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EMA/HMPC/194013/2017
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Cynara cardunculus* L. (syn. *Cynara scolymus* L.), folium

Final

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Cynara cardunculus</i> (= <i>Cynara scolymus</i> L.), folium
Herbal preparation(s)	a) Comminuted dried leaves for herbal tea b) Powdered dried leaves c) Dry extract of dried leaves (DER 2-7.5:1), extraction solvent water d) Dry extract of fresh leaves (DER 15-35:1), extraction solvent water e) Soft extract of fresh leaves (DER 15-30:1), extraction solvent water f) Soft extract of dried leaves (DER 2.5-3.5:1), extraction solvent ethanol 20% (V/V)
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in solid or liquid form for oral use
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1. Introduction

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

Latin Name: previously *Cynara scolymus* L., Asteraceae family (Compositae). In a recent botanical taxonomic revision of the genus *Cynara*, 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. subspecies *flavescens* Wiklund (ESCOP, 2009). The name of the monograph is also in accordance with the European Pharmacopoeia where the monograph is referred only to *Cynara cardunculus* (European pharmacopoeia Ed. 9.0; ref: 1866).

- Herbal substance(s)

According European pharmacopoeia, Ed. 9.0 (ref.: 1866) the name of the botanical species *Cynara scolymus* L. changed to *Cynara cardunculus* L. Pharmacopoeial grade artichoke leaf consists of the dried basal leaves of *Cynara cardunculus* L. containing a minimum 0.8% of chlorogenic acid (C₁₆H₁₈O₉; Mr 354.3) (dried drug). Botanical identification is carried out by thin-layer chromatography, macroscopic and microscopic evaluations, and organoleptic tests. The dried leaf must contain not less than 25% water-soluble extractive (BHP 1996; Pharmacopée Française, 1987; Blumenthal *et al.*, 2000; Bruneton, 1999). Artichoke (*Cynara cardunculus* syn=*C. scolymus* L.) is a perennial thistle originating in southern Europe around the Mediterranean (northern Africa and the Canary Islands) (Iwu, 1993). 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 involucre bracts and the base, known as the "heart"; the mass of inedible immature florets in the centre of the bud are called the "choke".

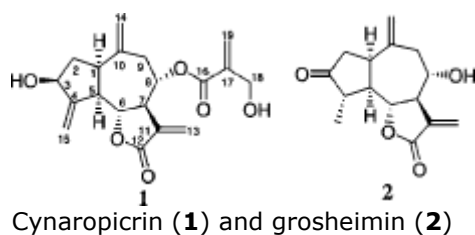
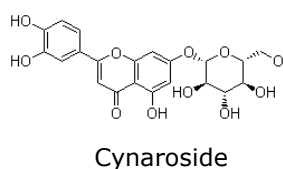
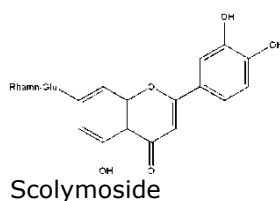
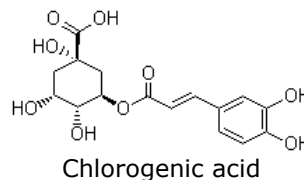
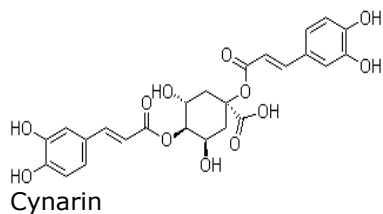
Its cultivation in Europe dates back to ancient Greece and Rome (Grieve, 1971). It is cultivated in North Africa as well as in other subtropical regions (Iwu, 1993). The material of commerce comes as whole or cut dried leaves obtained mainly from southern Europe and northern Africa (BHP, 1996). Furthermore, *Cynara* species contributed significantly to the Mediterranean agricultural economy, where more than 60% of the total world production came from Italy which was classified as the *Cynara cardunculus* (*C. scolymus*) (Asteraceae) native plant of the Mediterranean (North Africa and southern Europe) and popularly known in Brazil as artichoke. *Cynara cardunculus* (*C. scolymus*) is cultivated worldwide because of its nutritional benefits and medicinal properties.

Constituents (Dorne 1995; Maros *et al.*, 1966, 1968; Montini *et al.*, 1975; Samochowiec *et al.*, 1971)

- 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, , 0.4% bitter sesquiterpene lactones of which 47-83% is cynaropicrin and other sesquiterpene lactones (grosheimin, cynarotriol etc), as well as enzymes including

peroxidase The root and fully developed fruits and flowers are devoid of cynaropicrin; highest content reported in young leaves.

Moreover, 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 secondary metabolites. Other documented secondary metabolites include flavonoids, sesquiterpene lactones, polyphenols and caffeoylquinic acids.



- Herbal preparations:
 - a) Comminuted dried leaves for herbal tea
 - b) Powdered dried leaves
 - c) Dry extract of dried leaves (DER 2.5-7.5:1), extraction solvent water
 - d) Dry extract of fresh leaves (DER 15-35:1), extraction solvent water
 - e) Soft extract of fresh leaves (DER 15-30:1), extraction solvent water
 - f) Soft extract of dried leaves (DER 2.5-3.5:1), extraction solvent ethanol 20% (V/V)

- 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

Not applicable

1.2. Search and assessment methodology

The assessment is based on the sources mentioned in the list of references. Publications in other languages than English (at least abstract in English or other language available) were also included in the assessment.

Scientific databases: Scifinder, Scopus; HealLink, search date January 2017; key words: *Cynara scolymus*, *Cynara cardunculus*, artichoke leaf

Medical databases: Pubmed key words: *Cynara scolymus*, *Cynara cardunculus*, artichoke leaf

Pharmacovigilance resources: Not applicable

Other resources: Library of the National Kapodistrian University of Athens (Pharmacy and Pharmacognosy library)

Books, Book chapters, articles and letters in Journals, Medical press reviews, Acts of law and regulations

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from medicinal products marketed in EU

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Dry extract (DER 25-35:1); extraction solvent: water	Digestive complaints, regulation and improvement of lipid metabolism	Oral use, coated tablet adults 1 tablet contains 300 mg dry extract; 1 tablet 3 times daily	AT, WEU, since 2002
Dry extract (DER 25-35:1); extraction solvent: water 450 mg	Digestive complaints, regulation and improvement of lipid metabolism	Oral use, coated tablet adults 1 tablet contains 450 mg dry extract; 1 tablet 3 times daily	AT, WEU, since 2002
Dried expressed juice (no further details)	Improvement of digestion	Oral use, coated tablet adults 1 tablet contains 400 mg dried juice from 12.000 mg fresh leaves; 1-2 tablets 1 time daily	AT, WEU, since 2004
Dried expressed juice (no further details)	Dyspeptic disorders, post-treatment after hepatitis, chronic hepatopathies, subacute or chronic diseases of the biliary tract, after-care of cholecystectomy	Oral use, coated tablet adults 1 tablet contains 400 mg dried juice from 12.000 mg fresh leaves; 1-2 tablets 3 times daily	AT, WEU, since 2002
Dry extract (DER 4-6:1); standardized to >1.25%	Dyspeptic disorders, post-treatment after hepatitis, chronic hepatopathies, subacute or chronic diseases of the	Oral use, coated tablet contains 200 mg extract adults	AT, WEU, since 1992

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
caffeoylquinic acids	biliary tract, after-care of cholecystectomy	1-2 tablets 3 times daily	
Soft extract (DER 4-6:1); standardized to >0.5% caffeoylquinic acids	Dyspeptic disorders, post-treatment after hepatitis, chronic hepatopathies, subacute or chronic diseases of the biliary tract, after-care of cholecystectomy	Oral use, oral solution 5 ml solution contain 200 mg extract adults 5-10 ml 3 times daily	AT, WEU, since 2002
Dry extract (DER 3.8-5.5:1); extraction solvent: water	Digestive complaints, regulation and improvement of lipid metabolism	Oral use, capsule adults 1 capsule contains 400 mg dry extract; 1 capsule 3 times daily	AT, WEU, since 2002
Dry extract (DER 4-6:1); extraction solvent: water	Digestive complaints	Oral use, coated tablets adults 1 tablet contains 350 mg dry extract; 1-2 tablet 3 times daily	AT, TU, since 2000
Dry extract (no further details)	Digestive complaints	Oral use, coated tablets adults 1 tablet contains 300 mg dry extract; 1 tablet 3 times daily	AT, TU, since 1999
Dry extract (DER 4-6:1); extraction solvent: water	Dyspepsia	Oral use, capsule adults	AT, TU, since 1998

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		1 capsule contains 320 mg dry extract; 1-2 capsules 3 times daily	
Dry extract (DER 4-6:1); extraction solvent: water	Digestive complaints	Oral use, coated tablets adults 1 tablet contains 600 mg dry extract; 1 tablet 3 times daily	AT, TU, since 2000
Dry extract (no further details); extraction solvent: water	Digestive complaints	Oral use, coated tablets adults 1 tablet contains 400 mg dry extract; 1 tablet 3 times daily	AT, TU, since 1999
Powdered leaves	1) Enhances biliar excretion, after exclusion of serious pathologies 2) Cholagogue, after exclusion of serious pathologies. Minor increase in renal water excretion	Oral use, hard capsule adolescents and adults 1 capsule contains 200 mg ; 3-4 capsules 2 times daily	BE, WEU, since 2006
Dry "purified" extract (no further details), equivalent 1.875% chlorogenic acid	1) Enhances biliar excretion, after exclusion of serious pathologies 2) Cholagogue, after exclusion of serious pathologies. Minor increase in renal water excretion	Oral use, coated tablets adolescents and adults 1 tablet contains 200 mg dry extract; 3 tablets 2 times daily	BE, WEU, since 2000
Dry "purified" extract (no further details), equivalent 1.875%	1) Enhances biliar excretion, after exclusion of serious pathologies	Oral use, oral solution	BE, WEU, since 2000

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
chlorogenic acid	2) Cholagogue, after exclusion of serious pathologies. Minor increase in renal water excretion	adolescents and adults 1 ml contains 240 mg dry extract; 2.5 ml 2-4 times daily	
Dry extract (no further details)	1) Enhances biliar excretion, after exclusion of serious pathologies 2) Cholagogue, after exclusion of serious pathologies. Minor increase in renal water excretion	Oral use, coated tablets adolescents and adults 1 tablet contains 200 mg dry extract; 3 tablets 2-4 times daily	BE, WEU, since 1999
Cynara herbae	1) Enhances biliar excretion, after exclusion of serious pathologies 2) Cholagogue, after exclusion of serious pathologies. Minor increase in renal water excretion	Oral use, herbal tea 50-200 mg Cynara herbae per g tea	BE, Marketing Authorisations from 1962
Dry extract (DER 4-6:1) (no further details)	Dyspeptic symptoms and meteorism following fatty meals and meals which are difficult to digest, follow-up treatment by liver and biliary dysfunction	Oral use, coated tablet adults and children over 12 years: 1-2 tablets 3 times daily	BG, WEU, since 2001
Soft extract (DER 4-6:1) (no further details)	Dyspeptic symptoms and meteorism following fatty meals and meals which are difficult to digest, follow-up treatment by liver and biliary dysfunction	Oral use, oral solution adults and children over 12 years: 1-2 tea spoon 3 times daily	BG, WEU, since 2006

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Powdered dried leaves	Traditionally used to promote urinary and digestive elimination functions Traditionally used as a choloretic and cholagogue	Oral use, hard capsule adults 1 capsule contains 200 mg powdered herbal substance; 2 capsules 3 times daily Daily dose 1200mg	FR, TU, since 1988
Powdered dried leaves	Traditionally used to promote urinary and digestive elimination functions Traditionally used as a choloretic and cholagogue	Oral use, ampoule adults 1 ampoule (5 ml) contains 0.5 g powdered herbal substance; 1 ampoule 2 times daily	FR, TU, since 1994
Extract (no further details); extraction solvent: water	Traditionally used to promote urinary and digestive elimination functions Traditionally used as a choloretic and cholagogue	Oral use, ampoule adults 1 ampoule (15 ml) contains 0.3 g extract; 3 to 6 ampoules daily	FR, TU, since 1988
Dry aqueous extract (no further details)	Traditionally used to promote urinary and digestive elimination functions Traditionally used as a choloretic and cholagogue	Oral use, hard capsules adults 1 capsule contains 192.5 mg extract, 1-2 capsules 2 times daily	FR, TU, since 1990
Dry extract (DER 2-3.5:1); extraction solvent: water	Traditionally used to promote urinary and digestive elimination functions Traditionally used as a choloretic and	Oral use, hard capsules adults 1 capsule contains 200 mg extract, 1 capsule 2	FR, TU, since 1986

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	cholagogue	times daily	
<p>Dry extract from dried leaves (DER 2.5-3.5:1); extraction solvent: water</p> <p>Dry extract from fresh leaf (DER 15-30:1); extraction solvent: water</p>	Traditionally used to promote urinary and digestive elimination functions	<p>Oral use, coated tablets</p> <p>adults</p> <p>1 tablet contains 200 mg extract, 1-2 tablets 3 times daily</p>	FR, TU, since 1976
Soft extract from fresh leaves(DER 15-30:1); extraction solvent: water	Traditionally used to promote digestive elimination functions	<p>Oral use, solution</p> <p>adults</p> <p>20 g of extract/100 ml, 1 coffee spoon (3 ml)</p> <p>3 times daily (9 ml)</p>	FR, TU, since 1976
Soft extract (no further details); extraction solvent: water	Traditionally used to promote urinary and digestive elimination functions	<p>Oral use, ampoule</p> <p>adults</p> <p>1 ampoule (10 ml) contains 2 g extract, 1 ampoule 3 times daily</p>	FR, TU, since 1966
Dry extract (DER 5.8-7.5:1); extraction solvent: water	Traditional used to promote the digestion	<p>Oral use, coated tablet</p> <p>adults</p> <p>1 tablet contains 300 mg dry extract; 1 tablet 1-2 times daily</p>	DE, TU, at least since 1978
Dry extract from fresh artichoke leaves (DER 25-35:1), extraction solvent: water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	<p>Oral use, coated tablets</p> <p>adults</p>	DE, WEU, since 1978

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		1 tablet contains 450 mg dry extract; 1-2 tablets 3 times daily 1 tablet contains 300 mg dry extract; 2 tablets 3-4 times daily 1 tablet contains 150 mg dry extract; 2-4 tablets 3-4 times daily	
Dried expressed juice from fresh leaves (25-35:1); extraction solvent: water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, coated tablets adolescents and adults 1 tablet contains 400 mg dried expressed juice; 1 tablet 2 times daily	DE, WEU, since 2005
Dry extract (DER 3.8-5.5:1); extraction solvent: water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, hard capsule adults 1 capsule contains 200 mg dry extract; 1 capsule 3 times daily, if necessary 4 times daily	DE, WEU, since 1978
Dry extract (DER 4-6:1); extraction solvent: water	Dyspeptic complaints based on insufficient bile secretion like sense of fullness, flatulence, minor gastrointestinal spasms	Oral use, hard capsules adolescents and adults 1 capsule contains 200 mg dry extract; 2 capsules 3 times daily	DE, WEU, since 1978
Dry extract (DER 4-6:1); extraction solvent: water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, film tablets adolescents and adults 1 tablet contains 200 mg dry extract; 2 tablets 3	DE, WEU, since 1978

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		times daily	
Dry extract (DER 4-6:1); extraction solvent: water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, coated tablet adolescents and adults 1 tablet contains 220 mg dry extract, 2 tablets 3 times daily 1 coated tablet contains 232 mg dry extract; 2 coated tablets in the morning, 2 coated tablets at noon and 1 coated tablet in the evening 1 tablet contains 600 mg dry extract; 1 tablet 2 times daily	DE, WEU, since 1978 DE, WEU, since 1978 DE, WEU, since 2002
Dry extract (DER 4-6:1); extraction solvent: water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, hard capsules adolescents and adults 1 capsule contains 320 mg dry extract; 2 capsules 2 times daily 1 capsule contains 400 mg dry extract; 1 capsule 2-3 times daily	DE, WEU, since 1978 DE, WEU, since 1998
Dry extract (DER 4-6:1), extraction solvent water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, oral liquid adolescents and adults 10 ml liquid contains 400 mg dry extract; 10 ml liquid 3 times daily	DE, WEU, since 1978

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Dry extract (DER 5.8-7.5:1); extraction solvent: water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, coated tablets adolescents and adults 1 tablet contains 300 mg dry extract, 1 tablet 3 times daily	DE, WEU, since 1978
Dry extract from fresh artichoke leaves (DER 15-30:1), extraction solvent water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, coated tablet adolescents and adults 1 tablet contains 160 mg dry extract; 2 tablets 4 times daily oral use, film tablet 1 tablet contains 320 mg dry extract; 1 tablet 4 times daily	DE, WEU, since 1978 DE, WEU, since 2002
Soft extract (DER 2.5-3.5:1), extraction solvent ethanol 20% (V/V)	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, oral liquid adolescents and adults 100 g (=94.8 ml) liquid contain 33.333 mg soft extract; Single dose: 40 drops = 0.7 g Daily dose: 3 times daily = 2.1 g	DE, WEU, since 1978
Fluid extract (DER 1:0.9-1.1), extraction solvent ethanol 35% (V/V)	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, oral liquid adolescents and adults 1 ml liquid contains 1 ml fluid extract, 45 drops	DE, WEU, since 1978 The marketing authorisation was valid until 09/2008 and

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		fluid extract 4 times daily	expired because the company did not use it for 3 consecutive years
Dry extract <i>Cynarae scol. folium</i> (DER 3-6:1); extraction solvent: water	For digestive complaints, feeling of fullness, nausea, flatulence, gallbladder disease, to promote bile secretion (as cholagogue) , to promote fat digestion	Oral use, coated tablet adolescents, adults, elderly 1 tablet contains 400 mg extract, 1x3 times daily Duration of use not more 2-3 months. If the complaints reoccur the cure can be restarted after 1 month's break	HU, TU, since 2001
Cynarae folii extractum siccum Dry extract (DER 25-35:1); extraction solvent: water	Digestive complaints (e.g. stomach ache, feeling of fullness, flatulence)	Oral use, hard capsule 1 capsule daily	PL, TU, since 1967
Cynarae herba	Digestive complaints (feeling of fullness, nausea, flatulence) Adjuvant to a low fat diet in the treatment of mild to moderate hyperlipidaemia	Oral use, herbal tea 3 g herbal substance 1-3 times daily in hyperlipidaemia 1.5 g herbal substance 4 times daily *)	PL, TU, >30 years
Dry extract (DER 4-6:1); extraction solvent: water	Digestive complaints (feeling of fullness, nausea, flatulence, heartburn) Adjuvant to a low fat diet in the treatment of mild to moderate	Oral use, hard capsule contains 200 mg extract 1-2 capsules 1 time daily (digestive disorders) or 3-5 capsules daily (mild hyperlipidemia)	PL, WEU, since 1997

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	hyperlipidaemia		
Extractum fluidum (no further details)	Indicated in light forms of hyperlipidemia as additional treatment	Oral use, oral solution adults, adolescents and children 1 tea spoon 3 times daily	SK, WEU, since 1996
Dried leaves	Dyspepsia	Oral use, herbal tea adults up to 3 g per day (1 to 3 cups of tea per day)	ES, TU, since at least 1973
Powdered leaves	Dyspepsia	Oral use, tablets/capsules adults capsules containing 150; 175; 300; 500 mg; 600-1500 mg per day	ES, TU, since at least 1973
Dry extract(DER 4-6:1); extraction solvent: water	Digestive complaints such as indigestion, upset stomach, nausea, feeling of fullness, flatulence, particularly caused by over indulgence of food and drink, based on traditional use only	Oral use, hard capsule contains 200 mg extract adults, elderly 1 capsule 2 times daily	UK,TU, since 2009

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

**) this posology was accepted in 2011 for the comminuted dried leaves for herbal tea because the herba contains mainly the dried leaves of the plant*

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

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 as THMP, containing *Cynara scolymus* together with *Gentiana lutea* and *Curcuma longa*
- Germany: seven authorised combination products with *Matricariae flos*, *Taraxaci herba cum radix*, *Menthae piperitae folium*, *Millefolii herba*, *Foeniculi amari fructus*, *Helichrysi flos*

In Austria there are also products on the market as a combination with *Menthae piperitae folium*, *Taraxaci radix*, *Curcumae rhizoma* and *Silybi marianae fructus*. Or *Silybi marianae fructus*, *Taraxaci radix*.

In Belgium combinations products: Artichoke leaf extract with *Boldo folium*, *Hepaticae herba*, *Centaurii herba*, *Cardui benedicti herba*, *Fraxini folium*.

Information on other products marketed in the EU/EEA (where relevant)

No relevant data.

The following products referring to *Cynariae flos* and *herba* are also registered:

Cynariae flos: 3 expressed juices from fresh artichoke flower buds (1:0.6-0.9) on the market since 1978 in Germany as Traditional herbal medicinal product for mild digestive complaints for use by adults and adolescents. The recommended dose is: 10 ml expressed juice 2-3 times daily.

Cynariae herba: 1 fluid extract from artichoke herb (1:2.4-5.2), extraction solvent: ethanol on the market since 1978 for TU in Germany.

2.1.2. Information on products on the market outside the EU/EEA

Not applicable

2.2. Information on documented medicinal use and historical data from literature

The artichoke was used as a food and medicine by the ancient Egyptians, Greeks, and Romans. Artichoke leaf has been used as a choleric and diuretic in traditional European medicine since Roman times (Bianchini & Corbetta 1977). Artichoke (*C. scolymus* L., 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. Artichokes were introduced to the United States in the 19th century, to Louisiana by French immigrants and to California by Spanish immigrants.

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. Artichoke is the primary flavour of an Italian liquor.

The Commission E reported choleric 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 choleric (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 choleric (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 medicines, leaf preparations are used for liver and gallbladder problems, diabetes, high cholesterol, hypertension, anemia, diarrhea (and elimination in general), fevers, ulcers, and gout.

In Germany, artichoke leaf is used as a choleric (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 paediatric medicine, herbs with a relatively low bitter value such as artichoke leaf are used for the treatment of appetite disorders (Schilcher, 1997).

Preparations of artichoke are used for bloating, nausea, and impairment of digestion (Bruneton, 1999). In France, several pharmaceutical forms of artichoke leaf extracts are also in use since at least the last 35 years (Pharm. Franc., 1987; Martindale, 1993; WHO Monographs, 2009; ESCOP monographs supp. 2009).

Worldwide ethnomedical uses (Iwu, 1993)

Europe	For bile insufficiency, cancer, detoxification, dyspepsia, gallbladder disorders, high cholesterol, hyperglycaemia, 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, seborrhis, 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

2.3. Overall conclusions on medicinal use

Based on information obtained from Member states and data retrieved from handbooks as well as from the market overview in EU (Table 1) it can be concluded that the following preparations and uses of artichoke leaves fulfil the criteria for traditional use:

Table 2: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Comminuted dried leaves for herbal tea Cynarae herba for herbal tea	Dyspepsia	Oral use, herbal tea up to 3 g a day (divided into 1 to 3 cups of tea /day)	Spain since 1973
	Digestive complaints (feeling of fullness, nausea, flatulence) Adjuvant to a low fat diet in the treatment of mild to moderate hyperlipidaemia	Oral use, herbal tea 3 g herbal substance 1-3 times daily 1.5 g herbal substance 4 times daily)	Poland (more than 30 years) *
Powdered dried leaves	Dyspepsia	Oral use adults 600-1500 mg a day divided in 2-4 doses	Spain, since at least 1973
	Traditionally used to promote urinary and digestive elimination functions Traditionally used as a cholaretic and cholagogue	Oral use adults: 400 mg powdered herbal substance 3 times daily Daily dose 1200 mg	France since 1988
Dry extract (DER 2-3.5:1); extraction solvent:	Traditionally used to	Oral use	France since 1986

* This posology for comminuted dried leaves for herbal tea is based to existing data on Cynarae herba which have been on use in Poland in use for more than 30 years with the same indication, and is mainly consisting in dried leaves of the plant

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
water	<p>promote urinary and digestive elimination functions</p> <p>Traditionally used as a choleric and cholagogue</p>	<p>adults</p> <p>200 mg 2 times daily</p>	
Dry extract from dried leaves (DER 2.5-3.5:1); extraction solvent: water	Traditionally used to promote urinary and digestive elimination functions	<p>Oral use</p> <p>adults</p> <p>200 - 400 mg 3 times daily</p>	France since 1976
Dry extract (DER 3.8-5.5:1); extraction solvent: water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	<p>Oral use</p> <p>adults</p> <p>200 mg 3 times daily, if necessary 4 times daily</p>	Germany since 1978
Dry extract (DER 4-6:1); extraction solvent: water	Dyspeptic complaints based on insufficient bile secretion like sense of fullness, flatulence, minor gastrointestinal spasms	<p>Oral use (solid dosage form)</p> <p>adolescents and adults</p> <p>400 mg 3 times daily</p>	Germany since 1978
	Dyspeptic complaints, particularly based on functional affections of the biliary tract	<p>Oral use (solid dosage form)</p> <p>adolescents and adults</p> <p>440 mg 3 times daily</p>	Germany, WEU, since 1978
		<p>Oral use (solid dosage form)</p> <p>adolescents and adults</p> <p>464 mg in the morning,</p>	Germany, WEU, since 1978

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		464 mg at noon and 232 mg in the evening	
		Oral use (solid dosage form) adolescents and adults 400 mg 3 times daily	Germany, WEU, since 1978
		Oral use (liquid dosage form) adolescents and adults 400 mg 3 times daily	Germany, WEU, since 1978
		Oral use (solid dosage form) adolescents and adults 640 mg 2 times daily	Germany, WEU, since 1978
Dry extract (DER 5.8-7.5:1); extraction solvent: water	Traditional used to promote the digestion	Oral use, adults 300 mg 1-2 times daily	Germany, TU, at least since 1978
	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use adolescents and adults 300 mg 3 times daily	Germany, WEU, since 1978
Dry extract from fresh leaves (DER 15-30:1); extraction solvent: water	Traditionally used to promote urinary and digestive elimination functions	Oral use adults 200 - 400 mg 3 times daily	France since 1976
	Dyspeptic complaints, particularly based on functional affections of	Oral use adolescents and adults 320 mg 4 times daily	Germany since 1978

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	the biliary tract		
Dry extract from fresh leaves (DER 25-35:1), extraction solvent: water	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, adults 450 - 900 mg 3 times daily	Germany since 1978
Soft extract of fresh leaves (DER 15-30:1), extraction solvent water	Traditionally used to promote digestive elimination functions	Oral use (liquid dosage form) 600 mg 3 times daily (20 g of extract/100 ml)	France since 1976
Soft extract (DER 2.5-3.5:1) of dried leaves, extraction solvent ethanol 20% (V/V)	Dyspeptic complaints, particularly based on functional affections of the biliary tract	Oral use, (liquid dosage form) adolescents and adults Single dose 700 mg 3 times daily Daily dose 2.1 g	Germany 1978

All herbal preparations mentioned above have been in medicinal use for 30 years or more according to literature and information provided by Member States.

The indications reported in the medicinal use can be reworded as a general indication for a "traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia with a sensation of fullness, bloating and flatulence."

Long-standing medicinal use for at least 30 years within the European Union is therefore demonstrated in the above indication for the following preparations for oral administration which are proposed for the monograph **on traditional use**.

a) Comminuted dried leaves for herbal tea as herbal tea for oral use.

Traditional medicinal use of this preparation is substantiated by extensive bibliography and the presence on the Spanish and Polish market for more than 30 years. The posology is based to existing data on *Cynarae folium* as well as on *Cynarae herba* which have been in use in Poland in use for more than 30 years with the same indication, and is mainly consisting in dried leaves of the plant. The daily dose in adults and adolescents over 12 years is 1.5 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion 4 times daily (in Poland) or up to 3 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion daily (in Spain) as herbal tea for oral use.

b) Powdered dried leaves in solid or liquid dosage forms for oral use.

Traditional medicinal use of this preparation is substantiated by the presence of medicinal products Spain since at least 1973 and in France since 1988.

Daily dose: 600-1500 mg, divided in 2-4 doses (according to the broader range used in Spain)

c) Dry extract of dried leaves (DER 2-7.5:1), extraction solvent water in solid or liquid dosage forms for oral use as it is considered possible bracketing the following preparations:

- dry extract (DER 2-3.5:1) of dried leaves in solid dosage forms for oral use; extraction solvent: water (marketed in France since 1986): 200 mg 2 times daily (in adults).
- dry aqueous extract; DER 2.5-3.5:1 dried leaf (marketed in France since 1976): 200-400 mg 3 times daily (in adults)
- dry extract (DER 3.8-5.5:1); extraction solvent: water (marketed in Germany since 1978): 200 mg 3 times daily, if necessary 4 times daily (in adults)
- dry extract (DER 4-6:1), extraction solvent water (marketed in Germany since 1978): 400-440 mg 3 times daily or 464 mg in the morning, 464 mg at noon and 232 mg in the evening or 640 mg 2 times daily
- dry extract (DER 5.8-7.5:1), extraction solvent water (marketed in Germany since 1978): 300 mg 1-3 times daily (adults)

Therefore the posology agreed by HMPC for the Dry extract of dried leaves (DER 2-7.5:1), extraction solvent water ranges as follows: single dose: 200-640 mg; daily dose 400-1320 mg.

d) Dry extract of fresh leaves (DER 15-35:1), extraction solvent water in solid dosage forms for oral use as it is considered possible bracketing the following preparations:

- dry aqueous extract from fresh leaves (DER 15-30:1), marketed in France since 1976 (200-400 mg 3 times daily) and in Germany since 1978 (320 mg 4 times daily in adults and adolescents)
- dry extract of fresh leaves (DER 25-35:1), extraction solvent water, marketed in Germany since 1978 (450-900 mg 3 times daily in adults)

Therefore the posology agreed by HMPC for the Dry extract of fresh leaves (DER 15-35:1), extraction solvent water ranges as follows: single dose: 200-900 mg; daily dose 600-2700 mg. This is broader in

comparison with the previous version of the monograph (single dose: 300-600 mg, daily dose: 900-2400mg).

e) Soft extract of fresh leaves (DER 15-30:1), extraction solvent water, in liquid dosage forms for oral use, marketed in France since 1976 (600 mg 3 times daily). Single dose: 600 mg, daily dose: 1800 mg

The monograph adopted in 2011 included a daily dose of 600-1200 mg (in divided doses of 200 mg) as posology for the soft extract of the fresh leaves (DER 15-30:1), extraction solvent water. It was decided to maintain in the monograph only the posology expressed as mg extract and to delete the pharmaceutical dosage form.

f) Soft extract of dried leaves (DER 2.5-3.5:1), extraction solvent ethanol 20% (V/V), in liquid dosage forms for oral use, marketed in Germany since 1978 (700 mg 3 times daily in adolescents and adults). Single dose 0.7 g; daily dose 2.1 g.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

Artichoke leaf has shown cholesterol-lowering and lipid-lowering activity in rats and humans (Lietti 1977). Studies have demonstrated carminative, spasmolytic, antiemetic and choleric properties.

Results from *in vivo* studies, suggest that artichoke leaf has shown hepatoprotective and hepatostimulating properties (Adzet *et al.*, 1987i; 1987ii; Maros *et al.*, 1966). Antidyspeptic effects are mainly attributed to increased choleresis (ESCOP, 2003).

3.1.1.1. In vitro experiments

Choleric and hepatobiliary effects

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

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, 1995i). The choleric effect of expressed juice from fresh artichoke was investigated in isolated perfuse rat liver. Expressed 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.*, 2005). By testing fractions of the 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 expressed 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 expressed 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 (no further detail) on tauroolithocholate-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 dose-dependent manner when added simultaneously with the bile acid. However, prevention also occurred when the hepatocytes were pre-incubated with the extracts, indicating that absorption of the bile acid to components of the extracts was not involved (Gebhardt 2002i). 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, 1987i; 1987ii). 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.*, 1987i). 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 extract /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, 1997ii). 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, 1997i). The liver protective actions of artichoke have been also tested and reported by (Maros *et al.*, 1966; Aktay *et al.*, 2000; Speroni *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 reported by Emendorfer and co-workers in two publications (Emendorfer *et al.*, 2005i, 2005ii).

3.1.1.2. In vivo experiments

Hepatobiliary and hepatoprotective effects

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-dependend 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 deproteinised aqueous extract of artichoke leaf, administered orally to partially hepatectomised 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 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 LD₅₀ 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; LD₅₀ 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% caffeoylquinic acids, 25 mg/kg body weight). Through 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.*, 1987ii).

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 49% in bile acid concentration respectively (Saenz Rodriguez *et al.*, 2002).

The pharmacological effects of 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 semi-purified 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 ($p < 0.05$). Intra-gastric administration of the same extracts (400.0 mg/kg bw, total extract and 200.0 mg/kg bw of the semi-purified extract) also increased gastrointestinal motility by 11% and 14%, respectively ($p < 0.05$) (Lietti, 1977).

The effects of an extract from 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 choleric effects of the extract were similar to those of the reference compound de-hydrocholic 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 ($p < 0.01$) (Saenz Rodriguez *et al.*, 2002).

The choleric 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 choleric 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 choleric 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.*, 1987i).

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 intraperitoneally 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 it was significantly lowered ($p=0.05-0.02$) by cynarin after intraperitoneal administration (2 x200 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).

Table 3: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Pressed juice from fresh artichoke	Pressed juice, undiluted and diluted 1:3 and 1:5	<i>In vitro</i> in isolated perfuse rat liver	Gebhardt 1995i	A cholestatic effect induced in the cultures by lithocholate was inhibited by the extract
Fresh juice of artichoke leaf and dry aqueous extract (4:1)	Several concentrations	<i>In vitro</i> in isolated perfuse rat liver	Matuschowski <i>et al.</i> , 2005	The choleric effect of 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 no correlation with the content of caffeoylquinic acids was evident
Aqueous extract of the leaves(no	0.08 to 0.5 mg/ml	<i>In vitro</i>	Gebhardt 2002i	Prevent the formation of canalicular membrane

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
further detail)				transformations in a dose-dependent manner when added simultaneously with the bile acid
Several fractions from artichoke and cynaropicrin as well with other Brazilian traditionally used medicinal plants	Several concentration have been assayed	<i>In vitro</i> on guinea pig ileum	Maros T <i>et al.</i> , 1966; Aktay G <i>et al.</i> , 2000; Speroni E <i>et al.</i> , 2003, Emendorfer <i>et al.</i> , 2005i, 2005ii	Antihepatotoxic activity
Artichoke leaf extracts, cynarin and, caffeic acid	Three consecutive doses of 500.0 mg/kg bw of an extract of the crude drug, administered by gavage 48, 24 and 1 hour before CCl ₄ intoxication	<i>In vivo</i> in rats	Adzet 1987ii; 1987ii	Hepatoprotective activity of cynarin against carbon tetrachloride -induced toxicity in isolated rat hepatocytes was compared with other phenolic compounds produced a significant decrease in glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase direct bilirubin and glutathione levels, indicating a reduction in the potential for hepatotoxicity
Artichoke leaf extract	95µg leaf extract/ml	<i>In vitro</i>	Gebhardt and Fausel 1997ii	The liver protective actions of artichoke are reported
Deproteinized aqueous extract of artichoke leaf Chlorogenic acid Cynarin	Orally 0.5 ml/animal daily for 21 days Chlorogenic acid orally at 5-40 mg/kg bw Cynarin single intravenous administration (7-166 mg/kg bw)	<i>In vivo</i> in rats	Maros <i>et al.</i> , 1968 Preziosi 1956, 1958, 1959, 1960	Significantly increased liver tissues regeneration as measured by residual liver weight, mitotic index and percentage of dinucleated liver cells stimulated choleresis (70%) and peristaltic activity (40%) in a concentration depended manner. A dose-dependent increase in bile

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
				flow of up to 95% and an increase in biliary-excreted cholesterol were observed
A purified acid-rich, butanolic extract of artichoke leaf	10 mg/kg i.p	<i>In vivo</i> , in mice	Mortier <i>et al.</i> , 1976	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
Two hydroethanolic extracts of fresh artichoke	400mg/kg body weight of total extract or 200mg/kg of purified extract i.p.	<i>In vivo</i> , in rats	Bombardelli <i>et al.</i> , 1977	Both extracts stimulated choleresis significantly increasing the bile dry residue and the total cholate secretion (p<0.05)
Aquous extract of artichoke leaf,	orally 500 mg/kg bw 48 hours, 24 hours and 1 hours before inducing liver intoxication with carbon tetrachloride	<i>In vivo</i> , in rats	Adzet <i>et al.</i> , 1987i	Improved liver function
Undefined artichoke leaf fluid extract	0.45 mg/kg body weight i.p.	<i>In vivo</i>	Saenz Rodriguez <i>et al.</i> , 2002	Produced increases of 32% in bile flow and 49% in bile acid concentration respectively
Two aqueous alcoholic extracts of the fresh leaves	At a dose of 200.0 mg/kg bw and a semi-purified extract at a dose of 25.0 mg/kg bw) i.p	<i>In vivo</i> in rats	Lietti 1977	Stimulated choleresis, and significantly increased bile dry residue and total cholate secretion
Crude drug	400.0 mg/kg bw orally, acute administration	<i>In vivo</i> in rats	Sainz Rodriguez <i>et al.</i> , 2002	At the highest dose a significant increase of bile formation and flow was observed after single

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
	and repeated administration twice a day for 7 consecutive days			and repeated administration ($p < 0.01$)
Four extracts of the leaves (not described)	1 and 2 g/kg bw	<i>In vivo</i>	Speroni <i>et al.</i> , 2003]	Extracts 1, 2 and 4 did not show significant choleric 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 choleric activity
Powdered artichoke aerial parts	Orally at 110 mg/kg bw for 120 days	<i>In vivo</i> in rats	Samochowicz 1959, 1962i, 1962ii, 1962iii Samochowicz 1971 Saenz Rodriguez 2002	Lowered increases in serum and liver cholesterol and prevented the formation of atherosclerotic plaques

3.1.2. Secondary pharmacodynamics

Antioxidant and cytoprotective effects

Antioxidant and cytoprotective effects of an artichoke leaf aqueous dry extract (DER 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. EC₅₀ 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, 1995ii, 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 tested by flow cytometry using phorbol 12-myristate-13-acetate as the stimulant. The extract strongly inhibited the generation of reactive oxygen species with an EC₅₀ 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 enzymes glutamine oxaloacetic transaminase and glutamic pyrovic transaminase (Adzet *et al.*, 1987i, 1987ii). Artichoke leaf aqueous dry extract at dose of 20 µg/ml retarded Cu²⁺-mediated oxidation of human low density lipoproteine (LDL) in a dose-dependent 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 concentration-dependent 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- Garcia *et al.*, 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 tryptan 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 synthetase 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).

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 (Truillas *et al.*, 2003). Antioxidative activities have been reported for *Cynara* extracts (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 14C-acetate in primary cultured rat hepatocytes in a concentrations of 0.007-0.1 mg/ml produced moderate 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 EC₅₀ of approximately 30 µM. In human hepatic (HepG2) cells the maximum response of luteolin was more than 80% and the EC₅₀ 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 1997I; 1997ii; 1998). Subsequently it was demonstrated that artichoke extracts inhibit cholesterol biosynthesis from 14C-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 from cynaroside may occur in the human body (Gebhardt 1998; Gebhardt 2001, 2002i, 2002ii; Brown & Rice Evans, 1990; Fritsche *et al.*, 2002).

Cynara scolymus is thought among the herbs dealing with serum cholesterol reduction (Thompson 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).

Antimicrobial effects

The antibacterial and antifungal activities of artichoke extracts as well as of their phenolic compounds have been reported several authors (Zhu *et al.*, 2004, 2005; Yang *et al.*, 2005; Stoev *et al.*, 2004).

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 (Mahmoodabadi *et al.*, 2007).

3.1.3. Safety pharmacology

No information available except toxicity data presented under section 3.2 below.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

Antidyspeptic and choleric effects are mainly attributed to increased choleresis (Kraft, 1997; ESCOP 2003). At present, the mechanism of action of artichoke and its main compounds cannot be considered clarified.

Results from *in vitro* and *in vivo* studies in animals with artichoke extracts as well support the traditional use as digestion stimulant and for relief of digestive and dyspeptic problems such as dyspepsia with a sensation of fullness, bloating and flatulence.

Other possible pharmacodynamic actions such as antimicrobial, antioxidant, cytoprotective as well as antiatherosclerotic and antihypercholesterolaemic properties with increased elimination of cholesterol and inhibition of hepatocellular de novo cholesterol biosynthesis have been observed in various *in vitro* and *in vivo* test systems.

The traditional use of *Cynarae folium* for the symptomatic relief of digestive disorders such as dyspepsia with a sensation of fullness, bloating and flatulence is supported by the long standing use and the above mentioned pharmacological data.

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

No data available.

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

3.3.1. Single dose toxicity

Herbal preparations

The oral LD₃₀ and intraperitoneal LD₁₀ 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 LD₄₀ and intraperitoneal LD₅₀ were 2000 mg/kg and 265 mg/kg respectively (Bombardelli *et al.*, 1977).

The oral and intraperitoneal median lethal doses of a hydroalcoholic extract of the leaves in rats were 2 g/kg and 1 g/kg body weight, respectively (Lietti, 1977).

Cynarin

The LD₅₀ of cynarin in mice was determined as 1900 mg/kg body weight. Upon administration intraperitoneally to rats at 800 mg/kg or intravenously to rabbits at 1000 mg/kg per hour, cynarin produced no apparent side effects or signs or toxicity (Preziosi, 1958).

3.3.2. Repeat dose toxicity

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).

External application of a leaf extract to the skin of white rats, at doses of 1-3 g/kg body weight 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.*, 2003i; WHO monographs 2009).

3.3.3. Genotoxicity

Several studies on mutagenicity/genotoxicity of *Cynara scolymus* (syn *C. cardunculus*) are available.

Antimutagenic potential of *Cynara scolymus*:

Three different triterpenoid saponins (cynarasaponins) from involucre bracts of artichoke were isolated and their antimutagenic effect was assessed. The antimutagenic effect of these substances was estimated against acridine orange (AO)- and ofloxacin-induced damage of chloroplast DNA in *Euglena gracilis* assay. These cynara saponins were experimentally confirmed to exhibit different, statistically significant activity in reducing damage of chloroplast DNA of the flagellate *Euglena gracilis* induced by AO and ofloxacin ($p < 0.05-0.01$). 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 cynara saponins to reduce the chloroplast DNA lesion was not elucidated. (Križková *et al.*, 2004).

The potential antimutagenic activity of an extract (details unknown) from artichoke 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 cisplatin by the extract from artichoke was evaluated in the cell revitalisation assay by measuring cell viability via Trypan blue exclusive assay using mouse leukemia cells L1210. 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. The artichoke extract statistically significantly reduced the genotoxic effect of EMS. In the cell revitalisation assay, extract from artichoke enhanced the cytotoxic/cytostatic effect of cis-Pt. The artichoke extract significantly lowered the recovery of cisplatin pre-treated mouse leukemia cells (Miadokova *et al.*, 2006).

An extract of artichoke (*Cynara cardunculus* L.) (details unknown) was investigated for its potential antigenotoxic and antioxidant effects using four experimental model systems. In the *Saccharomyces cerevisiae* mutagenicity/antimutagenicity assay, *Cynara cardunculus* L. 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 *Cynara cardunculus* L. 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 free radical scavenging assay, *Cynara cardunculus* L. exhibited considerable antioxidant activity. The SC_{50} value representing 0.0054% *Cynara cardunculus* L. corresponds to an antioxidant activity of 216.8 μ M ascorbic acid which was used as a reference compound. Although the mechanism of *Cynara cardunculus* L. action still remains to be elucidated, different possible mechanisms are probably involved in the *Cynara cardunculus* L. antigenotoxic effects. The authors concluded that *Cynara cardunculus* L. is of particular interest as a suitable candidate for an effective chemopreventive agent. (Miadokova *et al.*, 2008).

In an *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 0.03 mmol/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%) (Edenharder *et al.*, 2003).

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 recognised 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 Kuzstelak, 1993).

Recent studies have investigated genotoxicity of ALE (Artichoke Leaf Extract). Both genotoxic and antigenotoxic effects were observed depending on the concentrations investigated, high doses of ALE (5mg/ml and 2 g/kg in cell line and mice studies, respectively) showed mutagenic effects, while lower doses showed protective antioxidant effects (Jacociunas *et al.*, 2013a). The aim of the study was to evaluate the capacity of *Cynara scolymus* L. leaves extract (LE) to cause chromosomal instability and cytotoxicity in Chinese hamster ovary cells (CHO) employing the cytokinesis-block micronucleus (CBMN) cytome assay. Cells were treated with four concentrations of *Cynara scolymus* for two exposure times: 1 h and 24 h. Our findings showed that LE did not increase the frequencies of nucleoplasmic bridges (NPBs) and nuclear bud (NBUD). However, all concentrations of the extract produced increments in micronuclei frequencies (MNi) in both exposure times, when compared to the negative control. No significant differences were observed in the nuclear division cytotoxicity index (NDCI), reflecting the absence of cytotoxic effects associated to LE. The results demonstrated the ability of *C. scolymus* LE to promote chromosomal mutations which are, probably, a result of the pro-oxidant activity of LE constituents such as flavonoids and chlorogenic acids. The authors suggested that high concentrations of artichoke could pose a risk associated to its consumption.

The genotoxicity of bloom head (BHE) and leaf (LE) extracts from artichoke (*Cynara scolymus* L.), and their ability to modulate the mutagenicity and recombinogenicity of two alkylating agents (ethyl methanesulfonate–EMS and mitomycin C–MMC) and the intercalating agent bleomycin (BLM), were examined using the somatic mutation and recombination test (SMART) in *Drosophila melanogaster*. Neither the mutagenicity nor the recombinogenicity of BLM or MMC was modified by co- or post-treatment with BHE or LE. In contrast, co-treatment with BHE significantly enhanced the EMS-induced genotoxicity involving mutagenic and/or recombinant events. Co-treatment with LE did not alter the genotoxicity of EMS whereas post-treatment with the highest dose of LE significantly increased this genotoxicity. This enhancement included a synergistic increase restricted to somatic recombination. These results show that artichoke extracts promote homologous recombination in proliferative cells of *D. melanogaster* (Jacociunas *et al.*, 2014).

3.3.4. Carcinogenicity

Caffeic acid (and chlorogenic acid)

The International Agency for Research on Cancer (IARC) has evaluated caffeic acid for its potential carcinogenicity (Anonymous 1993). After dietary administration of high doses of caffeic acid (intakes 2-3 g/kg body weight), 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 0.7-0.8 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 metabolise caffeic acid to the same metabolites and hydrolyse chlorogenic acid to caffeic acid.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

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 1 mg per ml of culture medium (Gebhardt 1997i, 1995i, 1995ii, 1997i; 1997ii).

3.3.8. Conclusions

Artichoke extracts promote homologous recombination in proliferative cells of *D. melanogaster* (Jacociunas *et al.*, 2014). Other, *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. The use in pregnancy and lactation is not recommended due to lack of data.

Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

Due to the lack of preclinical safety (especially genotoxicity) a list entry for *Cynarae folium* cannot be recommended.

3.4. Overall conclusions on non-clinical data

Pharmacokinetics

No data available.

Toxicology

Various extracts of *Cynara cardunculus* (= *C. scolymus*) demonstrated low acute toxicity. It should be also noted that all carcinogenicity (and other associated) studies available, conducted on caffeic acid 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 adequate mutagenicity or genotoxicity studies were available. Antimutagenic potential of artichoke has been reported but they seem incomplete.

There are no data on reproductive and developmental toxicity.

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

The hepatobiliary effects of Artichoke extracts including influence on choleresis, blood lipid and cholesterol lowering effects were investigated in several clinical trials. Petrowicz *et al.*, 1997 tested the lipid-lowering effects of an artichoke leaf standardised dry aqueous extract (4.5-5:1) in 44 healthy volunteers over 12 weeks in a randomised double-blind, placebo-controlled study.

The anti-dyspeptic and gastrointestinal effects of artichoke leaf aqueous dry extract (3.8-5.5:1), were studied by Fintelmann *et al.*, 1996 in a multicentre open study in 553 patients with dyspeptic complaints. The daily dose was generally 3-6 capsules of artichoke leaf a 320 mg per capsule. The global efficacy assessed by the physicians was excellent or good in 87% of cases.

Fintelmann & Petrowicz, 1998 used the same extract at a daily dosage of 3-6 capsules (320 mg per capsule in a 6-month open study of 203 patients with dyspeptic complaints). The global efficacy assessed by the physicians was excellent or good in 85.7% of cases.

Marakis *et al.*, 2002, 2003 observed in a post-marketing study that a standardised artichoke leaf extract (water >80°C, DER 4-6:1, minimum 0.3% flavonoids) also reduces symptoms of dyspepsia. The authors observed that artichoke leaf extract ameliorates upper gastro-intestinal symptoms in otherwise healthy subjects suffering from dyspepsia.

Holtmann *et al.*, 2003ii studied in a double-blind, randomised placebo controlled, multicenter trial (RCT) the efficacy of artichoke leaf extract ((water > 80°C DER 4-6:1), capsules, 2x320 mg three times daily), in patients with functional dyspepsia and irritable bowel syndrome (IBS) with some positive results.

According to the monographs of the Commission E and ESCOP and earlier published clinical studies the artichoke leaf preparation was acceptable superior to placebo in the treatment of patients with functional dyspepsia, while the safety profile was very good.

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

Different studies provided information on pharmacokinetic 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. After two days of a low-polyphenol diet 10 healthy volunteers were treated with 3x320 mg of an artichoke leaf aqueous 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 a series of studies were performed in a screening approach to predict

impending interactions (Hilgendorf & Döppenschmidt, 2003). Human liver microsomes were used for screening, using 8 standard subtype-specific CYP substrates. The testing included ethanolic extracts of *Serenoa repens* (*Sabal serrulata*, SR), *Hypericum perforatum*, *Harpagophytum procumbens*, *Piper methysticum* (Kava, KA) and *Cynara scolymus*. At extract concentrations derived from dose recommendations provided by German authorities (Commission E), different effects of the various plants were observed. The extracts of herbal drugs broadly used in Germany accomplish inhibition as well as activation of human CYP activity *in vitro* while detailed results concerning *Cynara* are not presented.

The metabolism and disposition of two different leaf extracts (extract A: dicaffeoylquinic acids 28.9%, flavonoids 8.8%; extract B: dicaffeoylquinic acids 6.2%, flavonoids 0.9%) were investigated in healthy volunteers enrolled in a two-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 (Wittemer *et al.*, 2002, 2005).

The active constituents of Artichoke Leaves Extracts have not been detected in human plasma or urine. Several metabolites detected in human plasma have been identified as being derived from mono and dicaffeoylquinic acids, and from flavanoids that are known active phenolic constituents of artichoke extract. The metabolites caffeic acid, ferulic acid, and isoferulic acid achieved peak plasma concentrations within 1 hour and declined over 24 hours, demonstrating a near biphasic profile. The hydrogenated metabolites dihydrocaffeic acid and dihydroferulic acid were detected after 6 to 7 hours, suggesting the involvement of more than one pathway in processing caffeoylquinic acids. Peak plasma concentration of luteolin was reached within 30 minutes, with elimination showing a biphasic profile (Salem *et al.*, 2015; Wittemer *et al.*, 2005).

A method was developed for the simultaneous determination of the hydroxycinnamates caffeic, dihydrocaffeic, ferulic, dihydroferulic, and isoferulic acid and the flavonoid luteolin in human plasma as metabolites derived from artichoke leaf water extract (water > 80°C, DER 4-6:1). Selectivity and sensitivity towards the target compounds were achieved by using the HPLC method with electrochemical array detection. Calibration curves were constructed in the ranges 2.1-51.7 ng/ml hydroxycinnamates caffeic, 2.0-76.7 ng/ml dihydrocaffeic, 2.2-53.7 ng/ml ferulic, 2.1-79.2 ng/ml dihydroferulic, 1.1-52.6 ng/ml isoferulic acid and 2.1-258.6 ng/ml flavonoid luteolin. Values for within-day and between-day precision and accuracy were in accordance with the international guidelines for validation of bioanalytical methods. The authors concluded that this method is appropriate for analysing samples from bioavailability and pharmacokinetic studies after oral administration of artichoke leaf extract (Wittemer & Veit, 2003).

In order to get more detailed information about absorption, metabolism and disposition of Artichoke leaf extract (water > 80°C, DER 4-6:1), 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 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, its methylated derivatives ferulic acid and isoferulic acid and the hydrogenation products dihydrocaffeic acid and dihydroferulic acid were identified as metabolites derived from caffeoylquinic acids. Except of dihydroferulic acid all of these compounds were present as sulfates or glucuronides. Peak plasma concentrations of total caffeic acid, ferulic acid and isoferulic acid

were reached within 1 hour and declined over 24 hours showing almost biphasic profiles. In contrast maximum concentrations for total dihydrocaffeic acid and dihydroferulic acid were observed only after 6-7 hours, indicating two different metabolic pathways for caffeoylquinic acids. Luteolin administered as glucoside was recovered only from plasma and urine as sulfate or glucuronide but neither in form of genuine glucosides nor as free luteolin. Peak plasma concentrations were reached rapidly within 0.5 hour. The elimination showed a biphasic profile (Wittemer *et al.*, 2005).

After oral consumption of cooked edible heads of *Cynara scolymus* L. (cultivar Violetto di Provenza) a pilot study (Azzini *et al.*, 2007) investigated the absorption and metabolism of bioactive molecules in human subjects. Results showed a plasma maximum concentration of 6.4 (standard deviation=sd 1.8) ng/ml for chlorogenic acid after 1 hour and its disappearance within 2 hours ($p < 0.05$). Peak plasma concentrations of 19.5 (sd 6.9) ng/ml for total caffeic acid were reached within 1 hour, while ferulic acid plasma concentrations showed a biphasic profile with 6.4 (sd 1.5) ng/ml and 8.4 (sd 4.6) ng/ml within 1 hour and after 8 hours respectively. The authors observed a significant increase of dihydrocaffeic acid and dihydroferulic acid total levels after 8 hours ($p < 0.05$). 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. The study shows the absorption pathways of hydroxycinnamic acids after consumption of edible cooked artichoke in human subjects.

4.2. Clinical efficacy

4.2.1. Dose response studies

There are no dose response studies available.

4.2.2. Clinical studies (case studies and clinical trials)

Blood lipid and cholesterol lowering effects

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

Decrease in cholesterol, triglycerides, three fatty acids, phospholipids and α -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 (defined as ethanolic extract from the aerial parts of artichoke) containing 0.09% or polyphenols (Wojcicki *et al.*, 1981).

In a comparative study, 73 patients with primary hyper-triglyceridaemia resistant to treatment with clofibrate were treated daily for 1 month with 9 tablets containing an undefined artichoke extract (this extract was defined as ethanolic extract of the aerial parts of artichoke, *Cynarae herba*), each tablet 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 40% of the patients, respectively (Wojcicki *et al.*, 1982).

In an open study, 403 patients with functional gallbladder disorders were treated with an undefined artichoke extract (2 tablets twice daily, each containing 375 mg of extract standardised 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 (Held, 1991-cited in ESCOP 2009).

In a randomised double-blind, placebo-controlled study, the lipid-lowering effects of an artichoke leaf standardised dry aqueous extract (4.5-5:1) were investigated in 44 healthy volunteers over 12 weeks. The mean initial concentrations were very low in both the verum (204.2 mg/dl, n=22) and placebo (203 mg/dl, n=22) groups in volunteers with initial cholesterol >230 mg/dl. 640 mg 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. 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, treatment with the extract led to a significant difference (p=0.022) for triglycerides compared to placebo (Petrowicz *et al.*, 1997).

In a multicentre, randomised, 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 (Englisch *et al.*, 2000).

In a study with an average duration of about 24 days, in 54 patients the effect of a standardised preparation (aqueous artichoke leaf extract 3.8-5.5:1) 3x320 mg was measured in comparison with placebo or fibre. The average lowering of cholesterol in all test patients with verum was 16.8% compared to 10% in all patients with placebo. This difference was statistically significant. A stronger cholesterol lowering effect was observed with a simultaneous dose of fibre. The lowering of LDL was similar to that of total cholesterol. The LDL/HDL-quotient was 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. Dropouts or side effects were similar between verum and placebo groups. Adverse events/side effects reported were for the verum: hypersensitivity reactions [SOC (sense of coherence): immune system disorders], n=1 and for the placebo: flatulence [SOC: gastrointestinal disorders], n=1; Other adverse events reported were nausea, headache, sleep disturbances and stomach ache without any information whether they occurred in the verum or in the placebo group (Schmiedel, 2002).

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 non-invasive 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. Lupatteli *et al.* investigated 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. $4.5 \pm 2.4\%$, $p < 0.01$), 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 $p < 0.05$). The authors concluded that artichoke dietary supplementation seems to positively modulate endothelial function in hypercholesterolemia (Lupatteli *et al.*, 2004).

Bundy *et al.* studied the effect of artichoke leaf extract on plasma lipid levels and general well-being in otherwise healthy adults with mild to moderate hypercholesterolemia. One hundred and thirty one adults were screened for total plasma cholesterol in the range 6-8 mmol/l, with 75 suitable volunteers randomised onto the trial. Volunteers consumed 1280 mg of a standardised artichoke leaf extract (not further detailed given) 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 (Bundy *et al.*, 2008).

Assessor's comment:

In conclusion, artichoke leaf extract consumption resulted in a modest but 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

In a double-blind placebo-controlled cross-over clinical trial, the choleric effect of a single dose of an artichoke product was investigated in 20 male volunteers with acute or chronic metabolic disorders. The group was randomised separated in two 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 standardised dry aqueous extract (4.5-5:1) of artichoke leaf extract in 50 ml water) or a placebo of similar appearance was administered via an intraduodenal probe, the subject having empty stomach on test days. The monitored bile secretion was significantly higher ($p < 0.01$) in the verum group: 127% higher at 30 minutes after administration, 151% after 60 minutes (the maximum effect) and 94% after 90 minutes. Results after 120 minutes and 150 minutes were also significantly higher ($p < 0.05$). Placebo treatment stimulated bile secretion to a lesser extent, with a maximum increase of 39% after 30 minutes. No adverse or relevant changes in laboratory safety parameters were observed (Kirschhoff *et al.*, 1994).

Kraft summarised 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 (Kraft, 1997).

Antidyspeptic and gastrointestinal effects

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 complaints 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 approximately 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%. The global efficacy assessed by the physicians was excellent or good in 87% of cases (Fintelmann, 1996).

The same extract at a daily dosage of 3-6 capsules (320 mg per capsule) was evaluated in a 6-month open study of 203 patients with dyspeptic complaints. After 21 weeks of treatment, the overall improvement of 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 in 171 and 170 patients decreased by 10.9% and 11%, respectively. From determinations in 159 patients, LDL-cholesterol decreased by 15.8% and HDL-cholesterol increased by 6.3%. The global efficacy assessed by the physicians was excellent or good in 85.7% of cases. No adverse reactions were reported (Fintelmann & Petrowicz, 1998).

A post-marketing study suggests that high doses of standardised artichoke leaf extract (water >80°C, DER 4-6:1, minimum 0.3% flavonoids) may reduce symptoms of dyspepsia. As a follow-up the efficacy of a low-dose artichoke leaf extract on amelioration of dyspeptic symptoms and improvement of quality of life were investigated. The study was an open, dose-ranging postal study. Healthy patients with self-reported dyspepsia were recruited through the media. The Nepean Dyspepsia Index (NDI) and the State-Trait Anxiety Inventory were completed at baseline and after 2 months of treatment with artichoke leaf extract, 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 artichoke leaf extract shows promise to ameliorate upper gastro-intestinal symptoms and improve quality of life in otherwise healthy subjects suffering from dyspepsia (Marakis *et al.*, 2002, 2003).

Assessor's comment:

The results of this open study add some evidence to the traditional 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.* assessed the efficacy of artichoke leaf extract ((water > 80°C DER 4-6:1), capsules, 2x320 mg three times daily), in the treatment of patients with functional dyspepsia and irritable bowel syndrome (IBS). In a double-blind, randomised placebo controlled, multicentre 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 artichoke leaf extract LI 120 preparation 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 as assessed by the Nepean Dyspepsia Index (NDI). 247 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 artichoke leaf extract than with the placebo (8.3±4.6, vs. 6.7±4.8, p<0.01). Similarly, patients treated with artichoke leaf extract 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 (Holtmann *et al.*, 2003i; 2003ii).

Assessor's comment:

the artichoke leaf preparation was better to placebo in the treatment of patients with functional dyspepsia. The safety profile was good, adverse events (sense of coherence (SOC): gastrointestinal disorders) mostly classified as mild or moderate and self-resolving. One serious reaction (moderate bilateral anexitis; (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.

Other effects

In a placebo-controlled, double-blind study in malaria patients, a purified aqueous dry extract from fresh artichoke leaf juice administration intramuscularly (100 mg per day) and orally (1600 mg per 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 was attributed to hepatoprotective effects of the artichoke extract (Wone *et al.*, 1986).

Irritable bowel syndrome

Irritable bowel syndrome (IBS), characterised 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 post-marketing surveillance study was performed to assess its effects on IBS. A subgroup of patients (n=279) with symptoms of IBS 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 IBS 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).

Bundy *et al.*, performed a subset analysis of a previous dose-ranging, open, postal study with artichoke leaf extracts, 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 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/diarrhoea" 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 score in the subset after treatment. This report supports previous findings that artichoke leaf extract ameliorates symptoms of IBS, plus improves health-related quality-of-life. Artichoke leaf extract (extraction solvent: water; 5:1) 320 or 640 mg per day was used for the study (Bundy *et al.*, 2004).

Assessor's comment:

This study evaluated the therapeutic value of artichoke leaf extract in those patients with dyspepsia who suffer from IBS. The analysis was performed on a subset of patients from a previously performed study in patients with dyspepsia and indicated that artichoke leaf extract may be of positive value in IBS patients for the symptoms assigned to dyspepsia. Especially the condition of alternating constipation/diarrhoea responded well to the artichoke extract treatment. Although not placebo controlled, this study/subset analysis yields evidence for a possible value of artichoke leaf extract in

IBS, which is currently not an approved indication of artichoke products. Adverse events/side effects were not reported.

Table 4: Clinical studies on humans

Type	Study design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Wojcicki & Winter 1975	Observational study	Daily dose : 900 mg Artichoke extract (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 ($p, 0.05$) Lack of side effects	Mean deviation before and after treatment	Small study too low number of objects
Wojcicki <i>et al.</i> , 1982	Comparative study	Undefined ALE (9 tablets, of 5 mg of polyphenolic acids , $n=25$) or 0.75 g or 1.5 g cynarin <i>per os</i> 1 month	73 patients	Primary hypertriglyceridaemia resistant to treatment with clofibrate	The ALE 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	The model values (x) of all examined parameters (cholesterol content, lipid parameters) prior and after treatments in subgroups with and without amelioration	Not well defined artichoke extract, short period study
Kirschhoff <i>et al.</i> , 1994	Double-blind, placebo-controlled , cross-over study	1.92 g standard dry water extract (4.5-5:1) of artichoke leaf (6x 320 mg) or placebo administered <i>via</i> an intraduodenal probe	20 males in two subgroups	Patients with acute or chronic metabolic disorders	Monitored bile secretion after 30, 60 90, 120 and 150 minutes: bile secretion higher ($p < 0.01$) in verum group: 127% higher 30 min after administration, 151% after 60	All analyses in concordance with good clinical practice-guidelines and	Small study too low number of objects lasting only

Type	Study design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
					min (the maximum effect) and 94% after 90 minutes result a after 120 min and 150 min were also significantly higher (p<0.05). Placebo treatment maximum increase 39% after 30 minutes	statistical analyses	2.5 hours
Fintelman n 1996	Multicentre open study	Daily dose 3-6 caps. ALE aqueous dry extract (3.8-5.5:1, 320 mg per capsule) <i>per os</i> 43.5 days	553 patients with dyspeptic complaints	Dyspepsia digestive complaints	Digestive complains declined within 6 weeks of treatment. All symptoms improved 71%. Meteorism reduction approximately 66%, 76% for abdominal pain, 82% for nausea 88% for emesis. In subgroup of 302 patients, total cholesterol decreased 11.5% and triglycerides 12.5%	Mean deviation before and after treatment	Due to the open study design the study only supports the plausibility
Kraft 1997	Post-marketing surveillance studies overview	Daily dose 3-6 capsules aqueous artichoke leaf dry extract (3.8-5.5:1), 320 mg per capsule <i>per os</i> 4 to 6 weeks	417 to 557 patients in total	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. Artichoke preparations were well tolerated (up to 95% of cases) with a low rate of side-effects	No special data reported, as data are coming from an overview of different studies performed	A mixture of different patients and inclusion criteria
Petrowicz <i>et al.</i> ,	Randomised double-blind,	640 mg dry water extract 3 times daily <i>per os</i>	44 health volunteers	Volunteers with initial cholesterol >230	Lipid lowering effects Decreased concentration of total cholesterol (p=0.015) and	The mean differences before and	Small number of subjects

Type	Study design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
1997	placebo-controlled study Efficacy, tolerability	Placebo 12 weeks	Verum=22 Placebo=22 No one dropped out	mg/dl($n_v-n_p=3$)	triglycerides ($p=0.01$) compared to placebo. Cholesterol >220 mg/dl ($n_v-n_p=5$), significant different ($p=0.012$) for triglycerides compared to placebo	after the treatment calculated using a fixed-effect model	reported insufficient data
Fintelman & Petrowicz 1998	Multicentre open study, safety, Efficacy, Tolerability	Daily dose 3-6 capsules aqueous dry extract (3.8-5.5:1, 320 mg per capsule) <i>per os</i> 6 months	203 patients	Dyspepsia digestive complaints	After 21 weeks treatment improvement of symptoms 66% e.g. vomit by 84%, abdominal pain 78%, nausea 76%, flatulence 70% and meteorism 69%. Total blood cholesterol -triglycerides, in 171 among patients decreased by 10.9% and in 159 patients LDL-cholesterol decreased by 15.8% and HDL- cholesterol by 6.3%. Global efficacy by the physicians excellent or good in 85.7% of cases No adverse effects	The mean differences before and after the treatment were calculated	Due to the open study design the study only supports the plausibility
Englisch <i>et al.</i> , 2000	Multicentre randomised placebo-controlled, double-blind study	Fresh artichoke leaf water extract (25-35:1) Daily 1800 mg (n=71) or placebo (n=72) as	143 patients	Patients with hyperlipoprotein aemia (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 significantly superior ($p=0.0001$) to those in	The primary criteria for efficacy were defined as difference of the changes of	Small study, short duration

Type	Study design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		coated tabs <i>per os</i> 6 weeks			placebo group (8.6% and 6.3% respectively) LDL/HDL ratio decreased by 20.2% in verum group and 7.2% in the placebo group	total cholesterol and changes of γ -GT in the blood, calculated as baseline adjusted between baseline (day 0) and endpoint (day 42 \pm 3) Adjustments were made by analysis of covariance (ANCOVA)	
Schmiedel 2002	Placebo study	Standardised preparation (aqueous ALE 3.8-5.5:1) (comparison with placebo) 3x320 mg 24 days	54 patients	Patients with hyperlipoprotein-aemia	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 Interesting side effects: verum: hypersensitivity reactions [SOC: immune system disorders] n=1; placebo: flatulence [SOC:	Average of the calculated differences between baseline and endpoint	Small number of subjects; short duration

Type	Study design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
					gastrointestinal disorders] n=1; adverse effects nausea, headache, sleep disturbances and stomach ache without information whether they occurred in the verum or in placebo group		
Lupatteli <i>et al.</i> , 2004		20 ml per day of frozen artichoke juice 6 weeks	28	28 moderately hyperlipemic patients 10 hyperlipemic patients men and women	Lipid lowering effects Controls showed 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)	Differences between groups were made by ANOVA. Data were analysed by SPSS statistical package	Very small study with short duration
Bundy <i>et al.</i> , 2008	Randomised, double blind placebo controlled trial	1280 mg (320 x 4) 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	Analysis of variance (ANOVA) was used to test for differences in mean values within groups. Statistical analyses were	Small study with no significant differences between groups were observed

Type	Study design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
					between groups statistically significant (p=0.025). No significant differences between groups were observed for LDL cholesterol, HDL cholesterol or triglyceride levels	performed using SPSS	for LDL cholesterol, HDL cholesterol or triglyceride levels
Marakis <i>et al.</i> , 2003	Open, dose-ranging postal study	320 or 640 mg of ALE daily 2 months	516/454 completed the study	516 participants 454 completed the study self-reported dyspepsia. Nepean Dyspepsia Index and State-Trait Anxiety Inventory were completed at baseline	Dyspepsia digestive complaints: significantly reduction of all dyspeptic symptoms, with an average reduction of 40% in global dyspepsia score. Health-related quality of life significantly improved compared with baseline. ALE ameliorates upper gastrointestinal symptoms and improves in healthy suffering from dyspepsia. side effects: constipation: n=2; loose stool: n=2; flatulence: n=1 [SOC: gastrointestinal disorders]	Results are expressed as means. Analysis was performed using MINITAB	Due to the open study design the study only supports the plausibility of the application of Cynarae extract. High drop-out number of subjects
Holtmann <i>et al.</i> , 2003	Double-blind, randomised controlled trial (RCT)	(ALE) [(water>80°C DER 4-6:1), 2x320 mg t.i.d], 6 weeks	247 patients	Patients with functional dyspepsia	Treatment of functional dyspepsia (FD) Quality of Life (QOL) as assessed by the Nepean Dyspepsia Index (NDI)	All analyses followed good clinical practice-guidelines. A two side t-test	Short duration of the study

Type	Study design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
					<p>Functional dyspepsia</p> <p>Data from 244 patients (129 active treatment, 115 placebo) were suitable statistical analysis.</p> <p>All symptom improvement was significantly higher with ALE than with the placebo (8.3±4.6, vs. 6.7±4.8, p<0.01). ALE showed significant greater improvement in global quality-of-life scores (NDI) compared with placebo-treated patients (41.1±47.6 vs. -24.8±35.6, p<0.01)</p>	<p>was used for the analysis of the primary and secondary outcome. In case of deviation from the normal distribution the Wilcoxon U-test was used instead of the t-test</p>	
Bundy <i>et al.</i> , 2004	Open, study	ALE (extraction solvent: water; DER 5:1) 320 or 640 mg per day 2 months		Patients with dyspepsia dealing with irritable bowel syndrome (IBS)	Significant fall in IBS incidence of 26.4% (p<0.001) after ALE; NDI (Nepean Dyspepsia Index) total symptom score significantly decreased by 41% (p<0.001) after ALE. Significant improvement 20% in NDI total quality-of-life (QOL)	McNemar test for dichotomous data, test was used to ascertain baseline differences in mean NDI symptoms and QOL scores (quality of life);analysis of	Open study supports the plausibility

Type	Study design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
						variance (ANOVA) used to test for differences in mean values within groups	

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

Long standing use and safety of preparations of *Cynarae folium* is supported by pharmacological studies, current findings of physiological properties and result from clinical studies. However, the available clinical data are not sufficient to support a well-established use indication.

5. Clinical Safety/Pharmacovigilance

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

The clinical safety evaluation of *Cynarae folium* is based on the considerable traditional experience and on the results from clinical studies.

5.2. Patient exposure

According to the above referred clinical trials:

Kraft, 1997 summarises 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 where artichoke preparations (daily dose 3-6 caps artichoke leaf, aqueous dry extract (3.8-5.5:1, 320 mg per capsule)) per os were well tolerated (up to 95% of cases) with a low rate of side-effects.

The same extract (Fintelmann & Petrowicz, 1998) was evaluated in a 6-month open study of 203 patients with dyspeptic complaints. After 21 weeks of treatment, no adverse reactions were reported.

A post-marketing study (Marakis *et al.*, 2002, 2003) indicated that high doses of standardised artichoke leaf extract (water >80°C, DER 4-6:1, minimum 0.3% flavonoids) could reduce symptoms of dyspepsia. Of the 516 participants, 454 completed the study. Adverse event/side effects observed were constipation: n=2; loose stool: n=2; flatulence: n=1 gastrointestinal disorders. The safety profile was very good, adverse events (sense of coherence, 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).

In conclusion, all data obtained from clinical trials, showed a good safety profile of artichoke leaf preparations in for patients with functional dyspepsia. The undesirable effects reported slight diarrhoea with abdominal spasm, epigastric complaints like nausea, and heartburn have been reported. The frequency is not known.

Contraindications

Hypersensitivity to the active substance or to plants of the Asteraceae family (Compositae).

In contrast to the monograph of *Curcumae longae* rhizome, the monograph of *Cynara folium* includes the following contra-indication: "Obstruction of bile duct, cholangitis, liver disease, gallstones and any other biliary disorders that require medical supervision and advice."

This contra-indication is included in the monograph because according to a double-blind placebo-controlled cross-over study Kirchhoff *et al.*, artichoke extract increases bile secretion (Kirchhoff *et al.*, 1994).

5.3. Adverse events, serious adverse events and deaths

Data from products on the European market and clinical trials indicate that generally the herbal preparations of artichoke are well tolerated. Slight diarrhoea with abdominal spasm, epigastric complaints like nausea, and heartburn has been reported. The frequency is not known.

Allergic reactions may occur. The frequency is not known.

If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.

One (serious) case was related to the treatment with a medicinal product containing artichoke leaf dry extract. 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 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 a commercial product (2 ampoules per day) for slimming on 6 November 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 administration of the product 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. 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.

Anaphylactic reaction to inulin: A 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. 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 (Franck *et al.*, 2005).

Acute oedema of the tongue: a life-threatening condition. This paper focuses on a number of life-threatening cases of acute tongue oedema. 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 (Gadban *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 expose 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* (Miralles *et al.*, 2003).

Assessor's comment:

A total of 5 cases with adverse reactions during treatment with Cynara have 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

None reported

5.5.1. Use in children and adolescents

No data available.

5.5.2. Contraindications

Hypersensitivity to the active substance or to plants of the Asteraceae family (Compositae).

Due to stimulation of bile secretion, Obstruction of bile duct, cholangitis, liver disease, gallstones and any other biliary disorders that require medical supervision and advice are contraindicated.

5.5.3. Special Warnings and precautions for use

The use in children under 12 years of age has not been established due to lack of adequate data.

5.5.4. Drug interactions and other forms of interaction

None reported

5.5.5. Fertility, pregnancy and lactation

One publication reviews herbal infusions used for induced abortion (Ciganda & 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.

No fertility data.

5.5.6. Overdose

No data available.

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

No data available.

5.5.8. Safety in other special situations

Not applicable

5.6. Overall conclusions on clinical safety

Only mild adverse events were reported in all published clinical trials. Slight diarrhoea with abdominal spasm, epigastric complaints like nausea, and heartburn have been reported. The frequency is not known.

Allergic reactions may occur (artichoke belongs to Asteraceae–Compositae family). The frequency is not known.

If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.

The use in children under 12 years of age has not been established due to lack of adequate data.

Hypersensitivity to the active substance or to plants of the Asteraceae family (Compositae).

Due to the available clinical data (Kirchhoff *et al.*, 1994), showing stimulation on bile secretion, contrary to other herbal medicinal products with similar indication (like *Curcumae longae rhizoma*), for artichoke it is agreed at HMPC to keep :“Obstruction of bile duct, cholangitis, liver disease, gallstones and any other biliary disorders that require medical supervision and advice”, as a contraindication(section 4.3 on the monograph) and not as a special warning and precaution for use (section 4.4)“.

The use in children under 12 years of age has not been established due to lack of adequate data.

Interactions with other medicinal products and other forms of interaction have not been reported.

6. Overall conclusions (benefit-risk assessment)

Artichoke is characterised by the phenolic acid constituents. Experimental studies (*in vitro* and *in vivo*) support some of the uses of artichoke. Traditionally, the choleric and cholesterol-lowering activities of globe artichoke have been attributed to cynarin (Lietti, 1977). Studies in animals and humans have

suggested that these effects may in fact be due to the monocaffeoylquinic acids and cynarin present in artichoke (e.g. chlorogenic and neochlorogenic acids). 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); even though, these effects have not yet been documented in clinical studies.

There are no sufficient data from well-designed clinical trials to support well-established use in this indication. Therefore the medicinal use of artichoke leaf has to be regarded as traditional in the sense of Dir. 2004/24/EC. However, the outcome of the clinical trials supports the plausibility in the proposed indication.

Moreover, the following herbal preparations are for more than 30 years on the European market and are proposed to be included in the monograph for Traditional Use:

- a) Comminuted dried leaves for herbal tea
- b) Powdered leaves
- c) Dry extract of dried leaves (2-7.5:1), extraction solvent water
- d) Dry extract of fresh leaves (15-35:1), extraction solvent water
- e) Soft extract of fresh leaves (15-30:1), extraction solvent water
- f) Soft extract of dried leaves (DER 2.5-3.5:1), extraction solvent ethanol 20% (V/V)

These herbal preparations are indicated for the symptomatic relief of digestive disorders such as dyspepsia with a sensation of fullness, bloating and flatulence, based on long standing use.

Only mild adverse events were reported in all published clinical trials. A total of 5 cases with adverse reactions during treatment with artichoke have been identified in the literature, which did not alter the benefit risk ratio.

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

As there is no adequate data on genotoxicity the establishment of a European Union List Entry is not supported.

Annex

List of references