EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 September 2011
EMA/HMPC/350089/2011
Committee on Herbal Medicinal Products (HMPC)

This document was valid from 13 September 2011 until 27 March 2018.

(EMA/HMPC/150218/2009)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Cynara scolymus* L., folium as released for public consultation on 15 January 2011 until 15 April 2011.

	Organisations and/or individuals
1	Laboratoires Pierre Fabre
2	European Scientific Cooperative on Phytotherapy (ESCOP)
3	Herbapol S.A.
4	Association of the European Self-Medication Industry (AESGP)

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
Laboratoires Pierre Fabre	The Laboratoires Pierre Fabre appreciates the draft for a community herbal monograph on *Cynara scolymus* L.*, folium* prepared by the Committee on Herbal Medicinal Products (HMPC). *However we have comments to § 2 Qualitative and quantitative composition and § 4.2 Posology and method of administration.*	
ESCOP	ESCOP appreciates the draft for a Community Herbal Monograph on "Cynara scolymus L., folium" prepared by the Committee on Herbal Medicinal Products (HMPC). The draft assessment report gives a comprehensive overview of the accumulated scientific knowledge on Cynara scolymus L. folium over the last decades. Nevertheless, we have concerns with regard to the assessment as "traditionally used" only and the following specific comments should be taken into consideration before finalising the community herbal monograph and the assessment report.	
W.Z.Z. Herbapol S.A.	Considering data reviewed in the Draft Assessment Report along with several dozen years of medicinal use of Cynara scolymus preparations in the complemetary treatment of patients with dyslipidemias we suggest populating the section *Well-established use* with description of the herbal preparations that have been assessed in the several existing published clinical studies. This is of great importance for the preservation of that treatment modality and sustaining public awareness of lipid-lowering effects of artichoke since the guideline on the assessment of clinical safety and efficacy in the preparation of community herbal monographs (EMEA/HMPC/104613/2005) precludes the possibility to address this indication in the *Traditional use* section. Hitherto several medicinal products have obtained Marketing Authorization with indications including	

Interested party	Comment and Rationale	Outcome
	complementary treatment in arteriosclerosis prohylaxis; however, until now there are only few published reports of adverse reactions and no evidence of lack of efficacy. The lipid-lowering action of artichoke preparations has been corroborated by the substantial body of evidence. The Cochrane Collaboration Report (Wider B, Pittler MH, Thompson-Coon J, Ernst E. Artichoke leaf extract for treating hypercholesterolemia. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.: CD003335. DOI: 10.1002/14651858.CD003335.pub2) enumerated three randomized clinical trials with total number of 262 participants univocally presenting positive clinical findings in patients treated with Cynara scolymus preparations. As Cochrane Review concluded that the scarce clinical evidence warrants further studies to support lipid-lowering action of artichoke, however, taking into account robust evidence of longstanding medicinal use in the complementary therapy patients with dyslipidemias we suggest to add herbal preparations of Cynara scolymus in the the *Well-established use* section.	
W.Z.Z. Herbapol S.A.	Considering similar definitions of terms folium and herba included in internal specifications of marketing authorisation holders we suggest the monograph should include data relating to both of the above mentioned herbal substances. It seems reasonable especially in some member states, including Poland, were the previous editions of national pharmacopoeias lacked monographs of Cynara scolymus folum or herba. Moreover the contemporary definition of Cynara scolymus folium has been introduced into European Pharmacopoeia only recently.	
AESGP	AESGP in principle welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for Cynarae folium-containing products, should facilitate mutual recognition in Europe.	

Interested party	Comment and Rationale	Outcome
	There are many products on the market which have been authorised as well-established medicinal use products (e.g. in Germany), hence a well-established use should be reflected in the monograph. However, in case a well-established use is not accepted for these authorised products, and although a monograph doe s not bear direct influence on authorised well-established use herbal medicinal products, as a precautionary measure and to pre-empt any potential issues, we would like to see them added to the traditional use column. The preparations have been the basis for preparation of the Commission E (1988, revision 1990) and ESCOP (and 2003). Their posology corresponds to the ESCOP monographs, and one of these products has been registered as “traditionally used” in Germany. A further one has been granted a traditional registration in the UK in 2009 (DigestHerb Capsules), see Public Assessment Report of MHRA **(encl 1)**.	

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and quantitative composition **Traditional use**	**Laboratoires Pierre Fabre**	Comment: In section ii) c) Herbal preparations, it is mentioned one quality of dry extract: "Dry extract (DER 3.8-7.5:1), extraction solvent water". We would like to inform you that the dry extract (native drug extract ratio 2-6:1, extraction solvent: water) has also a medicinal traditional use throughout a period of at least 15 years in the Community: On the one hand, dry aqueous extract is mentioned in the "Avis aux fabricants concernant les demandes d'autorisations de mise sur le marché de spécialités pharmaceutiques à base de plantes » edited by the Ministère des Affaires sociales et de l'Emploi in 1986 (*i.e* 25 years), On the other hand, this extract is used in the specialty ELUSANES® Artichaut which obtained a marketing authorization in 1986 in France according to this official document. This specialty has been marketed since more than 25 years. Proposed change: We propose to extend the DER in section ii) c) Herbal preparations: Dry extract (DER 2.0-7.5:1), extraction solvent water.	Cannot be endorsed as this dry extract "Dry extract (DER 2-6:1), extraction solvent water" does not fulfil the criteria of at least 30 years of use as requested by Directive 2004/24 EC for qualification as a traditional herbal medicinal product (since 1986, it has only 25 years).

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and quantitative composition	**ESCOP**	***Well-established use*** We would like to add the following preparation under the "well-established medicinal use": "Dry extract (4-6 :1) extraction solvent water" **Comments:** Published data on this herbal preparation fulfil the requirements for well-established use as defined in the respective Guideline EMEA/HMPC/104613/2005 (see comments under 4.2 Posology and method of administration).	
2. Qualitative and quantitative composition	**W.Z.Z. Herbapol S.A.**	We suggest to add the following herbal preparation in the section *Traditional use* and *Well-established use*: Cynarae herbae extractum siccum (3-5:1) extraction solvent – ethanol 50% [v/v] **Rationale:** The above mentioned herbal preparation has been granted Marketing Authorization in Poland on 11th May, 1981 and has been actively marketed for 30 years. Therapeutic indications includes: Traditional use in digestive complaints, complementary to a low fat diet in the treatment of mild to moderate hyperlipidaemia, as a protective measure in people exposed to the action of toxic substances (i.e. carbon disulfide) (1,2). **References:** 1. First Marketing Authorization Certificate of Cynarex:	Cannot be endorsed - the proposed extract Cynarae herbae extractum siccum (3-5:1) Extraction solvent – ethanol 50% [v/v] Refers to the aerial part (herba) and not to the leaves of Cynara and does not comply with the published monograph and the existing Ph. Eur. Monograph referring to the "Cynarae folium". In case of a special interest a request for a preparation of a monograph on Herba Cynara may be submitted. For information, the proposed extract was added to the AR under Cynara herba products in the overview of marketed product all over Europe.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Cynarae herbae extractum siccum (3-5:1) extraction solvent – ethanol 50% [v/v] Poland, 11.05.1981 [English translation] ***2.*** Cynarex - Summary of Product Characteristics, 11.12.2008 [English translation]	
2. Qualitative and quantitative composition	**AESGP**	**Well-established medicinal use:** **We propose to classify the dry extract (4-6:1, extraction solvent: water) with a daily dose of 1920 mg as "well-established use".** Reasons: The study Holtmann 2003 is a double-blind, randomised controlled trial which fulfils the requirements of a study of "good quality" and thus the respective HMPC guideline on the minimum requirements for "well-established use". The Assessment Report includes a positive statement on efficacy (p. 32 f., p. 40) for the tested dry extract (4-6:1). The product is marketed in Germany as Hepar-SL forte by Cassella-med GmbH & Co.KG (marketing authorisation number 6163618.01.00). The following products have been authorised in Germany as well-established medicinal use products.	All the proposed products have been included in the AR. The study of Holtman of 2003 has been referred to in the AR, but a detailed and accepted definition of functional dyspepsia is missing, thus the well-established use is not proved adequately.

<table>
<tr><th>Section number and heading</th><th>Interested party</th><th>Comment and Rationale</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Company</th><th>Product</th><th>Marketing authorisation/ registration number</th></tr>
<tr><td>Aliud Pharma GmbH</td><td>Cynara AL</td><td>41679.00.00</td></tr>
<tr><td>Stada GmbH</td><td>Heparstad 400 mg Hartkapseln</td><td>41676.00.00</td></tr>
<tr><td>Cassella-med GmbH & Co.KG</td><td>Cholagogum Nattermann Artischocke Kapsel</td><td>43566.00.00</td></tr>
<tr><td>Bionorica SE</td><td>CynaScol K&P</td><td>44777.00.00</td></tr>
<tr><td>Salus Pharma GmbH</td><td>Losapan Kapseln</td><td>41237.00.00</td></tr>
<tr><td>Inter Pharma Arzneimittel GmbH</td><td>Artischocke 400 mg K&P</td><td>45338.00.00</td></tr>
<tr><td>Dolorgiet GmbH & Co. KG</td><td>Chol-Art</td><td>41365.00.00</td></tr>
<tr><td>Dr. Dünner</td><td>Artischocke Kräutertabletten</td><td>6305256.00.00</td></tr>
<tr><td>Ardeypharm</td><td>Ardeycholan</td><td>43511.00.00</td></tr>
<tr><td>Cefak</td><td>Cefacynar</td><td>44776.00.00</td></tr>
<tr><td>Rodisma-Med Pharma GmbH</td><td>Natu-Hepa 600 mg</td><td>52053.00.00</td></tr>
<tr><td>Homöopathisches Laboratorium A. Pflüger GmbH & Co. KG</td><td>Hepagallin N</td><td>6240193.00.00</td></tr>
</table>
</td><td>The same extracts with same indications cannot be kept in both sides TU and WEU even if the posology is different.</td></tr>
</table>

Section number and heading	Interested party	Comment and Rationale	Outcome
		Traditional use: We propose to add the following extract: Dry extract (4-6:1), extraction solvent: water. We assume that this extract is covered by the dry extract 3.8-7.5:1 but this should be made clear as many products on the market declare a DER of 4-6:1. The difference between this dry extract and the dry extract proposed above for the well-established medicinal use is the posology. The proof of tradition for Artischocke Kräutertabletten which was submitted to the German health authority is attached as a confidential document **(encl. 2)**. Furthermore we propose to add the following: **Dry extract (9-11:1) extraction solvent ethanol 15%**. This extract is part of a combination product marketed as Salus Gallexier Kräuter Dragee in Germany. A table with proofs of tradition as well as references on the tradition are attached **(encl. 3)**. Furthermore, ethanolic extracts from Artichoke leaf are traditionally used as well. This can be shown in the attached references which are not yet included in the HMPC list **(encl. 4-8)**.	The tradition of dry extraction of (4-6:1) extraction solvent water is fulfilled, therefore the extract 3.8-7.5:1 (including 4-6:1) is fully covered. Dry extract (9-11:1) extraction solvent ethanol 15% is part of a combination. The proof of tradition can be accepted only for the combination preparation. But this monograph is about mono-preparations of artichoke leaves only. Ref (4) is referred in Cynarae herba again-R. F. Weiss “Lehrbuch der Phytotherapie” 3. Auflage 1974 [(Neurochol®- Tropfen) und Dragees (Neurochol®-Dragees) 30 bis 60 Tropfen täglich einer Kombination mit 15 g alkoholischer Auszug aus

Section number and heading	Interested party	Comment and Rationale	Outcome
		For the well-established medicinal use, we propose the same indications as for the traditional use: "For the symptomatic relief of digestive disorders such as dyspepsia with a sensation of fullness, bloating and flatulence."	*Herba Cynarae scol*. (1:1) in 100 g Zubereitung ca. 0,14 g bis 0,28 g Drogenäquivalente pro Tag 2 bis 6 Dragees täglich einer Kombination mit 40 mg eines wäss. TE aus *Herba Cynarae scol* (8.1) ca. 0,64 g bis 1,9 g Drogenäquivalente pro Tag] The same indication in both sides TU and WEU cannot be endorsed.
4.1 Therapeutic indications	**ESCOP**	**Well-established use** We suggest adding under "Well-established use": "Digestive complaints (such as dyspepsia with a sensation of fullness, boating and flatulence) due to hepatobiliary disturbances". **Comments:** The above-mentioned herbal preparation fulfils the requirements for the well-established medicinal use as defined in the respective HMPC Guideline (see comments under 4.2 Posology and method of administration).	The WEU is not endorsed. The existing clinical trials indicate that the artichoke leaf extracts (water dry extract of dried and fresh leaves separately) are somehow effective against functional dyspepsia and irritable bowel syndrome and exhibit lipid lowering effects. These activities are not adequately documented, therefore the well-established use cannot be supported.
4.1 Therapeutic indications	**W.Z.Z. Herbapol S.A.**	Considering the above mentioned preparation in the section *Well-established use* we suggest to add: - complementary to a low fat diet in the treatment of mild to moderate hyperlipidaemia, - as a protective measure in people exposed to the action of toxic substances (i.e. carbon disulfide). **Rationale:** Trials performed between 1975 and 1981 substantiated	Not endorsed as there is not enough evidence. Provided information refers mainly to Cynara herba and not to Cynara leaves. The references have been added to the List of References.

Section number and heading	Interested party	Comment and Rationale	Outcome
		indications for protective use in workers chronically exposed to carbon disulfide (3,4 and 5). Wójcicki et al corroborated beneficial effects of Cynarae herbae extractum siccum (3-5:1) in patients with mild to moderate hyperlipidaemia as shown by a statically significant change in triglyceride serum level in a subgroup of patients with positive response to treatment (6). **References:** 1. Wójcicki J, Winter S. Effect of preparation Cynarex on the blood serum lipids level of the workers exposed to the chronic action of carbon disulphide. *Medycyna Pracy* 1975; 26:213-217 [English translation] 2. Woyke M, Cwajda H, Wójcicki J, Kosmider K. Platelets aggregation in workers chronically exposed to carbon disulphide and subjected to prophylactic effects of Cynarex preparation. *Med Pracy* 1981; 32:261-264 [English translation] 3. Palacz O, Czepita D, Wójcicki J. Electroretinographic investigations in subjects in chronic exposure to carbon disulphide. III. Cynarex effect on ERG related to blood lipid pattern. *Klin Oczna* 1981; 83:223-5 [English translation] 4. Wójcicki J, Olejak B, Pieczul-Mróz J, Torbus-Lisiecka B, Bukowska H, Gregorczyk J. The use of Cynarex in the treatment of primary hyperlipidemia. Study Report. Szczecin, Poland. 1980. (previously unpublished) [English translation]	Was already listed in the draft LoR. Was already listed in the draft LoR. Was already listed in the draft LoR. It has been added in the LoR and AR.

Section number and heading	Interested party	Comment and Rationale	Outcome
4.2 Posology and method of administration	**ESCOP**	**<u>Traditional use</u>** **Posology** Under a) read "Daily dose of 6 g (3 g ~~1-~~2 times ~~per day corresponding to 600 mg dry aqueous extract,~~ or 1.5 g 4 times ~~per day~~)". **<u>Well-established use</u>** For the well-established use, we propose: **"Posology** *Adolescents, adults and elderly* Dry extract (4-6:1) extraction solvent water: Daily dose: 1920 mg (640 mg three times per day) *Use in children* The use in children under 12 years of age is not recommended. **Duration of use** Long term use is possible in consultation with a doctor. **Method of administration** Oral use." **Comments**: Amongst six clinical studies performed with different artichoke leaf preparations, one randomized double-blind study including 244 patients with functional dyspepsia [1] fulfils the requirements for well-established use as defined in the Guideline EMEA/HMPC /104613/2005. The overall improvement (from patient self-rating	The proposal is partially endorsed and the posology was changed as follows: "Daily dose of 6 g (3 g 1-2 times or 1.5 g 4 times)"; the information is coming from Poland. The WEU is not accepted as it was explained above. The existing clinical trials indicate that the artichoke leaf extracts (water dry extract of dried and fresh leaves separately) is somehow effective against functional dyspepsia and irritable bowel syndrome and also for its lipid lowering effects, but not

Section number and heading	Interested party	Comment and Rationale	Outcome
		scores for change in dyspeptic symptoms over 6 weeks of treatment) was significantly greater with artichoke leaf extract (2 x 320 mg, thrice daily) than with placebo (8.3 vs. 6.7; p<0.01). Global quality-of-life scores as assessed by the Nepean Dyspepsia Index improved significantly more in patients treated with artichoke leaf extract than in patients in the placebo group (–41.1 vs. –24.8; p<0.01). Additionally, a double-blind, placebo-controlled, cross-over pharmacological study in humans, also fulfilling quality requirements, evaluated choleretic effects [2]. It contributes to understand the mechanism of action of artichoke leaf. The study, which included 20 volunteers with acute or chronic metabolic disorders, showed that mean bile secretion was significantly higher in the verum group which received 1920 mg of the aqueous artichoke leaf dry extract (p<0.01): 127% higher 30 minutes after administration, 151% after 60 minutes (the maximum effect) and 94% after 90 minutes. Results after 120 minutes and 150 minutes were also significantly higher (p<0.05) in the verum group. **References:** [1] Holtmann G, Adam B, Haag S, Collet W, Grünewald E, Windeck T. Efficacy of artichoke leaf extract in the treatment of patients with functional dyspepsia: a six-week placebo-controlled, double-blind, multicentre trial. Aliment Pharmacol Ther 2003;18:1099-105. [2] Kirchhoff R, Beckers C, Kirchhoff GM, Trinczek-Gärtner H, Petrowicz O, Reimann HJ. Increase in choleresis by means of	adequately documented, so the Well Established Use cannot be supported. The safety profile was very good according the results given by the existing clinical trials which were performed for 6 weeks of the treatment. The proposal is endorsed that the use is safe for at least 2-3 weeks under TU. Both references have been already listed in the LoR and they have been evaluated in the AR (the one by Kirchhoff *et al.* in the English version).

Section number and heading	Interested party	Comment and Rationale	Outcome
		artichoke extract. Phytomedicine 1994;1:107-15. Also published in German as: Kirchhoff R, Beckers C, Kirchhoff G, Trinczek-Gärtner H, Petrowicz O, Reimann H-J. Steigerung der Cholerese durch Artischockenextrakt. Ergebnisse einer plazebokontrollierten Doppelblindstudie. Ärztl Forsch 1993;40:1-12.	
4.2 Posology and method of administration **Traditional use**	**Laboratoires Pierre Fabre**	Comment: The posology applied for ELUSANES® Artichaut since 1986 in France is 2 capsules per day. Each capsule contains 200 mg of dry extract. Proposed change: We propose to add in sections: Posology c) • Dry extract (DER 2.0-7.5:1), Daily dose 400-900 mg (in doses of 200, 300, or 600 mg).	The proposal cannot be endorsed as the product referred to has been on the market for less than 30 years.
4.2 Posology and method of administration	**ESCOP**	**Well-established medicinal use:** For the **well-established used dry extract (4-6:1, extraction solvent: water)** we suggest the following: *Daily dose: 1920 mg (three times 640 mg)* Reasons: The study of Holtmann 2003 demonstrated the efficacy of the dry extract (4-6:1, extraction solvent: water) with a daily dose of 1920 mg (three times daily 640 mg).	Not endorsed, explained above.

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<tr><td></td><td></td><td>
Traditional use:

As stated under Section 2, we propose to add the dry extract (4-6:1), extraction solvent: water with a daily dose of up to 1320 mg.

For the dry extract (4-6:1), extraction solvent: water, we propose to add:

Adults and adolescents from 12 years on: Up to 1320 mg, e.g. 400 mg 2-3 times daily, 600 mg 2 times daily or 440 mg 3 times daily.

The individual dosages of the preparations containing the dry extract (4-6:1), extraction solvent: water, are listed as follows.
<table>
<tr><th>Product</th><th>Single dose</th><th>Daily dose</th></tr>
<tr><td>Cynara AL</td><td>400 mg</td><td>1200 mg</td></tr>
<tr><td>Heparstad 400 mg Hartkapseln</td><td>400 mg</td><td>1200 mg</td></tr>
<tr><td>Cholagogum Nattermann Artischocke Kapsel</td><td>400 mg</td><td>1200 mg</td></tr>
<tr><td>CynaScol K&P</td><td>400 mg</td><td>1200 mg</td></tr>
<tr><td>Losapan Kapseln</td><td>400 mg</td><td>1200 mg</td></tr>
<tr><td>Artischocke 400 mg K&P</td><td>400 mg</td><td>1200 mg</td></tr>
<tr><td>Chol-Art</td><td>400 mg</td><td>1200 mg</td></tr>
<tr><td>Artischocke Kräuter Tabletten</td><td>320 mg (+ 300 mg powdered artichoke leaves)</td><td>960 mg (+ 900 mg powdered artichoke leaves)</td></tr>
<tr><td>Ardeycholan</td><td>400 mg</td><td>1200 mg</td></tr>
<tr><td>Cefacynar</td><td>400 mg</td><td>1200 mg</td></tr>
<tr><td>Natu-Hepa 600 mg</td><td>600 mg</td><td>1200 mg</td></tr>
<tr><td>Hepagallin N</td><td>440 mg</td><td>1320 mg</td></tr>
</table>
</td><td>Not endorsed, explained above (the extract is already covered by the given extract 3.8-7.5:1).</td></tr>
</table>

Section number and heading	Interested party	Comment and Rationale	Outcome
		For the **dry extract (9-11:1) extraction solvent ethanol 15%**, the following posology applies: *235-352.8 mg extract corresponding to 2.1-3.9 g of the herbal drug.* In the Assessment Report the posology of product **Cynara 400 mg capsule** is not listed (page 7 and 15, United Kingdom). The product is registered as DigestHerb hard capsules in the UK (registration number THR 23056/0005). This should be corrected in the Assessment Report because this product complies with the criteria of the HMPC draft monograph.	This extract is not accepted as it is referred only to a very complicate mixture. The proposal is endorsed. The information on the Cynara leaves extract referring the commercial product you refer to was not provided before. It was corrected accordingly.