15 January 2013
EMA/HMPC/113041/2010
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Cichorium intybus* L., radix

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Cichorium intybus* L., radix
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use
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1. Introduction

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

- Herbal substance(s)

***Cichorium intybus* Linnaei,**

Cichorium intybus L., is an erect perennial herb 80±90cm in height usually with bright blue flowers, rarely white or pink. It has a fleshy taproot up to 75 cm in length.

Cichorium intybus is a member of the *Asteraceae* family. The genus *Cichorium* consists of six species with major distribution areas in Europe and Asia. Member of the species are cultivated in Europe for salad leaves, chicons (blanched buds), or for roots (var. sativum), which are baked, ground, and used as a coffee substitute and additive.

The name of the plant is derived from Greek and Latin. *Cichorium* originates from χ_ω (kio)(I go) = χωρ_ov and chorion = field i, ie, in connection with the occurrence of the plant stands. "*Intybus*" is partly derived from the Greek _ντομος (éntomos) = cut, because of the leaves, and partly from the Latin in = in and = tubus tube, to indicate the hollow stem.

Popular common names of the plant are (Common) chicory, bluesailor's succory and coffee weed.

Chemical composition:

The chemical constituents of the plants can be summarised as follows:

(Boeuf *et al.* 2001, Bridle *et al.* 1984, Dauchot *et al.* 2009, de Kraker *et al.* 2003, Ernst *et al.*1995, Krebsky *et al.* 1999, Gordon and Flood 1980, Gupta *et al.*,1986, Gupta *et al.* 1991,Gupta *et al.* 2000, Hance *et al.* 2007, Leclercq 1983, Molan *et al.* 2003, Monde *et al.* 1990, Piet *et al.* 1996, Roberfroid 2000, Rossetto *et al.*2005)

Flowers:
cynadin 3-malonylglucoside (Bridle *et al.*1984), delphinidin 3,5-di-O-(6-O-malonyl-beta-D-glucoside) and delphinidin 3-O-(6-O-malonyl-beta-D-glucoside)-5-O-beta-D-glucoside, delphinidin 3-O-beta-D-glucoside-5-O-(6-O-malonyl-beta-D-glucoside), delphinidin 3,5-di-O-beta-D-glucoside and 3-O-p-coumaroyl quinic acid has been identified(Nørbæk *et al.* 2002).

Stem:
coumarins as umbelliferon, esculetin (6,7-dihydrocumarin) scopoletin, esculetin and cichorin (esculetin 7-O-β—D-glucosid)

Leaves:
caffeic acid, chichoric acid, these also as monoester of quinic acid, many flavonoids, as isorhamnetine, apigenin, apigenin-7-O-L-arabinoside, luteolin-7-O –glucuronide, quercetin -3-O – glucuronide, campheroil -3-O-glucoside, C-glycosilflavone, selenium compounds.

Roots:
Cichoriolide A, cichoriosides A, B and C from the root together with nine other known sesquiterpene lactones (Seto *et al.* 1988).

Root Milk Juice:

Sesquiterpene lactones of guajanolid type, lactucin and lactucopicrin (8-p-Hydroxyphenylacetillactucin).

A large number of sesquiterpenolactones have been isolated from *Cichorium intybus* (see Figure 1) (Bais and Ravishankar 2001)

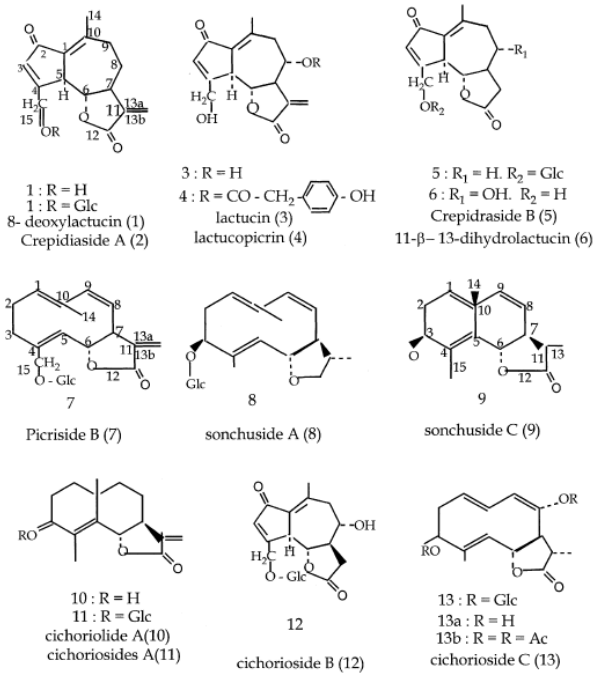

Figure 1. Sesquiterpene lactones isolated from *Cichorium intybus* (Bais and Ravishankar 2001)

The main sesquiterpene lactones are lactucin, 8 deoxylactucin, and lactucopicrin. There are found in the roots and the heads of the plant and are considered to be responsible for the bitter taste of chicory. The leaves and roots also contain traces amount of bitter of other sesquiterpene lactones such as guaianolides, lactupin, deoxylactupin, eudesmonolides and guanomanolides (Bais and Ravishankar 2001)

- Herbal preparation(s)

Comminuted herbal substance.

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

According to the information provided by the National Competent Authorities[1], only one herbal medicinal product containing *Cichorium intybus* as single ingredient is registered/ or authorised in the European Union. The product, a herbal tea of chicory roots is on the Polish market for 18 years. It is used an adjuvant in digestive complaints and lack of appetite. The recommended dose is 1.5 g, twice daily.

There are several combination products on the EU market:

Poland:

- **Zioła metaboliczne (*Species metabolicae)*** *containing Graminis rhizoma, Violae tricoloris herba, Cichorii radix, Urticae folium, Phaseoli pericarpium and Rhei radix. It is on the market for at least 20 years and is used as an adjuvant in skin disorders (juvenile acne) connected with abnormal metabolism*
- **Zioła poprawiające trawienie (*Species digestivae)*** *containing Cichorii radix, Angelicae radix, Carvi fructus, Absinthii herba, Gentianae radix. It is on the market for 20 years and is used as an adjuvant in lack of appetite, digestive complaints (meteorism, rebounding)*
- **Herbal tea** *(Betulae folium, Cichorii radix, Equiseti herba and Uvae ursi folium). This product is on the market for 14 years and is used for the treatment of mild urinary system inflammations*

In Germany the following fixed combinations are on the market for more than 30 years:

- Tea: Foeniculi fructus 20 g, Centaurii herba 5 g, Thymi herba 5 g, Absinthii herba 10 g, Millefolii herba 10 g, Calendulae flos 2 g, Cichorii herba 38 g, Menthae pip. folium 5 g, Aurantii pericarpium 5 g; Indication: Cholangitis, Cholecstitis, chronic hepatitis, gastroenteritis, atony of the stomach (old licence of rights, not accepted by BfArM)
- Oral liquid containing extracts of *Cichorium intybus* L., root / *Geum urbanum* L., root (Clove Root rhizome) / *Melissa officinalis* L., folium (Melissa leaf) / *Citrus aurantium* L. ssp. *Aurantium, epicarpium et mesocarpium* (bitter-orange epicarp and mesocarp) / *Centaurea benedicta* L. herba / *Artemisia absinthium* L., herba (wormwood herb). Extraction solvent: ethanol 96 % V/V / liqueur wine (1/22) Indication: traditionally used to support stomach function
- Oral liquid containing extracts of *Cichorium intybus* L., root / *Geum urbanum* L., root (Clove Root rhizome) / *Melissa officinalis* L., folium (Melissa leaf) / *Citrus aurantium* L. ssp. *Aurantium, epicarpium et mesocarpium* (bitter-orange epicarp and mesocarp) / *Centaurea benedicta* L., herba / *Artemisia absinthium* L., herba (wormwood herb. Extraction solvent: ethanol 70 % V/V / liqueur wine (1/22) Indication: traditionally used to support stomach function

[1] Data are collected using the template entitled 'Document for information exchange for the preparation of the assessment report for the development of Community monographs and for inclusion of herbal substance(s), preparation(s) or combinations thereof in the list' (EMEA/HMPC/137093/2006)

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised products
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised products
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised products
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	At least three products authorised containing *Cichorium intybus* in fixed combinations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised products
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised products
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised products
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	One single and three combination products

Member State	Regulatory Status				Comments
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised products
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised products
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised products

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

1.3. Search and assessment methodology

Date: September 2011

Search terms: "*Cichorium intybus*" and "chicory"

Databases: Pubmed, Toxnet, Pharmacutical Abstracts

Handbooks and textbooks on the topic were also used.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The medicinal use of chicory is in the Community documented in pharmacognosy texts and handbooks dating from 1938 (Madaus 1938; Scholz 2006); The Complete German Commission E Monographs (Blumenthal 1998).

In France, chicory root is included in the "Notice to manufacturers concerning marketing authorisation applications for plant-based medicinal products" (Ministry of social affairs and solidarity 1990).

A monograph for Cichorii radix is included in the official collection of herbal drug monographs (Český farmaceutický kodex, first edition, 1993). This monograph replaced the Czech technical standard ON 86 7033 - Kořen čekankový (chicory) published in 1967.

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

According to Scholz, the root as well as leaf/root mixtures of chicory are used for mild dyspeptic disorders and lack of appetite (Scholz 2006) The use of a tea of the roots in digestive disorders and loss of appetite was already reported in 1938 by Madaus (Madaus 1938). Other sources mention the

use of the roots as a tonic, a blood purifier, against internal and external bleeding, catarrh of the stomach, and jaundice (Hoppe 1949, 1958).

Decoctions from the root are used as a bitter tonic/stomachic, mild laxative, to promote liver function and diuresis (Poletti *et al.* 1989).

In France, a herbal tea from the root is traditionally used for the following indications (Ministry of social affairs and solidarity 1990):

- In symptomatic treatment of digestive disorders such as: flatulence, slow digestion, belching, epigastric distension.
- Traditionally used to promote renal and digestive elimination functions. Traditionally used choleretic or cholagogue.
- Traditionally used as adjuvants in slimming diets. Traditionally used to promote renal elimination functions).

The use of the herb is mentioned in two sources Braun (2009) and Hoppe (1958). Braun mentions the use of a tea containing 1 gram of herb but provides no information on what the tea is used for. According to Hoppe (1958) the herb is used as a tonicum. However no posology is given.

A mixture of the leaves and roots is described in French Pharmacopoeia (edition VII) and The Italian Pharmacopoeia (Edition V). No data is available on the ratio herb /root (Scholz 2006).

A German Commission E monograph exists for the dried above-ground part and/or roots for use in dyspepsia and loss of appetite (Blumenthal 1998).

Based on the available information listed above the following indication is proposed:

Traditional herbal medicinal product for the relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence and slow digestion) and temporary loss of appetite.

The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

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

The following posologies were found in literature:

Poletti *et al.* (1989): A handful of comminuted roots are cooked in 1 litre of water for 30 minutes. One cup of this preparation should be used before each meal.

Madaus (1938): Daily dose: 6 g in two glasses of water as a tea infusion; to be taken during the day.

Scholz (2006): Mixture of leaf/root or root only; daily dose of 3 g comminuted roots as an infusion or a decoction of 2-4 g in 250 ml water once daily.

No posology was found for the leaves.

In the German Commission E monograph, an average daily dose of 3 g herb or “equivalent preparation” is recommended. The monograph defines the herb, the dried above-ground part and/or roots (Blumenthal 1998).

Based on the posologies mentioned above the following posologies are included in the monograph:

Herbal tea: 2-4 g of the comminuted herbal substance in 250 ml of boiling water as a herbal infusion once daily.

Herbal tea: 2-4 g of the comminuted herbal substance in 250 ml of water as a decoction once daily.

3. Non-Clinical Data

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

Hepatoprotective activity

Gadgoli and Mshra (1997) reported a hepatoprotective effect against CCl_4 and paracetamol induced hepatoxicity. Intraperitoneal administration of an aqueous extract of chicory seeds in a dose of 30 to 50 mg/kg body weight to albino rats, resulted in a reduction of the elevation of hepatic enzymes induced by CCl4 and paracetamol, with significant ($p<0.001$) differences between treated and control rats.

Zafar and Mujahid (1998) observed a hepatoprotective activity against CCl_4 and paracetamol intoxication in rats after intraperitoneal administration of 50-150 mg/kg of an aqueous (1:10) extract from *Cichorium* roots. Hepatic enzymes and histopathology were analysed. Both, the natural root extract and the root callus extract were tested. The latter was found to be more active.

Sultana *et al.* (1995) observed, *in vitro*, a protective activity against oxidative damage of calf thymus DNA by free radicals of an ethanol extract of *Cichorium intybus* herb. A concentration-dependent inhibition, ranging from 15% to 55 % of the free radicals DNA damage, was observed.

Ahmed *et al*. (2003) tested different fractions of an alcoholic extract and one phenolic compound AB-IV of seeds of *Cichorium intybus* for anti-hepatotoxic activity on carbon tetrachloride (CCl(4))-induced liver damage in albino rats. The degree of protection was measured using biochemical parameters like aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALKP), and total protein (TP). Oral administration of 500 mg/kg of a methanol fraction and 250 mg/kg of compound AB-IV were found to possess a potent anti-hepatotoxic activity comparable to the standard drug silymarin (Silybon-70). The histopathological study of the liver was also carried out, wherein the methanolic fraction and compound AB-IV showed almost complete normalisation of the tissues as neither fatty accumulation nor necrosis was observed.

Ahmed *et al.* (2003 and 2008) reported the anti-hepatotoxic activity of cichotyboside, a sesquiterpene glycoside from the seeds of *Cichorium intybus*, against CCl4 induced liver damage in albino rats. Oral administration of 50 mg/kg cichotyboside once daily for six days resulted in a significant ($p<0.001$) reduction the elevated levels of liver enzymes (SGOT, SGPT, ALKP) and in an increase in total protein and albumin, respectively, using the usual metabolic parameters.

Choleretic effect

According to Scholz (2006), a choleretic effect was observed in rats after intraduodenal administration of a water extract of the roasted *Cichorium* root at a dose of 750 to 1250 mg/kg body weight.

Cholesterol absorption

Kim (2000) reported for chicory root extract a decrease in cholesterol absorption by 30% ($p<0.05$) in the jejunum and by 41% ($p<0.05$) in the perfused ileum. Kim (2002) reported antioxidative effects of *Cichorium intybus* root extract on LDL (low density lipoprotein) oxidation. The water extract of

Cichorium intybus showed an antioxidative effect on LDL and inhibitory effects on the production of thiobarbituric acid reactive substance and the degradation of fatty acids in LDL.

Antimalarial activity

Bischoff *et al.* (2004) identified the light-sensitive sesquiterpene lactones lactucin and lactucopicrin, extracted from *Cichorium intybus* roots, as antimalarial compounds. Both substances exhibited *in vitro*, activity against a HB3 clone of the Honduras-1 strain of Plasmodium falciparum. Inhibitory lactone concentrations that completely prevented parasite growth in cell cultures were 10 μg/ml for lactucin and 50 μg/ml for lactucopicrin.

Analgesic and sedative activity

Wesołowska *et al.* (2006) tested lactucin, lactocopicrin and 11β,13-dihydrolactucin from *Cichorium intybus* for analgesic and sedative activity in mice. The compounds showed significant ($p<0.0001$) analgesic effects at doses of 15 and 30 mg/kg in the hot plate test similar to that of ibuprofen at a dose of 30 mg/kg. Lactucopicrin was found to be the most active.

Antidiabetic effects

Pushparaj *et al*. (2007) investigated an ethanolic extract of *Cichorium intybus* herb for its anti-diabetic activity on male Sprague Dawley rats treated streptozotocin. A dose of 125 mg/kg body weight influenced oral glucose tolerance test and the same amount given orally for 14 days reduced serum glucose by 20%, triglycerides by 91% and cholesterol by 16%. No changes in the insulin secretion were observed during the experiment, whereas hepatic Glc-6-Pase activity was markedly reduced.

Antiflammatory activity

Kim *et al.* (1999) investigated the effect of an aqueous extract of *Cichorium intybus* on mast cell-mediated immediate type allergic reactions in mice. The extract was found to dose-dependently (10-1000 mg/kg intraperitoneal), inhibiting the anaphylactic reaction induced by a compound 48/80 (not further specified).

Cavin *et al*. (2005) observed *in vitro,* that a ethyl acetate chicory root extract produced a marked inhibition of prostaglandin E(2) (PGE(2)) production in human colon carcinoma HT29 cells treated with the pro-inflammatory agent TNF-alpha. Two independent mechanisms of action were identified: (1) an inhibition of the induction by TNF-alpha of cyclooxygenase 2 (COX-2) protein expression and (2) a direct inhibition of COX enzyme activities with a significantly higher selectivity for COX-2 activity. The inhibition of TNF-alpha-dependent induction of COX-2 expression was mediated by an inhibition of NF-kappaB activation. Guaianolide 8-deoxylactucin, was identified as the key inhibitor of COX-2 protein expression present in chicory root extract.

Antitumor activity

Hazra *et al.* (2002) reported a tumour-inhibitory effect of an ethanolic extract of chicory root against Ehrlich ascites carcinoma in mice. Significant results were obtained after intraperitoneal administration of from 300 to 700 mg/kg /day divided over 8 doses.

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

No data available.

Interaction with drug metabolism

Rasmussen *et al.* (2011) studied *in vivo* the effect of dried chicory root on cytochrome P450 enzymes in porcine liver. Oral administration of chicory root for 16 days to pigs increased the mRNA expression of CYP1A2, 2A and 2E1; and the protein expression of CYP1A2 and 2A. The activities of CYP1A2 and 2A were increased.

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

Acute toxicity

According to Scholz (2006) no deaths were observed in mice after oral administration of 625 mg/kg body weight or intraperitoneal administration of 125 mg/kg body weight of a water extract of the roasted roots.

Scholz (2006) reports that the LD_{50} of 8900 mg/kg body weight was observed with an unspecified root extract.

Chronic toxicity

Schmidt *et al.* (2007) performed a 28-day sub-chronic toxicity study in male and female rats, to evaluate the safety of a chicory root extract. Measurements included clinical observations, body weights, food consumption, clinical pathology, gross necropsy and histology. There were no treatment-related toxic effects from chicory extract administered orally at 70, 350 or 1000 mg/kg/day.

Reproductive and developmental toxicity

Prakash *et* Mathur (1976) observed in rats that oral administration of 200 mg/kg of a dry ethanol 50% extract of the root from day 1 to 7 or then between day 14 to 16 of pregnancy, resulted in the loss of foetuses in 24 of 30 rats tested (84%).

Roy-Choudhury and Venkatakrishna-Bhatt (1983) observed that oral administration of 8.7 g/kg body weight of an aqueous suspension of chicory root coffee to Swiss mice resulted in a degeneration of seminiferous tubules and atrophy of the Leydig cells in the treated animals. No effects were observed at 4.35 g/kg body weight. The mechanism of action of the high dose of the chicory aqueous root extract on the Swiss mice genital tract is unknown.

Behnam-Rassouli *et al.* (2010) investigated the effect of an aqueous extract of *Chicorium intybus* L. leaves on the offspring sex ratio in rat. Eleven rats in experimental groups 1 and 2 were intraperitoneally injected with either 1 or 0.7 g/kg body weight (LD_{50} = 2.244 g/kg) of an aqueous extract of chicory leaves for 30 days at 72 hours intervals. A significant effect on the sex ratio of the rat offspring was observed after intraperitoneal administration of chicory leaf extract.

Genotoxicity

Schmidt *et al.* (2007) reported that a defatted 95% ethanolic chicory root extract rich in sesquiterpene lactones showed with and without metabolic activation no mutagenic activity in the Ames test although it was cytotoxic to certain strains of Salmonella at higher doses.

3.4. Overall conclusions on non-clinical data

Non-clinical data demonstrates a broad spectrum of activities *Cichorii intybus* preparations. Several metabolic effects, such as a cholesterol lowering effect and anti-diabetic effect were observed. However effects were only observed with very high dose. The observed choleretric effect supports the traditional use for digestive disorders.

Toxicological data on *Cichorum intybus* is very limited. Studies with the tea or decoctions of the roots are lacking. Many toxicity studies were performed with ethanol extracts. Consequently extrapolation of the data to the aqueous tea/infusions is problematic. Oral administration of a high dose of the roasted roots was found to affect spermatogenesis in mice. Because this effect was not observed in low dose it is not likely that the oral intake of substantial lower amounts as herbal tea will affect spermatogenesis in men.

The studies on the Ames test are very promising. However because the experiments were performed with a defatted 95% ethanol extracts the data cannot be used to support the safety of the herbal tea.

Nonetheless, neither the chemical composition nor the long-term widespread use in the European Community suggests that there is a high risk associated with the use *Cichorum intybus*. Moreover, the alimentary use of roasted chicory roots is widespread in the Community and chicory extract is Generally Recognised as Safe (GRAS) by the FDA and appears on the Everything Added to Food in the United States (EAFUS) list.

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 pharmacokinetic data are available for *Cichorium intybus*' constituents.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No dose response studies have been performed available.

4.2.2. Clinical studies (case studies and clinical trials)

Schumacher *et al.* (2011) studied the effect of chicory coffee on the blood and plasma viscosity and platelet aggregation. They observed that daily intake of 300 ml chicory coffee for one week produced variable effects on platelet aggregation, depending on the inducer used for the aggregation test. Whole blood and plasma viscosity were both significantly decreased, along with serum MIF levels, after one week of chicory coffee consumption.

Olsen *et al.* published in 2010 the results of a Phase 1, placebo-controlled, dose escalation trial with chicory root extract (not further specified) in patients with osteoarthritis of the hip or knee. A total of 40 patients were enrolled in 3 cohorts and were treated with escalating chicory doses of 600 mg/day, 1200 mg/day and 1800 mg/day for 1 month. Results: in the highest dose cohort, 18 patients who completed treatment per protocol were analysed for efficacy. In this group, 13 patients showed at least 20% improvement in the defined response domains of pain, stiffness and global assessment: 9 of 10 (90%) patients randomised to active treatment with chicory and 4 of 8 (50%) patients randomised to placebo (P = 0.06). In general, the treatment was well-tolerated. Only one patient who was treated with the highest dose of chicory had to discontinue treatment due to an adverse event. The authors conclude that the results of this pilot study suggest that a chicory root extract could play a role in the management of osteoarthritis.

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

No data available.

4.3. Overall conclusions on clinical pharmacology and efficacy

In literature several studies with a hydrolysate of inulin isolated from chicory can be found. These studies are not included in this assessment because the product studied cannot be classified as a herbal preparation. Moreover, this product has neither a well-established nor a traditional medicinal use in the Community.

Only two clinical studies with chicory root could be retrieved. Both are pilot studies and are therefore considered to be insufficient to support a well-established use indication for chicory root. The traditional use in the proposed indications is made plausible by pharmacological data.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

In the literature, several cases of occupational allergy and contact dermatitis due to professional exposure to *Cichorium intybus* are reported (e.g. Friis *et al.* 1975, Nemery and Demedts 1989, Cadot *et al.* 2003, Helbling *et al.* 1997, Pirson *et al.* 2009). These cases are not discussed in detail because they are not considered to be relevant for the monograph.

5.3. Adverse events and serious adverse events and deaths

None reported.

5.4. Laboratory findings

None reported.

5.5. Safety in special populations and situations

No data available.

5.6. Overall conclusions on clinical safety

No reports of (serious) adverse events and deaths could be found in literature. The only cases reported are for allergy to chicory. These cases are mainly related to professional exposure. However, because the *Asteracea* family is a known source of allergic problems, a contra-indication for hypersensitivity to the active substance and members of the *Asteracea* will be included.

6. Overall conclusions

Cichorum intybus root has a long tradition of use in Europe. Despite this long tradition, the herbal substance is not described the European Pharmacopoeia or in an official Pharmacopoeia of an EU member state.

The traditional use of the roots in digestive disorders and loss of appetite is well documented in several handbooks and is considered plausible on the basis of the chemical composition and pharmacological data. *Cichorum intybus* roots contain bitter sesquiterpenes which could stimulate appetite and the choleretic activity observed in animal studies supports the use in digestive disorders.

Two clinical studies with chicory root could be retrieved. Both studies are pilot studies and are therefore considered to be insufficient to support a well-established use indication for chicory root.

There is insufficient data to support a traditional use monograph for *Cichorum intybus* leaves. Data is available on the use of mixtures of the leaves and root material. Because the leaf/root ratio of these mixtures is not documented no monograph was developed for the mixture.

The use of the herb as single ingredient is described in only two sources. Because none of these sources provide a clear posology and use, they are considered to be insufficient to demonstrate a traditional use of the herb in the European Union.

Toxicological data on *Cichorum intybus* root is very limited. Studies with the tea or decoctions of the roots are lacking. Nonetheless, neither the chemical composition nor the long-term widespread use in the European Community suggests that there is a high risk associated with the use *Cichorum intybus*. Moreover, the alimentary use of roasted chicory roots as coffee surrogate is widespread in the Community. Furthermore, chicory extract is Generally Regarded as Safe (GRAS) by the FDA and appears on the Everything Added to Food in the United States (EAFUS) list.

Cichorum intybus is a member of the *Asteracea* family. In view of the documented allergic reactions and cross-sensitivities with species of the *Asteracea* family, it is recommended that *Cichorum intybus* should be avoided by individuals with a known hypersensitivity to any sesquiterpene containing members of the *Asteraceae* family.

In conclusion, available data supports the use of *Cichorum intybus* root in the European Union as a "*traditional herbal medicinal product for the relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence, and slow digestion) and temporary loss of appetite*. The specified indication is plausible and there as are no safety concerns. Therefore, the benefit/risk balance is considered positive. However, because adequate safety data is lacking, a list entry is not recommended.

There is insufficient data to support a traditional use monograph for *Cichorum intybus* leaves and herb.

Annex

List of references