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Committee on Herbal Medicinal Products (HMPC)

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

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., oleum
Herbal preparation(s)	Soya-bean oil, refined
Pharmaceutical form(s)	Herbal preparations in liquid dosage forms for use as a bath additive.
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Note: This draft assessment report is published to support the public consultation of the draft European Union monograph on *Glycine max* (L.) Merr., oleum. 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.



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1. Introduction

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

- Herbal substance(s)

Not applicable.

- Herbal preparation(s)

Soya bean oil, refined, is fatty oil obtained from seeds of by *Glycine max* (L.) Merr. by extraction and subsequent refining in accordance with the European Pharmacopoeia (01/2010:1473). 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 major fatty acids are linoleic acid (48-58%), oleic acid (17-30%), palmitic acid (9-13%), linolenic acid (5-11%) and stearic acid (2.5-5%). Soya bean oil, refined, also contains myristic acid (maximum 0.2 %), palmitoleic acid (maximum 0.3 %), arachidic acid (maximum 1.0 %), eicosenoic acid (maximum 1.0 %) and behenic acid (maximum 1.0 %) (European Pharmacopoeia 01/2010:1473).

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"):

Herbal preparations in liquid dosage forms for use as a bath additive:

Soya bean oil, refined (*Soiae oleum raffinatum*)

Fatty oil obtained from the seeds of *Glycine max* (L.) Merr. by extraction and subsequent refining in accordance with the European Pharmacopoeia (01/2010:1473)

In addition to the herbal preparations reported as constituents of medicinal products, there is a broad range of dietary and cosmetic soya products on the market. Please note that dietary (including food supplements) and cosmetic soya products are not covered by this assessment report. Likewise, soya bean oil emulsions for parenteral nutrition 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: A PubMed search on the MeSH term 'soybean oil' found 2,249 citations in May 2016. Thus, to be able to find relevant articles among this high number of citations, the following PubMed search builder option subheadings were chosen: ("Soybean Oil/administration and dosage"[Mesh] OR "Soybean Oil/adverse effects"[Mesh] OR "Soybean Oil/antagonists and inhibitors"[Mesh] OR "Soybean Oil/blood"[Mesh] OR "Soybean Oil/metabolism"[Mesh] OR "Soybean Oil/pharmacokinetics"[Mesh] OR "Soybean Oil/pharmacology"[Mesh] OR "Soybean Oil/physiology"[Mesh] OR "Soybean Oil/therapeutic use"[Mesh] OR "Soybean Oil/toxicity"[Mesh]). The search found 1,220 citations. The titles of 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.

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, Cochrane Database of Systematic Reviews

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

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

Table 1: Overview of data on soya bean oil, refined obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
1. Soya bean oil, refined	Treatment of dry, itchy skin such as e.g. with atopic eczema, adjuvant treatment in seborrhoeic dermatitis, eczema infantile, neurodermatitis, ichthyosis and psoriasis	Bath additive, 84.75 g/100 g Full bath: 30–45 ml/bath. Other types of baths: 1 ml/5 L. Children: 5 ml/25 L	Since 1992, CZ, bibliographical
2. Soya bean oil, refined	For the supportive treatment of dermatosis with dry, itching skin such as e.g. -endogenous eczema (neurodermitis) -diaper dermatitis (nappy rash) -eczema due to washing -psoriasis	Bath additive, 89.65 g/100 g Full bath (100 L) adults: 30-40 ml. Child bath: (50 L) 20 ml If the skin is very dry, the double or triple amount can be used. Shower bath with direct application on skin 20 ml 2-3 times/week Bath temperature: do not exceed 36°C In case of pruritus: 32°C Duration of bath: 15-20 min (adults/adolescents). A few minutes (babies and young children)	Since 1996, DE, WEU
3. Soya bean oil, refined	For the supportive treatment of dermatosis with dry and itchy skin, such as endogenous eczema (neurodermitis), psoriasis, ichthyosis, pruritus senilis, diaper dermatitis, eczema due to washing	Bath additive, 78.1 g/100 g Full bath (100 L): 34.2 g, sitting bath (50 L): 17.1 g, partial bath (25 L): 8.55 g, full bath for babies (25 L): 8.55 g 10-20 min (for babies and young children: several minutes) 2-3 times/week Shower bath with direct application on skin: no amount given Bath temperature: do not exceed 36°C In case of pruritus: 32°C	At least since 1976, DE, WEU
4. Soya bean oil, refined	For the supportive treatment of dermatosis with dry and itchy skin, such as endogenous eczema (neurodermitis), psoriasis, ichthyosis, pruritus senilis, diaper dermatitis, eczema due to washing	Bath additive, 89.65 g/100 g Full bath (100-150 L): 30 ml, partial bath (30 L, e.g. bath for children): 5 ml, partial bath (5 L): 1 ml, 10-20 min (for babies and young children several minutes) 2-3 times/week Shower bath with direct application on skin: 20 ml Bath temperature: do not exceed 36°C In case of pruritus: 32°C	At least since 1976, DE, WEU
5. Soya bean oil, refined	For the supportive treatment of dermatosis with dry and itchy skin, such as endogenous eczema (neurodermitis), psoriasis, ichthyosis, pruritus senilis, diaper dermatitis, eczema due to washing	Bath additive, 80 g/100 g Full bath (100 L): 15-30 g, max. 20 min (for young children several minutes) 2-3 times/week Bath temperature: do not exceed 36°C In case of pruritus: 32°C	At least since 1976, DE, WEU

Active substance	Indication	Pharmaceutical form	Regulatory Status
6. Soya bean oil, refined	For the supportive treatment of dermatosis with dry and itchy skin, such as endogenous eczema (neurodermitis), psoriasis, ichthyosis, pruritus senilis, diaper dermatitis, eczema due to washing	Bath additive, 71.05 g/100 g Full bath (150 L): 15-45 ml, partial bath and bath for children (25 l): 2.5-7.5 ml Max. 20 min, 2-3 times/week Bath temperature: do not exceed 36°C In case of pruritus: 32°C	At least since 1976, DE, WEU
7. Soya bean oil, refined	For the supportive treatment of dermatosis with dry and slightly itchy skin, such as endogenous eczema (neurodermitis), psoriasis, ichthyosis, pruritus senilis, eczema such as diaper dermatitis, eczema due to washing	Bath additive, 84.75 g/100 g Full bath (150 L): 30-45 ml, bath for children(25 L): 5 ml, partial bath (5 L): 1 ml, Max. 20 min (for babies and young children several minutes), 2-3 times/week Bath temperature: do not exceed 36°C In case of pruritus: 32°C	At least since 1976, DE, WEU
8. Soya bean oil, refined	For the supportive treatment of dermatosis with dry and slightly itchy skin, such as endogenous eczema (neurodermitis), psoriasis, ichthyosis, pruritus senilis, eczema such as diaper dermatitis, eczema due to washing	Bath additive, 71.05 g/100 g Full bath (150 l): 30-45 ml, bath for children (25 l): 5 ml, partial bath (5 l): 1 ml, Max. 20 min (for babies and young children several minutes), 2-3 times/week Bath temperature: do not exceed 36°C. In case of pruritus: 32°C	Since 2013, DE, WEU
9. Soya bean oil, refined	Dry skin conditions including those associated with dermatitis and eczema.	Bath additive, 84.75 g/100 g For full bath (approx. 100 L): 20ml, for child's bath (approx. 25 L): 5 ml, for partial bath (approx. 5 litres): 2.5ml In particularly dry skin, 2-3 times the above quantities can be used. Generally, 2-3 baths should be taken weekly. For babies and infants a daily bath is recommended. The temperature of the bath water should not exceed 36°C as the regreasing effect is diminished at higher temperatures. For the treatment of pruritus the temperature should be 32°C or as low as can be tolerated. The bath should not be longer than 20 minutes. In the case of infants and small children a bath of only a few minutes is mostly sufficient. The duration of the therapy depends on the course of the disease.	Since 1998, UK, WEU
10. Soya bean oil, refined	Dry skin conditions including those associated with dermatitis and eczema.	Bath additive, 83,35 g/ 100 g For full bath (approx. 100 L): 20 ml, for child's bath (approx. 25	Since 2008, UK, WEU

Active substance	Indication	Pharmaceutical form	Regulatory Status
		<p>L): 5 ml, for partial bath (approx. 5 L): 2.5 ml.</p> <p>In particularly dry skin, 2-3 times the above quantities can be used.</p> <p>Generally, 2-3 baths should be taken weekly. For babies and infants a daily bath is recommended.</p>	

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

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

According to the Martindale The Extra Pharmacopoeia refined soya bean oil has emollient properties and is used as a bath additive in the treatment of dry skin conditions (Martindale, 1989).

Hager's Handbuch der Pharmazeutischen Praxis describes the cosmetic use of soya oil as a bath additive for dry skin conditions (Hänsel *et al.*, 1993).

2.3. Overall conclusions on medicinal use

According to the market overview and literature, soya bean oil, refined, fulfils 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 according to Directive 2004/24/EC. However, therapeutic indications associated with dermatitis, psoriasis, ichthyosis and eczema of different etiology require medical expertise. These indications are not appropriate for self-care and thus inappropriate indications for traditional herbal medicinal products. In harmonisation with other EU herbal monographs within the same therapeutic area, the traditional use indication for the symptomatic relief of dry skin conditions associated with mild recurrent eczema is considered appropriate.

Table 2: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Soya bean oil, refined Herbal preparations in liquid dosage forms for use as a bath additive.	Traditional herbal medicinal product used for the symptomatic relief of dry skin conditions associated with mild recurrent eczema. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long- standing use.	<i>Children, adolescents, adults and elderly</i> Single dose 71.05-89.65 g/100 g Full bath (approximately 100- 150 L): 15-45 ml Partial bath (approximately 25- 50 L): 5-15 ml Partial bath (approximately 5 L): 1-2.5 ml Children's bath (approximately 50 L): 20 ml Children's bath (approximately 25 L): 2.5-10 ml Shower bath with direct application on skin: 20 ml In particularly dry skin, 2-3 times the above quantities can be used. 2-3 times per week. <u>Duration of bath:</u> <i>Adolescents, adults and elderly</i> Maximum 20 minutes. <i>Children</i> A few minutes.	At least since 1976, DE, since 1992 CZ and since 1998 UK.

There are no clinical studies on soya bean oil as bath additive in the scientific literature. Therefore, Article 10a of Directive 2001/83/EC as amended (well-established use) is considered not fulfilled.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

No data found.

3.1.2. Secondary pharmacodynamics

No data found.

3.1.3. Safety pharmacology

No data found.

3.1.4. Pharmacodynamic interactions

No data found.

3.1.5. Conclusions

There are no non-clinical pharmacological data on soya bean oil in the literature.

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

No data found.

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

3.3.1. Single dose toxicity

No data found.

3.3.2. Repeat dose toxicity

No data found.

3.3.3. Genotoxicity

Soya bean oil was tested for genotoxicity at three different concentrations (6, 12 and 24% oil) in the Drosophila wing somatic mutation and recombination assay. The results indicate that the oil produces genotoxic effects when tested without any previous frying or boiling processes. The results after boiling soya oil during fifteen, thirty and sixty minutes showed a decrease of its genotoxic potential (Demir *et al.*, 2012).

3.3.4. Carcinogenicity

No data found.

3.3.5. Reproductive and developmental toxicity

No data found.

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 bean oil is scarce. Genotoxicity, carcinogenicity, reproductive and developmental toxicology have not been fully evaluated.

3.4. Overall conclusions on non-clinical data

Non-clinical information on the pharmacology and safety of soya bean oil is scarce. Genotoxicity, carcinogenicity, reproductive and developmental toxicology have not been fully evaluated. Since the genotoxic potential of soya bean oil 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.

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

No data found.

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

No data found.

4.2. Clinical efficacy

No data found.

4.2.1. Dose response studies

No data found.

4.2.2. Clinical studies (case studies and clinical trials)

No data found.

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

No data found.

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no data on clinical pharmacology or efficacy available for soya bean oil to support a well-established use indication.

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.

According to the European Commission database 'CosIng', which provides information on cosmetic substances and ingredients (contained in the Cosmetics Regulation EC No 1223/2009, Cosmetics Directive 76/768/EEC and Inventory of Cosmetic Ingredients), soya bean oil can be used without restriction in cosmetics and is classified as an emollient (CosIng, 2016).

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 the public statement it is stated that for refined soya bean oil a reduction of protein content may be assumed. However, it has not been established if this reduction is sufficient for prevention of severe allergic reactions. Thus, refined soya bean oil cannot be considered non-allergenic and no safe threshold for topical oil preparations can be defined (EMA/HMPC/138139/2005).

In the information obtained from the market overview of medicinal products containing soya bean oil, skin rashes and hypersensitivity have been reported. The frequencies are not known.

Accidental eye contact may cause keratitis, see section 5.5.3.

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 bean oil has been used as a bath additive for children for more than 30 years.

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 accordance with the information obtained from the market overview, full baths are contraindicated in cases of open wounds, large skin injuries, acute skin diseases, high fever, severe infections, severe circulatory disturbances and cardiac insufficiency.

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.

Eye contact may cause keratitis and should be avoided. In cases of accidental eye contact, the eye should be rinsed immediately with cold water. If eye irritation remains, a doctor or a qualified health care practitioner should be consulted (EMA/HMPC/138139/2005).

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 available.

5.5.6. Overdose

According to the information obtained from the market overview, accidental oral intake of soya bean oil may lead to nausea, vomiting and diarrhoea. In case of vomiting aspiration could occur, therefore, vomiting should not be induced. If signs of aspiration occur, such as coughing, wheezing, fever, and chest discomfort, a doctor or a qualified health care practitioner should be consulted.

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

Soya bean oil 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

Cutaneous use of refined soya bean oil as a bath additive for the symptomatic relief of dry skin conditions associated with mild recurrent eczema has a long standing medicinal use in the EU. If patients with known hypersensitivity to soya, peanut and to other plants of the Fabaceae (legume) family and to birch pollen are excluded, a traditional use in adults is considered safe from a clinical point of view.

6. Overall conclusions (benefit-risk assessment)

Based on the information obtained from Member States and literature, medicinal use of soya bean oil, refined, has been reported in the EU/EEA at least since 1976. Refined soya bean oil has been used as a bath additive in the treatment of dry skin in association with different dermatological diagnosis, such as dermatitis, psoriasis, ichthyosis and eczema of different etiology. There are no clinical studies on soya bean oil as bath additive in the scientific literature. Therefore, Article 10a of Directive 2001/83/EC as amended (well-established use) is not considered fulfilled.

According to the market overview and literature, soya bean oil, refined, fulfils 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 according to Directive 2004/24/EC. However, therapeutic indications associated with dermatitis, psoriasis, ichthyosis and eczema of different etiology require medical expertise. These indications are not appropriate for self-care and thus inappropriate indications for traditional herbal medicinal products. In harmonisation with other EU herbal monographs within the same therapeutic area, the traditional use indication for the symptomatic relief of dry skin conditions associated with mild recurrent eczema is considered appropriate.

If patients with known hypersensitivity to soya, peanut and to other plants of the Fabaceae (legume) family and to birch pollen are excluded, a traditional use in adults is considered safe from a clinical point of view.

Non-clinical data on safety of soya bean oil is scarce. Genotoxicity, carcinogenicity, reproductive and developmental toxicology have not been fully evaluated. Since the genotoxic potential of soya bean oil 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: Skin disorders and minor wounds

Annex

List of references