25 November 2010
EMA/HMPC/150209/2009
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Cynara scolymus* L., folium

<Based on Article 10a of Directive 2001/83/EC as amended (well-established use)>

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Cynara scolymus* L., Cynarae folium
Herbal preparation(s)	• Comminuted or powdered herbal substance for herbal tea • Powdered herbal substance • Dry extract (DER 3.8-7.5:1), extraction solvent water • Soft extract fresh leaves (DER 15-30:1), extraction solvent water • Dry extract fresh leaves (DER 25-35:1), extraction solvent water
Pharmaceutical forms	Comminuted or powdered herbal substance as herbal tea for oral use. Herbal preparations in solid or liquid form for oral use

Note: This draft Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Cynara scolymus* L., folium. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the 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

Latin Name: *Cynara scolymus* L., *Asteraceae* family (*Compositae*)
In a recent botanical taxonomic revision of the genus Cynara [ESCOP 2009] it has been accepted that the leafy cardoon (*Cynara cardunculus* L.) and the globe artichoke (*Cynara scolymus* L.) are two cultivars of a new subspecies *Cynara cardunculus* L. subsp. *flavescens* Wiklund [ESCOP 2009]. Nevertheless, the botanical name, *Cynara scolymus* has been kept for the monograph, in accordance with the European Pharmacopoeia (*Cynara scolymus)* not distinguishing morphologically the two types of the plant cultivars (globe artichoke and leafy cardoon).

Pharmacopoeial Name: Cynarae folium
Other Names: The name has originated from ardi shauki (أرضي شوكي), which is Arabic for ground-thorn, through the **Italian**: articiocco, **English**: globe artichoke, **French**: artichaut, **German**: Artischocke, **Hungarian**: articsóka level, **Latvian name**: artišoka lapas, **Greek**: Κινάρα, **Swedish**: kronärtskocka, **Dutch**: artisjok, **Portuguese**: alcachofra, **Croatian**: artičoka, **Turkish**: enginar, **Russian**: артишок, **Spanish**: alcachofa, alcachofera.

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

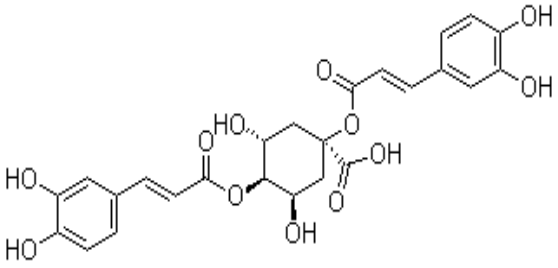
- Herbal substance(s)

Pharmacopoeial grade artichoke leaf consists of the dried basal leaves of *Cynara scolymus* L. containing a minimum 0.8 % of chlorogenic acid ($C_{16}H_{18}O_9$; M_r 354.3) (dried drug). Botanical identification is carried out by thin-layer chromatography (TLC), macroscopic and microscopic evaluations, and organoleptic tests. The dried leaf must contain not less than 25% water-soluble extractive [BHP 1996; Pharm. Franc. 1987; Blumenthal et al. 2000; Bruneton 1999].

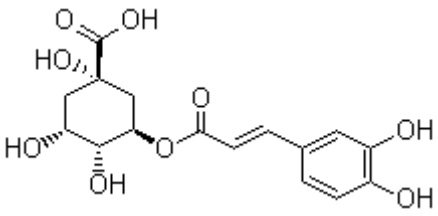
Globe Artichoke (*Cynara scolymus* L.) is a perennial thistle originating in southern Europe around the Mediterranean (northern Africa and the Canary Islands) [Leung & Foster, 1996]. It grows to 1.5-2 m tall, with arching, deeply lobed, silvery glaucous-green leaves 50–80 cm long. The flowers develop in a large head from an edible bud about 8–15 cm diameter with numerous triangular scales; the individual florets are purple. The edible portion of the buds consists primarily of the fleshy lower portions of the involucral bracts and the base, known as the "heart"; the mass of inedible immature florets in the center of the bud are called the "choke."

Its cultivation in Europe dates back to ancient Greece and Rome [Grieve 1971]. It is cultivated in North Africa as well as in other subtropical regions [Iwu 1993]. The material of commerce comes as whole or cut dried leaves obtained mainly from southern Europe and northern Africa [BHP 1996].
Artichoke leaf contains up to 2% phenolic acids, mainly 3-caffeoylquinic acid (chlorogenic acid), plus 1.3-di-O-caffeoylquinic acid (cynarin), and caffeic acid; 0.4% bitter sesquiterpene lactones of which 47-83% is cynaropicrin; 0.11.0% flavonoids including the glycosides luteolin-7-β-rutinoside (scolymoside), luteolin-7-β-D-glucoside and luteolin-4-β-D-glucoside; phytosterols (taraxasterol); sugars; inulin; enzymes; and a volatile oil consisting mainly of the sesquiterpenes β-selinene and caryophyllene [Hänsel et al. 1992, 1994; Leung & Foster 1996; Meyer-Buchtela 1999; Newall et al. 1996].
Analytically, artichoke's main plant chemicals are caffeic acid, caffeoylquinic acids, chlorogenic acid, cyanidol glucosides, cynaragenin, cynarapicrin, cynaratriol, cynarin, cynarolide, decanal, eugenol, ferulic acid, flavonoids, folacin, glyceric acid, glycolic acid, heteroside-B, inulin, isoamerboin, lauric acid, linoleic acid, linolenic acid, luteolin glucosides, myristic acid, neochlorogenic acid, oleic acid, palmitic acid, phenylacetaldehyde, pseudotaraxasterol, scolymoside, silymarin, sitosterol, stearic acid,

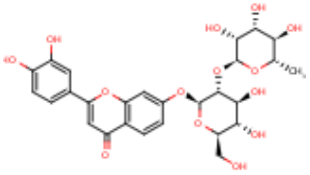
stigmasterol, and taraxasterol [Dorne 1995; Maros et al. 1966, 1968; Montini et al. 1975; Samochowiec et al. 1971].



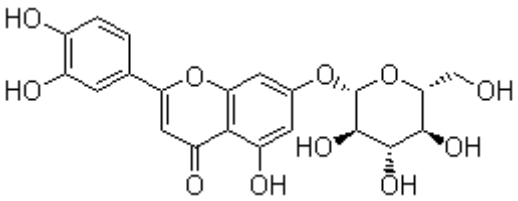
Cynarin



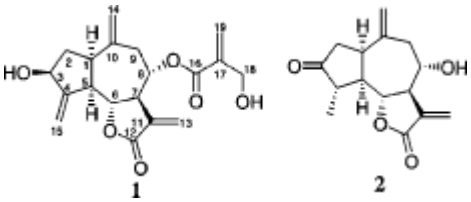
Chlorogenic acid



Scolymoside



Cynaroside



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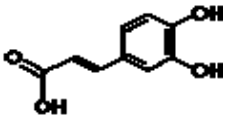
Cynaropicrin (**1**) and grosheimin (**2**)



Caffeic acid

The artichoke is popular for its pleasant bitter taste, which is attributed mostly to a plant chemical called cynarin found in the green parts of the plant. Cynarin is considered one of artichoke's main biologically active chemicals. It occurs in the highest concentration in the leaves of the plant, which is why leaf extracts are most commonly employed in herbal medicine. Other documented "active" chemicals include flavonoids, sesquiterpene lactones, polyphenols and caffeoylquinic acids.

- Herbal preparation(s)

Concerning the information provided by the Member States the intended use of the following preparations is:

TU

- Comminuted or powdered leaves for herbal tea (Belgium, Germany, Spain and Poland)

- Powdered leaves (France)

- Dry extract (DER 3.8-7.5:1), extraction solvent water (Poland, Germany)

- Dry extract fresh leaves (DER 25-35:1), extraction solvent water (Poland)

- Soft extract fresh leaves (DER 15-30:1), extraction solvent water (France)

- 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.

For combination products there is the following information in European market:

- Spain: Combinations products: Artichoke extract with laxative products or with Boldo extract

- Sweden: There is one combination product, a so called natural remedy, containing *Cynara scolymus* together with *Gentiana lutea* and *Curcuma longa*

- **Germany: Seven authorized combination products** with Matricariae flos, Taraxaci herba cum radix, Menthae piperitae folium, Millefolii herba, Foeniculi amari fructus, Helichrysi flos

Therefore the combinations of artichoke are not proposed for the monograph/list.

- Vitamins

Not applicable.

- Minerals

Not applicable.

1.2. Information about products on the market in the Member States

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Finland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Also in combinations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
Hungary	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known

Member State	Regulatory Status				Comments
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Poland	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Also combinations
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

Member State	Regulatory Status
Member state	products, indications
Austria	**TU** **Preparations:** 1) dry extract, DER 4-6:1, solvent water 350 mg 2) dry extract (no further details) 300 mg 3) dry extract, DER 4-6:1, solvent water 320 mg 4) dry extract, DER 4-6:1, solvent water 600 mg 5) dry extract, solvent water (no further details) 400 mg **Since:** 1) 2000; 2) 1999; 3) 1998; 4) 2000; 5) 1999 **Pharmaceutical form:** 1), 2), 4), 5) coated tablet 3) capsules **Posology** for oral use in adults: 1) 3 x daily 30-1-2 coated tablets 2), 4), 5) 3 x daily 30-1 coated tablet 3) 3 x daily 30-1 -2 capsules **Indications** : 1), 2), 4), 5) Digestive complaints 3) Dyspepsia **Risks:** No adverse effects known.

Member State	Regulatory Status
	There are also products in the market as a combination with Menthae pip. folium, Taraxaci radix, Curcumae rhizoma and Silybi marianae fructus. Or Silybi marianae fructus, Taraxaci radix **WEU** **Preparations:** 1) dry extract, DER 25-35:1, solvent water 300 mg 2) dry extract, DER 25-35:1, solvent water 450 mg 3) dry expressed juice from 12000 mg fresh leaves 400 mg 4) dry extract, DER 4-6:1, standardized to >1.25% caffeoylquinic acids 5) soft extract, DER 4-6:1, standardized to >0.5% caffeoylquinic acids 5 ml contain 200 mg 6) dry extract, DER 3.8-5.5:1, solvent water 400 mg 7) dry expressed juice from 12000 mg fresh leaves 400 mg **Since:** 1), 2), 6), 7) 2002; 3) 2004; 4), 5) 1992 **Pharmaceutical form:** 1), 2), 3), 4), 7) coated tablet 5) solution for oral intake 6) capsules **Posology** for oral use in adults: 1) oral, 3 x daily 300 mg 2) oral, 3 x daily 450 mg 3) oral, 1 x daily 1-2 coated tablets 4) oral, 3 x daily 1-2 coated tablets 5) oral, 3 x daily 5-10 ml 6) oral, 3 x daily 1 capsule 7) oral, 3 x daily 1-2 coated tablets **Indications:** 1), 2), 6) Digestive complaints, regulation and improvement of lipid metabolism 3) Improvement of digestion 4), 5), 7) dyspeptic disorders, post-treatment after hepatitis, chronic hepatopathies, subacute or chronic diseases of the biliary tract, after-care of cholecystectomy **Risks**: 4), 5), 7) None known 1), 2) Rarely mild laxative effects 6) hypersensitivity reactions
Belgium	**WEU** **Preparations:** 1) powdered leaves 2), 3) dry "purified" extract, equiv 1.875% chlorogenic acid (no further details) 4) dry extract (no further details) **Since:** 1) 2006; 2), 3) 2000; 4) 1999 **Pharmaceutical form**: 1) capsules, hard; 200 mg powder per capsule

Member State	Regulatory Status
	2) coated tabs; 200 mg extract/tab 3) oral solution; 240 ml extract/ml 4) coated tabs; 200 mg extract/tab **Posology** for oral use in adults and adolescents: 1) 2 times 3 to 4 caps daily 2) 2 times 3 tablets daily 3) 2-4 times 2.5 ml daily 4) 2-4 times 3 tabs daily **Indications:** 1) enhances biliar excretion, after exclusion of serious pathologies 2) cholagogue, after exclusion of serious pathologies. Minor increase in renal water excretion. Marketing Authorisations for the teas date from 1962 50-200 mg Cynara herb per g tea **Combinations products**: Artichoke leaf extract with Boldo folium, herba hepaticae, Centaurii herba, Cardui benedicti herba, Fraxini folium
Bulgaria	**WEU** **Preparations**: 1) dry extract, DER 4-6:1, tablets 2) soft extract (DER 4-6:1), liquid **Since:** 1) 2001; 2) 2006 **Pharmaceutical form:** 1) coated tablet 5) solution for oral intake **Posology** for oral use in adults (children over 12 years): 1) adults 1-2 tablets 3 times daily 2) adults 1-2 tea spoon 3 times daily **Indications:** 1), 2) dyspeptic symptoms and meteorism following fatty meals and meals which are difficult to digest, follow-up treatment by liver and biliary disfunction **Risks**: 1), 2) hypersibility, diarrhoea, flatulence, nausea
Cyprus	Not known.
Czech Republic	No authorized herbal medicinal products containing Cynarae folium as a single drug preparation are on the market.
Denmark	No authorized herbal medicinal products containing Cynarae folium as a single drug preparation are on the market.
Estonia	Not known.
Finland	No authorized herbal medicinal products containing Cynarae folium as a single drug preparation are on the market.

Member State	Regulatory Status
France	**TU** **Preparations:** 1), 2) powdered dried leaves 3) aqueous extract 4) dry aqueous extract 5) dry aqueous extract , DER 2-3.5:1 6), 7) dry aqueous extract; DER 2.5-3.5:1 dried leaf or DER 15-30:1 fresh leaf 8) soft aqueous extract **Since:** 1) 1988; 2) 1994; 3) 1988; 4) 1990; 5) 1986; 6-7) 1976; 8) 1966 **Pharmaceutical form:** 1), 4), 5) Hard capsules 6) coated tablet 2), 3), 7), 8) solution for oral intake **Posology** for oral use in adults: 1) hard capsule 3 times daily 200 mg of powdered drug/capsule 2) 1 ampoule (5 ml) 2 times daily (0.5 g of powdered drug/ ampoule) 3) 3 to 6 ampoules (15 ml) daily (0.3 g of extract/ampoule) 4) 1 to 2 hard capsules 2 times daily (192.5 mg of extract/capsule) 5) 1 hard capsule 2 times daily (200 mg of extract/capsule) 6) 1 to 2 coated tablets 3 times daily (200 mg of extract/tablet) 7) 1 coffee spoon 3 times daily (20 g of extract/100 ml) 8) 1 ampoule (10 ml) 3 times daily (2 g of extract/ampoule) **Indications:** 1-5) Traditionally used to promote urinary and digestive elimination functions. Traditionally used as a choleretic and cholagogue 6-8) Traditionally used to promote urinary and digestive elimination functions **Risks:** None reported
Germany	**TU** **Preparations:** dry extract (DER 5.8-7.5:1), extraction solvent water **Since:** 1978 **Pharmaceutical form:** coated tablet **Posology** for oral use in adults: 1 coated tablet contains 300 mg dry extract 1-2 times daily 1 coated tablet **Indications**: traditional used to promote the digestion **Risks:** Adverse reactions: slight diarrhoea with abdominal spasm, epigastric complaints like nausea and heartburn, reactions of hypersensitivity like exanthema. Interactions: concomitant use may decrease the efficacy of anticoagulants (coumarin

Member State	Regulatory Status
	derivates like Phenprocoumon, Warfarin). Tight monitoring is necessary. **Seven (7) authorized combination products** with Matricariae flos, Taraxaci herba cum radix, Menthae piperitae folium, Millefolii herba, Foeniculi amari fructus, Helichrysi flos Moreover the following authorized products for **TU**: **Cynariae flos**: 3 expressed juices from fresh artichoke flower buds (1:0.6-0.9) on the market since 1978, expr. juice, for TU **Cynariae herba:** 1 fluid extract from artichoke herb (1:2.4-5.2), extraction solvent: ethanol on the market since 1978, liquid, for TU **WEU** **Preparations:** 1), 3-11), 14-16), 18-19), 21-23), 27-34), 36), 38), 43) dry extract (DER 4-6:1), extraction solvent water 2, 26) dried expressed juice from fresh artichoke leaves (DER 25-35:1), extraction solvent water 12, 39-40) dry extract from fresh artichoke leaves (DER 25-35:1), extraction solvent water 13, 41, 42) dry extract (DER 5.8-7.5:1), extraction solvent water 17) fluid extract (DER 1:0.9-1.1), extraction solvent ethanol 35% (v/v) 20) dry extract (DER 3.8-5.5:1), extraction solvent water 25, 35) dry extract from fresh artichoke leaves (DER 15-30:1), extraction solvent water 37) soft extract (DER 2.5-3.5:1), extraction solvent ethanol 20% (v/v) **Since:** 1, 14, 16) 2000; 2) 2005; 3, 6, 9, 15, 18, 21-24) 1998; 4, 7, 10, 12, 13, 17, 19, 20, 35-42) 1978; 5, 11) 1999; 8, 28-31, 43) 2003; 25, 27, 32) 2002; 26) 2006; 33, 34) 2004 **Pharmaceutical form:** 1, 3, 5, 6, 9-11, 14-16, 18, 20-24, 38) hard capsule 2, 4, 8, 12, 13, 26-36, 39-43) coated tablet 7, 25) film tablet 17, 19, 37) oral liquid **Posology** for oral use: Adults and adolescents over 12 years 1, 3, 6, 9, 14-16, 18, 21-24) 1 hard capsule contains 400 mg dry extract; 1x3 times daily 2, 26) 1 coated tablet contains 400 mg dried expressed juice; 2 times daily 1 coated tablet 4) 1 coated tablet contains 232 mg dry extract; 5 coated tablets per day in the following order: 2 coated tablets in the morning, 2 coated tablets at noon and 1 coated tablet in the evening 5) 1 hard capsule contains 400 mg dry extract; 2-3 times daily 1 hard capsule 7) 1 film tablet contains 200 mg dry extract; 3 times daily 2 film tablets 8, 27-34, 43) 1 coated tablet contains 600 mg dry extract; 2 times daily 1 coated

Member State	Regulatory Status
	tablet 10) 1 hard capsule contains 200 mg dry extract; 3 times daily 2 hard capsules 11) 1 hard capsule contains 400 mg dry extract; 3 times daily 1 hard capsule 12) 1 coated tablet contains 450 mg dried expressed juice; 1-2 coated tablets 13, 41, 42) 1 coated tablet contains 300 mg dry extract 17) 1 ml liquid contains 1 ml fluid extract; 4 times daily 45 drops fluid extract 19) 10 ml liquid contains 400 mg dry extract; 3 times daily 2 teaspoons (=10 ml) of liquid 20) 1 hard capsule contains 200 mg dry extract; 3 times daily 1 hard capsule, if necessary 4 times daily 25) 1 film tablet contains 320 mg dry extract; 4 times daily 1 film tablet 35) 1 coated tablet contains 160 mg dry extract; 4 times daily 2 coated tablets 36) 1 coated tablet contains 220 mg dry extract; 3 times daily 2 coated tablets 37) 100 g (=94.8 ml) liquid contains 33.333 mg soft extract; 3 times daily 40 drops 38) 1 hard capsule contains 320 mg dry extract; 2 times daily 2 hard capsules 39) 1 coated tablet contains 300 mg dry extract; Adults: 3-4 times daily 2 coated tablets 40) 1 coated tablet contains 150 mg dry extract; Adults: 3-4 times daily 2-4 coated tablets **Indications :** 1, 3, 6, 7, 9, 11-16, 18-25, 39-42) dyspeptic complaints, particularly based on functional affections of the biliary tract 2, 4, 5, 8, 17, 26-38, 43) dyspeptic complaints, particularly based on functional affections of the biliary tract 10) dyspeptic complaints based on insufficient bile secretion like sense of fullness, flatulence, minor gastrointestinal spasms **Risks:** 1–43) Adverse reactions: slight diarrhoea with abdominal spasm, epigastric complaints like nausea and heartburn, reactions of hypersensitivity like exanthema. Interactions: concomitant use may decrease the efficacy of anticoagulants (coumarinderivates like Phenprocoumon, Warfarin). Tight monitoring is necessary.
Greece	No authorized herbal medicinal products containing Cynarae folium as a single drug preparation are on the market.
Hungary	**TU** **Preparations:** 400 mg Cynarae scol. folium extr. sicc (3-6:1, extraction solvent water) **Since:** 2001 **Pharmaceutical form:** Dragée, coated tablet **Posology** for oral use in adults 3x1 dragée: The use is not recommended in children under 12 years of age because of the lack of available experience. Duration treatment: Until the existence of the complaints but not more 2-3 months. If the complaints reoccur the cure can be restarted but at least one month's break

Member State	Regulatory Status
	should be kept. **Indications:** For digestive complaints, feeling of fullness, nausea, flatulence, gallbladder disease, to promote bile secretion (as cholagogue) , to promote fat digestion **Risks:** Contraindication: Obstruction of bile duct, cholangitis, hepatitis, hypersensitivity to artichoke or other species of the Compositae. Warnings: Patients with cholelithiasis should take artichoke leaf only after consulting a health care professional. Interactions: There are no data on concomitant use of Artichoke leaf with other preparations. Pregnancy, 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. Adverse effects: mild digestive system disturbances may occur in rare cases; allergic reactions might occur in sensitized patients.
Iceland	Not known.
Ireland	Not known.
Italy	Not known.
Latvia	No authorized herbal medicinal products containing Cynarae folium as a single drug preparation are on the market.
Lithuania	Not known.
Luxembourg	Not known.
Malta	Not known.
Netherlands	Not known.
Norway	Not known.
Poland	**TU** **Preparations:** 1) Cynarae herbae extractum sicuum (3-6:1), extraction solvent water 2) Cynarae herbae tinctura (1:5), extraction solvent ethanol 70% (v/v) 3) Cynarae folii extractum siccum (25-35:1), extraction solvent water 4) Cynarae herbae extractum siccum (4:1), extraction solvent ethanol 50% (v/v) 5) Cynarae herba –herbal tea **Since:** 1, 3) 1967; 2, 4) 1997; 5) since many years **Pharmaceutical form:** 1) capsule, hard 2) oral liquid 3) capsule, hard 4) tablets 5) herbal tea

Member State	Regulatory Status
	Posology 1) oral use, 3-4 capsules daily 2) oral use, 10 ml 3 times daily 3) oral use, 1 capsule daily 4) oral use, 2 tablets once a day (digestive disorders) or 2 tablets 3 times daily (hyperlipidaemia) 5) oral use: 3 g (of the dried Cynarae herba in one glass of bolding water–as infusion) 1-3 times daily or in hyperlipidaemia 1.5 g (of the dried Cynarae herba in one glass of bolding water – as infusion) 4 times daily **Indications :** 1, 3) digestive complaints (e.g. stomach ache, feeling of fullness, flatulence) 2) digestive complaints and hepatobiliary disturbances 4) digestive complaints and hepatobiliary disturbances. Adjuvant to a low fat diet in the treatment of mild to moderate hyperlipidaemia, 5) digestive complaints (feeling of fullness, nausea, flatulence). Adjuvant to a low fat diet in the treatment of mild to moderate hyperlipidaemia. **Risks:** Mild gastro-intestinal disturbances reactions may occur in rare cases; allergic reactions might occur in sensitized patients. **WEU** **Preparations**: Cynarae folii extractum aq siccum (4-6:1), extraction solvent: water **Since:** 1997 **Pharmaceutical form**: capsule, hard **Posology:** for oral use, 1-2 capsules once a day (digestive disorders) or 3-5 capsules daily (mild hyperlipidemia) **Indications:** digestive complaints (feeling of fullness, nausea, flatulence, heartburn)- Adjuvant to a low fat diet in the treatment of mild to moderate hyperlipidaemia **Risks**: Mild gastro-intestinal disturbances reactions may occur in rare cases; allergic reactions might occur in sensitized patients
Portugal	No authorized herbal medicinal products containing Cynarae folium as a single drug preparation are on the market.
Romania	Not known.
Slovakia	**WEU** **Preparations:** extractum fluidum **Since:** 1996 **Pharmaceutical form**: oral solution

Member State	Regulatory Status
	Posology for oral use: (tea spoon for 3 times a day) **Indications:** Indicated in light forms of hyperlipidemia as additional treatment. Indicated for adults, adolescents and children **Risks:** None reported
Slovenia	Not known.
Spain	**TU** **Preparations:** 1) Dried leaves for oral use as herbal tea or 2) Powdered leaves in pharmaceutical forms for oral use At least since 1973 **Pharmaceutical form:** 1) Herbal tea 2) Tablets/Capsules **Posology** for oral use in adults: 1) up to 3 g a day (1 to 3 caps of tea a day) 2) 600-1500 mg a day (Caps of 150; 175; 300; 500 mg) **Indications:** Dyspepsia **Risks**: None reported **Combinations products:** Combination of Artichoke with laxative products and with Boldo extract
Sweden	There is one combination product, a so called natural remedy, containing *Cynara scolymus* together with *Gentiana lutea* and *Curcuma longa*.
United Kingdom	Not known

1.3. Search and assessment methodology

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The artichoke was used as a food and medicine by the ancient Egyptians, Greeks, and Romans. Artichoke leaf has been used as a choleretic and diuretic in traditional European medicine since Roman times [Bianchini & Corbetta 1977]. Artichoke (*Cynara scolymus* L., (*Asteraceae*) is widely cultivated in Mediterranean countries, particularly in Italy, the sprout being consumed as a vegetable. Globe artichokes were first cultivated at Naples around the middle of the 15th century, and are said to have been introduced to France by Catherine de "Medici". The Dutch introduced artichokes to England, where they were growing in Henry VIII's garden at Newhall in 1530. They were introduced to the

United States in the 19th century, to Louisiana by French immigrants and to California by Spanish immigrants.

2.2. Information on traditional/current indications and specified substances/preparations

2.2.1.1. Type of tradition, where relevant

European tradition

2.2.1.2. Evidence regarding the indication/traditional use

The alcoholic extract of the leaves, currently used for the production of bitter liqueurs (about 10 g of dried leaves per litre), has been documented as a traditional folk remedy for dyspeptic disorders. Especially artichoke is the primary flavor of the Italian liquor.
The *Commission E* reported choleretic activity [Blumenthal et al. 2000; ESCOP 2009].
The *British Herbal Pharmacopoeia* reported hepatic action [BHP 1996].
The *Merck Index* reported the therapeutic category of cynarin, an active principle of artichoke, as choleretic [Budavari 1996].

The *African Pharmacopoeia* indicates its use for the treatment of liver dysfunction as well for its diuretic and anti-atherosclerotic actions [Iwu 1993].

Traditional medicinal uses of artichoke pertain to liver function as its leaves are considered choleretic (bile increasing), hepatoprotective, cholesterol-reducing, and diuretic [Kirchhoff et al. 1994]. Artichoke has been used in traditional medicine for centuries all over Europe as a specific liver and gallbladder remedy and several herbal drugs based on the plant are used as well for high cholesterol and digestive and liver disorders. Other uses around the world include treatment for dyspepsia and chronic albuminuria. Artichoke is also often used to mobilize fatty stores in the liver and detoxify it, and as a natural aid to lower cholesterol. In Brazilian herbal medicine systems, leaf preparations are used for liver and gallbladder problems, diabetes, high cholesterol, hypertension, anemia, diarrhea (and elimination in general), fevers, ulcers, and gout. Artichoke leaf has shown cholesterol-lowering and lipid-lowering activity in rats and humans [Lietti 1977]. Human studies have validated carminative, spasmolytic, antiemetic and choleretic actions [Kraft 1997].

In vivo, artichoke leaf has demonstrated hepatoprotective and hepatostimulating properties [Adzet et al. 1987; Maros et al. 1966].

In Germany, artichoke leaf is used widely as a choleretic [BAnz 1998; Meyer-Buchtela 1999] for its lipid-lowering, hepato-stimulating, and appetite-stimulating actions since at least thirty years [Hänsel et al. 1992, 1994; Meyer-Buchtela 1999]. Moreover, in German pediatric medicine, herbs with a relatively low bitter value such as artichoke leaf are considered suitable for the treatment of appetite disorders [Schilcher 1997].

Preparations of artichoke have been used for bloating, nausea, and impairment of digestion [Bruneton 1999]. It is specifically indicated for "dyspeptic syndrome" though its proven lipid-lowering actions suggest that it may also be useful as a prophylactic against atherosclerosis [Kraft 1997]. Artichoke leaf has shown cholesterol-lowering and lipid-lowering activity in rats and humans [Lietti 1977]. Human studies have validated carminative, spasmolytic, antiemetic, and choleretic actions [Kraft 1997].

In France, several pharmaceutical forms of Artichoke leaf extracts are also in use since the last thirty years [Pharm. Franc. 1987; Martindale 1993; WHO Monographs 2009; ESCOP monographs supp. 2009].

WORLDWIDE ETHNOMEDICAL USES

Europe	for bile insufficiency, cancer, detoxification, dyspepsia, gallbladder disorders, high cholesterol, hyperglycemia, jaundice, liver disorders, nausea
Brazil	for acne, anaemia, arthritis, arteriosclerosis, asthma, bile insufficiency, blood cleansing, bronchitis, diabetes, diarrhea, dyspepsia, digestive disorders, dandruff, fever, flatulence, gallbladder disorders, gallstones, gout, heart function, haemorrhage, haemorrhoids, high cholesterol, hypertension, hyperglycaemia, inflammation, kidney insufficiency, liver disorders, nephritis, obesity, prostatitis, rheumatism, seborriasis, ulcers, urethritis, urinary disorders, and as an astringent and vasoconstrictor
Dominican Republic	for bile insufficiency, digestive problems, gallbladder disorders
Haiti	for oedema, hypertension, kidney disorders, liver problems, urinary insufficiency
Mexico	for cystitis, gallstones, hypertension, liver disorders

The following herbal substances and herbal preparations are for more than 30 years on the European market and are proposed for the monograph **on traditional use**.

a) Comminuted or powdered leaves for herbal tea (Belgium, Germany, Spain, Poland)

b) Powdered leaves (France)

c) Dry extract (DER 3.8-7.5:1), extraction solvent water (Poland, Germany)

d) Dry extract fresh leaves (DER 25-35:1), extraction solvent water (Poland)

e) Soft extract fresh leaves (DER 15-30:1), extraction solvent water (France)

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

Posology and indications of the traditional herbal substance and preparations of artichoke

Indications: traditionally used

a) Traditional herbal medicinal product to promote digestion (against dyspepsia, digestive complaints) (Germany)

b) Traditional herbal medicinal product against digestive complaints (e.g. stomach ache, feeling of fullness, flatulence) and/or adjuvant to a low fat diet in the treatment of mild to moderate hyperlipidaemia (Poland)

c) Traditional herbal medicinal product against biliar disturbances, biliar colic

d) Adjuvant to allow fat diet in the treatment of mild to moderate hyperlipidaemia (for reducing cholesterol (ES)

e) Traditionally used to promote urinary and digestive elimination functions. Traditionally used as a choleretic and cholagogue (France)

The therapeutic indication which has been accepted by the MLWP is:

Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia 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.

Posology:

Generally it has been proposed an average oral daily dose: for hypercholesterolaemia and dyspepsia, 1–2 g of a dried aqueous extract [Englisch et al. 2000; 27. Petrowicz et al. 1997; Holtmann 2003]. While for adults daily dose: 5–10 g of crude drug; or equivalent galenical preparations for oral use [Blumenthal et al. 2000; *Hagers Handbuch der Drogen* 2003, WHO monographs, Vol. 4 2009]

a) Comminuted or powdered dried leaves for herbal tea
Daily dose of 6 g (3 g x 1-2 times per day corresponding to 600 mg dry aqueous extract, or 1.5 g x 4 times per day)

b) Powdered dried leaves
Daily dose of 600-1500 mg (in doses of 150, 175, 300, 500 mg)

c) Dry extract (DER 3.8-7.5:1) extraction solvent water
Daily dose 600-900 mg (in doses of 200, 300, or 600 mg)

d) Soft extract of fresh leaves (DER 15-30:1), extraction solvent water
Daily dose of 600-1200 mg (in doses of 200 mg) or in liquid form daily 9 ml (20 g of extract/100 ml)

e) Dry extract fresh leaves (DER 25-35:1), extraction solvent water
Daily dose 900 mg
Single dose up to 450 mg daily

In Germany exist also the following authorized products for TU:
Cynariae flos
3 expressed juices from fresh artichoke flower buds (1:0.6-0.9) on the market since 1978, expressed juice, for TU
Cynariae herba
1 fluid extract from artichoke herb (1:2.4-5.2), extraction solvent ethanol on the market since 1978, liquid, for TU

3. Non-Clinical Data

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

Constituents

Acids Phenolic, up to 2%. Caffeic acid, mono- and dicaffeoylquinic acid derivatives, e.g. cynarin (1.3-di-O-caffeoylquinic acids) and chlorogenic acid (mono derivatives).
Flavonoids 0.1-2%. Flavone glycosides e.g. luteolin-7-β-D-rutinoside (scolymoside), luteolin-7- β-D-glucoside and luteolin-4-β-D-glucoside.
Volatile oils Sesquiterpenes, β-selinene and caryophyllene (major); also eugenol, phenylacetaldehyde, decanal, oct-1-en-3-one, hex-1-en-3-one, and non-trans-2-enal.
Other constituents Phytosterols (taraxasterol and β-taraxasterol), tannins, glycolic and glyceric acids, sugars, inulin, enzymes including peroxidase, cynaropicrin and other sesquiterpene lactones

(grosheimin, cynarotriol etc). The root and fully developed fruits and flowers are devoid of cynaropicrin; highest content reported in young leaves.

Primary pharmacodynamics

Antioxidative, hepatoprotective and choleretic effects of artichoke leaf extracts as well as lipid-lowering and anti-atherogenicactivity with increased elimination of cholesterol and inhibition of hepatocellular de novo cholesterol biosynthesis have been demonstrated in various in vitro and in vivo test systems. Antisyspeptic effects are mainly attributed to increased choleresis [Kraft 1997; ESCOP 2003].

Choleretic effect

The following information was retrieved from ESCOP (2003), while similar results are reviewed by Hager (1992) Hager ROM 2004 [Hänsel 1992; Blaschek 2002].

- ***In vitro* experiments**

Antioxidant and cytoprotective effects

Antioxidant and cytoprotective effects of an artichoke leaf aqueous dry extract (4.5:1) were demonstrated in primary cultures of rat hepatocytes exposed to t-butyl hydroperoxide (t-BHP). When added simultaneously or prior to t-BHP, the extract inhibited lipid peroxidation in a concentration-dependent manner down to 0.001 mg/ml [Gebhardt 1997i; 1997ii]. Several characteristic polyphenolic constituents of artichoke leaf were effective in reducing t-BHP- induced melondialdehyde production EC_{50} values were 7, 8.1, 12.5, 15.2 and 28 µg/ml for luteolin caffeic acid, chlorogenic acid, cynarin and luteolin-7-glucoside respectively. The extract also prevented loss of intracellular glutathione by t-BHP [Gebhardt 1995i, 1996, 1997i, 1997ii; Gebhardt et al. 1998]. The effect of an artichoke leaf aqueous dry extract (4.5:1) on free radical production was also studied in human polymorphonuclear cells was tasted by flow cytometry using phorbol 12-myristate-13-acetate as the stimulant. The extract strongly inhibited the generation of reactive oxygen species with an EC_{50} of 0.23 µg/ml [Perez-Garcia et al. 2000].
Cynarin and caffeic acid showed significant cytoprotective activity ($p<0.01$ at 1 mg/ml) against carbon tetrachloride in isolated rat hepatocytes, reducing leakage of the liver anzymes glutamine oxaloacetic transaminase and glutamic pyrovic transaminase [Adzet et al. 1987]. Artichoke leaf aqueous dry extract at t-20 µg/ml retaded Cu^{2+}-mediated oxidation of human low density lipoproteine (LDL) in a dose –depended manner: the effect was attributed in part to luteolin 7-glucoside (as well as caffeoylquinic acids) [Brown &Rice-Evans 1990].
An aqueous dried extract (9:2) of the leaves was studied in human leukocytes to assess activity against oxidative stress. The extract (median effective concentration 0.23 µg/ml) produced a concentrationdependent inhibition of oxidative stress when cells were stimulated with agents that generate reactive oxygen species: hydrogen peroxide, phorbol- 12-myristate-13-acetate and *N*-formyl-methionyl-leucyl-phenylalanine. Cynarin, caffeic acid, chlorogenic acid and luteolin, constituents of artichoke leaf extracts, also showed a concentration-dependent inhibitory activity in the above models, contributing to the antioxidant activity of the extract in human neutrophils [Pérez- García 2000].

A study measured the effects of aqueous and ethanol extracts of the leaves on intracellular oxidative stress stimulated by inflammatory mediators, tumour necrosis factor alpha and oxidized low-density lipoprotein (ox-LDL) in endothelial cells and monocytes. Both extracts inhibited basal and stimulated reactive oxygen species production in endothelial cells and monocytes, in a dose-dependent manner. In endothelial cells, the ethanol extract (50.0 µg/ml) significantly reduced ox-LDL-induced intracellular reactive oxygen species production by 60% ($p<0.001$) and the aqueous extract (50 µg/ml) reduced ox-LDL-induced intracellular reactive oxygen species production by 43% ($p<0.01$). The ethanol extract

(50 µg/ml) reduced ox- LDL-induced intracellular reactive oxygen species production in monocytes by 76% (p<0.01). Effective concentrations of 25–100 µg/ml were well below the cytotoxic levels of the extracts which started at 1.0 mg/ml as assessed by lactate dehydrogenase leakage and trypan blue exclusion [Zapolska-Downar et al. 2002].

The flavonoids from artichoke (*Cynara scolymus* L.) have been studied in human endothelial cells for their up-regulate endothelial-type nitric-oxide synthase gene expression by [Li et al. 2004] while the phenolic compounds of the plant have been further studied for such antioxidative activities [Wang et al. 2003] and several other products from artichoke extracts showed similar activities [Llorach et al. 2002]. A study by Cervellati et al. (2002), focused on the antioxidant effects of artichoke extract in cultured blood vessel cells and reported that the extract demonstrated "marked protective properties against oxidative stress induced by inflammatory mediators". Artichoke's antioxidant properties were also confirmed in others studies that focused on human cells under various induced oxidative stresses [Jimenez-Escrig et al. 2003; Sarawek et al. 2008]. The water leaf extract of the plant has assayed and referred to possess strong antioxidative, anti-inflammatory and antiproliferative properties [Trouillas et al. 2003]. Antioxidative activities have been reported from Cynara extracts also from [Li et al. 2004; Stoev SD et al. 2004; Jimenez-Escrig et al. 2003; Wang et al. 2003; Llorach et al. 2002; and Cervellati et al. 2002].

Antiatherosclerotic and antihypercholesterolaemic activities

Artichoke leaf aqueous dry extract (4.5:1) inhibited the biosynthesis of cholesterol from ^{14}C-acetate in primary cultured rat hepatocytes in a concentrations of 0.007-0.1 mg/ml produced moderate I inhibition of about 20% at 1 mg/ml the inhibition was about 80% [Gebhardt 1995ii, 1998]. At 50-100 µg/ml, caffeic acid and cynarin produced negligible inhibition chlorogenic acid 10-15% and cynaroside (luteolin 7-glucoside) 19-22% but luteolin 51-63% [Gebhardt 1998]. When cynaroside was incubated with β-glucosidase, maximum inhibition of 50-60% was observed with an EC_{50} of approx. 30 Mµ. In human hepatic (HepG2) cells the maximum response of luteolin was more than 80% and the EC_{50} value was slightly higher. It was concluded that luteolin (a minor constituent) and indirectly its glucoside, cynaroside, seem to be mainly responsible for the inhibition of hepatic biosynthesis of cholesterol by artichoke leaf extracts [Gebhardt 1997, 1998]. Subsequently it was demonstrated that artichoke extracts inhibit cholesterol biosynthesis from. ^{14}C-acetate in primary cultured rat hepatocytes, inhibition in human hepatic (HepG2) cells in weak unless they have been pre-treated with β-glucosidase. This was explained by the fact the rat hepatocytes contain more endogenous β-glucosidase, enabling release of luteolin from its glucoside, cynaroside. Since β-glucosidase is present in the intestinal tract and in the liver, release of luteolin fron cynaroside may occur in the human body [Gebhardt & Hanika 1999; Gebhardt 2001, 2002i, 2002ii; Brown & Rice Evans JE. et al. 1990; Fritsche et al. 2002].
Cynara scolymus is thought among the herbs dealing with serum cholesterol reduction [Thomson Coon et al. 2002, 2003], while it has been recently referred in the literature the activity of artichoke juice which improves endothelial function in hyperlipidaemia [Lupattelli et al. 2004].

Hepatobiliary effects

In vitro an artichoke leaf aqueous dry extract enhanced the secretion of biliary substances in bile canaliculi reformed in primary cultures of hepatocytes. A cholestatic effect induced in the cultures by lithocholate was inhibited by the extract [Gebhardt 1996]. The effect of pressed juice (sap) from fresh artichoke activity was investigated in isolated perfuse rat liver. Pressed juice, undiluted and diluted 1:3 and 1:5, produced dose-dependent increase in bile flow of up to 150%, 125% and 112% respectively detectable 20 minutes after addition and reaching maximum value 10 minutes later. Bile acid production remained almost unchanged [Matuschowski et al. 1997]. By testing fractions of present

juice, it was shown that phenolic constituents were mainly responsible for the choleric action the strongest effects on both choleresis and bile acid production being exerted by mono-and dicaffeoylquinic acids. In further experiments with isolated perfuse rat liver a different pressed juice (from fresh artichoke flower buds) produced a comparable increase in bile flow and increased bile acid excretion by up to 128%. In contrast dried pressed juice (16:1 from flower buds) and dry aqueous extract (4:1) from artichoke leaf increase bile flow without significantly increasing bile acid secretion and no correlation with the content of caffeoylquinic acids was evident.

Antihepatotoxic activity

The effects of an aqueous extract of the leaves on taurolithocholate-induced cholestatic bile canalicular membrane distortions were studied in primary cultured rat hepatocytes using electron microscopy. Artichoke extracts at concentrations between 0.08 and 0.5 mg/ml were able to prevent the formation of canalicular membrane transformations in a dosedependent manner when added simultaneously with the bile acid. However prevention also occurred when the hepatocytes were preincubated with the extracts, indicating that absorption of the bile acid to components of the extracts was not involved [Gebhardt 2002]. The hepatoprotective activity of cynarin against carbon tetrachloride (CCl4)-induced toxicity in isolated rat hepatocytes was compared with other phenolic compounds. Only cynarin and, to a lesser extent, caffeic acid showed a cytoprotective effect [Adzet 1987]. Treatment of rats with three consecutive doses of 500.0 mg/kg bw of an extract of the crude drug, administered by gavage 48, 24 and 1 h before CCl4 intoxication, produced a significant decrease in glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase (also known as alanine aminotransferase or ALT), direct bilirubin and glutathione levels, thus indicating a reduction in the potential for hepatotoxicity [Adzet et al. 1987]. Primary cultures of rat hepatocytes exposed to *tert*-butyl hydroperoxide were used for characterizing the antioxidative and hepatoprotective potential of an aqueous extract of the crude drug and some selected constituents. Addition of *tert*-butyl hydroperoxide to the culture media resulted in enhanced lipid peroxidation as measured by the production of malondialdehyde and enhanced cytotoxicity detected by leakage of lactate dehydrogenase. The extract added prior to or simultaneously with *tert*-butyl hydroperoxide reduced both phenomena with a median effective concentration (EC50) of 95.0 and 12.0 µg leaf powder/ml respectively. Furthermore, the aqueous extract prevented the loss of intracellular glutathione caused by *tert*-butyl hydroperoxide. Several polyphenolic and flavonoid constituents of the extract were found to reduce malondialdehyde production. The median effective concentration values were 8.1, 12.5, 15.2 and 28 µg/ml for caffeic acid, chlorogenic acid, cynarin and cynaroside, respectively [Gebhardt and Fausel 1997]. Primary rat hepatocyte cultures exposed to *tert*-butyl hydroperoxide or cumene hydroperoxide were used to assess the antioxidative and protective potential of aqueous extracts of the leaves. Both hydroperoxides stimulated the production of malondialdehyde, particularly when the cells were pretreated with diethylmaleate in order to diminish the level of cellular glutathione. Addition of the extract did not affect basal malondialdehyde production, but prevented the hydroperoxide-induced increase of malondialdehyde formation in a concentration-dependent manner when presented simultaneously with or prior to the peroxides. The effective concentrations were as low as 0.001 mg/ml [Gebhardt 1997]. The liver Protective Actions of artichoke have been also tested and reported by [Maros T et al. 1966; Aktay G et al. 2000; Speroni E et al. 2003].

Gastrointestinal effects

The antispasmodic activity of several fractions from artichoke and cynaropicrin as well with other Brazilian traditionally used medicinal plants, on guinea-pig ileum has been demonstrated by [Emendorfer et al. 2005i, 2005ii].

Antimicrobial effects

The antibacterial and antifungal activities of artichoke extracts as well as of their phenolic compounds have been assayed [Zhu XF et al. 2004, 2005; Yang B et al. 2005; Stoev SD et al. 2004].

- ***In vivo* experiments**

Hepatobiliary and hepatoprotective affects

Chlorogenic acid administered orally to rats at 5-40 mg/kg body weight significantly stimulated choleresis (70%) and peristaltic activity (40%) in a concentration depended manner. A dose-depended increase in bile flow of up to 95% and an increase in biliary-excreted cholesterol were observed following a single intravenous administration of cynarin (7-166 mg/kg body weight) in the bile fistula rat model. Choleresis was still observed 4 hours after administration of 100 or 166 mg/kg body weight [Preziosi 1956, 1958, 1959, 1960].

A deproteinized aqueous extract of artichoke leaf, administrated orally to partially hepatectomized rats at 0.5 ml/animal daily for 21 days, significantly increased liver tissues regeneration as measured by residual liver weight, mitotic index and percentage of dinucleated liver cells [Maros et al. 1966]. In further experiments using the same methodology, the deproteinized extract accelerated the increase in liver weight, induced pronounced hypereamia and increased the percentage of binuclear hepatocytes and the content of ribonucleic acid in liver cells [Maros et al. 1968].

Intraperitoneal administration of a purified acid-rich, butanolic extract of artichoke leaf at 10 mg/kg protects mice against toxicity induced by ethanol: the LD_{50} for treated mice was 6.8 g ethanol/kg compared to 5.6 g ethanol/kg for the control group. The effect of the artichoke extract could be reproduced by administration of a mixture of citric, malic, succinic and hydroxymethylecrylic acids (2.5 mg/kg: LD_{50} of 7.1 g ethanol/kg) [Mortier et al. 1976].

Two hydroethanolic extracts of fresh artichoke [Bombardelli et al. 1977] were administered *i.p* to groups of rats: a total extract (19% caffeoylquinic acids, 200 mg/kg body weight) and a purified extract enriched in phenolic compounds (46% caffeoylquinicacids, 25 mg/kg body weight). Though bile duct cannulation it was shown that both extracts stimulated choleresis significantly increasing the bile dry residue and the total cholate secretion ($p<0.05$) [Lietti 1977]. The same extracts administered orally (400 mg/kg body weight of total extract or 200mg/kg of purified extract) increased gastrointestinal propulsion in rats by 11% and 14% respectively ($p<0.05$).
An aqueous extract of artichoke leaf (2.2% caffeoylquinic acids, 0.9% luteolin 7-glucoside) administered orally to rats at 500 mg/kg body weight 48 hours, 24 hours and 1 hours before inducing liver intoxication with carbon tetrachloride , improved liver function as measured by decreased levels of bilirubin glutathione and liver enzymes [Adzet et al. 1987].
In bile duct cannulated rats an undefined artichoke leaf fluid extract (0.45 mg/kg body weight) administered *i.p.* produced increases of 32% in bile flow and 495 in bile acid concentration respectively [Saenz Rodriguez et al. 2002].

Two aqueous alcoholic extracts of the fresh leaves (total extract containing 19% caffeoylquinic acids, at a dose of 200.0 mg/kg bw and a semipurified extract containing 46% caffeoylquinic acids, at a dose of 25.0 mg/kg bw) were assessed in rats. Intraperitoneal administration stimulated choleresis, and significantly increased bile dry residue and total cholate secretion ($p<0.05$). Intragastric administration of the same extracts (400.0 mg/kg bw, total extract and 200.0 mg/kg bw of the semipurified extract) also increased gastrointestinal motility by 11% and 14%, respectively ($p<0.05$) [Lietti 1977].
The effects of an extract of the crude drug on bile flow and the formation of bile compounds in anaesthetized rats after acute administration and repeated oral administration (twice a day for 7 consecutive days) were studied. A significant increase in bile flow was observed after acute treatment

with the extract as well as after repeated administration. The choleretic effects of the extract were similar to those of the reference compound dehydrocholic acid. Total bile acids, cholesterol and phospholipid were determined by enzymatic assays. At the highest dose (400.0 mg/kg bw), a significant increase was observed after single and repeated administration ($p<0.01$) [Saınz Rodriguez et al. 2002].
The choleretic effects of four extracts of the leaves (not described) were assessed in vivo in a study in rats. Extracts 1, 2 and 4 did not show significant choleretic activity at a dose of 1.0 and 2.0 g/kg bw. Extract 3, however, was found to induce an increase of bile flow, which was gradual and sustained. Cynarin and chlorogenic acid, administered as pure compounds, did not show choleretic activity at any of the doses tested and neither of them decreased the malondialdehyde content in liver [Speroni et al. 2003].
Treatment of rats with three consecutive doses of 500.0 mg/kg bw of an extract of the crude drug, administered by gavage 48, 24 and 1 h before CCl4 intoxication, produced a significant decrease in glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase (also known as alanine aminotransferase or ALT), direct bilirubin and glutathione levels, thus indicating a reduction in the potential for hepatotoxicity [Adzet et al. 1987].

Lipid-lowering and anti-atherogenic effects

Powdered artichoke aerial parts, administered orally at 110 mg/kg body weight for 120 days to rats fed on an atherogenic diet, lowered increases in serum and liver cholesterol and prevented the formation of atherosclerotic plaques [Samochowiec 1959, 1962i, 1962ii]. After 60 days on an atherogenic diet, 110 mg/kg body weight of powdered artichoke aerial parts, administered orally to rats daily for 10 weeks, lowered serum cholesterol by 36% compared to 25% in the control group [Samochowiec 1962iii].
Two hydroethanolic extracts of fresh artichoke a total extract (19% caffeoylquinic acids 100 mg/kg body weight) and a purified extract (46% caffeoylquinic acids 25 mg/kg body weight), administered intraoeritoneally to rats four times over a 28-hours period after inducing hyperlipidaemia with Triton WR1339, decreased total cholesterol by 14% and 45% and triglycerides by 18% and 33% respectively [Saenz Rodriguez 2002].

Cynarin (100 and 200 mg/kg body weight) administered intravenously to rabbits, lowered serum cholesterol by about 20% Triton WR 1339-induced hypercholesterolaemia. In rats was significantly lowered (p=0.05-0.02) by cynarin after intraperitoneal administration (2*200 mg/kg body weight) [Preziosi 1958]. Cynarin injected at 30 mg/kg /day significantly lowered the increases in total serum lipids ($p<0.05$) and esterified serum fatty acids ($p<0.001$) induced in rats by giving them 15% ethanol instead of drinking water for 20 days [Samochowiec 1971].

Other effects

The preventive effect of hydroalcoholic *Cynara scolymus* extract on appearance of type 1 diabetes mellitus in male rats has been studied by [Mahmoodabadi et al. 2007].

3.1.1. Conclusions on traditional use

Based on information obtained from Member states and data retrieved from handbooks it can be concluded that the following extracts and uses of artichoke leaves fulfil the criteria for traditional use:

- Comminuted or powdered dried leaves for herbal tea
- Powdered leaves
- Dry extract (DER 3.8-7.5:1) extraction solvent water

- Soft extract fresh leave (DER 15-30:1), extraction solvent water
- Dry extract fresh leaves (DER 25-35:1), extraction solvent water

Safety pharmacology

No information except toxicity data presented under 3.2 below

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

After two days of a low-polyphenol diet to 10 healthy volunteers, they have been treated with 3 x 320 mg of an artichole leaf aquaeus dry extract (4-6:1; caffeoylquinic acids 34.3 mg/g, flavonoids 5.6 mg/g) every 4 hours (at 0.4 and 8 hours). Phenolic derivatives present in the artichoke extract were not detected in the urine either as conjugates or aglycons; however b-glucuronidase treatment of urine revealed the presence of ferulic, isoferulic, dihydroferulic and vanillic acids as major metabolites of caffeoylquinic acids [Rechner et al. 2001].

In order to investigate potential inhibition or activation of cytochrome P450 (CYP) isoforms by extracts of popular herbal drugs in a screening approach to predict impending interactions [Hilgendorf & Döppenschmidt 2003]. Methods: Human liver microsomes were employed for screening, using 8 standard subtype-specific CYP substrates. The testing included ethanolic extracts of *Serenoa repens* (*Sabal serrulata*, SR), *Hypericum perforatum* (HY), *Harpagophytum procumbens* (HP), *Piper methysticum* (Kava, KA) and *Cynara scolymus* (CY). Organic solvent was removed for testing. At extract concentrations derived from dose recommendations provided by German Authorities (Commission E), differential effects of the various plants were observed. The effects ranged from strong activation of enzymatic turnover, i.e. HP: 272 ± 12% ($p<0.001$) of control (mean ± SD, n=3) for CYP2E1 to almost complete abolition of activity, e.g. for HY: 3 ± 0.7% ($p<0.0001$) for 3A4 and 0% ($p<0.0001$) for 2C8. Overall, most pronounced inhibitory effects were observed for HY (0% ($p<0.0001$) to 73 ± 2% ($p<0.001$)) and KA (5 ± 4% ($p<0.001$) to 92 ± 9% (not significant)), while HP exhibited inhibitory (2C19:59 ± 1% ($p<0.0001$)) as well as stimulatory effects (2E1: see above). The extracts of herbal drugs broadly used in Germany accomplish inhibition as well as activation of human CYP activity *in vitro*. Detailed results concerning *Cynara* are not presented.

[Wittemer et al. 2002, 2005]. A variety of mono- and dicaffeoylquinic acids (CCA) and flavonoids have been described as the main constituents of artichoke (*Cynara scolymus*) extract. Among them chlorogenic acid, cynarine and the flavonoid luteolin-7-O-glucoside (cynaroside) are the most prominent. A wide range of in-vitro activities of artichoke have been established, e.g. antioxidative and choleretic actions and lipid reduction. Here, the metabolism and disposition of 2 different leaf extracts (extract A: (CCA 28.9%, flavonoids 8.8%; extract B: CCA 6.2%, flavonoids 0.9%) were investigated in healthy volunteers enroled in a 2-way crossover study. Neither the mono- and dicaffeoylquinic acids nor the flavonoids present in the extracts were detected in human plasma as their original moieties. No safety relevant information is provided, no change of the safety profile.

[Wittemer & Veit 2003]. Artichoke leaf extract (water>80°C, DER 4-6:1) Hepar SL®. A validated method was developed for the simultaneous determination of the hydroxycinnamates caffeic (CA), dihydrocaffeic (DHCA), ferulic (FA), dihydroferulic (DHFA), and isoferulic acid (IFA) and the flavonoid luteolin (LUT) in human plasma as metabolites derived from artichoke leaf extract. The method involves sample preparation followed by separation using high-performance liquid chromatography on reversed-phase material with a polar end capping (Aqua-C (18), 250Î4.6 mm). Selectivity and sensitivity towards the target compounds were achieved by electrochemical array detection (CoulArray). Calibration curves were constructed in the ranges 2.1-51.7 ng/mL (CA), 2.0-76.7 ng/mL

(DHCA), 2.2-53.7 ng/mL (FA), 2.1-79.2 ng/mL (DHFA), 1.1-52.6 ng/mL (IFA) and 2.1-258.6 ng/mL (LUT). Values for within-day and between-day precision and accuracy were in accordance with the international guidelines for validation of bioanalytical methods. It is concluded that this newly developed method is appropriate for analysing samples from bioavailability and pharmacokinetic studies after oral administration of artichoke leaf extract. The authors describe a validated HPLC method for the determination of prominent artichoke leaf extract metabolites in human plasma. The availability of this method may stimulate further systematic investigation into the metabolic fate of artichoke leaf constituents.

[Wittemer et al. 2005]. Artichoke leaf extract (water>80°C, DER 4-6:1) Hepar SL®. In order to get more detailed information about absorption, metabolism and disposition of ALE, two different extracts were administered to 14 healthy volunteers in a crossover study. Each subject received doses of both extracts. Extract A) administered dose: caffeoylquinic acids equivalent to 107.0 mg caffeic acid and luteolin glycosides equivalent to 14.4 mg luteolin. Extract B) administered dose: caffeoylquinic acids equivalent to 153.8 mg caffeic acid and luteolin glycosides equivalent to 35.2 mg luteolin. Urine and plasma analysis were performed by a validated HPLC method using 12-channel coulometric array detection. In human plasma or urine none of the genuine target extract constituents could be detected. However, caffeic acid (CA), its methylated derivates ferulic acid (FA) and isoferulic acid (IFA) and the hydrogenation products dihydrocaffeic acid (DHCA) and dihydroferulic acid (DHFA) were identified as metabolites derived from caffeoylquinic acids. Except of DHFA all of these compounds were present as sulfates or glucuronides. Peak plasma concentrations of total CA, FA and IFA were reached within 1 h and declined over 24 h showing almost biphasic profiles. In contrast maximum concentrations for total DHCA and DHFA were observed only after 6-7 h, indicating two different metabolic pathways for caffeoylquinic acids. Luteolin administered as glucoside was recovered from plasma and urine only as sulfate or glucuronide but neither in form of genuine glucosides nor as free luteolin. Peak plasma concentrations were reached rapidly within 0.5 h. The elimination showed a biphasic profile. This well designed pharmacokinetic study reveals interesting insights into the fact of *Cynara* leaf extract constituents after oral administration. However, at the presence status these data are of no relevance for the risk benefit ratio of artichoke leaf preparations. No change of the safety profile.

Absorption and metabolism of bioactive molecules after oral consumption of cooked edible heads of *Cynara scolymus* L. (cultivar Violetto di Provenza) in human subjects: a pilot study **[Azzini et al. 2007].**

The current growing interest for natural antioxidants has led to a renewed scientific attention for artichoke, due not only to its nutritional value, but, overall, to its polyphenolic content, showing strong antioxidant properties. The major constituents of artichoke extracts are hydroxycinnamic acids such as chlorogenic acid, dicaffeoylquinic acids caffeic acid and ferulic acid, and flavonoids such as luteolin and apigenin glycosides. *In vitro* studies, using cultured rat hepatocytes, have shown its hepatoprotective functions and *in vivo* studies have shown the inhibition of cholesterol biosynthesis in human subjects. Several studies have shown the effect on animal models of artichoke extracts, while information on human bioavailability and metabolism of hydroxycinnamates derivatives is still lacking. Results showed a plasma maximum concentration of 6·4 (sd 1.8) ng/ml for chlorogenic acid after 1 h and its disappearance within 2 h ($P<0·05$). Peak plasma concentrations of 19·5 (sd6·9) ng/ml for total caffeic acid were reached within 1 h, while ferulic acid plasma concentrations showed a biphasic profile with 6·4 (sd1·5) ng/ml and 8·4 (sd4·6) ng/ml within 1 h and after 8 h respectively. The authors observed a significant increase of dihydrocaffeic acid and dihydroferulic acid total levels after 8 h ($P<0·05$). No circulating plasma levels of luteolin and apigenin were present. The study confirms the bioavailability of metabolites of hydroxycinnamic acids after ingestion of cooked edible *Cynara scolymus* L. (cultivar Violetto di Provenza). The study shows the absorption pathways of hydroxycinnamic acids after consumption of edible cooked artichoke in human subjects. No safety relevant information is given, no change of the safety profile.

3.2.1. Assessor's overall conclusions on pharmacokinetics

Six different studies provide information on pharmakinetic properties after the administration of water extracts of leaf artichoke to healthy volunteers. In all cases none of the constituents of the extracts have been detected in human plasma or urine. Caffeic acid its methylated derivatives ferulic and isoferulic acids and the hydrogenated products dihydrocaffeic and dihydroferulic acid were identified as metabolites from caffeoylquinic acids; except for dihydroferulic acid all of the other compounds were found as sulfates or glucuronides. The luteolin administered as glucosides was recovered from plasma and urine only as sulfate or glucuronide.

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

Acute toxicity

Herbal preparations. The oral LD_{30} and interperitoneal LD_{10} in male rats of hydroalcoholic total extract of artichoke leaf (19% caffeoylquinic acids) were determined as >2000 mg/kg and >1000 mg/kg body weight respectively. With a purified extract (46% caffeoylquinic acids) the oral LD_{40} and intraperitoneal LD_{50} were 2000 mg/kg and 265 mg/kg respectively [Bombardelli et al. 1977].

In primary cultures of rat hepatocytes no cytotoxic effects from an artichoke leaf aqueous dry extract (4.5:1) were observed at concentrations of up to 1mg per ml of culture medium [Gebhardt 1997, 1995i, 1995ii, 1996].

Cynarin. The LD_{50} of cynarin in mice was determined as 1900 mg/kg body weight. Upon administration intraperitoneally to rats at 800 mg/kg or inravenously to rabbits at 1000 mg/kg/hour, cynarin produced no apparent side effects or signs or toxicity [Preziosi 1958].

Sub-acute toxicity

Cynarin. Cynarin administered intraperitoneally to adult rats for 15 days at doses of 50-400 mg/kg/day produced no macroscopic or histological abnormalities or changes in blood parameters [Preziosi 1958].

The oral and intraperitoneal median lethal doses of a hydroalcoholic extract of the leaves in rats were 2.0 g/kg and 1.0 g/kg bw, respectively [Lietti 1977]. External application of a leaf extract to the skin of white rats, at doses of 1.0–3.0 g/kg bw for 21 days, did not produce any toxic effects or have any cumulative effects on haematological parameters or the biochemistry of rats. No skin-irritating or eye-irritating effects were observed in guinea-pigs [Holtmann et al. 2003; WHO monographs 2009].

Chronic oral toxicity

Cynarin. Cynarin administered intraperitoneally to rats daily for 40 days at 50-400 mg/kg/day caused no changes in overall condition or blood parameters. Increased body weight and significantly increased kidney weight ($p<0.01$) were observed only in animals treated with 400 mg/kg and significantly increased liver weight ($p<0.01$) in animals treated with 100-400 mg/kg. Some rats treated with cynarin at 100,200 and 400 mg/kg showed irrigative- degenerative changes in liver and kidneys most evident in rats receiving 400 mg. Young rabbits treated intravenously with cynarin at 50 mg/kg/day for 30 days remained in good condition with no evidence of toxicity from extensive haematological and histological investigation [Preziosi 1958].

Caffeic acid (and chlorogenic acid)

International Agency for Research on Cancer (IARC) has evaluated caffeic acid for its potential carcinogenicity (IARC Monographs Volume 56). After dietary administration of high doses of caffeic acid (intakes 2-3 g/kg bw), there were high incidences of forestomach hyperplasia and renal tubular-cell hyperplasia in mice of both sexes and an increase in forestomach squamous-cell papillomas and carcinomas in male mice and renal-cell adenomas in female mice. In rats, a high dietary intake (about 07-0.8 g/kg) of caffeic acid produced squamous-cell papillomas and carcinomas of the forestomach in animals of each sex and a few renal-cell adenomas in males.
Oral administration of caffeic acid in combination with known carcinogens resulted in enhancing or inhibiting effects depending upon the carcinogen and the time of administration. The IARC (1993) working group decided that caffeic acid is possibly carcinogenic to humans (Group 2B), because there is sufficient evidence in experimental animals for the carcinogenicity of caffeic acid. No data were available on the carcinogenicity of caffeic acid to humans (it should be noted that the recent review on coffee carcinogenicity came to the conclusion, that caffeine drinking is generally protective as regards to cancer [Nkondjock 2009]). The Working Group noted that humans and experimental animals metabolize caffeic acid to the same metabolites and hydrolyse chlorogenic acid to caffeic acid. In vitro and in vivo genotoxicity tests were generally negative, except increased gene mutations and chromosomal aberrations in cultured rodent cells at high exposures; no evaluation was made regarding these positive findings.

Genotoxicity

Several studies on mutagenicity/ genotoxicity of *Cynara scolymus* are available.

Antimutagenic potential of *Cynara scolymus*.

[Križková et al. 2004]. Three different triterpenoid saponins (cynarasaponins) from involucral bracts of Artichoke were isolated and their antimutagenic effect was assessed. Using spectrophotometric method it was shown that all three substances possess very good absorptive capability. The antimutagenic effect of these substances was estimated against acridine orange (AO)- and ofloxacin-induced damage of chloroplast DNA in Euglena gracilis assay. These cynarasaponins were experimentally confirmed to exhibit different, statistically significant activity in reducing damage of chloroplast DNA of the flagellate E. gracilis induced by AO and ofloxacin (p_t<0.05-0.01). These findings suggest that the antimutagenic effect of these compounds against AO-induced chloroplast DNA impairment could be a result of their absorptive capacity. As far as ofloxacin is concerned, a possible mechanism of the reduction of the chloroplast DNA lesion was not elucidated so far.

[Miadokova et al. 2006]. The potential antimutagenic activity of ECC was assayed by a test on sex-linked recessive lethal mutations detection in Drosophila melanogaster males treated with ethylmethane sulfonate (EMS). The possible enhancement of cytostatic/cytotoxic effect of cis-Pt by ECC was evaluated in the cell revitalization assay by measuring cell viability via Trypan blue exclusive assay using mouse leukemia cells L1210. Results: EMS was both toxic and genotoxic in D. melanogaster males. It statistically significantly increased the frequency of sex-linked recessive lethal mutations in comparison to the negative control. Furthermore, ECC statistically significantly reduced the genotoxic effect of EMS. It acted in a desmutagenic manner via EMS inactivation. In the cell revitalization assay, ECC enhanced the cytotoxic/cytostatic effect of cis-Pt. The therapeutic potential of ECC was established on the basis of statistically significantly lowered recovery of cis-Pt pre-treated mouse leukemia cells in the presence of ECC. Concluisons: The results imply that the extract isolated from artichoke C. cardunculus L. has marked beneficial activities (antimutagenic and therapeutic effect enhancing) and its potential biomedical application in the combination therapy of cancer and some neurodegenerative diseases may be suggested.

[Miadokova et al. 2008]. The extract of artichoke *C. cardunculus* L. (CCE) was investigated for its potential antigenotoxic and antioxidant effects using four experimental model systems. In the *Saccharomyces cerevisiae* mutagenicity/antimutagenicity assay, CCE significantly reduced the frequency of 4-nitroquinoline-N-oxide- induced revertants at the ilv1 locus and mitotic gene convertants at the trp5 locus in the diploid *Saccharomyces cerevisiae* tester strain D7. In the simultaneous toxicity and clastogenicity/anticlastogenicity assay, it exerted an anticlastogenic effect against N-nitroso-N'-methylurea-induced clastogenicity in the plant species *Vicia sativa* L. On the contrary, despite CCE not being mutagenic itself, in the preincubation Ames assay with metabolic activation, it significantly increased the mutagenic effect of 2-aminofluorene in the bacterial strain *Salmonella typhimurium* TA98. In the 1.1-diphenyl-2- picrylhydrazyl (DPPH) free radical scavenging assay, CCE exhibited considerable antioxidant activity. The SC_{50} value representing 0.0054% CCE corresponds to an antioxidant activity of 216.8 µM ascorbic acid which was used as a reference compound. Although the mechanism of CCE action still remains to be elucidated, different possible mechanisms are probably involved in the CCE antigenotoxic effects. It could be concluded that CCE is of particular interest as a suitable candidate for an effective chemopreventive agent.

[Edenharder et al. 2003]. After *in vivo* mouse bone marrow micronucleus assay, homogenates of artichoke among other vegetables and fruits reduced induction of micronuclei by benzo[a]pyrene (BaP) by 43-50%. The flavonoids quercetin and its glucoside isoquercitrin, administered orally in doses of 0.03mmol/kg body weight simultaneously with intraperitoneally given BaP, reduced the number of micronuclei in polychromatic erythrocytes of the bone marrow of mice by 73 and 33%. Ten-fold higher concentrations, however, reversed the effects with a particular strong increase observed with isoquercitrin (+109%; quercetin: +16%).

The genotoxic effects of flavonoid constituents present in the crude drug (quercetin and luteolin) were assessed in two short-term bacterial assays. In *Salmonella typhimurium* (strains TA1538 uvrB- and TA1978 uvrB+) the flavonoids did not induce damage in the DNA as recognized by UvrABC nuclease. Results of the SOS-chromotest in *Escherichia coli* K-12 strains PQ37 and PQ243 indicated that the flavonoids only weakly induced the SOS system [Czeczot and Kusztelak 1993].

Teratogenicity

No data available.

3.3.1. Assessor's overall conclusions on toxicology

Various extracts of Cynara scolymus seemed to be of low acute or subchronic toxicity potential. It should be also noted that all carcinogenicity (and other associated) studies available are not up to current standards. The current consensus is that forestomach tumours in rodents after high irritating exposures are less relevant for human risk assessment [Proctor et al. 2007]. The same opinion applies also to rodent renal adenomas. No mutagenicity or genotoxicity studies were available. There are no data on teratogenicity or carcinogenicity. Antimutagenic potential of artichoke has been reported but they seem incomplete.

3.4. Overall conclusions on non-clinical data

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

Primary pharmacodynamics

Antioxidative, hepatoprotective and choleretic effects of artichoke leaf extracts as well as lipid-lowering and anti-atherogenicactivity with increased elimination of cholesterol and inhibition of hepatocellular de novo cholesterol biosynthesis have been demonstrated in various in vitro and in vivo test systems. Antidyspeptic effects are mainly attributed to increased choleresis [Kraft 1997; ESCOP 2003].

4.1.1.1. Assessor's overall conclusions on pharmacodynamics

At present, the mechanism of action of artichoke and its main compounds cannot be considered clarified.

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

Data on the pharmacokinetics of artichoke's constituents are not available.

4.2. Clinical Efficacy

4.2.1. Dose response studies

4.2.2. Clinical studies (case studies and clinical trials)

- **Blood lipid and cholesterol lowering effects**

[Petrowicz et al. 1997]. In a randomized double-blind, placebo-controlled study, the lipid-lowering effects of an artichoke leaf aqueous dry extract standardized dry aqueous extract (4.5-5:1) were investigated in 44 healthy volunteers over 12 weeks. The mean initial concentration were very low in both the verum (204.2 mg/dl, n=22) and placebo (203.0 mg/dl , n=22) groups in volunteers with initial cholesterol>230mg/dl(n_v-n_p=3), 640mg of extract three times daily significantly decreased concentration of total cholesterol (p=0.015) and triglycerides (p=0.01) compared to placebo in volunteers with initial cholesterol >220 mg/dl (n_v-n_p=5), serum cholesterol was not significantly different (p=0.14) after treatment with the extract compared to placebo : however a significant difference (p=0.012) could be detected for triglycerides. In volunteers with initial cholesterol >210 mg/dl (n_v=10,n_p=7), treatment with the extract led to a significant difference (p=0.022) for triglycerides compared to placebo.

[Wojcicki & Winter 1975]. Daily administration of 900mg of an artichoke extract with a maximum polyphenolic acids content of 5.5% to 10 industrial workers with long term occupational exposure to carbon disulfide for 30days significantly lowered blood levels of cholesterol (p<0.02) free fatty acids , phospholipids and total lipids (p, 0.05).

[Wojcicki et al. 1981]. Decreases in cholesterol, triglycerides, three fatty acids, phospholipids and β-lipoproteins were observed in 30 healthy elderly subjects after daily administration for 6 weeks of 0.45 or 0.9 g of an undefined artichoke extract containing 0.09% or polyphenols.

[Wojcicki et al. 1982]. In a comparative study, 73 patients with primary hyper-triglyceridaemia resistant to treatment with clofibrate were treated daily for 1 month with an undefined artichoke extract(9 tablets , each containing 5 mg of polyphenolic acids , n=25) or with cynarin (0.75 g, n=28 or 1.5 g, n=20). The artichoke extract exerted significant total lipid-, triglyceride-, and phospholipids-lowering, effects in about 56% of the patients , whereas 0.75 g or 1.5 g of cynarin improved lipid parameters in 61% or 405 of the patients respectively.

[Heid 1991]. In an open study, 403 patients with functional gall bladder disorders were treated with an undefined artichoke extract (2 tablets twice daily, each containing 375 mg of extract standardized to 1% caffeoylquinic acids). After 4 weeks of treatment, complains such as nausea, stomach pains or loss of appetite had disappeared in more than 52% of patients and symptoms had improved in more than 80% of patients.

[Englisch et al. 2000]. In a multicentre, randomized, placebo-controlled, double- blind study, the effect of a fresh artichoke leaf aqueous dry extract (25-35:1) was investigated in 143 patients with hyperlipoproteinaemia (cholesterol >280 mg/dl) . Patients received either 1800 mg of artichoke extract (n=71) or placebo (n=72) daily as coated tablets for 6 weeks. In the verum group reductions of total cholesterol (18.5%) and LDL- cholesterol (22.9%) from baseline to end of treatment were significantly superior (p=0.0001) to those in the placebo group (8.6% and 6.3% respectively). The LDL/HDL ratio decreased by 20.2% in the artichoke extract group and 7.2% in the placebo group.

[Schmidel 2002]. Lowering of the cholesterol level by artichoke and fibre. A lowering of the cholesterol level by artichoke preparations have been known for a long time. In this study with 54 test patients at an average duration of about 24 days the effect of a standardized preparation (aqueous artichoke leaf extract 3.8-5.5:1) (Hepar-POS) was measured in comparison with placebo of fibre. The average lowering of cholesterol in all test patients with verum was 16.8% compared to 10.0% in all patients with placebo. This difference was statistically significant. An even stronger cholesterol lowering effect could be found tendentious with a simultaneous dose of fibre. The lowering of LDL is similar to that of total cholesterol. The LDL/HDL-quotient could be lowered in the verum and fibre groups while it rose slightly in the placebo group. Patients with flatulence obtained under verum a significant improvement on their troubles while the troubles remained unchanged under placebo. Under verum, no more dropouts or side effects than under placebo were found. The investigated extract was found to be effective in lipid lowering treatment. Adverse events/side effects: verum: hypersensitivity reactions [SOC: immune system disorders] n=1; placebo: flatulence [SOC: gastrointestinal disorders] n=1; further adverse events reported were nausea, headache, sleep disturbances and stomachache without any information whether they occurred in the verum or in the placebo group. No change of the safety profile.

[Lupatteli et al. 2004]. Artichoke juice improves endothelial function in hyperlipaemia. Artichoke extracts have been shown to produce various pharmacological effects, such as the inhibition of cholesterol biosynthesis and of LDL oxidation. Endothelial dysfunction represents the first stage of atherosclerotic disease; it is usually evaluated in humans by a noninvasive ultrasound method as brachial flow-mediated vasodilation (FMV) and by the determination of several humoral markers such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin. Aim of the study was to investigate the effects of dietary supplementation with artichoke leaf pressed juice on brachial FMV of hyperlipemics. The authors studied 18 moderately hyperlipemic patients (LDL cholesterol > 130 <200 mg/dl and/or triglycerides >150 <250 mg/dl) of both genders and 10 hyperlipemic patients, matched for age, sex and lipid parameters. All subjects were under isocaloric hypolipidic diet. A basal determination of serum lipids, soluble VCAM-1, ICAM-1, E-selectin and brachial FMV was performed. Thereafter patients were given 20 ml/die of frozen artichoke juice. The same parameters were repeated after 6 weeks. After artichoke treatment there was an increase of triglycerides (156 +/- 54 vs 165 +/- 76 mg/dL, p <0.05) and a reduction of total cholesterol (261 +/-

37 vs 244 +/- 38 mg/dL, p <0.05) and LDL cholesterol (174 +/- 31 vs 160 +/- 34 mg/dL, p <0.05). Controls showed a significant decrease in total and LDL cholesterol (respectively: 267 +/- 22 vs 249 +/- 20 mg/dL and 180 +/- 24 vs 164 +/- 23 mg/dL, both p <0.001). After artichoke there was a decrease in VCAM-1(1633 +/- 1293 vs 1139 +/- 883 ng/mL, p <0.05) and ICAM-1(477 +/- 123 vs 397 +/- 102 ng/mL, p <0.05), brachial FMV increased (3.3 +/- 2.7 vs 4.5 +/- 2.4%, p <0.01), while controls did not exhibit significant changes in VCAM-1, ICAM-1, E-selectin and brachial FMV. Univariate analysis showed that, in artichoke patients, changes of VCAM-1 and ICAM-1 were significantly related to changes in brachial FMV (respectively: r=-0.66 and r=-0.62; both p <0.05). In conclusion, artichoke dietary supplementation seems to positively modulate endothelial function in hypercholesterolemia. The vasodilatory effect of artichoke leaf pressed juice has been studied. Due to the small sample size the results have to be viewed as preliminary and need confirmation by further human studies. The target parameters assessed in this study are not directly related to approved indications of artichoke leaf preparations. Adverse events/side effects: not reported. No change of the safety profile.

[Bundy et al. 2008]. The objective of this trial was to assess the effect of artichoke leaf extract (ALE) on plasma lipid levels and general well-being in otherwise healthy adults with mild to moderate hypercholesterolemia. 131 adults were screened for total plasma cholesterol in the range 6.0-8.0 mmol/l, with 75 suitable volunteers randomised onto the trial. Volunteers consumed 1280 mg of a standardised artichoke leaf extract (ALE), or matched placebo, daily for 12 weeks. Plasma total cholesterol decreased in the treatment group by an average of 4.2% (from 7.16 (SD 0.62) mmol/l to 6.86 (SD 0.68) mmol/l) and increased in the control group by an average of 1.9% (6.90 (SD 0.49) mmol/l to 7.03 (0.61) mmol/l), the difference between groups being statistically significant (p=0.025). No significant differences between groups were observed for LDL cholesterol, HDL cholesterol or triglyceride levels. General well-being improved significantly in both the treatment (11%) and control groups (9%) with no significant differences between groups. In conclusion, ALE consumption resulted in a modest but favourable statistically significant difference in total cholesterol after 12 weeks. In comparison with a previous trial, it is suggested that the apparent positive health status of the study population may have contributed to the modesty of the observed response.

Assessor's comment: In conclusion, artichoke leaf extract consumption resulted in a modest but favourable statistically significant difference in total cholesterol after 12 weeks. In comparison with a previous trial, it is suggested that the apparent positive health status of the study population may have contributed to the modesty of the observed response.

- **Hepatobiliary effects including influence on choleresis**

[Kirschhoff et al. 1994]. In one double-blind placebo-controlled cross-over study, clinical trial, **20** male volunteers with acute or chronic metabolic disorders. The choleretic effect of a single dose was investigated. The group was separated in two randomized subgroups of 10, either 1.92 g of the extract (the contents of 6 proprietary capsules each containing 320 mg of extract plus excipients of a standardized dry aqueous extract (4.5-5:1) of artichoke leaf extract (Hepar SL forte, Seturner, Germany) in 50 ml water or a placebo of similar appearance was administered via an intraduodenal probe, the subject having empty stomach on test days. Monitoring of bile secretion was significantly higher (p<0.01) in the verum group: 127% higher 30 min after administration, 151% after 60 min. (the maximum effect) and 94% after 90 min result a after 120 min and 150 min were also significantly higher (p<0.05). Placebo treatment stimulated bile secretion to a lesser extent, with a maximum increase of 39% after 30 min. No adverse or relevant changes in laboratory safety parameters were observed.

[Kraft 1997]. An article by Kraft summarized various post-marketing surveillance studies conducted on patients with dyspepsia and/or diseases of the liver or bile duct. The studies included anywhere from **417 to 557** patients and treatment duration ranged from 4 to 6 weeks. Statistically significant

reduction of symptoms (e.g., abdominal pain, bloating, flatulence, and nausea) was reported for the surveillance studies referred to in this paper. Artichoke preparations were well tolerated (up to 95% of cases) with a low rate of side-effects.

- **Antidyspeptic and Gastrointestinal effects**

[Fintelmann 1996]. A multicentre open study with average treatment duration of 43.5 days was conducted in **553** patients with dyspeptic complaints. The daily dose was generally 3-6 capsules of artichoke leaf aqueous dry extract (3.8-5.5:1, 320 mg per capsule). Digestive complains declined in a clinically relevant and statistically significant manner within 6 weeks of treatment, the overall symptoms improved by about 71%. Compared to initial values, the subjective score reduction was approx. 66% for meteorism, 76% for abdominal pain, 82% for nausea and 88% for emesis. In subgroup of 302 patients, total cholesterol decreased by 11.5% and triglycerides by 12.5% while HDL-cholesterol showed a minimal rise of 2.3%. Global efficacy assessed by the physicians was excellent as good in 87% of cases.

[Fintelmann & Petrowicz 1998]. The same extract at a daily dosage of 3-6 capsules (320 mg per capsule) was evaluated in a 6-monthopen study of **203** patients with dyspeptic complains. After 21 weeks of treatment, the overall improvement in symptoms was 66% compared to initial values, e.g. vomiting by 84%, abdominal pain by 78%, nausea by 76%, flatulence by 70% and meteorism by 69%. Concentration of total blood cholesterol and triglycerides, determined tin 171 and 170 patients decreased by10.9% and 11.0% respectively. From determinations in **159** patients, LDL-cholesterol decreased by 1508% and HDL- cholesterol increased by 6.3%. Global efficacy assessed by the physicians was excellent or good in 85.7% of cases. No adverse reactions were reported.

[Marakis et al. 2002, 2003]. A recent post-marketing study indicated that high doses of standardised artichoke leaf extract (ALE) (water >80°, DER 4-6:1, min. 0.3% flavonoids) may reduce symptoms of dyspepsia. To substantial these findings, this study investigated the efficacy of a low-dose ALE on amelioration of dyspeptic symptoms and improvement of quality of life. The study was an open, dose-ranging postal study. Healthy patients with self-reported dyspepsia were recruited through the media. The Nepean Dyspepsia Index and the State-Trait Anxiety Inventory were completed at baseline and after 2 months of treatment with ALE, which was randomly allocated to volunteers as 320 or 640 mg daily. Of the **516** participants, 454 completed the study. In both dosage groups, compared with baseline, there was a significant reduction of all dyspeptic symptoms, with an average reduction of 40% in global dyspepsia score. However, there were no differences in the primary outcome measures between the two groups, although relief of state anxiety, a secondary outcome, was greater with the higher dosage (P=0.03). Health-related quality of life was significantly improved in both groups compared with baseline. The authors conclude that ALE shows promise to ameliorate upper gastro-intestinal symptoms and improve quality of life in otherwise healthy subjects suffering from dyspepsia.

Assessor's comment: The results of this open study add some evidence to the anyway well established use of artichoke leaf extract in functional dyspepsia. The relatively low doses which were found effective in this study are worth mentioning. However, as the study was uncontrolled the effectiveness of these low doses remains in question. Adverse event/side effects: constipation: n=2; loose stool: n=2; flatulence: n=1 [SOC: gastrointestinal disorders]. No change of the safety profile.

[Holtmann et al. 2003]. This study aimed to assess the efficacy of artichoke leaf extract (ALE) [(water > 80°C DER 4-6:1), Hepar SL capsules, 2x320 mg t.i.d], in the treatment of patients with functional dyspepsia (FD) and irritable bowel syndrome. In a double-blind, randomized placebo controlled, multicenter trial (RCT), of 6 weeks treatment, **247** patients with functional dyspepsia(ROME II criteria, but concomitant IBS symptoms, not dominating the clinical picture were allowed) were recruited and treated with either a commercial ALE LI 120 preparation (2x320 mg plant extract t.d.s.)

or a placebo. Patients with predominant reflux- or IBS-symptoms were excluded.The primary efficacy variable was the sum score of the patient's weekly rating of the overall change in dyspeptic symptoms (four-point scale). Secondary variables were the scores of each dyspeptic symptom and the quality of life (QOL) as assessed by the Nepean Dyspepsia Index (NDI). Two hundred and forty-seven patients were enrolled, and data from 244 patients (129 active treatments, 115 placebos) were suitable for inclusion in the statistical analysis (intention-to-treat). The overall symptom improvement over the 6 weeks of treatment was significantly greater with ALE than with the placebo (8.3 +/- 4.6, vs. 6.7 +/- 4.8, P < 0.01). Similarly, patients treated with ALE showed significantly greater improvement in the global quality-of-life scores (NDI) compared with the placebo-treated patients (41.1 +/- 47.6 vs. -24.8 +/- 35.6, P < 0.01). Safety parameters were comparable between both groups.

Assessor's comment: In accordance with the commonly accepted monographs of the Commission E. and ESCOP and earlier published clinical studies the artichoke leaf preparation was superior to placebo in the treatment of patients with functional dyspepsia. The safety profile was very good, adverse events [SOC: gastrointestinal disorders] mostly classified as mild or moderate and self-resolving. One serious reaction (moderate bilateral adnexitis; [SOC: infections and infestations]) occurred in the placebo group. No change of the safety profile but additional evidence for the indication of functional dyspepsia is concluded.

[Bundy et al. 2004]. A subset analysis of a previous dose-ranging, open, postal study, in adults suffering dyspepsia. Two hundred and eight (208) adults were identified post hoc as suffering with IBS. IBS incidence, self-reported usual bowel pattern, and the Nepean Dyspepsia Index (NDI) were compared before and after a 2-month intervention period. There was a significant fall in IBS incidence of 26.4% (p < 0.001) after treatment. A significant shift in self-reported usual bowel pattern away from "alternating constipation/diarrhea" toward "normal" (p < 0.001) was observed. NDI total symptom score significantly decreased by 41% (p < 0.001) after treatment. Similarly, there was a significant 20% improvement in the NDI total quality-of-life (QOL) score in the subset after treatment. This report supports previous findings that ALE ameliorates symptoms of IBS, plus improves health-related QOL. Artichoke leaf extract (extraction solvent: water; 5:1) 320 or 640 mg/per day0 was used for the study.

Assessor's comment: This study evaluates the therapeutic value of artichoke leaf extract in those patients with dyspepsia who suffer from irritable bowel syndrome. The analysis was performed on a subset of patients from a previously performed study in patients with dyspepsia and indicates that artichoke leaf extract may be of therapeutic value in IBS patients not only for the symptoms assigned to dyspepsia but also for other symptoms. Especially the condition of alternating constipation/diarrhoea responded very good to the artichoke extract treatment. Although not placebo controlled, this study/subset analysis yields evidence for a possible therapeutic value of artichoke leaf extract in the treatment of IBS, which is currently not an approved indication of artichoke products. Adverse events/side effects were not reported. No change of the safety profile.

- **Other effects**

[Wone et al. 1986]. In placebo placebo-controlled, double- blind study in malaria patients, a purified aqueous dry extract from fresh artichoke leaf juice administration intramuscularly (100 mg/day) and orally (1600 mg/day) for 3 days continuing the oral treatment on day 4 to 7 (n=46) or placebo (n=46) was given as additional treatment to standard quinine therapy. More rapid improvement in clinical symptoms of malaria observed in patients given artichoke therapy in addition to quinine were attributed to hepatoprotective effects of the artichoke extract.

- **Irritable bowel syndrome**

Irritable bowel syndrome, characterized by abdominal pain and altered bowel habit, has symptoms that overlap with those of dyspepsia. Since the crude drug is used for the treatment of dyspepsia, a postmarketing surveillance study was performed to assess its effects on irritable bowel syndrome. A subgroup of patients (*n*=279) with symptoms of irritable bowel syndrome was identified from a sample of individuals (*n*=553) with dyspeptic syndrome who were being monitored in a post marketing surveillance study of the extract for 6 weeks. Analysis of the data from the subgroup with irritable bowel syndrome revealed significant reductions in the severity of symptoms including abdominal pain, bloating, flatulence and constipation, and favourable evaluations of overall effectiveness by both physicians and patients [Walker et al. 2001].

Overview of clinical studies with artichoke

Study ID	**Study Dates Persons**	**Design Control type Study objective**	**Study &, Ctrl Drugs Dose, Route,**	**Duration**	**Gender M/F**	**Diagnosis Inclusion Criteria**	**Primary Efficacy Endpoint**
Wojcicki & Winter 1975	10 industrial workers	Efficacy, tolerability	Daily administration of 900 mg artichoke extr. Max. polyphenolic acids content 5.5%	30 days	10 industrial workers long term occupational exposure to carbon disulfide	Cholesterol lowering effects	significantly lowered blood levels of cholesterol (p<0.02) free fatty acids , phospholipids and total lipids (p, 0.05)
Wojcicki et al. 1982	73	Comparative study	Undefin. ALE (9 tablets, of 5 mg of polyphenolic acids , n=25) or 0.75 g or 1.5 g cynarin *per os* 1	1 month	73 patients with primary hyper-triglyceridaemia resistant to treatment with clofibrate	Lipid lowering effects	TheALE exerted significant total lipid-, triglyceride-,and phospholipids-lowering, effects in 56% of patients , whereas 0.75 g or 1.5 g of cynarin improved lipid parameters in 61% or 45% of patients
Kirschhoff et al. 1994	20	double-blind, placebo-controlled , cross-over study Efficacy, tolerability, safety	1.92 g (320x6) of stand.dry water extr.(4.5-5:1) of artichoke leaf (6 capsules -320 mg) in 50 ml water or placebo admnistr via an intraduodenal probe		20 males in two subgroups	acute or chronic metabolic disorders	bile secretion higher (p<0.01) in verum group: 127% higher 30 min after admin., 151% after 60 min. (the maximum effect) and 94% after 90 min result a after 120 min and 150 min were also significantly higher (p<0.05). Placebo treatm max. increase 39% after 30 min

Study ID	Study Dates Persons	Design Control type Study objective	Study &, Ctrl Drugs Dose, Route,	Duration	Gender M/F	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
Fintelmann 1996	553	multicentre open study, safety, Efficacy,	daily dose 3-6 caps. ALE aqueous dry extr. (3.8-5.5:1, 320 mg per capsule) *per os*	43.5 days	553 patients with dyspeptic complaints	Dyspepsia digestive complaints	Digestive complains declined within 6 weeks of treatm. All symptoms improved 71%. Meteorism reduction approx 66%, 76% for abdominal pain , 82% for nausea 88% for emesis. In subgroup of 302 patients, total cholesterol decreased 11.5% triglycerides 12.5%. Global efficacy by physicians excellent as good in 87% of cases No AEs
Kraft 1997	417 to 557 patients	post-marketing surveillance studies		4 to 6 weeks	417 to 557 patients	dyspepsia and/or diseases of the liver or bile duct	Statistically significant reduction of symptoms (e.g., abdominal pain, bloating, flatulence, and nausea) was reported for the surveillance studies referred to in this paper. Artichoke preparations were well tolerated (up to 95% of cases) with a low rate of side-effects
Petrowicz et al. 1997	44 healthvolunteers	randomized double-blind , placebo-controlled study Efficacy, tolerability	640 mg of dry water extr), 640 mg x3 daily *per os* Placebo	12 weeks	44 groups in volunteers with initial cholesterol >230 mg/dl(n_v-n_p=3)	Lipid lowering effects	Decreased concentration of total cholesterol (p=0.015) and triglycerides (p=0.01) to placebo in volunt. cholesterol >220 mg/dl (n_v-n_p=5), significant differ. (p=0.012) for triglycerides compared to placebo
Fintelmann & Petrowicz 1998	203	multicentre open study, safety, Efficacy, Tolerability,	daily dose 3-6 capsules ALE aqueous dry extract (3.8-5.5:1, 320 mg per capsule) *per os*	6 months	203 patients with dyspeptic complains	Dyspepsia digestive complaints	After 21 weeks treatm improvement of symptoms 66% e.g. vomit by 84% , abdominal pain 78% ,

Study ID	Study Dates Persons	Design Control type Study objective	Study &, Ctrl Drugs Dose, Route,	Duration	Gender M/F	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
		safety, Efficacy					nausea 76%, flatulence 70% and meteorism 69%. Total blood cholesterol -triglycrds, in 171 among patients decreas. 10.9% and in 159 determ. patients, LDL-cholesterol decreas. by 15.8% and HDL-cholesterol by 6.3%. Global efficacy by the physicians excellent or good in 85.7% of cases. No AEs
Englisch et al. 2000	143	Multicentrer andomized, placebo-controlled, double-blind study Efficacy, tolerability	fresh artichoke leaf water extr. (25-35:1) Daily 1800 mg (n=71) or placebo (n=72) as coated tabs *per os* 1	6 weeks	143 patients with hyperlipoproteinaemia (cholesterol >280 mg/dl)	Lipid lowering effects	In verum group reduction total cholesterol (18.5%) and LDL- (22.9%) from baseline to end of treatment signif. superior (p=0.0001) `to those in placebo group (8.6% and 6.3% respectively) LDL/HDL ratio decreased dy 20.2% in verum group and 7.2% in the placebo group
Schmidel 2002	54 test patients		Stand. preparation (aqueous ALE 3,8-5,5:1) (comparison with placebo	24 days	54 patients with hyperlipoproteinaemia (	Lipid lowering effects	The average lowering of cholesterol in all test patients with verum was 16.8 % compared to 10.0 % in all patients with placebo. This difference was statistically significant side effects: verum: hypersensitivity reactions [SOC: immune system disorders] n=1; placebo: flatulence [SOC: gastrointestinal disorders] n=1; ad. effe

Study ID	Study Dates Persons	Design Control type Study objective	Study &, Ctrl Drugs Dose, Route,	Duration	Gender M/F	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
							nausea, headache, sleep disturbances and stomachache without information whether they occurred in the verum or in placebo group
Lupatteli et al. 2004	28		20 ml/die of frozen artichoke juice	6 weeks	18 moderately hyperlipemic patients (LDL cholesterol > 130 <200 mg/dl and/or triglycerides >150 <250 mg/dl) 10 hyperlipemic patients males and women	Lipid lowering effects	Controls showed signif.decrease in total and LDL cholesterol (267 +/- 22 vs 249 +/- 20 mg/dL and 180 +/- 24 vs 164 +/- 23 mg/dL, both p <0.001). Also decrease in VCAM-1(1633 +/- 1293 vs 1139 +/- 883 ng/mL, p <0.05) and ICAM-1(477 +/- 123 vs 397 +/- 102 ng/mL, p <0.05), brachial FMV increased (3.3 +/- 2.7 vs 4.5 +/- 2.4%, p <0.01).
Bundy et al. 2008	131	randomized, double blind placebo controlled trial	1280mg (320 x 4) of a standardised artichoke leaf extract (ALE), or matched placebo, daily	12 weeks	131 adults	Lipid lowering effects	Plasma total cholesterol decreased in the treatment group by average of 4.2% (from 7.16 (SD 0.62) mmol/l to 6.86 (SD 0.68) mmol/l) and increased in the control group by an average of 1.9% (6.90 (SD 0.49) mmol/l to 7.03 (0.61) mmol/l), difference between groups statistically significant (p=0.025). No significant differences between groups were observed for LDL cholesterol, HDL cholesterol or triglyceride levels.

Study ID	Study Dates Persons	Design Control type Study objective	Study &, Ctrl Drugs Dose, Route,	Duration	Gender M/F	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
Kirschhoff et al. 1994	20	double-blind, placebo-controlled , cross-over study Efficacy, tolerability, safety	1.92 g (320x6) of stand.dry water extr.(4.5-5:1) of artichoke leaf (6 capsules -320 mg) in 50 ml water or placebo admnistr via an intraduodenal probe		20 males in two subgroups	acute or chronic metabolic disorders	bile secretion higher ($p<0.01$) in verum group: 127% higher 30 min after admin., 151% after 60min. (the maximum effect) and 94% after 90 min result a after 120 min and 150 min were also significantly higher ($p<0.05$). Placebo treatm max. increase 39% after 30 min
Marakis et al. 2003	516 454 completed the study	320 or 640 mg of ALE daily	open, dose-ranging postal study	2 months	516 participants 454 completed the study self-reported dyspepsia. Nepean Dyspepsia Index and State-Trait Anxiety Inventory were completed at baseline	Dyspepsia digestive complaints	significant reduction of all dyspeptic symptoms, with an average reduction of 40% in global dyspepsia score. Health-related quality of life signif. improved compared with baseline. ALE ameliorates upper gastro-intestinal symptoms and improves quality of life in healthy suffering from dyspepsia. side effects: constipation: n=2; loose stool: n=2; flatulence: n=1 [SOC: gastrointestinal disorders]
Holtmann et al. 2003	247 patients	(ALE) [(water > 80° C DER 4-6:1), Hepar SL capsules, 2x 320 mg t.i.d],	Double-blind, randomized controlled trial (RCT)	6 weeks	treatment of 247 patients with functional dyspepsia (FD) quality of life (QOL) as assessed by the Nepean Dyspepsia Index (NDI)	Functional dyspepsia	data from 244 patients (129 active treatment, 115 placebo) were suitable statistical analysis. All symptom improvement was signif. higher with ALE than with the placebo (8.3 +/- 4.6, vs. 6.7 +/- 4.8, $P < 0.01$). ALE showed

Study ID	Study Dates Persons	Design Control type Study objective	Study &, Ctrl Drugs Dose, Route,	Duration	Gender M/F	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
							signif. greater improvmn in global quality-of-life scores (NDI) compared with placebo-treated patients (41.1 +/- 47.6 vs. - 24.8 +/- 35.6, P<0.01).
Bundy et al. 2004	208 patients	ALE (extraction solvent: water; DER 1:5) 5:1) 320 or 640 mg/per day	subset analysis of a previous dose-ranging, open, postal study	2 months	IBS self-reported usual bowel pattern, and the Nepean Dyspepsia Index (NDI)	dyspepsia dealing with irritable bowel syndrome (IBS)	significant fall in IBS incidence of 26.4% (p<0.001) after ALE NDI total symptom score signif. decreased by 41% (p<0.001) after ALE. Signif. Improvement 20% in NDI total quality-of-life (QOL).

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

No information available.

4.3. Overall conclusions on clinical pharmacology and efficacy

In a multicentre, randomized , placebo-controlled , double- blind study by [Englisch et al. 2000], the effect of a fresh artichoke leaf aqueous dry extract (25-35:1) was investigated in 143 patents for its lipid lowering effects without obtaining convincing results: In the verum group, the reduction of total cholesterol was 18.5% and of LDL 22.9%. In another randomized double-blind, placebo-controlled study [Petrowicz et al. 1997] studied the same effects (lipid lowering effects) with a water extract of Cynara in 44 healthy volunteers. After 12 weeks, a decreased concentration of total cholesterol ($p=0.015$) and triglycerides ($p=0.01$) to placebo (volunt. cholesterol >220 mg/dl (n_v-n_p=5), significant differ. ($p=0.012$) for triglycerides compared to placebo) was reported. The groups were too small to adequately evaluate the final results. Finally, in the study of [Holtmann et al. 2003] it was aimed to assess the efficacy of artichoke leaf extract (water > 80° C DER 4-6:1, 2x 320 mg t.i.d), in the treatment of patients with functional dyspepsia (FD) and irritable bowel syndrome. In a double-blind, randomized placebo controlled, multicenter trial (RCT), 247 patients with functional dyspepsia (ROME II criteria, but concomitant IBS symptoms, not dominating the clinical picture were allowed) were recruited and treated with either a commercial preparation (2x320 mg plant extract t.d.s.) or a placebo. The overall symptom improvement over the 6 weeks of treatment was higher with Cynara extract than with placebo (8.3 +/- 4.6, vs. 6.7 +/- 4.8, $P<0.01$) with higher improvement in the global quality-of-life scores but enough detailed and accepted definition of functional dyspepsia.

Throughout all existing clinical trials, the efficacy was not supported sufficiently but the determined safety of the use of Cynara extracts was evaluated adequately.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

5.2. Patient exposure

5.3. Adverse events and serious adverse events and deaths

No major adverse events have been reported from clinical human pharmacological studies with preparations containing extracts of artichoke leaf involving over 1600 subjects and study duration of up to 2 years. Overall, 19 minor adverse events were reported; mainly gastrointestinal complaints [Fintelmann 1996; Fintelmann & Petrowicz 1998; Kirschhoff et al. 1993; Englisch 2000; Petrowicz et al. 1997; Wojcicki et al. 1975, 1981; Palacz et al. 1981; Woyke et al. 1981; Wone et al. 1986]. A systematic review of published human studies concluded that safety data for artichoke leaf extract indicate only mild and infrequent adverse effects [Pittler & Ernst 1998].

The following groups of adverse events / side effects are mentioned by the review authors:

- *Immune system disorders*

- allergic reactions

- *Metabolism and nutrition disorders*

- decreased appetite

- *Gastrointestinal disorders*

- flatulence

- *General disorders and administration site conditions*

- weakness
- hunger

Known allergies to artichokes and related species (*Asteraceae* or *Compositae*).

Obstruction of bile ducts. In case of gallstones, use only after consulting a physician.

5.3.1.1. Serious adverse events and deaths

One case (serious) was related to treatment with artichoke leaf dry extract containing medicinal products. The other 4 cases are related to allergic reactions following ingestion of artichoke or are connected to occupational situations, however, not transferable to the use of herbal medicinal products containing *Cynara*.

A 24-year–old woman was hospitalised on 30th of November 2005 because of asthenia and urticaria. She had neither any medical history nor any risks of virus infection or acute or chronic alcoholic intoxication. She had started consumption of Hepanephrol (2 ampoules/day) for slimming on 6 Nov 2005. Liver tests were normal in September 2005 on the occasion of a routine check. On 30 November 2005 she developed asthenia and urticaria requiring medical consultation. Clinical examination revealed no fever, no icterus, no signs of hepatocellular insufficiency and no signs of hepatic encephalopathy. Abdominal palpation revealed a painless abdomen without signs of hepatomegaly. There were no signs of thrombosis, and auscultation of the heart was normal. Hepatic enzymes were elevated as follows: ALAT 40 times higher than normal (N), ASAT 48 x N; GGT 1.3 x N, ALP 1.3 x N. Bilirubin and prothrombin were in normal range. Tests for hepatitis A, B, C, herpes, cytomegaly, Epstein-Barr, or toxoplasmosis were negative. Further tests were without findings. The ECG was normal. Ultrasound testing of the liver and the bile ducts didn't show any abnormal findings; no gallstones or signs of dilatation of the bile ducts or signs of chronic hepatopathy were found. The admistration of Hepanephrol was stopped on day of admission. Liver parameters improved within 3 weeks. A liver biopsy was not performed [Sinayoko et al. 2007].

Assessor's comment: As stated by the authors, a causal relationship is formally possible in this case because of a plausible temporal relationship and because of an improvement of the reaction following the discontinuation of the product. Thus, an intolerability or hypersensitivity reaction cannot completely be excluded here. However, the used product is insufficiently described including the relevance of the used dosage. In addition, the product was not used in the recommended indication (off label use). In summary, based on the available information it is assessed that this case report may not be directly transferred to other artichoke preparations as used in Germany. If a general advice not to use a product in case of known hypersensitivity is given in the SPC, no change of the safety profile is concluded; no other measures have to be taken.

[Franck et al. 2005]. Anaphylactic reaction to inulin: first identification of specific IgEs to an inulin protein compound. This case of an immediate allergic reaction resulting in an anaphylactic shock was not caused by an artichoke leaf preparation but two food products containing added inulin (Raftilose). However, differential diagnosis of this case led to the assumption of a cross-allergy with artichoke. Given the extremely rare occurrence of inulin allergy the probability of an allergic cross reaction after the intake of medicinal artichoke products in patients previously sensitised against inulin by consumption of other inulin containing food is considered to be extremely low. No change of the safety profile.

[Gabdnan et al. 2003]. Acute oedema of the tongue: a life-threatening condition. This paper focuses on a number of life-threatening cases of acute tongue edema. In one of ten cases reported in this paper the patient had consumed an "artichoke" prior to the event. The authors assess this case as being directly related to the artichoke consumption. However, as the artichoke was consumed as a food, it may have been that it was prepared with a spice dressing, or was otherwise prepared or concomitantly consumed with other, not mentioned food. Thus, the causality of artichoke for the adverse reaction is not assessable. However, the reaction must be assessed as possible in relation to artichoke which belongs to the family of *Asteraceae*. The - generally low - possibility of such reactions against any *Asteraceae* is well known and adequately addressed in most products with a warning label for patients with known allergy against any *Asteraceae* plant. No change of the safety profile.

[Miralles et al. 2003]. Occupational rhinitis and bronchial asthma due to artichoke (*Cynara scolymus*): Two cases of contact allergy are reported. Both cases involved vegetable warehouse workers who developed occupational rhinitis and bronchial asthma following exposition to artichokes. While the symptoms described in these cases are relatively severe the article also stresses that only two additional case reports of artichoke allergy were found in a Medline and Embase data base search. Both cases fit into the well known picture of rarely occurring allergy against Cynara. No change of benefit risk ratio.

Assessor's comment: A total of 5 cases with adverse reactions during treatment with Cynara has been identified in the literature, which did not change the benefit risk ratio.

5.4. Laboratory findings

None reported.

5.5. Safety in special populations and situations

No reports.

5.6. Intrinsic (including elderly and children) /extrinsic factors

No reports.

5.7. Drug interactions

Concomitant use with *Cynara* containing medicinal products may decrease the efficacy of anticoagulants (coumarin derivates like Phenprocoumon, Warfarin) [ESCOP 2009].

5.8. Use in pregnancy and lactation

In addition, one review deals with herbal infusions used for induced abortion [Ciganda and Laborde 2003]. In this paper, *Cynara* is only briefly mentioned in a table without any clinical proof. However, due to the lack of any data and in accordance with general medical practice, *Cynara*-containing herbal medicinal products should not be used during pregnancy and lactation.

5.9. Overdose

No information.

5.10. Drug abuse

No information.

5.11. Withdrawal and rebound

No information.

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

No information.

5.13. Overall conclusions on clinical safety

Only mild adverse events were reported in all published clinical trials. The pharmaceutical forms are therefore acceptable with respect to clinical safety.

6. Overall conclusions

Artichoke is characterized by the phenolic acid constituents, in particular cynarin. Experimental studies (*in vitro* and *in vivo*) support some of the result uses of artichoke. Traditionally, the choleretic and cholesterol-lowering activities of globe artichoke have been attributed to cynarin [Lietti 1977].

However, studies in animals and humans have suggested that these effects may in fact be due to the monocaffeoylquinic acids and cynarin present in artichoke (eg chlorogenic and neochlorogenic acids). Clinical trials investigating the use artichoke and cynarin in the treatment of hyperlipidaemia generally report positive results. However, further rigorous clinical trials are required to establish the benefit of globe artichoke leaf extract as a lipid – and cholesterol-lowering agent. Hepatoprotective and hepatoregenerating activities have been documented for cynarin *in vitro* and in animals rats. However, these effects have not yet documented in clinical studies.

The existing clinical trials indicate that the artichoke leaf extracts (water dry extract of dried and fresh leaves) is somehow effective against functional dyspepsia and also for its lipid lowering effects, but not adequately documented, so the Well Establish Use cannot be supported.

Moreover, the following herbal preparations are since a period of 30 years on the European market and are proposed in the monograph for Traditional Use:

a) Comminuted or powdered dried leaves for herbal tea

b) Powdered leaves

c) Dry extract (3.8-7.5:1), extraction solvent water

d) Soft extract fresh leaves (15-30:1), extraction solvent water

e) Dry extract fresh leaves (25-35:1), extraction solvent water

All the above herbal preparations have been proposed for traditional use, for the symptomatic relief of digestive disorders such as dyspepsia with a sensation of fullness, bloating and flatulence, based on long standing use.

The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use. A total of 5 cases with adverse reactions during treatment with Cynara have been identified in the literature, no change of benefit risk ratio.

Due to the lack of any data and in accordance with general medical practice, Cynara-containing herbal medicinal products should not be used during pregnancy and lactation.

Only mild adverse events were reported in all published clinical trials. The pharmaceutical forms are therefore acceptable with respect to clinical safety.

As there is no available data on genotoxicity, carcinogenity and reproducibility on fumitory extracts, the establishment of a Community List Entry is not possible because of safety concerns.

Annex

List of references