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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Centaurium erythraea* Rafn. s.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>Centaurium erythraea</i> Rafn. s. l. including <i>C. majus</i> (H. et L.) Zeltner and <i>C. suffruticosum</i> (Griseb.) Ronn. (syn.: <i>Erythraea centaurium</i> Persoon; <i>C. umbellatum</i> Gilibert; <i>C. minus</i> 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 (DER 1:1), extraction solvent ethanol 25% V/V d) Tincture (DER 1:5), extraction solvent ethanol 70% V/V e) Soft extract (DER 1:10), extraction solvent water
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid or solid dosage forms 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)

Centaurii herba consists of the whole or fragmented dried flowering aerial parts of *Centaureum 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., 2008).

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

Secoiridoid glucosides are the characteristic bitter-tasting constituents, principally (75%) swertiamarin and smaller amounts of gentiopicroside (gentiopicrin) and sweroside (bitterness value ca. 12,000) and centapicrin (bitterness value ca. 4,000.000). Other iridoids include bitter m-hydroxybenzoyl esters of sweroside, and de-acetylcentapicrin, centauroside (a dimeric secoiridoid), secologanin, 6'-m-hydroxybenzoyl-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 preparation(s)
 - a) Comminuted herbal substance for tea preparation
 - b) Powdered herbal substance
 - c) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V
 - d) Tincture (DER 1:5), extraction solvent ethanol 70% V/V
 - e) Soft extract (DER 1:10), extraction solvent water
- 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.

In Madaus (1938), Weiss (1974) and Van Hellefont (1985) are mentioned 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.

Phytochemical research data on major components in *Centaureum erythraea*

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

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

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

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 xanthenes (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 xanthenes occurring in the chloroform extract of small centaury aerial parts. The methodology developed was applied to twelve samples, and in all of them, nine xanthenes were identified and quantified (Valentão *et al.*, 2002).

With a new HPLC method a natural xanthone aglycone was isolated from *C. erythraea* herb and identified as 1,3,8-trihydroxy-5, 6,-dimethoxyxanthone (Aberham *et al.*, 2011).

Analytical marker

The Ph. Eur. monograph on *Centaurii herba* describes the TLC identity by means of analytical marker swertiamarin. Recent study results of Aberham *et al.* revealed that at room temperature the content of this constituent remained nearly unchanged, but reduced to 85% at high temperatures. After six months of storage the decomposition of gentiopicroside and sweroside was observed. The authors presented a validated HPLC method enabling the simultaneous determination of several bioactive constituents of *C. erythraea*, and concluded that xanthenes were stable under all conditions and suggested that these constituents may be more suitable analytical markers (Aberham *et al.*, 2011).

Metal concentration in herbal substance

After an investigation on metal concentration in plants in polluted industrial regions, Polish researchers concluded that *C. erythraea* was distinguished with the highest concentrations of Cd, Co, and Zn in plants. Therefore they concluded that careful selection is necessary of the sites for the collection of this medicinal plant (Brudzińska-Kosior *et al.*, 2012).

1.2. Search and assessment methodology

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

For updating this Assessment Report with actual information in order to revise the HMPC monograph of 2009, the database Embase has recently been searched with search term: 'Centaurium 2007-'.

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

In July-September 2014 a request was sent for information on marketed products containing *Centaurii herba* to the member states. A number of countries BE, DE, NL, UK answered that they have no authorised/registered medicinal products. DE thereby mentioned that in Germany there are 191 herbal teas containing centaury. In Austria there is one single component with this herb (Table 1) and several Member States (BG, CZ, EE, ES, LV, SI, SK) have authorised/registered combination (T)HMP's with centaury on the market (Table 2).

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
Comminuted herbal substance	Gastrointestinal complaints	Herbal tea 1 filter bag contains 1.4 g Adolescents, adults: 3-4 times daily 1 cup Children 6-12 years: 2-3 times daily 1 cup	AT (July 2014) THMP registered according to article 16a
Comminuted herbal substance	Digestive disorders and in Absence of appetite	Herbal tea (decoction) 1.5 g/glass, 2-4 times daily	PL (March 1995) Registered by drug institute daily
Comminuted herbal substance	Lack of appetite and digestive disorders (bloating, belching)	Herbal tea (decoction) 1 teaspoon (2g), 2-3 times daily	PL (December 2000) Registered by drug institute

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

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

Table 2: Overview of data obtained from marketed combination medicinal products

Member State (date of information)	Active substance	Indication	Pharmaceutical form	Regulatory status
BG (Sep 2014)	Combination coated tablet 18 mg centaurii herba, 18 mg levistici radix, 18 mg rosmarini folium	Traditional herbal medicinal product used as adjuvant therapy and for supplementation of specific measures administered in case of mild symptoms of inflammatory diseases of the urinary tract and for the prevention of renal gravel in adults and adolescents older than 12 years.	Coated tablets 2 tablets 3 times daily	THMP since 2013
CZ (Sep 2014)	Combination herbal tea Calami radix, Angelicae radix, Matricariae flos, Centaurii herba, Hyperici herba, Agrimoniae herba, Menthae piperitae herba, Rubi fruticosi folium, Foeniculi fructus	Relief of mild gastrointestinal disorders - stomachicum, carminativum, the product has mild spasmolytic, antiphlogistic and cholaretic effect	Herbal tea Posology: 1 tea bag/250 ml of boiling water 2-3 times daily	Combination product since 1971
EE	Combination Oral solution containing > 25 herbal substances	Traditional herbal medicine used orally: for functional disorders of gastrointestinal tract and as cholagogic	As generally tonisizing remedy Posology: 5 ml solution 2-3 times daily	Combination THMP since 2001
EE	Combination Oral solution containing: 1 ml (15 drops) solution contains: centaury extract (6 mg), lovage root extract (6 mg), rosemary leaf extract (6 mg). Extraction	Traditionally used for the supportive therapy in case of inflammatory diseases of the kidneys and the urinary tract, for the prevention of renal gravel.	Posology: 5 ml solution 3 times daily Risks: Allergic skin reactions, digestive disorders	Combination THMP since 2010

Member State (date of information)	Active substance	Indication	Pharmaceutical form	Regulatory status
	solvent is ethanol 59%. The medicinal product contains 19% ethanol V/V			
EE	Combination Coated tablet containing: centaury pulverized (18 mg), lovage root pulverized(18 mg), rosemary leaf, pulverized (18 mg)	Traditionally used for the supportive therapy in case of inflammatory diseases of the kidneys and the urinary tract, for the prevention of renal gravel	Posology: 2 tablets 3 times daily Risks: Allergic skin reactions, digestive disorders.	Combination THMP since 2010
ES (Sep 2014)	Combination Coated tablet Centaurii herba (18 mg) Levisticii radix (18 mg), Rosmarini folium (18 mg)	Supportive treatment and for the supplementation of specific measures in case of mild complaints within the frame-work of inflammatory diseases of the efferent urinary tract; for irrigation of the urinary tract in order to prevent the deposition of renal sand.	Film coated tablets	Combination THMP
LV (Sep 2014)	Combination oral solution 1 ml of solution contains extract (1:56) from 18 mg of mixture composed of Centaurii herba, Levisticii radix, Rosmarini folium (1:1:1). Extraction solvent – ethanol 59% (V/V).	Traditionally used for supportive treatment of mild urinary tract infections, as well as prophylactic measure against deposition of renal sand.	Oral drops, solution	Combination THMP since 2010
LV (Sep 2014)	Combination coated tablets 1 tablet contains 18 mg of powdered Centaurii herba, 18 mg	Traditionally used for supportive treatment of mild urinary tract infections, as well as prophylactic	Coated tablets	Combination THMP since 2010

Member State (date of information)	Active substance	Indication	Pharmaceutical form	Regulatory status
	of powdered Levistici radix, 18 mg of powdered Rosmarini folium.	measure against deposition of renal sand.		
SI (Oct 2014)	Combination coated tablets - <i>Centaurium erythraea</i> Rafn., herba 18,0 mg - <i>Levisticum officinale</i> Koch, radix 18,0 mg - <i>Rosmarinus officinalis</i> L., folium 18,0 mg	Supportive treatment of mild symptoms of inflammatory diseases of efferent urinary tract and - urinary dilution because of increased fluid intake which may prevent renal sand formation.	Adults and adolescents over 12 years: 2 tablets 3 times daily.	Combination THMP since 2013
SK (Aug 2014)	Combination Centaurii herba and other components	Inflammation of urine tract	Coated tablets 18 mg in 1 tablet Max. daily dose: Children from 6 to 11 years: 3 tablets per day From 12 years and adults: 6 tablets per day Single dose: 6-11 years: 1 tablets 12-adults: 2 tablets Duration of use: 3 -6 months	Combination THMP since 2010

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

No data available.

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

No data available.

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

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 States¹:

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 (1930), (Van Hellemont, 1985).

Erythraea centaurii extractum fluidum is described in: Belg. Pharm. III (before 1930) (Van Hellemont, 1985).

Extractum centaur. minor is described in: Belg. Pharm. II (Van Hellemont, 1985).

Extractum centaurii (a soft water based extract) is described in several handbooks (Erg.B.6, 1953; Van Hellemont, 1985; Pinkhof *et al.*, 1979; Hänsel *et al.*, 1992; Blumenthal, 1998; Blaschek *et al.*, 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), 1985 (Van 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; Van Hellemont, 1985).

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

Bisset (1994) mentioned 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.

¹ 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 *et al.*, 2005), see also 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 (Van Hellefont, 1985).

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) mentioned 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 Table 3.

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 topical application of an aqueous extract of centaury in the air pouch granula test (Berkan *et al.*, 1991; Hänsel *et al.*, 1992). The anti-inflammatory potential was recently evaluated by an *in vivo* experimental model based on the inhibition of acetic acid-induced increase in capillary permeability assessment. According to the results methanolic extract of *C. erythraea* displayed wound healing activity (Küveli Akkol *et al.*, 2013).

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.

Documentation regarding the posology

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

	Single dose	Daily dose
Madaus (1938)		1.5 g
Van Hellefont (1985)	1 g per cup infusion	
Weiss (1974)	1-2 teaspoon ² /cup before meals	
Martindale (1977)	30-60 ml infusion (1:20)	
BHP (1979)	2-4 g	
Blumenthal <i>et al.</i> (1998)		6 g
Bisset (1994)	2-3 g	
Newall (1994)	2-4 g	
ESCOMP (2003)	1-4 g in 150 ml water	

² 1 teaspoon = ca. 1.8 g (Bisset, 1994)

b) Powdered herbal substance

	Single dose	Daily dose
Madaus (1938)	1-2 g	
Van Hellemont (1985)	1-2 g	
Hänsel <i>et al.</i> (1992) (reference to Valnet (1983))	0.5 g 0.25 g	

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

	Single dose	Daily dose
ESCOP (2003)	2-4 ml	
Van Hellemont (1985)	0.6-1 g (progressive)	
Martindale (1977)	2-4 ml	
BHP (1979)	2-4 ml	
Hänsel <i>et al.</i> (1992)	2-4 ml	
Newall (1994)	2-4 ml	

d) Tincture (DER 1:5), extraction solvent ethanol 70% V/V

	Single dose	Daily dose
Van Hellemont (1985)	30 drops ³	
Hänsel <i>et al.</i> (1992)	2-5 g	

e) Soft extract (DER 1:10), extraction solvent water

	Single dose	Daily dose
Van Hellemont (1985)	100-200 mg	1 g
Blumenthal <i>et al.</i> (1998)		1-2 g
Hänsel <i>et al.</i> (1992)	0.2 g	1-2 g

In Table 3 information is given regarding the documented medicinal use, strength and posology for the main preparations of *Centaurii herba* as found in the phytotherapeutic handbooks.

³ 30 drops = ca. 1.5 g

Table 3: Overview of historical data

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
a) Cut herbal substance for tea preparation	Gastro-intestinal disorders, bitter stimulating appetite and increasing secretion of gastric juice	1-4 g up to 4 times daily	Madaus (1938) Van Hellefont (1985) Weiss (1974) Martindale (1977) BHP (1979) Blumenthal <i>et al.</i> (1998) Bisset (1994) Newall (1994) ESCOP (2003)
b) Powdered herbal substance	Dyspeptic and stomach disorders, lack of/stimulation of appetite	0.25-2 g up to 3 times daily	Madaus (1938) Van Hellefont (1985) Hänsel <i>et al.</i> (1992)
c) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V	Dyspeptic complains; lack of appetite	2-4 ml up to 3 times daily	ESCOP (2003) Van Hellefont (1985) Martindale (1977) BHP (1979) Hänsel <i>et al.</i> (1992) Newall (1994)
d) Tincture (DER 1:5), extraction solvent ethanol 70% V/V	Increasing sputum and gastric secretion; dyspepsy, diarrhoea, flatulence, stimulation of appetite	1.5-5 g up to 3 times daily	Van Hellefont (1985) Hänsel <i>et al.</i> (1992)
e) Soft extract (DER 1:10), extraction solvent water	Loss of appetite, dyspeptic complaints	0.2 g daily dose: 1-2 g	Hänsel <i>et al.</i> (1992) Van Hellefont (1985) Blumenthal <i>et al.</i> (1998)

2.3. Overall conclusions on medicinal use

Based on the documentation found in the handbooks, as listed above and the actual market data received from the Competent Authorities sufficient information was found for the cut herbal substance, powdered herbal substance, liquid extract, tincture and soft extract to justify at least 30 years of medicinal use including at least 15 years of the EU for the herbal substance *Centaurea herba* (Table 4).

All above mentioned preparations are for oral use, have a specified strength and posology and have indications suitable to the legal requirements in the relevant route of administration.

Table 4: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Comminuted herbal substance	Gastro-intestinal disorders, bitter stimulating appetite and increasing secretion of gastric juice	1-4 g up to 4 times daily	> 77 years

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Powdered herbal substance	Dyspeptic and stomach disorders, lack of/stimulation of appetite	0.25-2 g up to 3 times daily	> 77 years
Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V	Dyspeptic complaints; lack of appetite	2-4 ml up to 3 times daily	> 38 years
Tincture (DER 1:5), extraction solvent ethanol 70% V/V	Increasing sputum and gastric secretion; dyspepsy, diarrhoea, flatulence, stimulation of appetite	1.5-5 g up to 3 times daily	> 30 years
Soft extract (DER 1:10), extraction solvent water	Loss of appetite, dyspeptic complaints	0.2 g daily dose: 1-2 g	> 30 years

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

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).

Pharmacological activities of combination preparations

A concentration-dependant relaxant effect was observed in high-fat fed rats on spontaneous ileum contractions and on rat ileum pre-contracted with carbachol, after administration of a hydroethanolic extract of four herbs, including *Erythraea centaureum* (L.) Borkh, supporting its anti-dyspeptic activity. (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).

The essential oil, obtained by hydrodistillation of *C. erythraea* aerial parts, showed antimicrobial potential on *Escherichia coli*, *Salmonella enteritidis*, *Staphylococcus aureus* and *Bacillus cereus*; no antibacterial activity of the oil was observed on *Pseudomonas fluorescens* and *Listeria monocytogenes* (Jerkovic *et al.*, 2012).

Isolated swertiamarin showed anticholinergic activity, significantly inhibiting carbachol-induced contractions of the proximal colon in rats in a dose-dependent 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 *Centaureum 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 and Mauthner, 1996).

3.1.2. Secondary pharmacodynamics

Pharmacological activities of whole extracts of centaury herb

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 pre-treatment 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 hepatoprotective 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 hepatoprotective activity was also observed by histopathological examination of liver sections (Mroueh *et al.*, 2004).

Antioxidant activity of small centaury infusion has been reported (Valentão *et al.*, 2001; Valentão *et al.*, 2003). Antioxidant effects of methanol extracts of *Centaureum* species aerial parts was also confirmed by the study of Siler *et al.*, who investigated antioxidant capacity of different plant parts. The assays showed that above ground parts generally displayed up to 13 times higher antioxidant activity compared to roots, which might be related to higher phenolics content, especially flavonoids, in green plant organs. Secoiridoid glycosides showed no antioxidant activity (Siler *et al.*, 2014).

Tuluze *et al.* aimed to determine the antioxidant and antiulcer activities of an ethanolic extract of *C. erythraea* (SC) in aspirin (ASA) induced acute gastric ulcer model. The gastroprotective effect of SC was investigated in rats. After treatment by intragastric (i.g.) administration of 1 ml SC for 7 days, the ulcer index, oxidant and antioxidant levels were measured and compared. In the ASA plus SC group myeloperoxidase activity was lower, the glutathione and Vitamin A levels were determined higher and the percentage of lesion area (ulcer index) was significantly reduced, compared to the ASA group. The authors suggested that the SC extract protects against ASA-induced damage due to its antioxidizing activity (Tuluze *et al.*, 2011).

Antimicrobial activity for *C. erythraea* was found to be dependent on the extraction solvent used: the ethanolic extract showed inhibition zones against *Candida albicans*, *Streptococcus mutans*, *Staphylococcus aureus* and *Aggegrabacter actinomycetecomitans*; the hexane extract showed inhibition zones against *C. albicans*, *S. mutans*, *S. aureus* and the *n*-butanol extract showed inhibition zones against *C. albicans*, *S. mutans*, *S. aureus* and *A. actinomycetecomitans* (Pereira *et al.*, 2011)

Siler *et al.* demonstrated in their study on different *Centaureum* species that all tested methanolic extracts demonstrated appreciative **antibacterial** (0.05–0.5 mg/ml) and strong **antifungal** activity (0.1–0.6 mg/ml) (Siler *et al.*, 2014).

Several studies have been performed to investigate the **antidiabetic activity** of hydro-alcoholic extracts of *C. erythraea*.

Hamza *et al.* demonstrated that oral treatment (with 2 g/kg body weight extract for 18 weeks) of type 2 diabetes in mice, induced with a standardised high fat diet (HFD), a reduction in blood glucose concentrations, triglyceride, total cholesterol, serum insulin concentrations, serum insulin resistance and calorie intake (Hamza *et al.*, 2011) (reviewed by Harlev *et al.*, 2013).

The aim of Sefi *et al.* was to evaluate protective effects of *C. erythraea* leaf extract (65 mg/kg, as single dose by i.p. administration) against pancreas β -cells' damage and anti-oxidant defence systems in streptozotocin induced diabetic rats. They found a clear indication that the treatment exerted therapeutic protection in diabetes by decreasing oxidative stress and pancreatic β -cells' damage which might be attributed to its antioxidative potential (Sefi *et al.*, 2011).

In another animal study with streptozotocin (STZ) hyperglycaemic rats, Stefkov *et al.* concluded that obtained results indicated that treatment with *C. erythraea* extract (aerial parts, administered intragastrically (i.g) at different doses of 125-500 mg/kg body weight for 12 or 45 days) in STZ-diabetic rats regulated the elevated level of blood glucose and carbohydrate-related disturbances slightly better than the effect of glibenclamide. The regulation of the serum lipid status in diabetic rats was also reported. The authors suggested that the antihyperglycaemic effect could be influenced by the bitter compounds in the extract (flavonoids, iridoids and xanthenes) (Stefkov *et al.*, 2014).

Loizzo *et al.* found in their *in vitro* study evaluating the influence of the extraction procedure that the chloroform extract of *C. erythraea* exerted inhibitory activity on both digestive enzymes α -amylase and β -glucosidase, as the methanol and *n*-hexane extracts exhibited no inhibition (Loizzo *et al.*, 2008).

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

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

The traditional use of *Centaureum erythraea* Rafn. s.l., herba, as a (powdered) herbal drug, herbal tea, water extract 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.

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

General toxicity of gentiopicroside, swertiamarin and sweroside was determined in the brine shrimp lethality bioassay. LD₅₀ values measured for swertiamarin and sweroside were 8.0 µg/ml and 34 µg/ml, respectively. Podophyllotoxin, which was used as the positive control showed an LD₅₀ of 2.8 µg/ml (Kumarasamy *et al.*, 2003a; Kumarasamy *et al.*, 2003b).

The acute and subchronic toxicity of aqueous extract of *C. erythraeae* (CE) in rodents was studied by Tahraoui *et al.* For the acute study, the lyophilised CE-extract was administered to adult IOPS OFA mice in single oral doses of 1–15 g/kg given by gavage, and single intraperitoneal (i.p.) doses of 1–14 g/kg. General behavioural adverse effects, mortality, and latency of mortality were determined for up to 14 days.

In the sub-chronic dose study, the CE-extract was administered orally at doses of 100, 600 and 1200 mg/kg daily for 90 days to Wistar rats. Body weight and selected biochemical and haematological parameters were determined every 30 days and at the end of 90 days of daily administration; sections of liver and kidney were examined histologically for any signs of organ damage at the end of the treatment.

In the acute study in mice, there were no deaths or any signs of toxicity observed after oral administration of single doses of the CE-extract at any dose level up to the highest dose tested (15 g/kg), which was the no-observed-adverse-effect level (NOAEL). However, the mortality rate as well as the acute toxicity of the i.p. administered CE-extract increased progressively with increasing dose. The NOAEL for the i.p. dose was 6 g/kg while the lowest-observed-adverse-effect level (LOAEL) was 8 g/kg; the calculated acute toxicity (LD₅₀) of i.p. administered CE-extract in mice was 12.13 g/kg. In

sub-chronic studies in rats, the CE-extract administered orally at daily doses of 100, 600 and 1200 mg/kg for 90 days), did not cause any changes in haematological and biochemical parameters, except a small reduction of mean corpuscular volume, and a decrease in serum glucose and triglyceride levels at the higher doses. Histopathological examination of the liver and kidneys at the end of the study showed normal architecture suggesting no morphological disturbances.

The authors stated that because of the lack of toxicity of the CE-extract given by the oral route, and relatively high NOAEL values for the i.p. dose in the acute study in mice, as well as lack of mortality or clinically significant adverse changes in the biological and haematological parameters, and the morphology of liver and kidneys in rats after 90 days of daily dosing, it may be concluded that the CE-extract is relatively non-toxic. Also, in view of the doses consumed empirically in traditional medicine in Morocco, there is a wide margin of safety for the therapeutic use of *Centaurium erythraea* (Tahraoui *et al.*, 2010).

3.3.2. Repeat dose toxicity

No data available.

3.3.3. Genotoxicity

No data available.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

Toxicological data on centaury preparations are very limited. One published study was found on the acute and subchronic toxicity of aqueous extract and another on acute toxicity of some main constituents.

The acute toxicity (oral administration up to 15 g/kg) and subchronic toxicity (oral administration up to 1200 mg/kg for 90 days) of an aqueous extract was studied in mice. For the acute toxicity the NOAEL value was 15 g/kg, in the subchronic study no signs of toxicity have been observed. In the same study the NOAEL for intraperitoneal (i.p) administration was 6 g/kg and the calculated acute toxicity (LD₅₀) of i.p. administrated extract 12.13 g/kg. Compared to the therapeutically used preparations, these results demonstrated a wide safety margin for the use of centaury.

By an experimental study the LD₅₀ values for gentiopicroside, swertiamarin and sweroside were determined in the brine shrimp lethality bioassay; the results did not indicate any safety concern with respect to the medicinal human use of the whole extract.

Neither the data from the few available toxicity studies, nor the chemical composition, nor the long-term widespread use in the European Union suggest that there is a (potential) risk associated with the use of centaury extract.

Due to the lack of data on repeated dose toxicity, genotoxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, a list entry for *Centaurii herba* cannot be recommended.

3.4. Overall conclusions on non-clinical data

The traditional use of *Centaureum erythraea* Rafn. s.l., herba, as a (powdered) herbal drug, herbal tea, water extract 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.

Results from relevant experimental studies on centaury to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of *C. erythraea* preparations is scarce, the available toxicity data do not suggest any safety concern in relation to the oral medicinal use.

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

Oral administration of *C. erythraea* preparations can be regarded as safe at traditionally used doses. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

4. Clinical Data

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

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

4.2.1. Dose response studies

There are no dose response studies available.

4.2.2. Clinical studies (case studies and clinical trials)

No published data available.⁴ Clinical studies could not be found. Therefore, only the use as a traditional herbal medicinal product is recommended and a well-established use is not justified.

Combination preparations

In an open study on the treatment of urolithiasis with combination product containing 18 mg of each herb (Centaurii herba, Levistici radix, and Rosmarini folium), the results suggested this treatment is safe and supportive in addition to standard therapy (Ceban, 2012, Gaybullaev and Kariev, 2013). The prophylactic activity of the above mentioned product in (recurrent) urinary tract infection (UTI) was investigated in women. It appeared that daily intake of single doses six times a day, clearly modified quantity and quality of the urine compared to the control group (Vashchula *et al.*, 2013). The role of this combination product in the prophylaxis and treatment of UTI's in adults and children, and other gestational diseases in pregnancy, as well as the safety and tolerance was also confirmed in the review of clinical studies by Naber (Naber, 2012).

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

Not applicable, as there are no clinical study data available.

5. Clinical Safety/Pharmacovigilance

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

Not applicable, as there are no clinical safety data available.

5.2. Patient exposure

Aside from market presence and data from studies on a combination product, there are no concrete data concerning patient exposure.

If patients with known intolerance to Centaurii herba or plants of the Gentianaceae family are excluded, a traditional use is possible if administration follows the instructions as specified in the monograph.

5.3. Adverse events, serious adverse events and deaths

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

⁴ 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'. For the 5 years' revision additional search in database of Embase was done with the term '*Centaurium 2007*'.

One case report has been found, reporting a possible relation between the acute and cytolytic hepatitis and the intake of a herbal combination preparation (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).

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

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).

5.5.3. Special warnings and precautions for use

Due to lack of adequate data the use in children and adolescents under 18 years of age is not recommended.

5.5.4. Drug interactions and other forms of interaction

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

5.5.5. Fertility, pregnancy and lactation

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

No fertility data available as well.

5.5.6. Overdose

No toxic effects have been documented. After intake of high dosages, stomach disturbances and nausea have been reported (Van Hellefont, 1985).

5.5.7. 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.

5.5.8. Safety in other special situations

Not applicable.

5.6. 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.

On the basis of the information on its traditional use medicinal *Centaurii herba* containing preparations have proven not be harmful in the specified conditions of use (recommended indication/recommended preparations)

6. Overall conclusions (benefit-risk assessment)

The use of *Centaureum erythraea* Rafn. s.l., herba has a long tradition in Europe, mainly in mild dyspeptic/gastrointestinal disorders and in temporary loss of appetite.

As adequate clinical studies are lacking, well-established use for this herb is not justified.

The medicinal use has been documented continuously in well-known handbooks. Therefore, *Centaurii herba* fulfils the requirements of Directive 2004/24 EC as basis for classification as a traditional herbal medicinal product. The use of *Centaurii herba* containing preparations in above-mentioned indication 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 xanthenes, phenolic acids and other ingredients may contribute to the pharmacological activity of *Centaurii herba*.

Typical analytical marker is swertiamarin (Ph. Eur.), but also the group of xanthenes were recently found to be suitable analytical markers.

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

- a) Herbal tea: 1-4 g of the comminuted herbal substance in 200 ml of boiling water as a herbal infusion, up to 4 times daily;
- b) Powdered herbal substance: single dose 0.25-2 g, up to 3 times daily;
- c) Liquid extract (DER 1:1), ethanol 25% V/V: single dose: 2-4 ml, up to 3 times daily;
- d) Tincture (DER 1:5), extraction solvent ethanol 70% V/V: single dose: 1.5-5 g, up to 3 times daily;
- e) Soft extract (DER 1:10), extraction solvent 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, but it is difficult to extrapolate these to the whole extract. Available study data on acute and subchronic toxicity suggested that aqueous *Centaurii herba* extract can be used safely. Neither the chemical composition and experimental data for isolated compounds nor the long-term widespread use in the European Union suggest that there is a (potential) risk associated with the use of centaury extract; the safe use of centaury containing preparations has sufficiently justified.

Due to the lack of data on 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 European Union, 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.

Annex

List of references

The list of references has been added as a separate document.