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EMA/HMPC/648162/2022
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Cnicus benedictus* L., herba

Final

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Cnicus benedictus</i> L., herba
Herbal preparation(s)	a) Powdered herbal substance b) Comminuted herbal substance c) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V d) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 25% V/V
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid or solid dosage forms for oral use.
Rapporteur(s)	O. Palomino
Peer-reviewer	C. Purdel



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1. Introduction

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

- Herbal substance(s)

There is no European Pharmacopoeia monograph for the herbal substance.

A monograph exists in the Austrian Pharmacopoeia for *Cnici benedicti herba* (Kardobenediktenkraut: ÖAB 2009/007), the German Codex (DAC, 1986), the British Herbal Pharmacopoeia (1996) and the British Herbal Compendium (Bradley, 1992). Holy thistle (or blessed thistle) consists of the dried aerial parts of *Cnicus benedictus* L. (Asteraceae), collected when the plant is in flower.

Synonyms: *Centaurea benedicta* (Bernh.), Sp. Pl. ed. 2 1296 (1763); *Carbenia benedicta* (L.) Adans., Fam. Pl. 2: 116 (1763); *Carbenia benedicta* (L.) Arcang., Comp. Fl. Ital. 397 (1882); *Hierapicra benedicta* (L.) Kuntze, Revis. Gen. Pl. 347 (1881); *Carduus benedictus* (L.) Thell. in Bull. Herb. Boissier ser. 2 8: 788 (1908); *Cnicus benedictus* L., Sp. Pl. 826 (1753); *Calcitrapa lanuginosa* Lam., Fl. Fran. 2: 35 (1779), nom. illeg.; *Benedicta officinalis* Bernh., Syst. Verz. 159 (1800); *Cnicus benedictus* var. *kostchyi* Boiss., Fl. Orient. 3: 706 (1875); *Cnicus benedictus* var. *microcephalus* Boiss., Fl. Orient. 3: 705 (1875) (Castroviejo, 1986–2012).

Constituents: Blessed thistle contains sesquiterpene lactones including cnicin (bitter index = 1;1,800) (0,2-0,7%), and salonenolide, tannins (8%), high mineral content (mainly potassium, manganese, magnesium, and calcium), lignin lactones (lignanoides such as arctigenin, trachelogenin), phytosterols, triterpenoids, volatile oils (0.3%), phytosterols, and small amounts of flavonoids and polyacetylenes (Avula et al., 2022; Bradley, 1992; Leung and Foster, 1996; Newal et al., 1996; Wichtl and Bisset, 1994).

- Herbal preparation(s)

a) Powdered herbal substance

b) Comminuted herbal substance

c) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V

d) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 25%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, where applicable.

Not applicable.

1.2. Search and assessment methodology

Available literature on *Cnicus benedictus* (= *Centaurea benedicta*) in the electronic databases PubMed, Toxline and The Cochrane Library, and the incoming on the "Call for scientific data for use in HMPC assessment work on *Cnici benedicti herba*", were used for a literature search. Articles were filtered by using the following terms: *Cnicus benedictus*, *Centaurea benedicta*, holly thistle, blessed thistle. Also, books, book chapters, and articles and letters in journals and medical press reviews were assessed. No restrictions to language were applied. The search was performed twice: January 2022 and June 2022.

Results in PubMed: with the search term "*Cnicus benedictus*", 20 references were obtained in June 2022; search term "*Centaurea benedicta*", 2 results; search term "holly thistle", no results; search term "blessed thistle", 8 results.

Results in Toxline/National Library of Medicine: one complete reference was found for *Cnicus benedictus*, *Centaurea benedicta* or blessed thistle.

Results in The Cochrane Library: with the search term "blessed thistle", 12 results were obtained, mainly about the use of herbal medicines in women during breastfeeding.

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 marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
Cnici benedicti herba, comminuted	Supportive in mild digestive ailments and lack of appetite, as stimulant for the secretion of gastric juice	Comminuted herbal substance for herbal tea, decoction. 2 g (one teaspoon) pour with a glass (200 mL) of hot water. Bring to boil and boil under cover for 5 min. Set aside for 10 min., strain. Drink the herbal tea 2-3 times daily, 30 min. before meals.	NA, 1993, PL
Cnici benedicti herba, comminuted	Supportive in mild digestive ailments and lack of appetite, as stimulant for the secretion of gastric juice	Comminuted herbal substance for herbal tea, decoction. 3 g (one teaspoon) pour with a glass (200 mL) of hot water. Bring to boil and boil under cover for 5 min. Set aside for 10 min., strain. Drink the herbal tea 2 times daily, 30 min. before meals.	NA, 1993, PL
Cnici benedicti herba	Lack of appetite and digestive disturbances	1.0-2.0 g powdered herbal substance or pills. 5.0-10.0 g of comminuted herbal substance for infusion/decoction un 150 mL of water. Single dose before meals.	Informator Terapeutyczny, PL, 1955*
Cnici benedicti herba	Lack of appetite,	5.0-10.0 g of comminuted	Informator

Active substance	Indication	Pharmaceutical form	Regulatory Status
	digestive disturbances and as remineraliser Antiseptic in dermatological use	herbal substance for infusion/decoction un 200 mL of water. Single dose before meals.	Terapeutyczny, PL, 1955*

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

*In Poland, there were yearly lists of products approved for sell in pharmacies or medical-herbal shops, since the fifties of the 20th century; the official lists were distributed in pharmacies. The first registration system according to the European framework was held in the years of 1992-1993 in the Drug Institute in Warsaw, and most of the first registration certificates (IL/...) were extensions of registration of herbal medicines for which in the period of 1987-1992 were sent individual confirmations or agreements of the Ministry of Health.

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

Not applicable.

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

Not applicable.

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

Not applicable.

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

Blessed or "holy" thistle is an annual herb native to the Mediterranean region and western Asia. It was brought under cultivation in Europe during the sixteenth century and was mentioned as a heal-all in treatises of the Plague, from where the species name *benedictus* was derived (Blumenthal, 2000).

It has been used for more than 2000 years as a bitter, to stimulate appetite, enhance bile secretion, strengthen the liver, diminish jaundice, decrease flatulence and aid digestion. Different preparations have been also traditionally used as a diuretic, diaphoretic, emmenagogue, contraceptive, antipyretic, as a cure for bubonic plague sores and malaria, and as a general tonic/cure-all (Newall et al., 1996; Ulbricht et al., 2008). The external use of holy thistle preparations includes the treatment of gangrenous and indolent ulcers (Bradley et al., 1992; Newall et al., 1996).

The Hagers handbuch (Frerichs et al., 1938) reflects the use of holy thistle for the lack of appetite and as a bitter tonic.

In Poland, preparations of *Cnici benedicti* (*Herba Cardui benedicti*) for the lack of appetite and digestive disturbances, and also in dermatology as antiseptic, are shown in the Informator Terapeutyczny USL 1955 and 1959.

Currently, blessed thistle is used in the EU and USA as a bitter tonic to treat dyspepsia, flatulence and indigestion in the form of tablets, aqueous infusion, alcoholic fluid extract or tincture; it is also included as a flavouring agent in food, such as the Benedictine liqueur (Ulbricht, 2008; Wichtl and Biset, 1994), and is listed in the Belgium legislation as a vegetal specie to be included in Food Supplements (*Cnicus benedictus* L., aerial parts)(RD, 2017).

Table 2. Overview of historical data

Herbal preparation	Documented use / traditional use	Pharmaceutical form	Reference
Cnici benedicti herba	Aperitive, bitter tonic	Powder, tablets: 1-2 g. Herbal tea for infusion or decoction: 5.0-10.0 g in 150 mL water.	Frerichs et al., 1938
Cnici benedicti herba	Lack of appetite, anorexia, flatulent dyspepsia	Dried herb: 1.5-2 g in infusion. Liquid extract 1:1, 25% ethanol: 1.5-2 mL. Tincture 1:5, 25% ethanol): 3-6 mL.	BHC, 1992
Cnici benedicti herba	Anorexia, flatulent dyspepsia	Dried herb: 1.5-3.0 g or by infusion, 3 times daily. Liquid extract: 1:1 in 25% alcohol: 1.5-3.0 mL, 3 times daily.	Newal et al., 1996
Cnici benedicti herba	Loss of appetite, (flatulent) dyspepsia	Herbal substance: 4-6 g per day (cut herb or dried extract). Herbal tea: 1.5-2 g in 150 mL water, 3 times daily. Fluid extract 1:1 (g/mL): 1.5-2 mL, 3 times daily. Tincture 1:5 (g/mL): 7.5-10 mL, 3 times daily.	Blumenthal, 2000
Cnici benedicti herba	Stomachic, aperitive, spasmolytic, carminative, cholagogic	Herbal tea: 2 tea spoonful in boiling water; allow to steep for 30 min, then strain. Daily dose: 2-3 cups, 15-30 min before each meal. Tincture (1:5): 10-30 drops in a liqueur glass of water, several times per day.	Weiss & Fintelmann, 2000

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Cnici benedicti herba, comminuted	Supportive in mild digestive ailments and lack of appetite, as stimulant for the secretion of gastric juice	Comminuted herbal substance for herbal tea, decoction. 2 g (one teaspoon) pour with a glass (200 mL) of hot water. Bring to boil and boil under cover for 5 min. Set aside for 10 min., strain. Drink the herbal tea 2-3 times daily, 30 min. before meals.	NA, 1993, PL
Cnici benedicti herba, comminuted	Supportive in mild digestive ailments and lack of appetite, as stimulant for the secretion of gastric juice	Comminuted herbal substance for herbal tea, decoction. 3 g (one teaspoon) pour with a glass (200 mL) of hot water. Bring to boil and boil under cover for 5 min. Set aside for 10 min., strain. Drink the herbal tea 2 times daily, 30 min. before meals.	NA, 1993, PL
Cnici benedicti herba	Lack of appetite and digestive disturbances	1.0-2.0 g powdered herbal substance or pills. 5.0-10.0 g of comminuted herbal substance for infusion/decoction in 150 mL of water. Single dose before meals.	Informator Terapeutyczny, PL, 1955
Cnici benedicti herba	Lack of appetite, digestive disturbances and as reminaliser Antiseptic in dermatological use	5.0-10.0 g of comminuted herbal substance for infusion/decoction in 200 mL of water. Single dose before meals.	Informator Terapeutyczny, PL, 1955
Cnici benedicti herba	Aperitive, bitter tonic	Powder, tablets: 1-2 g. Herbal tea for	Frerichs et al., 1938

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		infusion or decoction: 5.0-10.0 g in 150 mL water.	
Cnici benedicti herba	Lack of appetite, anorexia, flatulent dyspepsia	Dried herb: 1.5-2 g in infusion. Liquid extract 1:1, 25% ethanol: 1.5-2 mL Tincture 1:5, 25% ethanol): 3-6mL 3 times daily.	BHC, 1992

Historical data and documented period of use in the EU support the evidence of traditional use of different preparations of blessed thistle for the temporary loss of appetite and for dyspepsia and mild spasmodic disorders of the gastrointestinal tract:

- 1.0-2.0 g of powdered herbal substance, before meals;
- 5.0-10.0 g of herbal substance or comminuted herbal substance as a tea preparation in 150-200ml of boiling water, before meals*;
- Liquid extract 1:1, 25% ethanol: 1.5-2 mL, 3 times daily;
- Tincture 1:5, 25% ethanol: 3-6 mL, 3 times daily.

* although blessed thistle is generally recommended as safe (GRAS), when taken at doses greater than 5 grams per cup of tea, it might cause stomach upset and vomiting (see also Section 5.3 Adverse reactions). Thus, for safety reasons, the posology recommended for this preparation as herbal tea might be decreased to 1.5-3g, 3 times daily. This posology is in accordance with the recommendations, the bibliographic references, and the most recent products in the market in the EU (since 1993).

Although some bibliographic references include the cutaneous use of blessed thistle as antiseptic, there are no medicinal products in the EU market and no information is available about the posology for that indication, so it cannot be considered as an indication with evidence of traditional use.

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

Sesquiterpene lactones present in blessed thistle are considered to be bitter constituents (mainly cynicin) which may be responsible of stimulating the taste buds causing a reflex increase in the secretion of saliva and gastric juice, this stimulating the appetite (BHC, 1992).

No pharmacological studies demonstrating this activity have been found.

3.1.2. Secondary pharmacodynamics

Antibacterial activity

Some studies reported the antibacterial activity for the whole dry herb, an aqueous extract of the herb, for isolated cnicin and for the essential oil (Vanhaelen-Fastré et al, 1973; Cobb, 1975; Vanhaelen-Fastré et al., 1972; Newall et al, 1996). Nevertheless, they are very old studies and no complete information is available.

Its antimicrobial activity has been attributed to cnicin and to its polyacetylene constituents (Vanhaelen-Fastré et al, 1968).

Anti-inflammatory activity

Isolated cnicin exhibited *in-vivo* antiinflammatory activity in the carrageenan rat paw oedema test, with virtual equivalence to indomethacin (Schneider et al, 1987).

3.1.3. Safety pharmacology

Although no specific studies have been found, high doses of holy thistle (more than 5.0 g per cup of tea) may irritate the stomach and cause vomiting (McGuffin, Botanical Safety Handbook, 1997).

3.1.4. Pharmacodynamic interactions

No interactions have been reported. Nevertheless, due to the possible mechanism of action of blessed thistle, some pharmacodynamics interactions may be suspected: as blessed thistle can increase stomach acid, taking blessed thistle might decrease the effects of some medications used to decrease stomach acid such as antacids, H₂-blockers and proton pump inhibitors (NLM, 2022).

3.1.5. Conclusions

The scientific information available on *Cnicus benedictus* L., herba pharmacological activity is limited and so it is scarce to support the proposed indication. Nonetheless, the chemical composition of the plant, rich in bitter principles, may be responsible of the increase in the secretion of digestive juices which in turn may exert aperitive and digestive effects.

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

No data are available for the herbal substance/herbal preparation.

Plants containing sesquiterpene lactones with an α -methylene- γ -lactone moiety are generally considered to be allergenic, although no documented hypersensitivity reactions to holy thistle were located. Allergic reactions may occur in individuals with known hypersensitivity to other members of the Asteraceae family (Newall et al., 1996).

3.3.1. Single dose toxicity

The acute toxicity (LD₅₀) of orally administered cnicin in mice is of 1.6-3.2 mmol/kg body weight (Schneider, 1987).

3.3.2. Repeat dose toxicity

No data available.

3.3.3. Genotoxicity

Schimmer et al. (1994) published an evaluation of commercial plant extracts in the Ames mutagenicity test. A tincture prepared from *Cnicus benedicti* L., herba (EtOH 60% 1:5) exhibited no mutagenicity at concentrations up to 200 µL/disc in the standard Ames assay on strains TA98 and TA100 of *Salmonella typhimurium* with and without metabolic activation.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

Blessed thistle may cause contact dermatitis; cross reactivity may occur with other members of the Asteraceae family (Ulbricht et al., 2008).

In the writhing-test during the assessment of its anti-inflammatory properties, cnicin caused abdominal pain in mice with ED50 of 6.2 µmol/kg body weight (Schneider et al 1987).

3.3.7. Other special studies

None reported.

3.3.8. Conclusions

There is no non-clinical information on the safety of *Cnicus benedictus* L., herba available. As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended. Due to the lack of adequate genotoxicity studies, a list entry cannot be recommended.

3.4. Overall conclusions on non-clinical data

There are no relevant experimental studies on *Cnicus benedictus* L., herba to support the proposed indications. The possible pharmacological effects associated to its chemical composition are not considered contradictory to the traditional uses.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of *Cnicus benedictus* L., herba is scarce.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed with the preparations included in the monograph.

4. Clinical Data

4.1. Clinical pharmacology

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

No data available.

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

No data available.

4.2. Clinical efficacy

No data available.

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

No clinical studies have been found on the effects of *Cnicus benedictus* L., herba on any disease.

Overall, the existing data do not meet the criteria for "well established medicinal use" in accordance with Directive 2001/83/EC. The plausibility of efficacy of the medicinal product is based on long-standing use and experience and allows the development of a EU herbal monograph on the traditional use of *Cnicus benedictus* L., herba.

5. Clinical Safety/Pharmacovigilance

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

No data available.

Although blessed thistle has sometimes been used traditionally as an abortifacient, safety and efficacy in this area have not been established (Ulbricht et al., 2008).

5.2. Patient exposure

Data obtained from post market surveillance (Ulbricht et al., 2008) indicated that blessed thistle, when taken at high doses (greater than 5 g per cup of tea) may cause stomach irritation and vomiting.

At gastrointestinal level, chronic ingestion of plants that contain $\geq 10\%$ tannins may cause gastrointestinal upset. Traditionally, blessed thistle is believed to stimulate gastric acid secretion and use may be inadvisable in patients with peptic ulcer disease (Ulbricht et al., 2008).

Blessed thistle has been shown to possess platelet-activating factor (PAF) antagonist properties, which in theory may cause increasing bleeding risk (Ulbricht et al, 2008). Nevertheless, this effect has not been proven in human studies.

Aside from market presence, there are no concrete data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

Gastric irritation and vomiting have been reported from high doses of blessed thistle (>5g per cup of tea) (Ulbricht et al. 2008).

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.5.1. Use in children and adolescents

No data available.

5.5.2. Contraindications

No data available.

5.5.3. Special Warnings and precautions for use

No data available.

5.5.4. Drug interactions and other forms of interaction

No data available.

5.5.5. Fertility, pregnancy and lactation

Blessed thistle has been used traditionally to stimulate menstruation or induce abortion, and therefore should be avoided during pregnancy (Ulbricht et al., 2008).

Although blessed thistle has been used traditionally to stimulate lactation, its use is not recommended during lactation due to the lack of safety information (Ulbricht et al., 2008).

5.5.6. Overdose

Not reported.

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

No data available.

5.6. Overall conclusions on clinical safety

On the basis of the information on its traditional use, the medicinal product proves not to be harmful in the specified conditions of use.

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

6. Overall conclusions (benefit-risk assessment)

Well-established use cannot be accepted for *Cnicus benedictus* L., herba, due to the lack of data on clinical efficacy, in accordance with Directive 2001/83/EC.

The data related to reproductive and developmental safety is scarce, so the use of *Cnicus benedictus* L., herba in pregnancy is not recommended. A European Union list entry is not supported due to lack of adequate data on genotoxicity.

Studies related to the toxicity of *Cnicus benedictus* L., herba and isolated constituents are scarce; nevertheless, and because of its long-standing use, no major safety concerns can be derived in relation to the use of *Cnicus benedictus* L., herba in the recommended posology and conditions of use.

Thus, medicinal use of *Cnicus benedictus* L., herba, fulfils all the requirements for Traditional Use in the European Union (self-medication character, specified strength/posology, appropriate route of administration, period of traditional use, plausibility and safety): it is well documented in several handbooks and marketed throughout a period of at least 30 years under Directive 2001/83/EC as powdered herbal substance (also in the form of tablets), comminuted herbal substance, liquid extract and tincture.

Traditional use has shown that *Cnicus benedictus* L., herba can be recognised as safe when used in recommended dosages under the conditions specified in the monograph, for the following therapeutic indications:

Indication 1) Traditional herbal medicinal product for the temporary loss of appetite.

Indication 2) Traditional herbal medicinal product for symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract.

Annex

List of references