



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

12 July 2016  
EMA/HMPC/220598/2016  
Committee on Herbal Medicinal Products (HMPC)

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

Draft

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Glycine max</i> (L.) Merr., lecithin
Herbal preparation(s)	Soya-bean lecithin (deoiled, enriched phospholipids from soya bean)
Pharmaceutical form(s)	Herbal preparations in liquid or solid dosage forms for oral use.
Rapporteur(s)	P. Claeson
Assessor(s)	E. Svedlund
Peer-reviewer	I. Chinou

Note: This draft assessment report is published to support the public consultation of the draft European Union monograph on *Glycine max* (L.) Merr., lecithin. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.



# Table of contents

<b>Table of contents</b> .....	<b>2</b>
<b>1. Introduction</b> .....	<b>4</b>
1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof ..	4
1.2. Search and assessment methodology .....	5
<b>2. Data on medicinal use</b> .....	<b>6</b>
2.1. Information about products on the market .....	6
2.1.1. Information about products on the market in the EU/EEA Member States .....	6
2.1.2. Information on products on the market outside the EU/EEA .....	10
2.2. Information on documented medicinal use and historical data from literature .....	10
2.3. Overall conclusions on medicinal use .....	11
<b>3. Non-Clinical Data</b> .....	<b>12</b>
3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	12
3.1.1. Primary pharmacodynamics .....	12
3.1.2. Secondary pharmacodynamics .....	13
3.1.3. Safety pharmacology .....	13
3.1.4. Pharmacodynamic interactions .....	13
3.1.5. Conclusions .....	13
3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	13
3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof .....	14
3.3.1. Single dose toxicity.....	14
3.3.2. Repeat dose toxicity.....	14
3.3.3. Genotoxicity .....	14
3.3.4. Carcinogenicity.....	14
3.3.5. Reproductive and developmental toxicity .....	14
3.3.6. Local tolerance .....	15
3.3.7. Other special studies.....	15
3.3.8. Conclusions .....	15
3.4. Overall conclusions on non-clinical data .....	15
<b>4. Clinical Data</b> .....	<b>16</b>
4.1. Clinical pharmacology .....	16
4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents.....	16
4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents.....	16
4.2. Clinical efficacy .....	16
4.2.1. Dose response studies.....	16
4.2.2. Clinical studies (case studies and clinical trials) .....	16
4.3. Clinical studies in special populations (e.g. elderly and children) .....	19
4.4. Overall conclusions on clinical pharmacology and efficacy.....	19
<b>5. Clinical Safety/Pharmacovigilance</b> .....	<b>19</b>
5.1. Overview of toxicological/safety data from clinical trials in humans.....	19

5.2. Patient exposure .....	19
5.3. Adverse events, serious adverse events and deaths.....	19
5.4. Laboratory findings.....	19
5.5. Safety in special populations and situations .....	19
5.5.1. Use in children and adolescents.....	19
5.5.2. Contraindications.....	20
5.5.3. Special warnings and precautions for use .....	20
5.5.4. Drug interactions and other forms of interaction.....	20
5.5.5. Fertility, pregnancy and lactation.....	20
5.5.6. Overdose.....	20
5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability .....	20
5.5.8. Safety in other special situations .....	20
5.6. Overall conclusions on clinical safety.....	20
<b>6. Overall conclusions (benefit-risk assessment).....</b>	<b>21</b>
<b>Annex .....</b>	<b>21</b>

# 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 deoiled, enriched phospholipids obtained from seeds of by *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:

1. Deoiled phospholipids from soya bean (soya lecithin)
2. Deoiled phospholipids from soya bean (soya lecithin) (*Lecithinum ex soya*)  
Soya lecithin contains (3-sn-phosphatidyl)choline, phosphatidylethanolamine and phosphatidylinositol. Pharmacopeial grade soya lecithin must contain a minimum 20% and maximum 31.6% phosphatidylcholine calculated on the dried substance (Blumenthal *et al.*, 2000).
3. Deoiled, 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 method.

Please note that dietary soya products (including food supplements) are not covered by this 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 Pharmacopeia 2015 (updated); U.S. Pharmacopeia National Formulary (USP 38-NF 33, 2015); NIH National Center 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 (deoiled phospholipids) obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
1. Deoiled 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. Deoiled, 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. Deoiled, 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. Deoiled, 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. Deoiled, 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 &gt;12 years: 2 capsules 3 times daily. Long-term use possible.</p>	<p>At least since 1990, DE, WEU</p>
<p>6-11. Deoiled, 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 &gt;12 years: 2 capsules 3 times daily. Long-term use possible.</p>	<p>Since 2005, DE, WEU</p>

12. Deoiled 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. Deoiled, enriched phospholipids from soya beans. The phospholipids are quantified to 73–79% phosphatidylcholine, contain up to 7% phosphatidylethanolamine 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. Deoiled, 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. Deoiled 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 physical and mental performance of the body. b) Treatment of mild hypercholesterolemia as an	Oral emulsion, 90 mg/ml Adults: 15 ml 3 times daily. The maximal dose is 3x30 ml. If the symptoms persist for more than 4 weeks or worsen during	Since 1993 (since 2012 THMP), HU, TU



Active substance	Indication	Pharmaceutical form	Regulatory Status
	adjuvant to dietary measures	the treatment the patients should consult with their physicians.	
18. Deoiled 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 per 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 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, see table 2 below.

**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

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Soya lecithin (deoiled, enriched phospholipids from soya bean) Herbal preparations in liquid and solid dosage forms for oral use.	<p>Traditional herbal medicinal product for the relief of temporary fatigue and sensation of weakness.</p> <p>The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.</p>	<p>Oral use: <i>Adolescents, adults and elderly</i></p> <p>Daily dose: 750-2700 mg 2-3 times daily</p> <p>The use in children under 12 years of age is not recommended.</p>	<p>Since 1966 AT, at least since 1976 DE, since 1993 HU, Steinegger and Hänsel, 1972</p>
	<p>Traditional herbal medicinal product used for the treatment of mild hypercholesterolemia if diet and other non-pharmacological actions (e.g. physical training, weight reduction) alone are insufficient.</p> <p>The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.</p> <p><u>Assessor´s comment:</u> This indication is not appropriate for self-care, see conclusion below.</p>	<p>Oral use: <i>Adolescents, adults and elderly</i></p> <p>Daily dose: 600-3000 mg 3 times daily</p> <p>The use in children under 12 years of age is not recommended.</p>	<p>Since 1966 AT, at least since 1976 DE, since 1993 HU, Hänsel, 1993, Blumenthal <i>et al.</i>, 2000</p>
	<p>Traditional herbal medicinal product used to improve subjective complaints e.g. loss of appetite, feeling of pressure in the right epigastrium due to hepatic damage.</p> <p>The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.</p> <p><u>Assessor´s comment:</u> This indication is not appropriate for self-care, see conclusion below.</p>	<p>Oral use: <i>Adolescents, adults and elderly</i></p> <p>Daily dose: 600-700 mg 3 times daily</p> <p>The use in children under 12 years of age is not recommended.</p>	<p>At least since 1976 DE, since 1998 CZ, since 1993 HU, Blumenthal <i>et al.</i>, 2000</p>

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 indications is not appropriate for self-medication. This indication cannot be considered acceptable for a traditional herbal medicinal product.

The clinical efficacy of soya lecithin in mild hypercholesterolemia, based on Article 10a of Directive 2001/83/EC as amended (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. 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, feeling of pressure in the right epigastrium due to hepatic damage. Hence, Article 10a of Directive 2001/83/EC as amended (well-established use) is not considered fulfilled.

### 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.

*Hypercholesterolemia*

In the scientific literature, there are some publications on the hypercholesterolemic properties of dietary soya lecithin in animals. However, since the composition of soya lecithin might differ between food and medicinal products, these studies are not included in the assessment report. In addition, reports on the effect of soya lecithin on lipid metabolism in healthy animals (i.e. normolipidaemic animals) have been excluded (see Annex 'List of references').

*Subjective complaints due to hepatic damage*

No data found.

### 3.1.2. Secondary pharmacodynamics

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).

### 3.1.3. Safety pharmacology

No data found.

### 3.1.4. Pharmacodynamic interactions

No data found.

### 3.1.5. Conclusions

Results from relevant experimental studies on soya lecithin to support the proposed indications are scarce.

## **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 administered 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 per day, 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. 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 scarce. 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, there 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 1g of DLPC labelled with 3H in choline and 14C in the two linoleic acid residues. Based on data from fecal 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 14C 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 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 food supplements, soya



lecithin products of unknown regulatory status, or unknown composition were excluded. Also, studies on healthy volunteers, patients on dialysis, patients with diabetes and patients with alcoholic fatty liver diagnosis were excluded (see Annex 'List of references'). The included studies are presented in table 3 below.

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.

**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 dietary polyenylphosphatidylcholine on metabolism of cholesterol and triglycerides in hypertriglyceridemia patients  Kesaniemi <i>et al.</i> , 1986	Open, non-randomised 2-armed cross-over study	<b>Treatment period 1:</b> First treatment period: 7 g safflower oil/day given orally. <b>Treatment period 2:</b> 10 g lecithin*/day given orally.  Each treatment was given for approx. 5 weeks. All patients were fed low-cholesterol diets.  *Prepared by Natterman Company, Cologne, Germany, containing 67% C18:2 fatty acids	10 subjects, 1F/9M, 45-70 yrs.	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  ter Welle <i>et al.</i> , 1974	Open, uncontrolled  Duration: 8 months	<b>Treatment:</b> oral soya lecithin*  Initial dose: 1.2 g per day for 4 months, followed by 2.4 g per day for another 4 months  *"Lecithine essentielle forte - Natterman-versuchspräparat v 5180" prepared by Nattermann Company, Cologne, Germany <b>Content:</b> soya lecithin, 300 mg; vitamin B1, 6 mg, vitamin B12, 6 µg; nicotinamide, 33 mg; and vitamin E-acetate, 6 mg	12 subjects; 9F/3M; 34-76 yrs	Patients with type II hypercholesterolemia  Baseline serum mean cholesterol levels ±S.E.M. were 11.00±0.91 mmol/l, indicating familial hypercholesterolemia. Three patients had elevated serum triglycerides.  All patients but two had a history of clinical atherosclerotic disease, e.g. angina pectoris and myocardial infarction.  Four patients were on a low cholesterol diet. No patient had diabetes.  Any hyperlipidaemia treatment was stopped some time before investigation	No clinically relevant changes were seen in total lipids, total cholesterol, triglycerides, phospholipids, total lipids in the lipoprotein fractions and the weight percentage of linoleic acid in serum cholesterol esters and serum lecithin	Difference in total lipids: - 1 <sup>st</sup> exp. period vs. 1 <sup>st</sup> control period, - 2 <sup>nd</sup> exp. period vs 1 <sup>st</sup> control period, - 2 <sup>nd</sup> control period vs. 1 <sup>st</sup> control period, and 2 <sup>nd</sup> exp. period vs. 2 <sup>nd</sup> control period, compared using Student's <i>t</i> -test	Small open, uncontrolled study not supporting a cholesterol lowering effect of soya lecithin (1.2-2.4 g).

### **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**

Very few studies on the cholesterol lowering effect of soya lecithin have been published during the last 20 years. In particular, there are only two studies on soya lecithin medicinal products found in the literature. The included studies by Kesaniemi et al., 1986 and ter Welle et al., 1974, are small, open and do not support a cholesterol lowering effect of soya lecithin. The studies are considered exploratory and no conclusion on the cholesterol lowering effect of soya lecithin can be drawn. The current requirements for well-established medicinal use according to Article 10a of Directive 2001/83/EC as amended is considered not 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 have 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**

Soya lecithin has no or negligible influence on the ability to drive and use machines.

### **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 or peanut to 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 indications 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. 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 as amended is considered not fulfilled.

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. 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, feeling of pressure in the right epigastrium due to hepatic damage. Hence, Article 10a of Directive 2001/83/EC as amended (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 or peanut to 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 scarce. 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*