of temporary fatigue and sensation of weakness. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.	Oral use: <i>Adults and elderly</i> Single dose: 750-2700 mg 2-3 times daily <i>Adolescents</i> Single dose: 750 mg 2 times daily The use in children under 12 years of age is not recommended.	Since 1966 AT, at least since 1976 DE, since 1993 HU, (Steinegger and Hänsel, 1972)

Soya lecithin has been used for the relief of temporary fatigue and sensation of weakness since 1966, i.e. traditional medicinal use according to Directive 2004/24/EC is considered fulfilled for this indication.

Soya lecithin as a medicinal product has also been used for more than 30 years in the EU/EEA for the treatment of mild hypercholesterolemia if diet and other non-pharmacological actions (e.g. physical training, weight reduction) alone are insufficient. However, the decision to initiate treatment of hypercholesterolemia requires a medical investigation which provides the medical doctor with the information necessary for the decision. Monitoring of the treatment effect and the necessary periodic re-evaluations also requires medical resources and expertise. Since diagnosis, initiation and monitoring of therapy for mild hypercholesterolemia require medical expertise this indication is not considered appropriate for self-medication. This indication cannot be considered acceptable for a traditional herbal medicinal product.

Authorised products with the indication mild hypercholesterolemia can be found on the EU market for more than 10 years. The clinical efficacy of soya lecithin, based on Article 10a of Directive 2001/83/EC (well-established use), is evaluated in section 4. "Clinical data".

Furthermore, soya lecithin has been used to improve subjective complaints e.g. loss of appetite, feeling of pressure in the right epigastrium due to hepatic damage in the EU/EEA at least since 1976. However, hepatic damage is not considered appropriate for self-care and this indication should not be considered acceptable for traditional herbal medicinal products.

Authorised products with the indication 'improvement of subjective complaints e.g. loss of appetite, feeling of pressure in the right epigastrium due to hepatic damage' can be found on the EU market for more than 10 years. The availability of clinical evidence for soya lecithin to establish recognised

efficacy and an acceptable level of safety based on Article 10a of Directive 2001/83/EC (well-established use), is evaluated in section 4. "Clinical data".

3. Non-Clinical Data

The amphipathic phospholipids make up the lipid bilayer found in all cell membranes and influence numerous cellular functions (Gundermann *et al.* 2011). The non-clinical safety has been reviewed by the Commission E in 1988 and 1994 (Blumenthal *et al.*, 2000).

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

3.1.1. Primary pharmacodynamics

In decreased performance such as fatigue and sensation of weakness

No data found. However, one experimental study indicates that soybean lecithin may improve memory impairment in aged rats (Suzuki *et al.*, 2001).

Hypercholesterolemia

In the scientific literature, there are some publications on the hypercholesterolemic properties of dietary soya lecithin in animals. Although this assessment report has focused on soya lecithin used as medicinal product some other publications are also mentioned.

Adding soya lecithin (3.4%) to the diet reduced non-HDL cholesterol in both cynomolgus monkeys and F1B hamsters (Wilson *et al.*, 1998). Also in Rhesus monkeys, lecithin supplementation to food reduced plasma cholesterol (Wong *et al.*, 1980).

Reduction of LDL cholesterol as well as an increase in the level of HDL cholesterol was observed in rats fed a hypercholesterolemic diet in combination with lecithin (2.5 or 0.7%) (Jimenez *et al.*, 1990). However, 6% soya lecithin had no effect on the serum cholesterol level in rats fed on a diet containing 0.5% cholesterol although lecithin compared to corn oil reduced cholesterol absorption (O'Mullane and Hawthorne, 1982).

Soybean lecithin reduced total plasma cholesterol without a decrease in HDLC in guinea pig fed by cholesterol diet (O'Brien and Corrigan, 1988).

Hepatic damage

Gundermann *et al.* reviewed in 2011 that cytoprotective properties of lecithin have been corroborated in 25 *in vitro* studies and in 145 *in vivo* experiments in 8 different animal species. In these studies, lecithin has primarily been administered to avoid hepatic toxicity induced by chemicals (e.g. carbon tetrachloride) or drugs (e.g. cyclosporine A) (Gundermann *et al.*, 2011).

Fatty liver with cholangitis with bile duct proliferation, cholestasis and fibrosis were induced in rabbits by atherogenic diet for 18 months. For rabbits receiving additional feeding of soya lecithin (3%) for an additional 4 months only some cholangitis with minimal fibrosis was observed (Hunt and Duncan, 1985).

Lecithin had both preventive and curative effect on ethanol-induced alteration on liver weights in rats (Das and Vasudevan, 2006). Pretreatment with lecithin also had a positive impact with reduction of D-galactosamine induced hepatotoxicity in rats (Raj *et al.*, 2011).

3.1.2. Secondary pharmacodynamics

No data found.

3.1.3. Safety pharmacology

No data found.

3.1.4. Pharmacodynamic interactions

No data found.

3.1.5. Conclusions

Relevant experimental studies on soya lecithin to support the proposed indication are limited since most experimental studies have poorly described extracts, inadequate posology or lack of relevant control groups. However, none of the reported pharmacological studies constitute any cause for safety concerns.

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

Absorption

The absorption rate following oral administration within 24 h is higher than 90% in animals (Gundermann *et al.*, 2011). The Commission E describes that phospholipids are degraded to lysophosphatidylcholine in the intestine and absorbed primarily in this form (animal data). In the gut wall, the phospholipids are in part re-synthesised (Blumenthal *et al.*, 2000).

Distribution

Phospholipids are primarily incorporated into the liver, with minor incorporation into other organs such as the gastrointestinal tract, spleen, lungs, muscles, kidneys and brain (Gundermann *et al.*, 2011).

In plasma, phosphatidylcholine and other phosphoglycerides are tightly bound to lipoproteins or albumin, or to both (Blumenthal *et al.*, 2000).

Metabolism

Phosphatidylcholine and other phosphoglycerides are degraded through a series of so-called phospholipases to fatty acids, choline and glycerine metabolites to be in turn re-synthesised in the liver and other organs (Blumenthal *et al.*, 2000).

Elimination

Renal excretion after a single dose in the first eight days was 17.4% of the administered dose in rats and 17.7% in rhesus monkeys. The excretion in the faeces was low, with 3–8% of the dose excreted in the first 5–7 days in rats. Hence, a considerable part of the phospholipids are thought to be incorporated in the cell membrane of different cells (Gundermann *et al.*, 2011).

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

3.3.1. Single dose toxicity

In the Commission E monograph on lecithin enriched extracts from soya bean, doses of phosphatidylcholine of up to 10 g/kg bw in mice and rats and 4.5 g/kg bw in rabbits given intravenous, intraperitoneally, and orally in a single dose are reported to be non-toxic (Blumenthal *et al.* 2000).

Phosphatidylinositol from soya lecithin at doses of up to 2 g/kg of was administrated once orally to male and female rats. There were no deaths or any clinical sign in any group throughout the observation period (Honda *et al.*, 2009).

3.3.2. Repeat dose toxicity

The “no-effect” dosage over 48 weeks administration to rats are above 3.75 g/kg bw/day, as reported in the Commission E monograph on lecithin enriched extracts from soya bean. Following repeated intravenous application over 12 weeks in rats, the lowest systemic toxic dosage was between 0.1 and 1 g/kg bw and lowest local toxic dosage at over 1 g/kg bw. In a four weeks study in dogs, the lowest toxic dosage was above 0.1 g/kg bw (Blumenthal *et al.*, 2000).

Phosphatidylinositol from soya lecithin was repeatedly administered orally to male and female rats at daily doses of 100, 300 and 1,000 mg/kg for 13 weeks. Neither death nor any toxicological signs during the administration period and no changes related to the test substance administered were observed in any group with regard to body weight, food consumption, ophthalmoscopy, hematology, blood biochemistry, necropsy, organ weights or histopathology. Based on these results, the no-observed-adverse effect level (NOAEL) was considered to be 1,000 mg/kg/day for male and female rats (Honda *et al.*, 2009).

3.3.3. Genotoxicity

No data have been found for soya lecithin. Genotoxic evaluation of phosphatidylinositol from soya lecithin has been carried out using the bacterial reverse mutation test (Ames test) and *in vitro* chromosome aberration test in compliance with the OECD guidelines for testing chemicals. In the Ames test, the strains *Salmonella typhimurium* TA100, TA1535, TA 98 and TA1537 and *Escherichia coli* WP2uvrA were used. The concentration range tested in Ames test with and without metabolic activation was 313-5000 µg/plate. In the *in vitro* chromosome aberration test cultured Chinese hamster lung fibroblast cells (CHL/IU) were used. The concentration range tested in the *in vitro* chromosome aberration test with and without metabolic activation was 313-5000 µg/ml. The results showed neither increases of revertant colonies nor chromosome aberration (Honda *et al.*, 2009).

3.3.4. Carcinogenicity

No data found.

3.3.5. Reproductive and developmental toxicity

In the Commission E monograph on lecithin enriched extracts from soya bean, doses of up to 3.75 g/kg bw in pregnant animals, animals embryos, and animal neonates showed no pathology of toxicity to reproduction. The lowest teratogenic or embryo-toxic dosage in rats following oral and

intravenous administration was more than 1 g/kg bw. In rabbits teratogenic dosages were greater than 1 g/kg bw for oral administration and greater than 0.5 g/kg bw in intravenous administration (Blumenthal *et al.*, 2000).

Two reproductive and developmental toxicity studies on dietary soya lecithin in rats have been found in the scientific literature (Bell and Lundberg, 1985; Bell and Slotkin, 1985). In the study by Bell and Lundberg, pregnant rat dams and offspring were exposed to a 5 or 2% soya lecithin preparation or a control diet. The authors report that sensorimotor deficits (reflex righting and swimming development) were seen in the 5% soya lecithin preparation group. Later, animals exposed to lifelong 5 or 2% soya lecithin preparations were hypoactive, had poor postural reflexes, and showed attenuated morphine analgesia. In another study by Bell and Slotkin, rats exposed perinatally to dietary commercial soya lecithin preparation showed alterations in sensorimotor development and brain cell maturation (latencies for righting responses measured on postnatal days 1-4 and negative geotaxis measured on postnatal days 5-8). In adulthood, morphine analgesia was reduced in the treated animals.

3.3.6. Local tolerance

The allergic potency of soya have been evaluated and presented in the 'Public statement on the allergenic potency of herbal medicinal products containing soya or peanut protein' (EMA/HMPC/138139/2005) (see section 5.3 Adverse events, serious adverse events and deaths).

3.3.7. Other special studies

Not relevant

3.3.8. Conclusions

Non-clinical information on the safety of soya lecithin is limited. No toxicological concerns are raised regarding the reported studies.

Genotoxicity and carcinogenicity have not been fully evaluated. Since the genotoxic potential of soya lecithin has not been fully evaluated, a European Union list entry cannot be recommended from a non-clinical point of view.

Reproductive and developmental toxicology have not been fully evaluated. In two publications on dietary soya lecithin in rats, the authors report developmental toxicity. Since the composition of soya lecithin might differ between food and medicinal products, the relevance of these studies for soya lecithin as active ingredient in medicinal products on the EEA market is not known. As there is limited information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

3.4. Overall conclusions on non-clinical data

The available documentation (information from literature, products available on the market and valid registrations within the EU) show a long-standing and on-going medicinal use of soya lecithin in the EU. During this time, no signals of safety concern have been identified (see also section 5 Clinical Safety/Pharmacovigilance).

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

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

Phospholipids make up the lipid bilayer found in all cell membranes and influence numerous cellular functions. Polyunsaturated fatty acids are basic constituents of the phospholipids, influencing membrane fluidity and modulating the activities of membrane-bound enzymes, carriers and receptors. Together with cholesterol and bile acids, phospholipids form mixed micelles in the gallbladder. In the human body phospholipids form parts of the lipoprotein particle complexes, such as very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL). The main task of lipoproteins is the transportation of lipophilic cholesterol and triglycerides in the bloodstream (Gundermann *et al.*, 2011).

Soya lecithin is claimed to have beneficial effects in hypercholesterolemia by reducing total cholesterol and low density lipoprotein cholesterol (LDL-C). The underlying mechanism(s) have not been elucidated (van Ee, 2009).

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

Absorption, distribution, metabolism and elimination of dilinoeylephosphatidylcholine (DLPC) have been reported in a study on five patients after single oral administration of 1 g of DLPC labelled with ^3H in choline and ^{14}C in the two linoleic acid residues. Based on data from faecal excretion and renal elimination measured up to 7 days, it was estimated that more than 90% was absorbed, either intact or after intestinal hydrolysis to lysophosphatidylcholine. Peak plasma ^3H levels were reached in 6 to 24 hours at about 20% of the total administered dose, whereas ^{14}C maximum was reached in 4 to 12 hours at about 28% of the total administered dose. A large portion of the radioactivity from labelled oral phosphatidylcholine appeared in phosphatidylcholine of plasma lipoproteins and red blood cells (Zierenberg *et al.*, 1982).

4.2. Clinical efficacy

In addition to the herbal preparations reported as constituents of medicinal products, there is a broad range of dietary soya products on the market. The composition of the bioactive compounds differs markedly between products and is affected by processing method. Therefore, only soya lecithin preparations included in medicinal products on the EEA-market are evaluated in this section.

4.2.1. Dose response studies

No relevant clinical study has been found.

4.2.2. Clinical studies (case studies and clinical trials)

Soya lecithin in decreased performance such as fatigue and sensation of weakness

There are no studies found concerning soya lecithin and effects on performance such as fatigue and sensation of weakness.

Soya lecithin in the treatment of mild hypercholesterolemia

For the data base search on soya lecithin in hypercholesterolemia, all clinical studies found, whether controlled or not, have been included. However, only studies on soya lecithin products as medicinal products on the EEA market were further evaluated. Studies on soya lecithin with unknown composition as well as unclear or irrelevant posology were excluded. Also, studies on healthy volunteers, patients on dialysis, patients with diabetes and patients with alcoholic fatty liver diagnosis were excluded (Kirsten *et al.*, 1989; Kirsten *et al.*, 1994). The included studies are presented in Table 3.

For the assessment on clinical efficacy of soya lecithin in hyperlipidemic treatment, the EMA document 'Guideline on clinical investigation of medicinal products in the treatment of lipid disorders' (EMA/CHMP/748108/2013) is considered appropriate to use. The guideline recommends:

- A relative reduction in low density lipoprotein cholesterol (LDL-C) levels is acceptable as a primary efficacy endpoint in patients with primary hypercholesterolemia, provided that claims in the label are restricted to a lipid lowering effect
- For medicinal products modifying lipid parameters other than LDL-C, demonstration of a positive clinical outcome in terms of morbidity or mortality is required
- Studies for the evaluation of efficacy or safety of a new lipid-modifying agent are mainly performed in patients with primary hypercholesterolemia and mixed hyperlipidaemia with moderate to very highly elevated LDL-C levels
- When specifically claimed, patients with familial hypercholesterolemia (heterozygous and homozygous) should normally be studied in separate clinical trials, based on their cholesterol levels and clinical genetic characteristics
- All measurements should be performed under standardised, fasting conditions following a dietary lead-in period with or without wash-out of appropriate duration
- Comparative studies with accepted therapy are expected for evaluating the efficacy and safety of newer lipid-modifying drugs
- Duration will depend on their expected outcome but should last at least a minimum of 3 months (for known mechanisms of action) and preferably up to 12 months (for others)

The guideline also discusses that blood lipid levels may be affected by other clinical conditions such as diabetes. If included, patients with type 2 diabetes mellitus should be represented in adequate numbers that will permit sub-group analysis and also evaluation of consistency with the overall results of the study.

Soya lecithin in subjective complaints due to hepatic damage

For the data base search on soya lecithin in hepatic damage, all clinical studies found, whether controlled or not, have been included. However, only studies on soya lecithin products as medicinal products on the EEA market were further evaluated and presented in table 4. The diverse study populations and results are inconclusive and the conditions not relevant for a TU product. The relevance of the studies presented in table 4 is therefore limited.

Table 3: Clinical studies on soya lecithin containing medicinal products on the EEA market in the treatment of hypercholesterolemia

Type	Study	Test Product(s)	Number of subjects	Subjects	Outcomes	Statistical analysis	Clinical relevance
To evaluate the effects of polyenylphosphatidylcholine on metabolism of cholesterol and triglycerides in hypertriglyceridemia patients Kesaniemi <i>et al.</i> , 1986	Open, non-randomised 2-armed cross-over study	<i>Treatment period 1:</i> First treatment period: 7 g safflower oil/day given orally. <i>Treatment period 2:</i> 10 g lecithin*/day given orally. Each treatment was given for approximately 5 weeks. All patients were fed low-cholesterol diets. <i>*Prepared by Natterman Company, Cologne, Germany, containing 67% C18:2 fatty acids</i>	10 subjects, 1F/9M, 45-70 years.	Patients with endogenous triglyceridemia (type 4 hyperlipoproteinemia) Five patients had coronary heart disease (CHD) or cerebrovascular disease (CVD), five patients had no CHD/CVD. No patient had fasting hyperglycaemia or required hypoglycaemic agents. No patient had congestive heart failure or evidence of liver failure or gastrointestinal disease.	Compared with safflower oil, lecithin feeding did not significantly affect plasma total cholesterol, LDL, HDL or TG.	Difference evaluated by paired <i>t</i> -test, $P < 0.05$	Small, open cross-over study not supporting a cholesterol lowering effect of high doses of lecithin (10 g) compared with safflower oil. No wash-out period between treatments described.
To study the effect of soya lecithin on blood lipid and lipoprotein values in patients with type II hyperlipoproteinemia	Open, uncontrolled Duration: 8 months	<i>Treatment:</i> oral soya lecithin* Initial dose: 1.2 g/day for 4 months, followed by 2.4 g/day for another 4 months <i>*"Lecithine essentielle forte - Natterman-versuchspräparat v</i>	12 subjects; 9F/3M; 34-76 years	Patients with type II hypercholesterolemia Baseline serum mean cholesterol levels \pm S.E.M. were 11.00 ± 0.91 mmol/L, indicating familiar hypercholesterolemia. Three patients had	No clinically relevant changes were seen in total lipids, total cholesterol, triglycerides, phosphor-	Difference in total lipids: - 1 st exp. period vs. 1 st control period, - 2 nd exp. period vs 1 st control period,	Small open, uncontrolled study not supporting a cholesterol lowering effect of soya lecithin (1.2-2.4 g).

Type	Study	Test Product(s)	Number of subjects	Subjects	Outcomes	Statistical analysis	Clinical relevance
ter Welle <i>et al.</i> , 1974		<p>5180" prepared by Nattermann Company, Cologne, Germany</p> <p>Content: soya lecithin, 300 mg; vitamin B1, 6 mg, vitamin B12, 6 µg; nicotinamide, 33 mg; and vitamin E-acetate, 6 mg</p>		<p>elevated serum triglycerides.</p> <p>All patients but two had a history of clinical atherosclerotic disease, e.g. angina pectoris and myocardial infarction.</p> <p>Four patients were on a low cholesterol diet. No patient had diabetes.</p> <p>Any hyperlipidaemia treatment was stopped some time before investigation</p>	<p>lipids, total lipids in the lipoprotein fractions and the weight percentage of linoleic acid in serum cholesterol esters and serum lecithin</p>	<p>- 2nd control period vs. 1st control period, and 2nd exp. period vs. 2nd control period, compared using Student's <i>t</i>-test</p>	

Table 4: Clinical studies on soya lecithin containing medicinal products with hepatic indications on the EEA market

Type	Study	Test Product(s)	Number of subjects	Subjects	Outcomes	Statistical analysis	Clinical relevance
<p>Evaluation of effects of lecithin in patients with chronic hepatitis B or C in combination with interferon alpha 2a or 2b.</p> <p>Duration: 24 or 48 weeks</p> <p>Niederau <i>et al.</i>, 1998</p>	<p>Double-blind, randomized, placebo-controlled, multicentre. The study was performed and monitored according to GCP and GLP.</p>	<p>S.c. injections of 5 million I.U. (hepatitis B) or 3 million I.U. (hepatitis C) IFN thrice weekly for 24 weeks.</p> <p>Additional oral medication with either 3x2 soya lecithin* (1.08 g/day)</p> <p><i>*Polyunsaturated phosphatidylcholine (PPC), 72-76% lecithin. Essentiale forte, Rhône-Poulenc Rorer GmbH, Cologne, FRG.</i></p>	<p>24 weeks: 272 patients; 137 lecithin, 135 placebo.</p> <p>48 weeks: 176 patients; 92 lecithin, 84 placebo</p>	<p>Patients with chronic hepatitis B or C. Diagnosed at least 3 months prior the study, evidence of viral replication for at least 6 months. All patients received interferon alpha treatment (IFN).</p> <p>Oral medication with either 3 lecithin capsules (0.18 g/capsule) or placebo twice per day.</p> <p>Treatment for 24 weeks. Responders (ALT decrease $\geq 50\%$) maintained treatment for further 24 weeks after cessation of IFN.</p> <p>Exclusion criteria: Current medication with immunosuppressive agents, heparin, oral anticoagulants, corticoids, liver therapeutics and antiviral agents including IFN if given during the previous 3 months, positive test for serum antibodies to HIV or hepatitis D, pregnancy, lactation or</p>	<p>Lecithin increased the response rate in patients with hepatitis C, but not in hepatitis B.</p>	<p>The rate of responders were compared using the asymptomatic χ^2-test for independent samples ($n > 100$). Fisher's exact test (two-tailed) was used for $n \leq 100$. Students' <i>t</i>-test was used for ALT-values. $p > 0.05$</p>	<p>Double-blind, randomized, placebo-controlled, according to GCP and GLP supporting hepatic indication, but with limited relevance.</p>

				absence of contraceptive use in women of childbearing age, contraindications for IFN; decompensated liver cirrhosis, hepatocellular carcinoma, auto-immune hepatitis, leukocyte count below $2 \times 10^9/L$, platelet count below $70 \times 10^9/L$, history of psychosis, depression or epilepsy, severe chronic disease, severe hypertension, disorders of blood coagulation, renal disease; creatinine ≥ 1.5 mg/dL.			
To investigate the effect of administration of essential phospholipids on plasma lipid parameters in patients with alcoholic fatty liver. Duration: 3 months. Turecky <i>et al.</i> , 2003	Open clinical trial	2 capsules of Essentiale forte (600 mg) 3 times/day	71 subjects 29 patients, 17M, 12F, mean age 48.9 years. 42 healthy subjects, 30M, 12F, mean age 38.8 years.	Patients suffered from alcoholic fatty liver with histologically verified liver steatosis. The control group was students and blood donors who showed no abnormalities on physical or laboratory tests.	Positive effect on hepatocyte integrity and subjective symptoms of patients with liver steatosis. No effect on plasma lipid parameters.	Gaussian distribution: Student's <i>t</i> -test for differentiating the averages and Pearson's correlation coefficient. Non-Gaussian distribution: Wilcoxon's test for comparing populations and Spearman's correlation coefficient.	Open study supporting hepatic indication, but with limited relevance.

<p>Pilot study to evaluate efficacy and safety of lecithin in a phase III clinical trial in patients with hepatic failure over one year period in a prospective randomised blinded controlled design.</p> <p>Treatment 6-8 weeks.</p> <p>Singh and Prasad, 1998</p>	<p>Randomized, double-blind, placebo-controlled</p>	<p>Lecithin (350 mg) x3/day for 6-8 weeks</p>	<p>70 subjects</p> <p>36 patients with fulminant hepatic failure, 16 lecithin, 20 placebo-controls</p> <p>34 patients with subacute hepatic failure, 14 lecithin, 20 placebo-controls</p>	<p>Fulminant hepatic failure was diagnosed on clinical features of hepatic encephalopathy occurring within 8 weeks after onset of jaundice together with impaired liver function. Supported by clinical and/or ultrasonographic evidence of small shrunken liver.</p> <p>The diagnosis subacute hepatic failure patients had hepatic encephalopathy developing after 8 weeks but within 6 months after onset of jaundice, clinically detectable ascites in acute hepatitis, absence of evidence of chronic liver disease by ultrasonography and/or upper gastrointestinal endoscopy.</p>	<p>Faster recovery after encephalopathy and lower mortality rate</p>	<p>Student's <i>t</i>-test for unpaired data and Fischer's exact probability test</p>	<p>Small, randomized, double blind, placebo-controlled study, lecithin dose ~1 g/d supporting hepatic indication, but with limited relevance.</p>
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<p>To determine the effectiveness of lecithin in preventing or reversing liver fibrosis in heavy drinkers</p> <p>Lieber <i>et al.</i>, 2003</p>	<p>Double-blind, randomized, placebo-controlled</p> <p>Duration: 2 years</p>	<p>3 tablets/day of lecithin* or placebo</p> <p><i>*From Rhône-Poulenc Rorer, Cologne, Germany</i></p>	<p>789 alcoholics, mean age: 48.8 years, M 97.3 %</p> <p>412 completed 24 months, 377 dropouts.</p>	<p>The average intake was 16 drinks (80 g) per day for ≥5 years (average 19 years).</p>	<p>Lecithin did not affect progression of liver fibrosis.</p>	<p>Analysis of variance for group comparison, χ^2 for categorical variables.</p>	<p>Double blinded, randomized, placebo controlled study not supporting hepatic indication and with limited relevance.</p>
<p>To study the effect of lecithin on HBsAg negative chronic active hepatitis</p> <p>Jenkins <i>et al.</i>, 1982</p>	<p>Prospective, randomized, double-blind, placebo-controlled</p> <p>Duration: 1 year</p>	<p>Lecithin* (3 g/day)</p> <p><i>*Essential Phospholipid, nattermann & Cie, Germany</i></p>	<p>30 patients, 8M, 22F</p>	<p>Patients with HBsAg negative chronic active hepatitis with biopsy with evidence of continuing disease activity, receiving immunosuppressive therapy (prednisolone 7.5-15 mg/day with/without azathioprine 50-75 mg/day)</p>	<p>Histological evidence of disease activity was reduced by lecithin.</p>	<p>Wilcoxon's Sum of Rank Test, $p < 0.05$</p>	<p>Double blinded, randomized, placebo controlled study supporting hepatic indication, but with limited relevance.</p>

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

No clinically relevant study in special populations has been found.

4.4. Overall conclusions on clinical pharmacology and efficacy

There are several clinical studies on the cholesterol lowering effect of soya lecithin, however, very few studies have been published during the last 20 years. In particular, there are only two studies on soya lecithin medicinal products found in the literature (Kesaniemi *et al.*, 1986; ter Welle *et al.*, 1974). Both studies are small, open and exploratory, and do not support a cholesterol lowering effect of soya lecithin. The current requirements for well-established medicinal use according to Article 10a of Directive 2001/83/EC is considered not fulfilled.

The effect of soya lecithin with hepatic indications has been studied in patients with different liver diseases such as chronic hepatitis (Niederau *et al.*, 1998; Jenkins *et al.*, 1982), hepatic failure (Singh and Prasad, 1998), alcoholic fatty liver (Turecky *et al.*, 2003) and alcoholic liver disease (Lieber *et al.*, 2003). Generally, the composition of the products used in these studies are not well described. Furthermore, none of the hepatic indications are relevant for self-treatment, the criteria for traditional herbal medicinal products can therefore not be considered fulfilled.

In the scientific literature, there are no clinical studies on soya lecithin in the improvement of subjective complaints e.g. loss of appetite, feeling of pressure in the right epigastrium due to hepatic damage. Hence, Article 10a of Directive 2001/83/EC (well-established use) is not considered fulfilled.

5. Clinical Safety/Pharmacovigilance

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

No data found.

5.2. Patient exposure

Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

Phospholipids are mainly obtained by food consumption (0.5-3 g/day from food) (Blumenthal *et al.*, 2000).

5.3. Adverse events, serious adverse events and deaths

Dietary soya products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations. The allergic potency of soya and peanut has been evaluated in the 'Public statement on the allergenic potency of herbal medicinal products containing soya or peanut protein' (EMA/HMPC/138139/2005).

In addition to allergic reactions, the information obtained from the market overview of medicinal products containing soya lecithin includes reports on gastrointestinal disorders (such as soft stool and diarrhoea) and skin reactions (such as urticaria, exanthema, and pruritus).

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

According to the information obtained from the market overview, soya lecithin used for the relief of temporary fatigue and sensation of weakness, has not been used in children under 12 years of age.

5.5.2. Contraindications

Cross-allergy has been reported for patients with known allergies to other legumes. IgE-cross reactions are also reported for patients with birch pollen allergy and associated food allergies (EMA/HMPC/138139/2005).

In the information obtained from the market overview of medicinal products containing soya lecithin, the antiphospholipid syndrome is contraindicated in some products on the market. However, in guidelines on the current treatment of antiphospholipid syndrome there are no recommendations that soya lecithin should be avoided for these patients (Lim, 2013; Tuthill 2009).

5.5.3. Special warnings and precautions for use

If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

5.5.4. Drug interactions and other forms of interaction

No interaction studies have been performed.

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. No fertility data are available.

5.5.6. Overdose

No case of overdose has been reported.

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

No studies on the effect on the ability to drive and use machines have been performed.

5.5.8. Safety in other special situations

Not applicable

5.6. Overall conclusions on clinical safety

Based on limited data from clinical experience, mainly cases of gastrointestinal discomfort and hypersensitivity reactions have been reported. The frequencies of the undesirable effects are not known.

Soya lecithin used for the relief of temporary fatigue and sensation of weakness, has a long standing medicinal use in the EU. If patients with known hypersensitivity to soya bean, peanut or other plants of the Fabaceae (legume) family and to birch pollen are excluded, a traditional use is considered safe if administration follows the instructions as specified in the monograph.

6. Overall conclusions (benefit-risk assessment)

Soya lecithin as a medicinal product has been used for more than 30 years in the EU/EEA for the treatment of mild hypercholesterolemia if diet and other non-pharmacological actions (e.g. physical training, weight reduction) alone are insufficient. However, the decision to initiate treatment of hypercholesterolemia requires a medical investigation which provides the medical doctor with the information necessary for the decision. Monitoring of the treatment effect and the necessary periodic re-evaluations also requires medical resources and expertise. Since diagnosis, initiation and monitoring of therapy for mild hypercholesterolemia require medical expertise this indication is not appropriate for self-medication. This indication cannot be considered acceptable for a traditional herbal medicinal product.

There are only two clinical studies on soya lecithin medicinal products found in the literature. Other studies have been excluded and not assessed. The included studies are small, open and do not support a cholesterol lowering effect of soya lecithin. The current requirements for well-established medicinal use according to Article 10a of Directive 2001/83/EC is considered not to be fulfilled.

Furthermore, soya lecithin has been used to improve subjective complaints e.g. loss of appetite and feeling of pressure in the right epigastrium due to hepatic damage, in the EU/EEA at least since 1976. Hepatic damage is not appropriate for self-care and this indication cannot be considered acceptable for traditional herbal medicinal products. In the scientific literature, there are no clinical studies on soya lecithin in the improvement of subjective complaints e.g. loss of appetite and feeling of pressure in the right epigastrium due to hepatic damage. Hence, Article 10a of Directive 2001/83/EC (well-established use) is considered not fulfilled.

Soya lecithin has been used for the relief of temporary fatigue and sensation of weakness, throughout a period of at least 30 years, including at least 15 years within the EU/EEA, i.e. traditional medicinal use according to Directive 2004/24/EC is considered fulfilled. If patients with known hypersensitivity to soya bean, peanut or other plants of the Fabaceae (legume) family and to birch pollen are excluded, a traditional use is considered safe if administration follows the instructions as specified in the monograph. The use in children under 12 years of age has not been established due to lack of adequate data.

Non-clinical data on pharmacology and safety of soya lecithin is limited. Genotoxicity, carcinogenicity, reproductive and developmental toxicology have not been fully evaluated. Since the genotoxic potential of soya lecithin has not been fully evaluated, a European Union list entry cannot be recommended from a non-clinical point of view. As there is limited information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Therapeutic area for browse search: Fatigue and weakness.

Annex

List of references