6 May 2026
EMA/HMPC/216488/2025
Committee on Herbal Medicinal Products (HMPC)

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

Draft - Revision 1

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)	*Glycine max* (L.) Merr., lecithinum (soya-bean lecithin)
Herbal preparation(s)	Soya-bean lecithin (de-oiled phospholipids from soya bean)
Rapporteur(s)	E. Svedlund (revision 1) P. Claeson (first version)
Assessor(s)	C. Löfberg (revision 1, non-clinical) S. Larsson (revision 1, clinical) E. Svedlund (first version)
Peer-reviewer	I. Chinou

Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Glycine max*, lecithinum. 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.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000
An agency of the European Union

Table of contents

1. Introduction

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

- Herbal substance(s)

Not applicable.

- Herbal preparation(s)

No official quality standard available.

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).

- There is a Ph.Eur monograph for Phospholipida ex soia ad injectabile (07/2019:2316), however, this monograph is dedicated explicitly to parenteral use.Relevant constituents for this assessment report

The main phospholipids are phosphatidylcholine (average 76% in lecithin), phosphatidylethanolamine and phosphatidylinositol (Blumenthal et al., 2000).

1.2. Search and assessment methodology

Scientific databases

☒ Scientific/Medical/Toxicological databases

PubMed was search 8 May 2024 using the following search terms and filters: (bean, soy[MeSH Terms] AND (2015:2024[pdat])) AND (lecithin[MeSH Terms]). 121 results.

☒ Pharmacovigilance databases

☒ data from EudraVigilance

☐ from other sources (e.g. data from VigiBase)

☐ Other

Books

☐

Regulatory practice

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

☒ Market overview (including pharmacovigilance actions taken in member states)

☒ PSUSA

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

☒ Ph. Eur. monograph

☐ Other

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

☒ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☐ Other

1.3. Main changes introduced in the first revision

The first revision was started because of the new safety information were found and considered relevant for the monograph sections 4.5 (interactions) and 4.8 (undesirable effects). Therefore, the main changes in the assessment report have been introduced in chapter 5 on clinical safety. In addition, the assessment report has been updated in accordance with the current assessment report template. The monograph has been updated in sections 4.2 (the posology for adults and elderly), 4.4 and 4.8.

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 obtained from marketed medicinal products.

Herbal substance/ preparation	**Indication**	**Posology and method of administration**	**Regulatory Status**
Phospholipids from soybean (lecithin)	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.	TU, since 1966 (THMP since 2010), AT
Phospholipids from soybean	Improvement of subjective symptoms like loss of appetite, feeling of pressure in the upper abdomen in case of toxic liver injury and in case of hepatitis	Hard capsule. 1 capsule contains 300 mg phospholipids. Adults and adolescents: initial dose 2 capsules 3 times daily; maintaining dose 1 capsule 3 times daily.	WEU, since 1974, AT (prescription only)
De-oiled, enriched phospholipids from soya beans	For the improvement of subjective symptoms such as loss of appetite, feeling of	Hard gelatine capsules, 300 mg/capsule	MA, since 1998, CZ

Herbal substance/ preparation	Indication	Posology and method of administration	Regulatory Status
	pressure in right upper epigastrium due to toxic-metabolic liver damage and in hepatitis.	2 capsules 3 times daily	
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, 600 mg/capsule 1 capsule 3 times daily	MA, since 2013, CZ
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.	WEU, at least since 1976, DE
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.	WEU, at least since 1976, DE
De-oiled, enriched phospholipids from soya beans	a) Mild hypercholesterolemia if diet and other non-pharmacological actions (e.g. physical training, weight reduction) alone are insufficient. This therapy is only justified	Capsule, soft, 300 mg/capsule >12 years: 2 capsules 3 times daily. Long-term use possible.	WEU, at least since 1990, DE

Herbal substance/ preparation	Indication	Posology and method of administration	Regulatory Status
	if an improvement of the cholesterol level is observable. 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. 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.		
De-oiled, enriched phospholipids from soya beans	a) Mild hypercholesterolemia if diet and other non-pharmacological actions (e.g. physical training, weight reduction) alone are insufficient. 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	Capsule, soft, 350 mg/capsule >12 years: 2 capsules 3 times daily. Long-term use possible.	WEU, since 2005, DE

Herbal substance/ preparation	Indication	Posology and method of administration	Regulatory Status
	incorrect nutrition (toxic-nutritive hepatic damage) and due to chronic hepatitis. 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.		
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.	WEU, since 2013, DE
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.	WEU, since 2013, DE
De-oiled, enriched phospholipids from soya beans	To improve subjective complaints e.g. loss of appetite, feeling of	Capsule, hard, 300 mg/capsule	WEU, since 2013, DE

Herbal substance/ preparation	Indication	Posology and method of administration	Regulatory Status
	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.	>12 years: 2 capsules 3 times daily. Long-term use possible	
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	WEU, at least since 1976, DE
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	TU, at least since 1976, DE
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 adjuvant to dietary measures	Oral solution, 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 the treatment the patients should consult with their physicians.	Healing product, since 1993, reclassified to THMP, 2012, withdrawn 2015, HU
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.	TU, since 2013, withdrawn 2019, HU

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. However, 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 of soya-bean lecithin is described or indicated, and where the herbal preparations have been properly described, are taken into account in the assessment report.

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 Expanded Commission E monograph, 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).

Table 2. Overview of historical data.

Herbal substance/ preparation	**Documented use / Traditional use**	**Posology and method of administration**	**Reference and date of the reference**
Lecithinum ex soya (soy lecithin)	Mild hypercholesterolemia, if dietary measures alone are not sufficient	Oral use Average daily dosage is 3.5 g	Hänsel, 1993, Commission E, 1988
Soy phospholipid with 73-79% (3-sn-phosphatidyl) choline (lecithin enriched extract from soybean)	a) less severe forms of hypercholesterolemia in which diet and other non-medical interventions (e.g. exercise, weight control) have not shown results b) 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	Daily dosage: 1.5-2.7 g phospholipid from soya bean with 73-79% (3-sn-phosphatidyl) choline in a single dose.	Commission E, 1994

Herbal substance/ preparation	Documented use / Traditional use	Posology and method of administration	Reference and date of the reference
	chronic hepatitis adjuvant therapy with phospholipids of soya beans is only indicated when improvement of symptoms is discernible from other therapy		

2.3. Overall conclusions on medicinal use

Table 3. Overview of evidence on period of medicinal use.

Herbal substance/ preparation	Indication	Posology and method of administration	Period of medicinal use
At least 10 years in the EU			
Soya-bean lecithin (de-oiled phospholipids from soya bean)	For enhancing physical and mental performance of the body	Oral solution, 90 mg/ml Adults: 1350 mg 3 times daily. The maximal dose is 2700 mg 3 times daily. Duration of use 4 weeks	1993-2015, HU
	Treatment of mild hypercholesterolemia as an adjuvant to dietary measures	Oral solution, 90 mg/ml Adults: 15 ml 3 times daily. The maximal dose is 3x30 ml. Duration of use 4 weeks	1993-2015, HU
	Mild hypercholesterolemia if diet and other non-pharmacological actions (e.g. physical training, weight reduction)	Capsule, soft, 350 mg/capsule Adults and adolescents: 700 mg 3 times daily. Long-term use possible.	WEU, since 2005, DE

Herbal substance/ preparation	Indication	Posology and method of administration	Period of medicinal use
	alone are insufficient. This therapy is only justified if an improvement of the cholesterol level is observable.		
At least 30 years including 15 years in the EU			
Soya-bean lecithin (de-oiled phospholipids from soya bean)	To support performance in case of physical and mental stress	Oral solution, 90 mg/ml Adults: 1350 mg 3 times daily Duration of use: should be used for 4 weeks minimum. Long term use possible.	Since 1966, AT
	To improve general condition in exhaustion and to strengthen the nerves	Oral solution, 500 mg/10 ml Adults and adolescents: 750 mg 2 times daily	At least since 1976, DE
	For supplementation of dietetic measures in case of hypercholesterolemia	Oral solution, 90 mg/ml Adults: 1350 mg 3 times daily Duration of use: should be used for 4 weeks minimum. Long term use possible.	Since 1966, AT
	Mild hypercholesterolemia if diet and other non-pharmacological actions (e.g.	Capsule, hard, 300 mg/capsule Adults and adolescents: 600 mg 3 times daily.	WEU, at least since 1976, DE

Herbal substance/ preparation	Indication	Posology and method of administration	Period of medicinal use
	physical training, weight reduction) alone are insufficient. This therapy is only justified if an improvement of the cholesterol level is observable.	Long-term use possible.	
		Granules, 3 g/sachet Adults and adolescents: 3 g 3 times daily Long-term use possible	WEU, at least since 1976, DE
	For the improvement of subjective symptoms such as loss of appetite, feeling of pressure in the upper abdomen/right upper epigastrium in case of toxic liver injury and in case of hepatitis	Capsule, hard, 300 mg/capsule Adults and adolescents: 600 mg 3 times daily; In AT: maintaining dose 300 mg 3 times daily.	WEU, since 1974, AT (prescription only), MA, since 1998, CZ,
		Capsule, hard, 600 mg/capsule 600 mg 3 times daily	MA, since 2013, CZ
	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. This therapy does not replace the abstinence of the toxic substances	Capsule, hard or soft, 300 mg or 600 mg/capsule Adults and adolescents: 600 mg 3 times daily. Long-term use possible.	WEU, at least since 1976, DE
		Capsule, soft, 350 mg/capsule Adults and adolescents: 700 mg 3 times daily. Long-term use possible.	WEU, since 2005, DE

Herbal substance/ preparation	Indication	Posology and method of administration	Period of medicinal use
	(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.		
Soy phospholipid with 73-79% (3-sn-phosphatidyl) choline (lecithin enriched extract from soybean)	a) less severe forms of hypercholesterolemia in which diet and other non-medical interventions (e.g. exercise, weight control) have not shown results b) 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	Daily dosage: 1.5-2.7 g phospholipid from soya bean with 73-79% (3-sn-phosphatidyl) choline in a single dose.	Commission E, 1994

Herbal substance/ preparation	Indication	Posology and method of administration	Period of medicinal use
	only indicated when improvement of symptoms is discernible from other therapy		

Clinical efficacy and safety based on Article 10a of Directive 2001/83/EC (well-established use), is evaluated in chapter 4 'Clinical data' and chapter 5 'Clinical Safety/Pharmacovigilance'. The non-clinical safety is evaluated in chapter 3 'Non-clinical data'.

Clinical safety for preparations that fulfil the criteria of medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, i.e. traditional medicinal use based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC is further evaluated in chapter 5 'Clinical Safety/Pharmacovigilance'. The non-clinical safety is evaluated in chapter 3 'Non-clinical data'.

Based on the information obtained from Member States and literature, soya lecithin has been used for the relief of temporary fatigue and sensation of weakness since 1966. In the first revision of the monograph, the posology for adults and elderly has been updated due to withdrawn product not fulfilling 30 years of medicinal use.

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.

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.

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).

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).

Assessor's comment:

No non-clinical studies that support the indication in the monograph has been found.

3.1.2. Secondary pharmacodynamics

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 feed 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 administrated 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, cholestatsis 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).

Assessor's comment:

No safety concerns have been identified from reported non-clinical secondary pharmacodynamic studies on hypercholesterolemia and hepatic damage.

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 lysophophatidylcholine 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 is 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 Expanded 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).

Assessor's comment:

There are no safety concerns from reported single dose toxicity studies.

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 Expanded 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 Sprague-Dawley rats at daily doses of 100, 300 and 1,000 mg/kg for 13 weeks in accordance with OECD guidelines 408 from 1998 i.e. Repeated Dose 90-day Oral Toxicity Study in rodents. 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).

Assessor's comment:

There are no safety concerns from reported repeat dose toxicity studies.

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 1997a and 1997b 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).

Assessor's comment:

No data have been found in the public domain for the herbal preparation included in the monograph. Tests on phosphatidylinositol from soya lecithin were negative.

3.3.4. Carcinogenicity

No data found.

3.3.5. Reproductive and developmental toxicity

In the Expanded Commission E monograph on lecithin enriched extracts from soya bean, doses of up to 3.75 g/kg bw in pregnant animals, animal 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.

Assessor's comment:

Adequate tests on reproductive toxicity have not been performed. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

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 toxicity studies

Not relevant.

3.3.8. Conclusions on toxicological data

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.

The following text is included in the monograph section 4.6: 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 is available.

The following text is included in the monograph section 5.3: Adequate tests on reproductive toxicity and genotoxicity have not been performed. Tests on carcinogenicity have not been performed.

3.4. Overall conclusions on non-clinical data

Results from relevant non-clinical studies are limited. No safety concerns have been identified.

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

There are numerous clinical studies performed with soya lecithin. In accordance with the guideline 'Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005 – Rev. 1), the assessment of well-establish use should also include if the products reported in the market overview can be considered as similar to the product studied in relevant clinical studies found in the literature (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States'). Therefore, the scope of the assessment in this section is fatigue and sensation of weakness, mild hypercholesterolemia, and subjective complaints due to hepatic damage. Only studies related to these indications are included below.

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 cholesterols 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).

Assessor's comment:

No relevant data available.

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 dilinoeylphosphatidylcholine (DLPC) have been reported in a study on five patients after single oral administration of 1 g of DLPC labelled with ^{3}H 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 ^{3}H 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).

Assessor's comment:

No data on the herbal preparation included in the monograph have been found.

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 medicinal products 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).

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 of 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.

Open studies

ter Welle et al., 1974, studied the effect of soya lecithin on blood lipid and lipoprotein values in 12 patients with type II hyper-lipoproteinemia. The study was open uncontrolled study. The patients were 9 women and 3 men between 34-76 years of age with type II hypercholesterolemia. Baseline serum mean cholesterol levels ±S.E.M. were 11.00±0.91 mmol/L, indicating familiar 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. Oral soya lecithin with an initial dose of 1.2 g/day for 4 months, followed by 2.4 g/day for another 4 months. Each tablet contained lecithin, 300 mg; vitamin B1, 6 mg, vitamin B12, 6 µg; nicotinamide, 33 mg; and vitamin E-acetate, 6 mg. The authors reported that no clinically relevant changes were seen in total lipids, total cholesterol, triglycerides, phosphor-lipids, total lipids in the lipoprotein fractions and the weight percentage of linoleic acid in serum cholesterol esters and serum lecithin.

Assessor's comment:

The study by ter Welle et al., 1974, is a small, open, uncontrolled study not supporting a cholesterol lowering effect of soya lecithin (1.2-2.4 g).

Kesaniemi et al., 1986, evaluated the effects of polyenylphosphatidylcholine on metabolism of cholesterol and triglycerides in hyper-triglyceridemia patients. The study was an open, non-randomised 2-armed cross-over study. The study included 10 subjects, 1 woman and 9 men between 45-70 years of age 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. All patients were fed low-cholesterol diets. In the first treatment period 7 g safflower oil/day was taken orally. In the second treatment period 10 g lecithin/day was taken orally. The lecithin contained 67% C18:2 fatty acids. Each treatment was given for approximately 5 weeks. The authors report that compared with safflower oil, lecithin feeding did not significantly affect plasma total cholesterol, LDL, HDL or TG. The difference was evaluated by paired t-test, $P<0.05$.

Assessor's comment:

The study by Kesaniemi et al., 1986 is an open cross-over study in 10 subjects with hyper-triglyceridemia. The high doses of lecithin (10 g) for five weeks did not affect plasma total cholesterol, LDL, HDL or TG levels compared with safflower oil. No wash-out period between treatments described. Overall, the study does not support a WEU indication in the monograph.

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 below.

Double-blind, randomized, placebo-controlled studies

Jenkins et al., 1982, investigated the effect of lecithin on HBsAg negative chronic active hepatitis in a randomized, double-blind, placebo-controlled study. Included patients had a biopsy with evidence of continuing disease activity and were treated with immunosuppressive therapy (prednisolone 7.5-15 mg/day with/without azathioprine 50-75 mg/day). Out of 30 patients (8 men and 22 women) included 15 received 3 g of lecithin daily for 1 year. The authors reported that histological evidence of disease activity was reduced by lecithin.

Assessor's comment:

The small study by Jenkins et al., 1992, does not correspond to an indication of a medicinal product in the EU for at least 10 years. Thus, the study could not be taken into account for a WEU indication in the monograph.

Niederau et al., 1998, evaluated the effects of lecithin in patients with chronic hepatitis B or C in combination with interferon alpha 2a or 2b. The study was double-blind, randomized, placebo-controlled, multicentre. The study was performed and monitored according to GCP and GLP. Patients with chronic hepatitis B or C, diagnosed at least 3 months prior the study, with evidence of viral replication for at least 6 months were included. 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 absence of contraceptive use in women of childbearing age, contraindications for IFN; decompensated liver cirrhosis, hepatocellular carcinoma, auto-immune hepatitis, leukocyte count below 2x109/L, platelet count below 70x109/L, history of psychosis, depression or epilepsy, severe chronic disease, severe hypertension, disorders of blood coagulation, renal disease; creatinine≥1.5 mg/dL. All patients received treatment with interferon alpha (IFN) s.c. injections of 5 million I.U. (hepatitis B) or 3 million I.U. (hepatitis C) IFN thrice weekly for 24 weeks. In addition, the patients took oral medication with either lecithin (Polyunsatureated phosphatidylcholine (PPC), 72-76% lecithin) 3 capsules (0.18 g/capsule) or placebo twice per day. 272 patients (137 lecithin, 135 placebo) were treated for 24 weeks. 176 responders (92 lecithin, 84 placebo) i.e. ALT decrease ≥50% maintained treatment for further 24 weeks after cessation of IFN. The authors report that lecithin increased the response rate in patients with hepatitis C, but not in hepatitis B.

Assessor's comment:

Niederau et al., 1998, studied the effects of lecithin (1.2 g) in patients with chronic hepatitis B or C in combination with interferon alpha 2a or 2b. The studied effects do not correspond to an indication of a medicinal product in the EU for at least 10 years. Thus, the study could not be taken into account for a WEU indication in the monograph.

Singh and Prasad, 1998, performed a 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. 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. 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 utrasonography and/or upper gastrointestinal endoscopy. 70 subjects were included; 36 patients with fulminant hepatic failure (16 lecithin, 20 placebo-controls) and 34 patients with subacute hepatic failure (14 lecithin, 20 placebo-controls). The treatment was 350 mg lecithin three times daily for 6-8 weeks. The authors report a faster recovery after encephalopathy and lower mortality rate for the lecithin groups.

Assessor's comment:

This small pilot study by Sinh and Prasad, 1998, in patients with hepatic failure does not correspond to an indication of a medicinal product in the EU for at least 10 years. Thus, the study could not be taken into account for a WEU indication in the monograph.

Lieber et al., 2003, investigated the effectiveness of lecithin in preventing or reversing liver fibrosis in heavy drinkers in a double-blind, randomized, placebo-controlled study. 789 subjects (mean age: 48.8 years, 97.3% men) had an average intake of 16 drinks (80 g) per day for ≥5 years (average 19 years). The treatment was 3 tablets/day of lecithin (Rhône-Poulenc Rorer, Cologne, Germany) or placebo. 412 completed the 24 months study i.e., 377 dropped out. The authors reported that lecithin did not affect progression of liver fibrosis.

Assessor's comment:

Lieber et al., 2003, reported that lecithin did not affect progression of liver fibrosis in heavy drinkers. Progression of liver fibrosis in heavy drinkers does not correspond to an indication of a medicinal product in the EU for at least 10 years. Thus, the study could not be taken into account for a WEU indication in the monograph.

Open studies

Turecky et al., 2003, investigated the effect of administration of essential phospholipids on plasma lipid parameters in patients with alcoholic fatty liver. Included patients suffered from alcoholic fatty liver with histologically verified liver steatosis took 2 capsules of 600 mg 3 times/day for 3 months. The control group was students and blood donors who showed no abnormalities on physical or laboratory tests. 71 subjects participated: 29 patients (17 men and 12 women, mean age 48.9 years) and 42 healthy subjects (30 men and 12 women, mean age 38.8 years). The authors report a positive effect on hepatocyte integrity and subjective symptoms of patients with liver steatosis, but no effect on plasma lipid parameters.

Assessor's comment:

Turecky et al., 2003, studied the subjective symptoms of patients with liver steatosis. However, the study was an open study and therefore not pivotal for a WEU indication in the monograph.

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

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

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

Soya lecithin in the treatment of mild hypercholesterolemia

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 and in most studies the soya lecithin composition is not sufficiently described. 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.

Soya lecithin in subjective complaints due to hepatic damage

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. The diverse study populations and results are inconclusive. Overall, the relevance of the studies presented is therefore limited.

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 market overview

The following safety information are included in the SmPC of products on the market:

Table 4. Safety information from products marketed in the EU/EEA.

Herbal substance/ preparation	**SmPC section**	**Safety information**	**Member State**
De-oiled enriched phospholipids from soya beans	4.5	Interactions with anticoagulants cannot be excluded. For this reason, the dose of the anticoagulant may need to be adjusted.	CZ

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

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).

Table 5. Overview of the patient exposure.

	Patients enrolled	**Patients exposed**	**Patients exposed to the proposed dose range**	**Patients with long term* safety data**

Placebo-controlled	1161	578	405	15 (3 g)
Open studies	51	51	22	12 (1.2-2.4 g)

* In general, this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Assessor's comment:

Phospholipid exposures are mainly obtained from food consumption.

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).

The International Birth Date (IBD) of soybean phospholipids (oral use) is 02 October 1957. In the outcome of the PSUSA/00010707/202110 on soybean phospholipids (oral use) with data lock point: 01/10/2021, the PRAC considers a causal relationship between soybean phospholipids (oral use) and increased blood pressure, palpitations, dizziness, and nausea and vomiting is at least a reasonable possibility. The PRAC concluded that the product information of products containing soybean phospholipids (oral use) should be amended accordingly. CMDh, on 19 July 2022, having considered the PSUR on the basis of the PRAC recommendation and the PRAC assessment report, agreed by consensus on the variation of the marketing authorisations of medicinal products containing soybean phospholipids (oral use). The scientific conclusions are as follows:

In view of available data on increased blood pressure, palpitations, dizziness, and nausea and vomiting from the literature, spontaneous reports including cases with a close temporal relationship and positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between soybean phospholipids (oral use) and increased blood pressure, palpitations, dizziness, and nausea and vomiting is at least a reasonable possibility. The PRAC concluded that the product information of products containing soybean phospholipids (oral use) should be amended accordingly.

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics Section 4.8

The following adverse reaction should be added under the SOC Investigations with a frequency "not known": **Increased blood pressure**

The following adverse reaction should be added under the SOC Cardiac disorders with a frequency "not known": **Palpitations**

The following adverse reaction should be added under the SOC Nervous system disorders with a frequency "not known": **Dizziness**

The following adverse reactions should be added under the SOC Gastrointestinal disorders with a frequency "not known": ~~stomach complaints~~ **Nausea; Vomiting**

Assessor's comment:

In the first version of the monograph the following adverse reactions are listed:

Allergic reactions including severe anaphylaxis and angioedema have been reported. The frequency is not known.
Skin reactions like pruritus, dermatitis, exanthema and urticaria have been reported. The frequency is not known.
Gastrointestinal disorders like stomach discomfort and diarrhoea have been reported. The frequency is not known.

The conclusion from PRAC that the product information of products containing soybean phospholipids (oral use) should be amended as presented above is considered relevant for the monograph. The following adverse reaction are listed in the first revision of the monograph:

Immune system disorders: anaphylaxis, angioedema. Frequency: not known.
Investigations: increased blood pressure. Frequency: not known.
Cardiac disorders: palpitations. Frequency: not known.
Nervous system disorders: dizziness. Frequency: not known.
Skin and subcutaneous tissue disorders: pruritus, dermatitis, exanthema, urticaria. Frequency: not known.
Gastrointestinal disorders: diarrhoea, nausea, vomiting. Frequency: not known.

The EudraVigilance database was searched on 7 February 2024 with the active substance (high level) contains: soya-bean, soybean, lecithinum, lecithin, soiae oleum, soya-bean oil, soiae, soybean phospholipids. In addition to information from the finalised PSUSA, no new safety issues could be identified that would trigger revision of the monograph. However, the case report from Ksouda et al. 2018 cited in chapter 5.5.4. were also found in the EudraVigilance database.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

The use in children under 12 years of age has not been established.

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).

Assessor's comment:

Hypersensitivity to the active substance, soya, peanut and to other plants of the Fabaceae (legume) family and to birch pollen is included in the monograph section 4.3 'Contraindications'.

5.5.3. Special warnings and precautions for use

Severe allergic reactions including anaphylaxis and angioedema have been reported.

Assessor's comment:

Since severe allergic reaction are listed in the monograph section 4.8 'Undesirable effects', the following warning is included in monograph section 4.4: Severe allergic reactions including anaphylaxis and angioedema have been reported (see section 4.8). Patients should be advised to immediately stop using the product in case of symptoms of allergic reactions.

5.5.4. Drug interactions and other forms of interaction

No interaction studies have been performed.

Ksouda et al. 2018 (in French) report a case of potential interaction between soy lecithin and Vitamin K antagonists in a 46 years-old woman in Tunisia. The patient was also treated with carbamazepine due to epilepsy since childhood. In addition, she took levothyroxine (25 µg/day) for hypothyroidism, venlafaxine (37.5 mg/day) for depression, and flecainide (100 mg/day), bisopropol (2.5 mg/day) and acenocoumarol (4 mg/day) for paroxysmal atrial fibrillation. Subtherapeutic INR values (1.4-1.7) were detected despite the gradually increase in dose of acenocoumarol. Despite replacing carbamazepin by levetiracetam and venlafaxine by sertraline, the INR remained low (1.5). Therefore, the acenocoumarol was replaced by fluindione (40 mg) but the INR remained at 1.5-1.7. After further investigation it was found that the patient was taking soy lecithin for hypercholesterolemia for three years and the patient was told to stop taking soy lecithin. Fifteen days after stopping soy lecithin, the INR values had increased to 2.26.

Cambria-Kiely reported in 2002 that a 70-year-old white man who was stable on warfarin therapy developed subtherapeutic INR values after ingesting soy protein in the form of soy milk. The subtherapeutic INR values could not be explained by factors known to reduce the INR such as noncompliance, new medications, other alternative therapies, increased physical activity, changes in medication storage, or increased consumption of vitamin K. INR values returned to therapeutic concentrations within 2 weeks after discontinuation of the soy milk. Repeated coagulation test results during the next 2 months remained within the normal range.

Assessor's comment:

Two published case reports on possible interactions with Vitamin K antagonists have been found in the literature. However, the report by Cambria-Kiely in 2002 was on soy milk product with unknown content of soy lecithin and the report by Ksouda et al. in 2018 was on a soy lecithin product in Tunisia with unknown posology and quality. Overall, there is not sufficient data to include such information in the monograph.

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 information available.

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. Considering the safety-profile of soya-bean lecithin, the following standard sentence should be included in MO section 4.7: 'Soya-bean lecithin has no or negligible influence on the ability to drive and use machines.'

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

Hypersensitivity to the active substance, soya, peanut and to other plants of the Fabaceae (legume) family and to birch pollen is included as a contraindication in the monograph.

The use in children under 12 years of age has not been established.

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. In line with recommendations from PRAC, increased blood pressure, palpitations and dizziness are also included in the monograph with frequency not known.

Since severe allergic reaction are listed adverse reactions in the monograph a warning that patients should be advised to immediately stop using the product in case of symptoms of allergic reactions is included in the monograph section 4.4.

6. Overall conclusions

Well established use monograph

The requirements for well-established use according to Article 10a of Directive 2001/83/EC are considered not fulfilled.

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.

Traditional use monograph

The requirements for traditional medicinal use according to Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC are considered fulfilled. It has been demonstrated that soya lecithin has been in traditional medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, with an acceptable level of safety for:

Herbal substance/ preparation	**Indication**	**Therapeutic area for browse search**	**Posology and method of administration**	**Duration of use**
Soya-bean lecithin (de-oiled phospholipids from soya bean)	Traditional herbal medicinal product used 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.	Fatigue and weakness	Oral use *Adults and elderly:* Single dose: 750-1350 mg 2-3 times daily Daily dose: 1500-4050 mg *Paediatric population:* Adolescents Single dose: 750 mg 2 times daily Daily dose: 1500 mg The use in children under 12 years of age has not been established.	If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Non-clinical data on pharmacology and safety of soya lecithin is limited. Genotoxicity, carcinogenicity, reproductive and developmental toxicology have not been fully evaluated.

As there is limited information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

List entry

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

Annex

List of references