EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 July 2015
EMA/HMPC/294187/2013
Committee on Herbal Medicinal Products (HMPC)

European Union herbal monograph on *Silybum marianum* (L.) Gaertn., fructus

Draft

Discussion in Working Party on European Union monographs and European Union list (MLWP)	May, July, November 2013 January, May, July, November 2014 January, May 2015
Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation	7 July 2015
Start of public consultation	22 July 2015
End of consultation (deadline for comments). Comments should be provided using this template to hmpc.secretariat@ema.europa.eu	31 October 2015
Rediscussion in MLWP	
Adoption by HMPC	

Keywords	Herbal medicinal products; HMPC; European Union herbal monographs; well-established medicinal use; traditional use; *Silybum marianum* (L.) Gaertn; Syn. *Carduus marianus* L.; Silybi mariani fructus; Milk thistle fruit

BG (bulgarski): Бял трън, плод	LT (lietuvių kalba): Margainių vaisiai
CS (čeština): plod ostropestřece mariánského	LV (latviešu valoda): Īstā mārdadža augļi
DA (dansk): Marietidselfrugt	MT (Malti): Għerq tax-Xewk tal-Madonna
DE (Deutsch): Mariendistelfrüchte	NL (Nederlands): Mariadistel
EL (elliniká): Σιλύβου μαριανού καρπός	PL (polski): Owoc ostropestu plamistego
EN (English): Milk thistle Fruit	PT (português): Cardo-mariano
ES (español): Cardo mariano, fruto de	O (română): fruct de armurariu
ET (eesti keel): maarjaohakavili	SK (slovenčina): Plod pestreca
FI (suomi): maarianohdake, hedelmä	SL (slovenščina): plod pegastega badlja
FR (français): Chardon-marie (fruit de)	SV (svenska): Mariatistel, frukt
HR (hrvatski): paskvičine peteljke	IS (íslenska):
HU (magyar): Máriatövis termés	NO (norsk): Marietistelfrukt
IT (italiano): Cardo mariano frutto	

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

European Union herbal monograph on *Silybum marianum* (L.) Gaertn., fructus

1. Name of the medicinal product

To be specified for the individual finished product.

2. Qualitative and quantitative composition[1, 2]

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended *Silybum marianum* (L.) Gaertn., fructus (Milk thistle fruit) i) Herbal substance Not applicable. ii) Herbal preparations Dry extract (DER 36-44:1), (extraction solvent: ethyl acetate) standardised to contain 40-65% silymarin, calculated as silibinin	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended *Silybum marianum* (L.) Gaertn., fructus (Milk thistle fruit) i) Herbal substance Not applicable. ii) Herbal preparations a) Comminuted herbal substance b) Powdered herbal substance c) Dry extract (DER 20-70:1), extraction solvent acetone 95% (V/V) d) Dry extract (DER 30-40:1), extraction solvent ethanol 96% (V/V) e) Dry extract (DER 20-35:1), extraction solvent ethyl acetate f) Dry extract (DER 26-45:1), extraction solvent ethyl acetate g) Liquid extract (DER 10-17:1), extraction solvent ethanol 60% (V/V)

3. Pharmaceutical form

Well-established use	Traditional use
Herbal preparations in solid dosage forms for oral use. The pharmaceutical form should be described by	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid or solid dosage forms

[1] The declaration of the active substance(s) for an individual finished product should be in accordance with relevant herbal quality guidance.
[2] The material complies with the Ph. Eur. monograph (ref.: 1860).

Well-established use	Traditional use
the European Pharmacopoeia full standard term.	for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.

4. Clinical particulars

4.1. Therapeutic indications

Well-established use	Traditional use
Herbal medicinal product for supportive treatment of alcoholic liver disease.	Traditional herbal medicinal product for the symptomatic relief of digestive disorders with a sensation of fullness, bloating and flatulence. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

4.2. Posology and method of administration[3]

Well-established use	Traditional use
Posology *Adults and elderly* Single dose: 173 – 186.7 mg extract standardized to a content of 108.2 mg silymarin, calculated as silibinin[4] Daily dose: 3 times daily The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use') **Duration of use** The average duration of use is 2 months. If the symptoms persist during the use of the medicinal product, a doctor or a pharmacist should be consulted. **Method of administration** Oral use.	**Posology** *Adults and elderly* Herbal preparation a) Comminuted herbal substance for tea preparation. Single dose: 3-5 g in 100 ml of boiling water, Daily dose: 2 or 3 times daily, before meals Herbal preparation b) Single dose: 300 mg – 600 mg Daily dose: 2-3 times daily, up to 1800 mg daily, before meals Herbal preparation c) Single dose: Dry extract corresponding to 120 mg silymarin, calculated as silibinin Daily dose: 3 times daily, up to 360 mg, before meals Herbal preparation d) Single dose: 200 mg dry extract Daily dose: 200 mg dry extract

[3] For guidance on herbal substance/herbal preparation administered as herbal tea or as infusion/decoction/macerate preparation, please refer to the HMPC 'Glossary on herbal teas' (EMA/HMPC/5829/2010 Rev.1).
[4] 108.2 mg silymarin (HPLC method, according Eur. Ph. monograph) correspond to 140 mg silymarin (DNPH)

Well-established use	Traditional use
	Herbal preparation e) Single dose: 162.5-250 mg dry extract Daily dose: 3-4 times daily Herbal preparation f) Single dose: 123-208.3 mg dry extract Daily dose: 3-4 times daily Herbal preparation g) Single dose: 15 ml equivalent to 392 mg soft extract Daily dose: 30 ml (2 times 15ml) equivalent to 784 mg soft extract The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use') **Duration of use** 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. **Method of administration** Oral use.

4.3. Contraindications

Well-established use	Traditional use
Hypersensitivity to the active substance and to other plants of the Asteraceae (Compositae) family.	Hypersensitivity to the active substance and to other plants of the Asteraceae (Compositae) family.

4.4. Special warnings and precautions for use

Well-established use	Traditional use
The use is not recommended in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted.	The use in children and adolescents under 18 years of age has not been established due to lack of adequate data. If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. For extracts containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of

Well-established use	Traditional use
	medicinal products for human use', must be included.

4.5. Interactions with other medicinal products and other forms of interaction

Well-established use	Traditional use
None reported.	None reported.

4.6. Fertility, pregnancy and lactation

Well-established use	Traditional use
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.	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.

4.7. Effects on ability to drive and use machines

Well-established use	Traditional use
No studies on the effect on the ability to drive and use machines have been performed.	No studies on the effect on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Well-established use	Traditional use
Mild gastrointestinal symptoms such as dry mouth, nausea, upset stomach, gastric irritation and diarrhoea may occur; headache; allergic reactions (urticaria, skin rash, pruritus, anaphylaxis, asthma) may occur. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.	Mild gastrointestinal symptoms such as dry mouth, nausea, upset stomach, gastric irritation and diarrhoea may occur; headache; allergic reactions (dermatitis, urticaria, skin rash, pruritus, anaphylaxis, asthma), have been reported. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.

4.9. Overdose

Well-established use	Traditional use
No case of overdose has been reported.	No case of overdose has been reported.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Well-established use	Traditional use
Pharmacotherapeutic group: Liver therapy, lipotropics Proposed ATC code: A05B	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

5.2. Pharmacokinetic properties

Well-established use	Traditional use
After oral administration, absorption is low and maximum plasma concentrations are reached after 4-6 hours. Silibinin and other individual components from silymarin are rapidly conjugated with sulphate and glucuronic acid in liver, then reaching plasma and bile. Metabolites are found mainly in the bile. Through this way, 20-40% of the initial dose is eliminated. Silymarin half-life is between 6 and 8 hours, with a maximum plasmatic concentration between 1.3-1.9 µg/ml.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

5.3. Preclinical safety data

Well-established use	Traditional use
Silymarin has proved nontoxic in rats and mice after oral doses of 2,500 mg or 5,000 mg/kg. In a 12 month study, rats received silymarin up to 2,500 mg/kg, showed no evidence of toxicity. No evidence of ante or postnatal toxicity in animals was reported, nor did silymarin affect fertility in rats. Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended, unless necessary for the safe use of the product. Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

6. Pharmaceutical particulars

Well-established use	Traditional use
Not applicable.	Not applicable.

7. Date of compilation/last revision

7 July 2015