European Medicines Agency
Evaluation of Medicines for Human Use

London, 12 March 2009
Doc. Ref.: EMEA/HMPC/105535/2008

ASSESSMENT REPORT ON *CENTAURIUM ERYTHRAEA* RAFN S. L. INCLUDING *C. MAJUS* (H. ET L.) ZELTNER AND *C. SUFFRUTICOSUM* (GRISEB.) RONN., HERBA, FOR THE DEVELOPMENT OF A COMMUNITY HERBAL MONOGRAPH

DISCUSSION IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST	March 2008 May 2008 July 2008
ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	2 July 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	15 November 2008
REDISCUSSION IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST (MLWP)	March 2009
ADOPTION BY HMPC	12 March 2009

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I. REGULATORY STATUS OVERVIEW[1]

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'

Member State	Regulatory Status				Comments[2]
Austria	■ MA	☐ TRAD	■ Other TRAD	■ Other Specify: as food supplement	C. herba in combination products
Belgium	■ MA	☐ TRAD	☐ Other TRAD	■ Other Specify: as food supplement	C. herba in combination products
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: Not Known	C. herba in combination products
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
Estonia	■ MA	☐ TRAD	■ Other TRAD	☐ Other Specify:	C. herba in combination products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
Germany	■ MA	■ TRAD	☐ Other TRAD	☐ Other Specify:	C. herba in combination products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

[1] This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.
[2] Not mandatory field

Member State	Regulatory Status				Comments[2]
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
Poland	☐ MA	■ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	C. herba in combination products
Spain	☐ MA	☐ TRAD	■ Other TRAD	☐ Other Specify:	C. herba in combination products
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No C. herba on market
United Kingdom	☐ MA	■ TRAD	☐ Other TRAD	☐ Other Specify:	C. herba in combination products

II. ASSESSMENT REPORT

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

(TRADITIONAL USE)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Centaurium erythraea* Rafn s. l. including *C. majus* (H. et L.) Zeltner and *C. suffruticosum* (Griseb.) Ronn. (syn.: *Erythraea centaurium* Persoon; *C. umbellatum* Gilibert; *C. minus* Gars.), herba (centaury herb) The material complies with the Ph. Eur. monograph (ref. 01/2005:0865).
Herbal preparation(s)	A) Comminuted herbal substance B) Powdered herbal substance C) Liquid extract (1:1; ethanol 25% v/v) D) Tincture (1:5; ethanol 70% v/v) E) Soft extract (1:10; water)
Pharmaceutical forms	Comminuted herbal substance as herbal tea or other herbal preparations in liquid or solid dosage forms for oral use.
Rapporteur(s)	Emiel van Galen/Burt Kroes
Assessor	Els Ensink

II.1 INTRODUCTION

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

Herbal substance[3]:

Centaurii herba consists of the whole or fragmented dried flowering aerial parts of *Centaurium erythraea* Rafn s. l. including *C. majus* (H. et L.) Zeltner and *C. suffruticosum* (Griseb.) Ronn. (syn.: *Erythraea centaurium* Persoon; *C. umbellatum* Gilibert; *C. minus* Gars.) (Ph. Eur.).

Constituents: (Popov, 1969; BHP, 1979; Aquino *et al.*, 1985; van der Sluis, 1985 ; Dombrowicz *et al.*, 1988; Hellemont, 1988; Hänsel *et al.*, 1992; Bisset, 1994; Schulz *et al.*, 1998; Valentão *et al.*, 2002; Bellavita, 2003; ESCOP, 2003)

Secoiridoid glucosides are the characteristic bittertasting constituents, principally (75%) swertiamarin and smaller amounts of gentiopicroside (gentiopicrin) and sweroside (bitterness value ca. 12,000) and centapricin (bitterness value ca. 4,000.000). Other iridoids include bitter m-hydroxybenzoyl esters of sweroside, and deacetylcentapicrin, centauroside (a dimeric secoiridoid), secologanin, 6'-m-hydroxy-benzoyl-loganin, dihydrocornin (a cyclopentane iridoid), gentioflavoside.

Analysis of different plant parts has shown a variety in the composition of the bitter ingredients. Due to the occurrence of the very bitter secoiridoid esters centapicrin and desacetylcentapicrin, fruits are more bitter than the flowers, leaves and stems. Swertiamarin is the major component in all parts of *C. erythraea*.

Secoiridoid alkaloids: gentianine and gentianidin;

Xanthones: 6 methoxylated xanthones, including eustomin (1-hydroxy-3,5,6,7,8-penta-methoxyxanthone) and 8-demethyl-eustomin and others;

Organic/Phenolic acids such as p-coumaric, o-hydroxyphenylacetic, ferulic, protocatechuic, sinapic, vanillic, syringic, hydroxyterephthalic and 2,5-dihydroxy-terephthalic acids and oleanolic acid (0.1%);

Phytosterols: β-sitosterol, stigmasterol, campesterol and others;

Coumarins: 5-formyl-2,3-dihydroisocoumarin;

Miscellaneous: flavone components and anthocyanes.

Herbal preparations specified for the individual final product

A) Comminuted herbal substance for tea preparation
B) Powdered herbal substance
C) Liquid extract (1:1; ethanol 25% v/v)
D) Tincture (1:5; ethanol 70% v/v)
E) Soft extract (1:10; water)

[3] According to the 'Procedure for the preparation of Community monographs for traditional herbal medicinal products' (EMEA/HMPC/182320/2005 Rev.2) and the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMEA/HMPC/182352/2005 Rev. 2).

Combination preparations with Centaurii herba

Madaus (1938), Weiss (1974) and Hellemont (1988) mention formulas containing Centaurii herba in combination with other herbal substances. At present authorised/registered combination products containing Centaurii herba are on the market in several EU Member States, amongst others: Czech Republic, Germany, United Kingdom, Austria, Poland, Spain and Estonia.

II.1.2 Information on period of medicinal use in the Community regarding the specified indication

Centaurium erythraea Rafn is used for many decades in the European Union mainly for the relief of digestive complaints (peptic discomfort) and lack of appetite. Centaurii herba was also used for the treatment of diabetes, snakebites, malaria, wounds and as an antipyretic, tonic and sedative. Preparations of this herb are described in different (old) Pharmacopoeias of European Member States[4]:

Centaurii herba (based on *Erythraea centaurium* Persoon) has been documented in DAB 6 (1936) and Ned. Pharm. III (1889) (van der Sluis, 1985).

Centaurii minoris herba is described in Pharmacopoeias of following member states: Austria, Czech Republic, Germany, Hungary, Poland, Romania and Spain (Martindale, 1977).

Erythraea centaurii herba florida is described: Ph. Ned. (1934), Belg. Pharm. IV (1940), (Hellemont, 1988).

Erythraea centaurii extractum fluidum is described in: Belg. Pharm. IV (1940) (Hellemont, 1988).

Extractum centaur. minor is described in: Belg. Pharm. IV (1940) (Hellemont, 1988).

Extractum centaurii (a soft extract) is described in the 'Ergänzungsband zum deutschen Arzneibuch' (EB 6, 1953) and (Hänsel *et al*., 1992; HagerRom, 2006).

Centaury – Centaurii herba is described in Eur. Ph. (Eur. Ph., 2008).

The medicinal use has also been documented in well-known handbooks dating from 1938 (Madaus), 1954 (Steinmetz), 1977 (Martindale), 1988 (Hellemont) and 1992 (Hänsel *et al.*) up to 2003 (ESCOP).

In ancient times Centaurii herba was used as a febrifuge in intermittent fever attacks, at dysmenorrhoea and as a sedative (Madaus, 1938; Hellemont, 1988).

According to Kneipp (1935) centaury has blood cleaning properties and is used for gastro-intestinal complaints, Madaus (1938) claims it to be the best remedy against gastric juice burning sensation.

Steinmetz (1954) describes *Erythraea centaurium* (common names: small centaury or small knapweed) to be a bitter stomachic and febrifuge, to be used in chlorosis and jaundice; it also 'purifies the blood, promotes the menses and improves the appetite'.

Bisset (1994) mentions its use as a bitter, for stimulating the appetite and increasing the secretion of the gastric juice, especially in chronic dyspeptic states and achylia. In folk medicine Centaurii herba was also employed as roborant and tonic.

[4] The various pharmacopoeias are not in agreement regarding the species of *Centaurium*. These discrepancies are due mainly to the confusion about the nomenclature and delimitation of *C. erythraea* s. l. and many synonyms are used in literature for *C. erythraea* Rafn (van der Sluis, 1985). Hybridisation occurs frequently causing morphological variability, resulting in taxonomic divergences. *C. erythraea* s. l. is an unresolved assemblage comprising diploid to hexaploid species related to *C. erythraea* subsp. *erythraea* (Mansion, 2005), see also II.1.1.

Centaury is used in dyspepsy and diarrhoea accompanied by liver and bile impairments or caused by an unbalanced diet and can be effective in flatulence (Hellemont, 1988).

According to Hänsel *et al.* (1992) Centaurii herba can be applied in dyspeptic and stomach disorders, and in lack of or for stimulation of appetite.

Newall (1994) mentions the traditional use of the infusion in anorexia.

In Germany extracts of Centaurii herba are components in registered gastrointestinal, cholagogue and urological remedies (Bisset, 1994; Walther, 2004).

For an overview on the documented applications of Centaurii herba , see II.3.2.

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

II.2.1.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Documentation regarding the route of administration

Oral administration is the main route of administration for Centaurii herba preparations.

Centaurii herba has also been used topically in the treatment of inflammations, wounds (Hänsel *et al.*, 1992), snakebites and eczema (Dweck, 1997).
Results from an animal study demonstrated a significant anti-inflammatory activity after application of an aqueous extract of centaury in the air pouch granula test (Berkan *et al*., 1991; Hänsel *et al.*, 1992).
However, in the handbooks detailed information on composition of the preparation, posology, duration of use and clinical data is lacking. Therefore, topical use as a traditional herbal medicinal product does not fulfil the requirements of Directive 2004/24/EC.

Phytochemical research data on major components in *Centaurium erythraea*

- Xanthones and the secoiridoids sweroside, swertiamarin and gentiopicrin have been identified in several *Centaurium* species. On the basis of chemical derivation, the authors concluded sweroside to be probably identical with the compound known as ‘kantaurin’ (van der Sluis, Labadie, 1981).

- An HPLC method was developed and used for the determination of gentiopicrin (gentiopicroside) in *Centaurium erythraea* (Kaluzova *et al*., 1995).

- Piatczak *et al*. (2006) demonstrated that the level of secoiridoids is modified by both transformation by *Agrobacterium rhizogenes* and by the development stage of transformed plants. The total content of the compounds (expressed as the sum of gentiopicroside, sweroside and swertiamarin) in transformed plants was 280 mg/g dry weight and was 8 times the content in the sample of commercially available *C. erythraea* herb.

- In the course of a phytochemical study of *C. erythraea*, six methoxylated xanthones (1,5-hydroxy-3-methoxyxanthone, 1-hydroxy-3,5,6-trimethoxyxanthone, 1-hydroxy-3,5,6,7-tetramethoxyxanthone, 1-hydroxy-3,5,6,7,8-pentamethoxyxanthone, 1-hydroxy-3,7,8-trimethoxyxanthone and 1,8-dihydroxy-3,5,6,7-tetramethoxyxanthone) were isolated and identified by spectroscopic means. Subsequently a detection method was developed for the determination of these and other methoxylated xanthones occurring in the chloroform extract of small centaury aerial parts. The methodology developed was applied to twelve samples, and in all of them, nine xanthones were identified and quantified (Valentão *et al*., 2002).

- Kumarasamy *et al*. (2003) isolated the two secoiridoid glycosides, swertiamarin and sweroside from the aerial parts of *Centaurium erythraea*.

Pharmacodynamics

Although the mechanism of action is still unclear, it is assumed that the bitter constituents stimulate the gustatory nerves in the mouth and give rise to an increase in the secretion of gastric juice and bile, thereby enhancing the appetite and digestion (Evans, 1996).

Pharmacological activities of whole extracts of centaury herb

- Increase in sputum (Hänsel *et al.*, 1992) and gastric juice secretion (Blumenthal *et al.*, 1998; Hänsel *et al.*, 1992).

- Antipyretic activity of a dry aqueous extract of centaury was observed in rats after administration of 50-100 mg/animal by gavage in a yeast-induced fever test (Berkan,1991; Hänsel *et al.*, 1992; Newall, 1994). The antipyretic properties are assumed to be due to the phenolic acid. No fever-lowering/antipyretic effects were observed after pretreatment with centaury (Newall, 1994).

- Anti-inflammatory activity of a dry aqueous extract of centaury was observed in Freund's adjuvant-induced polyarthritis in rats treated orally with 10-500 mg per day (Berkan, 1991). Inhibition of carrageenan-induced paw oedema by 40% has been found after oral intake of 100 mg/kg body weight of a dry ethanolic extract of centaury (Capasso *et al.*, 1983; Hänsel *et al.*, 1992; Newall, 1994).

- A diuretic effect was observed in rats after oral administration of 8% or 16% aqueous extract of centaury at 10 ml/kg body weight daily for one week, with the most effective dose for water and electrolyte excretion being 8%. From the fifth day of treatment urine volume increased significantly with the lower dose and both doses led to a significant increase of sodium, chloride and potassium excretion. At the end of the treatment a diminution in creatine clearance was observed (Haloui, 2000).

- A hepato-protective activity of a methanol extract of the leaves of *C. erythraea* was evaluated against acetaminophen-induced liver toxicity in rats. An oral dose of 300 mg/kg/day for 6 days or a single dose of 900 mg/kg for 1 day exhibited a significant protective effect by lowering serum glutamate oxaloacetate transaminase (SGOT), glutamate pyruvate transaminase (SGPT) and lactate dehydrogenase (LDH). The hepato-protective activity was also observed by histopathological examination of liver sections (Mroueh *et al.*, 2004).

- Antioxidant activity of small centaury infusion has been reported (Valentão, 2001; Valentão, 2003).

- An aqueous extract of *C. erythraea* did not show analgesic properties (Berkan, 1991).

Pharmacological activities of combination preparations

- A concentration-dependant relaxant effect was observed in rats fed on spontaneous ileum contractions and on rat ileum pre-contracted with carbachol, after administration of an hydroethanolic extract of four herbs, including *Erythraea centaurium* (L.) Borkh. (Botion *et al.*, 2005).

Pharmacological activities of isolated compounds in centaury herb

- Antimalarial properties of gentiopicrin have been mentioned in handbooks (Newall, 1994).

- Antibacterial activity could be observed for swertiamarin and sweroside; both compounds inhibited the growth of *Bacillus cereus*, *Bacillus subtilis*, *Citrobacter freundii* and *Escherichia*

coli. While swertiamarin was also active against *Proteus mirabilis* and *Serratia marcescens*, sweroside inhibited the growth of *Staphylococcus epidermidis* (Kumarasamy *et al*., 2002).

- Isolated swertiamarin showed anticholinergic activity, significantly inhibiting carbachol-induced contractions of the proximal colon in rats in a dose-dependant manner after oral administration at 150 mg/kg and 300 mg/kg body weight (Yamahara *et al*., 1991).
- Isolated gentianine, administered to rats at 100 mg/kg body weight, showed besides anti-ulcerogenic activity in the water immersion stress test an inhibitory action against gastric secretion (Yamahara *et al*., 1978).

- A depressive effect on the central nervous system is reported for mice treated orally with 30 mg/kg body weight gentianine. An inhibition of spontaneous movement activity and an increase of hexo-barbital induced sleeping time were observed (Yamahara *et al.*, 1978).

- Two methoxylated xanthone derivatives, eustomin and demethyleustomin, isolated from the aerial parts of *Centaurium erythraea* Rafn showed antimutagenic properties in Salmonella typhimurium strains TA98, TA100, and TA102. The antimutagenic character of the compounds was supported by the effects shown in post-treatment experiments as well as by results obtained with recA mutants of *E. coli* and *Bacillus subtilis*. Isolated eustomin at 50 µg/plate showed strong inhibition, 76% against 2-NF and 64% against 2-AA in strain TA-100; 8-demethyleustomin was also active, with results of 43% and 39% respectively, but no inhibition was detected from secoiridoid or polar fractions of centaury (Schimmer, Mauthner, 1996).

II.2.1.2 Assessor's overall conclusions on pharmacology

The traditional use of *Centaurium erythraea* Rafn, herba, as a (powdered) herbal drug, herbal tea or hydroalcoholic extract, for the relief of mild dyspeptic/gastrointestinal disorders/complaints and lack of appetite is well documented in a number of handbooks.

Results from *in vitro* and *in vivo* studies with extracts, and isolated constituents, support the traditional use as appetite and digestion stimulant.

Experimental data to support the antipyretic activity are very limited. In addition, no specific posology for this indication could be found. Therefore, the use as an antipyretic cannot be recommended.

II.2.2 Pharmacokinetics

II.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No data available.

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

No data available, no conclusion can be drawn.

II.2.3 Toxicology

II.2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

- No published data could be found on the toxicity of extracts of centaury. However one case report has been found, reporting a possible relation between the acute and cytolytic hepatitis and the intake of the herbal preparation Copaltra (containing *Coutarea latiflora* 50 mg and *Centaurium erythraea* 50 mg). As it concerned a combination product, no conclusions on the safety of *Centaurium* can be drawn (Wurtz *et al*., 2002).

- General toxicity of gentiopicroside, swertiamarin and sweroside was determined in the brine shrimp lethality bioassay. LD_{50} values measured for swertiamarin and sweroside were 8.0 microg/ml and 34 microg/ml, respectively. Podophyllotoxin, which was used as the positive control showed an LD_{50} of 2.8 microg/ml (Kumarasamy *et al*., 2003a; Kumarasamy *et al*., 2003b).

II.2.3.2 Assessor's overall conclusions on toxicology

Toxicological data on centaury are very limited. Experimental data are only available for isolated compounds. Nonetheless, neither the chemical composition nor the long-term widespread use in the European Community suggest that there is a (potential) risk associated with the use of centaury extract. Yet, due to the lack of data on acute and chronic toxicity, repeated dose toxicity, genotoxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, a list entry for Centaurii herba cannot be recommended.

II.3 CLINICAL DATA

Clinical studies could not been found. Therefore, only the use as a traditional herbal medicinal product is recommended but a well-established use is not justified.

II.3.1 Clinical Pharmacology

No data available.

II.3.1.1 Pharmacodynamics

No data available.

II.3.1.2 Pharmacokinetics

No data available.

II.3.2 Clinical Efficacy / Longstanding use and experience

For centaury herb the following medicinal uses have been reported in European handbooks:

* (Chronic) digestive/dyspeptic/gastro-intestinal problems: achylia, gastric juice burning, stomach, obstipation, anorexia, lack of appetite/appetite stimulation, chlorosis, jaundice, functional disturbances in the bile system etc.

Gastric juice burning sensation	Madaus (1938)
Blood cleaning action, so used for all kinds of GI-complaints	Kneipp (1935)
Bitter stomachic	Steinmetz (1954)
Increase in sputum and/or and gastric juice secretion (esp. in chronic states and achylia)	Blumenthal *et al*. (1998), Hänsel *et al*. (1992), Bisset *et al*. (1994)
Enhancing of appetite	Steinmetz (1954), Hellemont (1988), Bisset (1994), Newall (1994), ESCOP (2003)
Bitter stomachic to be used in chlorosis and	Steinmetz (1954)

jaundice	
As a tonic	Newall (1994)
All kinds of dyspeptic complaints	Hellemont (1988), ESCOP (2003)

* Fever/antipyretic

Febrifuge	Steinmetz (1954)
Intermittent fever attacks	Madaus (1938), Hellemont (1988)

II.3.2.1 Posology

There are no dose response studies available. The following posology is described in the literature:

A) Comminuted herbal substance for tea preparation (1:20)

	Single dose, up to 4 times daily	Daily dose
Madaus (1938)		1.5 g
Hellemont (1988)	1 g per cup infusion	
Weiss (1974)	1-2 teaspoon[5]/cup before meals	
Martindale (1977)	30-60 ml infusion	
BHP (1979)	2-4 g	
Blumenthal *et al.* (1998)		6 g
Bisset (1994)	2-3 g	
Newall (1994)	2-4 g	
ESCOP (2003)	1-4 g in 150 ml water	

B) Powdered herbal substance

	Single dose, up to 3 times daily	Daily dose
Madaus (1938)	1-2 g	
Hellemont (1988)	1-2 g	

[5] 1 teaspoon = ca. 1.8 g (Bisset, 1994)

Hänsel *et al.* (1992)	0.25-2 g	

C) Liquid extract (1:1; alcohol 25% v/v)

	Single dose, up to 3 times daily	Daily dose
ESCOP (2003)	2-4 ml	
Hellemont (1988)	0.6-1 g (progressive)	
Martindale (1977)	2-4 ml	
BHP (1979)	2-4 ml	
Hänsel *et al.* (1992)	2-4 ml	
Newall (1994)	2-4 ml	

D) Tincture (1:5; ethanol 70% v/v)

	Single dose, 3 times daily	Daily dose
Hellemont (1988)	30 drops[6]	
Hänsel *et al.* (1992)	2-5 g	

E) Soft extract (1:10; water)

	Single dose	Daily dose
Blumenthal *et al.* (1998)		1-2 g
Hänsel *et al.* (1992)	0.2 g	1-2 g

Proposed posology for the specified preparations

Specified preparation	Dosage
A) Cut herbal substance for tea preparation	single dose: 1-4 g, up to 4 times daily
B) Powdered herbal substance	single dose: 0.25-2 g, up to 3 times daily

[6] 30 drops = ca. 1.5 g

C) Liquid extract (1:1; ethanol 25% v/v)	single dose: 2-4 ml, up to 3 times daily
D) Tincture (1:5; ethanol 70% v/v)	single dose: 1.5-5 g, up to 3 times daily
E) Soft extract (1:10; water)	single dose: 0.2 g, daily dose: 1-2 g

Duration of use

No information could be found on the duration of use. As clinical safety studies are lacking, it is recommended to limit the duration of use to 2 weeks.

II.3.2.2 Clinical studies (case studies and clinical trials)

No published data available[7].

II.3.2.3 Clinical studies in special populations (e.g. elderly and children)

No published data available.

II.3.2.4 Assessor's overall conclusions on (clinical) efficacy / the traditional medicinal use

The available clinical data do not support well-established use.

The traditional use of *Centaurium erythraea* Rafn, herba, as a (powdered) herbal drug, herbal tea or hydroalcoholic extract, for the relief of mild dyspeptic/gastrointestinal disorders/complaints and lack of appetite is well documented in a number of handbooks. The traditional use is supported by pharmacological data.

II.3.3 Clinical Safety/Pharmacovigilance

II.3.3.1 Patient exposure

No data available.

II.3.3.2 Adverse events

None known (Newall, 1994; Blumenthal *et al.*, 1998; Walther, 2004).

II.3.3.3 Serious adverse events and deaths

No data available.

II.3.3.4 Laboratory findings

No data available.

II.3.3.5 Safety in special populations and situations

II.3.3.5.1 Intrinsic (including elderly and children) /extrinsic factors

No data available.

II.3.3.5.2 Drug interactions

[7] The electronic databases of PubMed, Embase and International Pharmaceutical Abstracts were searched with the search terms 'Centaurium erythraea' combined with 'human', 'clinical trial' , 'randomised controlled trial' and 'review'.

None known (Blumenthal *et al.*, 1998).

II.3.3.5.3 Use in pregnancy and lactation

No data available. In accordance with general medical practice, the product should not be used during pregnancy or lactation.

II.3.3.5.4 Overdose

No toxic effects have been documented. After intake of high dosages, stomach disturbances and nausea have been reported (Hellemont, 1988).

This information has not been included into the monograph because the dosage is not given in the reference.

II.3.3.5.5 Drug abuse

No data available.

II.3.3.5.6 Withdrawal and rebound

No data available.

II.3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed.

II.3.3.5.8 Contra-indications

Due to the reflexively stimulation of gastric juice secretion caused by bitter ingredients, products containing Centaurii herba must not be used in case of active peptic ulcer disease (Bisset 1994; Walther, 2004).

II.3.3.6 Assessor's overall conclusions on clinical safety

Clinical safety data are lacking. However, up to now no (serious) side effects have been reported. Furthermore, the chemical composition of centaury herb does not give reasons for safety concerns.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.
Data on use in children or adolescents are not available.

II.4 ASSESSOR'S OVERALL CONCLUSIONS

- The use of *Centaurium erythraea* Rafn has a long tradition in Europe, mainly in mild dyspeptic/gastrointestinal disorders and in temporary loss of appetite. The medicinal use has been documented continuously in well-known handbooks. Therefore, Centaurii herba fulfils the requirements of Directive 2004/24 EC for classification as a traditional herbal medicinal product. Its use in above-mentioned disorders is considered plausible on the basis of bibliographic and pharmacological data.

- The pharmacological activity is attributed to the whole extract; however emphasis is put on the group of secoiridoid glycosides ('bitters') with main components swertiamarin, gentiopicroside, centapicrin and sweroside. Also xanthones, phenolic acids and other ingredients may contribute to the pharmacological activity of Centaurii herba.

- Centaurii herba is used in the following pharmaceutical forms and posology:

A) Comminuted herbal substance for tea preparation: single dose: 1-4 g, up to 4 times daily;

B) Powdered herbal substance: single dose 0.25-2 g, up to 3 times daily;

C) Liquid extract (1:1; ethanol 25% v/v): single dose: 2-4 ml, up to 3 times daily;

D) Tincture (1:5; ethanol 70% v/v): single dose: 1.5-5 g, up to 3 times daily;

E) Soft extract (1:10; water): single dose: 0.2 g; daily dose: 1-2 g.

- Toxicological data on centaury is very limited. Experimental data is only available for isolated compounds. Nonetheless, neither the chemical composition nor the long-term widespread use in the European Community suggests that there is a (potential) risk associated with the use of centaury extract. Yet, due to the lack of data on acute and chronic toxicity, repeated dose toxicity, genotoxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, a list entry for Centaurii herba cannot be recommended.

- There are no clinical safety data for extracts of Centaurii herba. In the documentation of the traditional medicinal use within the Community, no serious adverse effects have been reported.

- Due to lack of data, Centaurii herba preparations cannot be recommended for children and adolescents below the age of 18 years, in pregnancy and lactation and must not be used in case of active peptic ulcer disease. During the public consultation, an interested party requested to include a posology for adolescents. This was not endorsed because the claim was not supported with experimental safety and/or exposure data.

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPH ON *CENTAURIUM ERYTHRAEA* RAFN, HERBA

III.2 LITERATURE REFERENCES