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SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Species amarae*

Draft

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Achillea millefolium</i> L. herba <i>Artemisia absinthium</i> L., herba <i>Centaurium erythraea</i> Rafn. s.l., herba <i>Cichorium intybus</i> L., radix <i>Gentiana lutea</i> L., radix <i>Marrubium vulgare</i> L., herba <i>Menyanthes trifoliata</i> L., folium <i>Taraxacum officinale</i> Weber ex Wigg., radix cum herba
Herbal preparation(s)	Combinations of the above mentioned herbal substances
Pharmaceutical form(s)	Comminuted herbal substances as herbal tea for oral use.
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Species amarae*. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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# 1. Introduction

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

- 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.

This assessment report refers to herbal tea combinations used in the therapeutic area 'loss of appetite'. Herbal substances contained in such combinations for which an assessment by the HMPC has been performed are Millefolii herba, Absinthii herba, Centaurii herba, Cichorii radix, Gentianae radix, Menyanthidis folium, Marrubii herba and Taraxaci radix cum herba<sup>1</sup>.

Herbal substances linked to the therapeutic area but not yet assessed by the HMPC (e.g. Aurantii amari epicarpium et mesocarpium) are not considered in this assessment report. Also Cinnamomi cortex was not considered in this assessment because this indication is not included in the European Union herbal monograph (EMA/HMPC/246774/2009); however, in the calculations was considered as active substance, not as an excipient, as an indication for the stimulation of appetite is reported for Cinnamomi cortex by ESCOP and Kommission E.

Additional herbal substances which may be combination partners but which are not linked to the therapeutic area are considered as excipients.

For the description of the herbal substances, their constituents, relevant pharmacopoeia monographs, non-clinical and clinical data please refer to the assessment reports of the single herbal substances.

## 1.2. Search and assessment methodology

The information regarding herbal tea combinations in the therapeutic area 'loss of appetite' was gathered from EU member states and the information provided by interested parties.

Standard handbooks of Phytotherapy were screened manually for relevant information.

Search in scientific databases for combinations did not provide any results.

For the scientific data on safety and efficacy of the single herbal substances contained in the combinations please refer to the assessment reports of the single herbal substances.

# 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

Not applicable

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

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<sup>1</sup> The Ph. Eur. monograph on Taraxaci herba cum radice (Ph. Eur. ref.: 1851) is referring to the same herbal substance included in EU monograph, *Taraxacum officinale* Weber ex Wigg., radix cum herba (EMA/HMPC/212895/2008)

**Table 1:** Overview of data obtained from marketed medicinal products

Herbal substances mentioned in brackets are considered as excipient (no plausible contribution to the traditional indication).

	<b>Active substance</b>	<b>Indication</b>	<b>Pharmaceutical form</b>	<b>Regulatory Status</b>
1	<b>Magentee I</b> 100 g herbal tea contain: 20 g Gentianae radix, 20 g Aurantii amari epicarpium et mesocarpium, 25 g Centaurii herba, 25 g Absinthii herba, 10 g Cinnamomi cortex	To stimulate appetite	Herbal tea 1 cup of a fresh warm infusion prepared from 2 teaspoonful (approx. 4 g) of herbal tea (steeping time 5-10 min) ½ hour before meals several times daily	1987, WEU, DE, Standard Marketing Authorisation
2	<b>Magentee II*</b> 100 g herbal tea contain: 10-25 g Angelicae radix, 15-30 g Millefolii herba, 10-25 g Centaurii herba, 10-25 g Absinthii herba	To stimulate appetite	Herbal tea 1 cup of a fresh warm infusion prepared from 2 teaspoonful (approx. 3-4 g) of herbal tea (steeping time 10-15 min) ½ hour before meals several times daily	1988, WEU, DE, Standard Marketing Authorisation
3	<b>Magentee III*</b> 100 g herbal tea combination contain: (10-35 g Melissaefolium), 10-35 g Millefolii herba, 30-50 g Absinthii herba	To stimulate appetite	Herbal tea 1 cup of a fresh warm infusion prepared from 2 teaspoonful (approx. 2-3 g) of herbal tea (steeping time 10-15 min) ½ hour before meals several times daily	1988, WEU, DE, Standard Marketing Authorisation
4	<b>Magentee IV*</b> 100 g herbal tea contain: 10-30 g Gentianae radix, 10-35 g Taraxaci herba cum radice, 10-35 g Centaurii herba	To stimulate appetite	Herbal tea 1 cup of a fresh warm infusion prepared from 2 teaspoonful (approx. 4 g) of herbal tea (steeping time 10-15 min) ½ hour before meals several times daily	1988, WEU, DE, Standard Marketing Authorisation
5	<b>Magentee V*</b> 100 g herbal tea combination contain: 10-30 g Gentianae radix, 10-35 g Millefolii herba, 10-25 g Centaurii herba, 10-25 g Absinthii herba	To stimulate appetite	Herbal tea 1 cup of a fresh warm infusion prepared from 2 teaspoonful (approx. 4 g) of herbal tea (steeping time 10-15 min) ½ hour before meals several times daily	1988, WEU, DE, Standard Marketing Authorisation
6	<b>Magentee VI*</b> 100 g herbal tea combination contain: 10-15 g Gentianae radix, 15-25 g Aurantii amari epicarpium et mesocarpium, 10-25 g Centaurii herba,	To stimulate appetite	Herbal tea 1 cup of a fresh warm infusion prepared from 2 teaspoonful (approx. 4 g) of herbal tea (steeping time 10-15 min) ½ hour before meals several times daily	1988, WEU, DE, Standard Marketing Authorisation

	Active substance	Indication	Pharmaceutical form	Regulatory Status
	10-20 g Absinthii herba			
7	2 g of herbal tea contain: (0.30 g Matricariae flos, comminuted); (0.28 g Foeniculi amari fructus, comminuted (0.24 g Menthae piperitae folium, comminuted); (0.22 g Anisi fructus, comminuted); (0.22 g Coriandri fructus, comminuted); 0.06 g Menyanthidis trifoliatae folium, comminuted; 0.06 g Centaurii herba, comminuted	Traditional herbal medicinal product to stimulate appetite in adults	Herbal tea Adults: 1 cup of an infusion prepared from 1 tablespoonful (approx. 2 g) herbal tea (steeping time 5-10 min) 2-3 times daily No longer than 2 weeks	1976, DE, TUR in 2013
8**	Menthae piperitae herba 525 mg Agrimoniae herba 375 mg Marrubii herba 375 mg Rhei radix 225 mg	Used for support of bile excretion in temporary loss of appetite, in mild bile disorders, flatulence. The product has mild spasmolytic, antiphlogistic and choleric effect.	Herbal tea Pour ¼ L of boiling water over 1 teabag, cover and steep for 5 - 10 minutes. Do not allow the tea to boil. Drink warm and unsweetened 3- times a day after meals.  Always prepare fresh.	SK, 1998  (less than 30 years)  CZ, 1997, TUR since 2011
9**	1 tea bag contains: Agrimoniae herba 250 mg Marrubii herba 250 mg Boldo folium 100 mg Frangulae cortex 100 mg Matricariae flos 100 mg Menthae piperitae herba 100 mg Taraxaci radix cum herba 100 mg	Adjuvant therapy of biliary tract disorders; the tea supports bile excretion, acts slightly laxative, used against flatulation, relieves tension in the abdomen, relieves feelings of fullness. For adults, adolescents and children 12 years of age.	Herbal tea Pour ¼ L of boiling water over 2 teabags, cover and steep for 5-10 minutes and then remove. Do not allow the tea to boil. Drink as warm as possible, 3 times daily, in sips before meals. Always prepare fresh.	SK, 1969 CZ, 1969
10**	1 tea bag contains: Angelicae radix 225 mg Calami radix 225 mg Matricariae flos 225 mg Agrimoniae herba 150 mg Centaurii herba 150 mg Hyperici herba 150 mg Menthae piperitae herba 150 mg Rubi fruticosi folium 150 mg Foeniculi amari fructus	For relief of mild gastrointestinal disorders - stomachicum, carminativum, the product has mild spasmolytic, antiphlogistic and choleric effect.	Herbal tea Tea bag: pour one cup (1/4 L) of boiling water over one infusion bag and allow to steep for 15 minutes in a covered cup or teapot. Drink warm 2-3 times / day, half-an-hour before meals. Always prepare a fresh serving, just before use.	SK, 1971 CZ, 1971

	Active substance	Indication	Pharmaceutical form	Regulatory Status
	75 mg			
11**	Angelicae radix 15,0 g Calami radix 15,0 g Matricariae flos 15,0 g Agrimoniae herba 10,0 g Centaurii herba 10,0 g Hyperici herba 10,0 g Menthae piperitae herba 10,0 g Rubi fruticosi folium 10,0 g Foeniculi amari fructus 5,0 g	For relief of mild gastrointestinal disorders stomachic, carminativum, the product has mild spasmolytic, antiphlogistic and choleric effect.	Herbal tea Loose tea: pour one cup (1/4 l) of boiling water over 1 spoonful (5 g) of loose tea and allow to steep for 15 minutes in a covered cup or teapot. Drink warm 2-3 times / day, half-an-hour before meals. Always prepare a fresh serving, just before use.	SK, 1971 CZ, 1971
12**	1 tea bag contains: Absinthii herba 300 mg Menthae piperitae herba 300 mg Millefolii herba 300 mg Hyperici herba 150 mg Levistici radix 150 mg Liquiritiae radix 150 mg Foeniculi dulcis fructus 150 mg	Used for support of bile excretion in temporary loss of appetite and in mild bile disorders, flatulence. The product has mild spasmolytic, antiphlogistic and choleric effect.	Herbal tea Pour 1/4l of boiling water over 1 teabag, cover and steep for 10 minutes. Do not allow the tea to boil. Drink warm and unsweetened 3-times a day after meals. Always prepare fresh.	SK, 1998 (less than 30 years) CZ, 1995, TUR since 2011
13**	Matricariae flos 375 mg Menthae piperitae herba 375 mg Althaeae radix 300 mg Liquiritiae radix 300 mg Foeniculi dulcis fructus 150 mg	Adjuvant therapy of mild indigestion, loss of appetite, flatulence, spasms and mild gastrointestinal inflammation	Herbal tea Pour 1/4l of boiling water over 1 teabag, cover and steep for 5 minutes. Do not allow the tea to boil. Drink 2-3-times a day, for infants serve in spoons or baby bottle. Always prepare a fresh serving, just before use.	SK, 1998 (less than 30 years)  CZ, 1995, TUR since 2011
14**	1 tea bag contains: Absinthii herba 300 mg Menthae piperitae herba 300 mg Millefolii herba 300 mg Hyperici herba 150 mg Levistici radix 150 mg Liquiritiae radix 150 mg Foeniculi dulcis fructus 150 mg	a) used in temporary loss of appetite b) used in mild dyspeptic/gastrointestinal disorders	Herbal tea 1 tea bag /250 ml of boiling water 3 times daily	CZ, 1995, switched to TUR 2011 (less than 30 years)

\*The active herbal substances must add up to at least 70% (m/m) of the herbal tea combination. Other ingredients – if they are used- can be Anisi fructus, Basilici herba, Rubi fruticosi folium, Foeniculi amari fructus, Coriandri fructus, Cyani flos, Aurantii amari flos, Calendulae flos, Rosmarini folium, or Salviae officinalis folium. Each other ingredient must not be more than 5 g of the herbal tea combination.

\*\*Ref 8; 9; 10; 11; 12; 13, 14- taking into account the indication is referring mainly to digestive disorders and the mode of administration is sometimes after the meals these references will not be

considered as "Species amarae"; these will be taken into account and included in Species digestivae (stomachicae) monograph.

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

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

Not applicable

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

Not applicable

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

Calculation of the mass of the single dose / daily dose when 'spoon' is referred:

Based on information from pharmaceutical industry the bulk density of herbal teas depends on the individual components as well as on the particle size.

For the assessment of the historical data, two types of spoon (coffee spoon and table spoon) were used.

The official information for the German Standard Marketing Authorisation mentions an equivalence of 1 teaspoon with 2-4 g of herbal tea combination. A similar calculation is cited in Fischer (1978).

According to ÖAB (1960) coffee spoon is equivalent to teaspoon, therefore for the posology, 1 teaspoon (coffee spoon) is calculated as 2 grams. It was accepted that one coffee spoon contains 2 g herbal tea

#### **Table 2:** Overview of historical data

Herbal substances mentioned in brackets are considered as excipient (no plausible contribution to the traditional indication).

	<b>Active substance</b>	<b>Indication</b>	<b>Pharmaceutical form</b>	<b>Reference</b>
15	Absinthii herba 20 parts Centaurii herba 20 parts Aurantii amari epicarpium et mesocarpium 20 parts Menyanthidis folium 10 parts Calami rhizoma 10 parts Gentianae radix 10 parts Cinnamomi ceylanici cortex 10 parts	Species amaricantes	Herbal tea Single dose 1.5 g/cup, as an infusion	Austrian Pharmacopoeia IX 1960  Hager, 1938
16	Radix angelicae 100 g Radix pimpinellae 100 g Herba centaurii 500 g Folium menthae piperitae 300 g	Species stomachicae	Herbal tea 1 coffee spoon (2g) /cup, as an infusion, 2 cups daily, ½ hour before meals	Czechoslovak Pharmacopoeia II. Edition, 1954 Karmazín et al, 1984
17	Herba absinthii 200 g Herba millefolii 200 g Herba menthae piperitae 200 g Radix levistici 100 g Herba hyperici 100 g Fructus foeniculi 100 g Radix liquiritiae 100 g	Species stomachicae	-	Czechoslovak Pharmacopoeia, IV. Edition, 1987
18	Absinthii herba 20 g Centaurii herba 20g Aurantii amari epicarpium et mesocarpium 25 g Menyanthidis folium 15 g Calami rhizoma 10 g Gentianae radix 10 g	Species amaricantes	Herbal tea 2 coffee spoons (4 g) /cup, as an infusion, 2 cups daily, ½ hour before meals	Czechoslovak Pharmacopoeia, II. Edition, 1954 Karmazín et al, 1984
19	Absinthii herba 15 g Centaurii herba 30 g Menyanthidis folium 15 g Herba menthae piperitae 15 g Calami rhizoma 10 g Gentianae radix 15 g	Species stomachicae	Herbal tea 1 coffee spoon (2g) /cup, as an infusion, 2-3 cups daily, ½ hour before meals	Karmazín et al, 1984
20	(Juniperi pseudo- fructus): Menyanthidis folium: (Sennae folium) 1:1:1.	Species amarae	Herbal tea One tablespoon (3 g)/ one cup of boiling water.	Dispensatorium Danicum 1938
21	Herba Cardui benedicti 20 g Millefolii herba 20 g Folium Menyanthidis trifoliatae 20g (Folium Menthae piperitae 15 g) (Radix Symphyti 15 g) (Fructus Carvi 10 g)	Species amarae	Decoction: 2-2½ spoons boil in water for 2-3 min. under cover, leave for 10 min. drink 100-150 ml, 3 times daily, ½ hour before meals	Farmakopea Polska III, 1954 Maly Poradnik Terapeutyczny, 1977 Gobiec, 1967



22	Herba Carduui Benedicti 2 parts Gentianae radix 2 parts Centaurii herba 2 parts Rhizoma Calami 0.25 parts (Fructus Cynosbati 2 parts) (Fructus Coriandri 0.5 parts)	Tonic appetitive tea	Herbal tea 2-3 spoons of infusion 2%; ½ hour before meals	Plante medicinale, Edit. Medicala, 1986
23	Absinthii herba 10 g Angelicae radix 10 g (Melissae folium 15 g) Marrubii herba 10 g (Foeniculi fructus 5 g)	Tonic appetitive tea	Herbal tea 1 table spoon (3 g)/ 1/4 L boiling water; drink one cup of tea (250 ml) with 25-30 min before each meal	Romania Produse Farmaceutice Romanesti, 1970
24	Gentianae radix 15 g Marrubii herba 10 g Centaurii herba 10 g Cichorii radix 10 g (Menthae piperitae herba 5 g)	Tonic appetitive tea	1-2 tablespoons (3 -6 g) infused in 1/4 L boiling water; 1 cup of tea (250 ml) before each meal	Romania Produse Farmaceutice Romanesti, 1970

### 2.3. Overall conclusions on medicinal use

**Table 3:** Absinthii herba in combinations

Combination partner	Amount Absinthii herba in combination (excl. excipients)	Single dose Absinthii herba / daily dose Frequency	Reference (# in tables 1 and 2)
Angelicae radix*	10-25% 33%	0.3-1 g/0.9-3 g, 3 times daily 1 g / 3 g, 3 times daily	2 23
Aurantii amari epicarpium et mesocarpium	25% 10- 20% 20% 20%	1 g / 3 g, 3 times daily 0.4- 0.8 g/1.2- 2.4 g, 3 times daily 0.3 g / - 0.8 g/1.6 g, 2 times daily	1 6 15 18
Calami rhizoma	20% 20% 15%	0.3 g/- 0.8 g/1.6 g, 2 times daily 0.3 g /0.6-0.9 g, 2-3 times daily	15 18 19
Cinnamomi cortex	25% 20%	1 g / 3 g, 3 times daily 0.3 g / -	1 15
Centaurii herba	25% 10-25% 10-25% 10-20% 20% 20% 15%	1 g / 3 g, 3 times daily 0.3-1 g/ 0.9-3 g, 3 times daily 0.4-1 g/1.2-3 g, 3 times daily 0.4-0.8 g/1.2-2.4 g, 3 times daily 0.3 g/- 0.8 g/1.6 g, 2 times daily 0.3 g/0.6-0.9 g, 2-3 times daily	1 2 5 6 15 18 19
Gentianae radix	25% 10-25% 10-20% 20% 20% 15%	1 g / 3 g, 3 times daily 0.4 - 1 g/ 1.2-3 g, 3 times daily 0.4 - 0.8g/ 1.2-2.4 g, 3 times daily 0.3 g/- 0.8 g /1.6 g, 2 times daily 0.3 g /0.6-0.9 g, 2-3 times daily	1 5 6 15 18 19
Marrubii herba	33%	1 g / 3 g, 3 times daily	23
Millefolii herba	10-25% 33-77% 10-25% 20%	0.3-1 g/ 0.9-3 g, 3 times daily 0.66- 2.31 g/1.98 - 6.93 g, 3 times daily 0.4-1 g/1.2- 3 g, 3 times daily	2 3 5 17
Menyanthidis folium	20% 20%	0.3 g / - 0.8 g/1.6 g, 2 times daily	15 18

Combination partner	Amount Absinthii herba in combination (excl. excipients)	Single dose Absinthii herba / daily dose Frequency	Reference (# in tables 1 and 2)
	15%	0.3 g /0.6-0.9 g, 2-3 times daily	19
<b>Summary</b>	<b>10-83%</b>	<b>Single dose 0.3 – 2.31 g</b> <b>Daily dose 0.6 – 6.93 g</b> <b>Frequency: 2-3 times daily</b> Monograph: Single dose: 1-1.5 g Daily dose: 2-3 g Frequency: -	

grey: no European Union herbal monograph developed so far; \*Public statement

Comments on Reference 3: Absinthii herba 46-83%; single dose: 0.92-2.49 g/daily dose: 2.76-7.47 g

According to Absinthii herba monograph the maximum daily dose corresponds to 3 g and the daily exposure to thujone has to be below 6.0 mg.

In order to comply with the EU monograph (EMA/HMPC/751490/2016) the percentage of Absinthii herba for a maximum daily of 6 g of combination corresponds to 50%. Therefore, in this case, the percentage of Absinthii herba should be limited to this value.

**Table 4:** Centaurii herba in combinations

Combination partner	Amount Centaurii herba in combination (excl. excipients)	Single dose Centaurii herba / daily dose Frequency	Reference (# in tables 1 and 2)
Absinthii herba	25%	1 g / 3 g, 3 times daily	1
	10-25%	0.3-1 g/0.9-3 g, 3 times daily	2
	10-25%	0.4- 1 g/1.2- 3 g, 3 times daily	5
	10-25%	0.4- 1 g/1.2- 3 g, 3 times daily	6
	20%	0.3 g / -	15
	20%	0.8 g/1.6 g, 2 times daily	18
	30%	0.6 g/ 1.2- 1.8 g, 2-3 times daily	19
Angelicae radix*	10-25%	0.3-1 g/0.9- 3 g, 3 times daily	2
	50%	1 g/2 g, 2 times daily	16
Aurantii amari epicarpium et mesocarpium	25%	1 g / 3 g, 3 times daily	1
	10- 25%	0.4- 1 g/1.2- 3 g, 3 times daily	6
	20%	0.3 g / -	15
	20%	0.8 g/1.6 g, 2 times	18
Calami rhizoma	20%	0.3 g/-	15
	20%	0.8 g/1.6 g, 2 times daily	18
	30%	0.6 g/1.2 – 1.8 g, 2-3 times daily	19
	32%	-	22
Cardui Benedicti herba	32%	-	22
Cinnamomi cortex	25%	1 g / 3 g, 3 times daily	1
	20%	0.3 g / -	15
Cichorii radix	22%	0.66-1.32 g/2-4 g, 3 times daily	24
Gentianae radix	25%	1 g / 3 g, 3 times daily	1
	10-35%	0.4-1.4 g/ 1.2-4.2 g, 3 times daily	4
	10-25%	0.4-1g/ 1.2-3 g, 3 times daily	5
	10-25%	0.4-1g/ 1.2-3 g, 3 times daily	6
	20%	0.3 g/-	15
	32%	-	22
	20%	0.8 g/1.6 g, 2 times daily	18
	30%	0.6 g/1.2-1.8 g, 2-3 times daily	19
	22%	0.66-1.32 g/2-4 g, 3 times daily	24
Marrubii herba	22%	0.66-1.32 g/2-4 g, 3 times daily	24
Millefolii herba	10-25%	0.3-1 g/ 0.9-3 g, 3 times daily	2

Combination partner	Amount Centaurii herba in combination (excl. excipients)	Single dose Centaurii herba / daily dose Frequency	Reference (# in tables 1 and 2)
	10-25%	0.4-1 g/1.2- 3 g, 3 times daily	5
Menyanthis folium	50% 20% 20% 30%	0.06 g/0.12-0.18 g, 2-3 times daily 0.3 g / - 0.8 g/1.6 g, 2 times daily 0.6 g/1.2-1.8 g, 2-3 times daily	7 15 18 19
Taraxaci radix cum herba	10-35%	0.4-1.4 g/ 1.2-4.2 g, 3 times daily	4
<b>Summary</b>	<b>10-50%</b>	<b>Single dose 0.06 – 1.4 g</b> <b>Daily dose 0.12 – 4.2 g</b> <b>Frequency: 2-3 times daily</b> Monograph: Single dose 1-4 g Daily dose: 4-16 g Frequency: 4 times daily	

grey: no European Union herbal monograph developed so far; \* Public statement

**Table 5:** Cichorii radix in combinations

Combination partner	Amount Cichorii radix herba in combination (excl. excipients)	Single dose Cichorii radix / daily dose Frequency	Reference (# in tables 1 and 2)
Centaurii herba	22%	0.66-1.32 g/2-4 g, 3 times daily	24
Gentianae radix	22%	0.66-1.32 g/2-4 g, 3 times daily	24
Marrubii herba	22%	0.66-1.32 g/2-4 g, 3 times daily	24
<b>Summary</b>	<b>22%</b>	<b>Single dose 0.66-1.32 g</b> <b>Daily dose 1-4 g</b> <b>Frequency: 3 times daily</b> Monograph: Single dose 2-4 g Daily dose: 2-4 g Frequency: once daily	

grey: no European Union herbal monograph developed so far;

**Table 6:** Gentianae radix in combinations

Combination partner	Amount Gentianae radix in combination (excl. excipients)	Single dose Gentianae radix / daily dose Frequency	Reference (# in tables 1 and 2)
Absinthii herba	20% 10-30% 10-15% 10% 10% 15%	0.8 g / 2.4 g, 3 times daily 0.4-1.2 g/1.2- 3.6 g, 3 times daily 0.4- 0.6 g/1.2- 1.8 g, 3 times daily 0.15 g / - 0.4 g/0.8 g, 2 times daily 0.3 g/0.6-0.9 g, 2-3 times daily	1 5 6 15 18 19
Aurantii amari epicarpium et mesocarpium	20% 10- 15% 10% 10%	0.8 g / 2.4 g, 3 times daily 0.4- 0,6 g/1.2- 1.8 g, 3 times daily 0.15 g / - 0.4 g/0.8 g, 2 times daily	1 6 15 18
Centaurii herba	20% 10-30% 10-30% 10-15% 10% 10% 15% 32% 33%	0.8 g / 2.4 g, 3 times daily 0.4-1.2 g/1.2- 3.6 g, 3 times daily 0.4-1.2 g/1.2- 3.6 g, 3 times daily 0.4- 0,6 g/1.2- 1.8 g, 3 times daily 0.15 g / - 0.4 g/0.8 g, 2 times daily 0.3 g/0.6-0.9 g, 2-3 times daily - 1-2 g/3-6 g, 3 times daily	1 4 5 6 15 18 19 22 24

Combination partner	Amount Gentianae radix in combination (excl. excipients)	Single dose Gentianae radix / daily dose Frequency	Reference (# in tables 1 and 2)
Cichorii radix	33%	1-2 g/3-6 g, 3 times daily	24
Calami rhizoma	10%	0.15 g / -	15
	10%	0.4 g/0.8 g, 2 times daily	18
	15%	0.3 g/0.6-0.9 g, 2-3 times daily	19
	32%	-	22
Cardui Benedicti Herba	32%	-	22
Cinnamomi cortex	20%	0.8 g / 2.4 g, 3 times daily	1
	10%	0.15 g / -	15
Marrubii herba	33%	1-2 g/3-6 g, 3 times daily	24
Millefolii herba	10-30%	0.4-1.2 g/1.2- 3.6 g, 3 times daily	5
Menyanthis folium	10%	0.15 g / -	15
	10%	0.4 g /0.8 g, 2 times daily	18
	15%	0.3 g/0.6-0.9 g, 2-3 times daily	19
Taraxaci radix cum herba	10-30%	0.4-1.2 g/1.2- 3.6 g, 3 times daily	4
<b>Summary</b>	<b>10-33%</b>	<b>Single dose 0.15 – 2 g</b> <b>Daily dose 1.2 – 6 g</b> <b>Frequency: 2- 3 times daily</b> Monograph: Single dose 0.6-2 g Daily dose: 0.6-6 g Frequency: 1-3 times daily	

grey: no European Union herbal monograph developed so far

**Table 7:** Marrubii herba in combinations

Combination partner	Amount Marrubii herba in combination (excl. excipients)	Single dose Marrubii herba / daily dose Frequency	Reference (# in tables 1 and 2)
Angelicae radix*	33%	1 g / 3 g, 3 times daily	23
Absinthii herba	33%	1g / 3 g, 3 times daily	23
Centaurii herba	22%	0.66-1.32 g/ 2-4 g, 3 times daily	24
Gentianae radix	22%	0.66-1.32 g/ 2-4 g, 3 times daily	24
Cichorii radix	22%	0.66-1.32 g/ 2-4 g, 3 times daily	24
<b>Summary</b>	<b>22-33%</b>	<b>Single dose 0.3 – 1.32 g</b> <b>Daily dose 0.9 – 4 g</b> <b>Frequency: 3 times daily</b> Monograph: Single dose 1-2 g Daily dose: 3-6 g Frequency: 3 times daily	

grey: no European Union herbal monograph developed so far; \* Public statement

**Table 8:** Menyanthis folium in combinations

Combination partner	Amount Menyanthis folium in combination (excl. excipients)	Single dose Menyanthis foium / daily dose Frequency	Reference (# in tables 1 and 2)
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Absinthii herba	10% 15% 15%	0.15 g / - 0.6 g/1.2 g, 2 times daily 0.3 g/0.6-0.9 g, 2-3 times daily	15 18 19
Cardui Benedicti herba	33%	-	21
Centaurii herba	50% 10% 15% 15%	0.06 g/0.12-0.18 g, 2-3 times daily 0.15 g / - 0.6 g/1.2 g, 2 times daily 0.3 g/ 0.6-0.9 g, 2-3 times daily	7 15 18 19
Gentianae radix	10% 15% 15%	0.15 g / - 0.6 g/1.2 g, 2 times daily 0.3 g/0.6-0.9 g, 2-3 times daily	15 18 19
Millefolii herba	33%	-	21
<b>Summary</b>	<b>10-50%</b>	<b>Single dose 0.06 – 0.6 g</b> <b>Daily dose 0.12 – 1.2 g</b> <b>Frequency: 2-3 times daily</b> Monograph: Single dose 0.4-1.6 g Daily dose: 0.78-3.9 g Frequency: 2-4 times daily	

Table 9: Millefolii herba in combinations

<b>Combination partner</b>	<b>Amount Millefolii herba in combination (excl. excipients)</b>	<b>Single dose Millefolii herba / daily dose Frequency</b>	<b>Reference (# in tables 1 and 2)</b>
Angelicae radix*	15-30%	0.45-1.2 g/1.35- 3.6 g, 3 times daily	2
Absinthii herba	15-30% 11-54 % 10-35% 20%	0.45-1.2 g/1.35- 3.6 g, 3 times daily 0.22-1.62g /0.66- 4.86 g, 3 times daily 0.4- 1.4 g/ 1.2- 4.2 g, 3 times daily -	2 3 5 17
Cardui Benedicti herba	33%	-	21
Centaurii herba	15-30% 10-35%	0.45-1.2 g/1.35- 3.6 g, 3 times daily 0.4- 1.4 g/ 1.2- 4.2 g, 3 times daily	2 5
Gentianae radix	10-35%	0.4- 1.4 g/ 1.2- 4.2 g, 3 times daily	5
Menyanthidis folium	33%	-	21
<b>Summary</b>	<b>10-54%</b>	<b>Single dose 0.22 – 1.62 g</b> <b>Daily dose 0.66 – 4.86 g</b> <b>Frequency: 3 times daily</b> Monograph: Single dose 2-4 g Daily dose: 6-16 g Frequency: 3-4 times	

grey: no European Union herbal monograph developed so far; \* Public statement

Table 10: Taraxaci herba cum radice in combinations

<b>Combination partner</b>	<b>Amount Taraxaci radix cum herba in combination (excl. excipients)</b>	<b>Single dose Taraxaci radix cum herba / daily dose Frequency</b>	<b>Reference (# in tables 1 and 2)</b>
Centaurii herba	10-35%	0.4-1.4 g/1.2- 4.2 g, 3 times daily	4

Gentianae radix	10-35%	0.4-1.4 g/1.2- 4.2 g, 3 times daily	4
<b>Summary</b>	<b>10-35%</b>	<b>Single dose 0.4 – 1.4 g</b> <b>Daily dose 1.2 – 4.2 g</b> <b>Frequency: 3 times daily</b> Monograph: Single dose 4-10 g Daily dose: 12-30 g Frequency: 3 times daily	

grey: no European Union herbal monograph developed so far

**Table 11:**

Numbers indicate the percentage of a herbal substance (left row) in a combination with other herbal substances (excipients excluded) based on documented traditional medicinal use. (Instructions and an example how to apply the table are given on the following page.)

Example: When Absinthii herba is combined with Gentianae radix then 10–25% of Absinthii herba is traditionally used in combinations. This combination contains 10–30% Gentianae radix.

	Absinthii herba	Centaurii herba	Cichorii radix	Gentianae radix	Marrubii herba	Millefolii herba	Menyanthis folium	Taraxaci herba cum radice	Range
Absinthii herba	-	10-25%	-	10-25%	33%	10-50%	15-20%	-	10-50%
Centaurii herba	10-30%	-	22%	10-35%	22%	10-25%	20-50%	10-35%	10-50%
Cichorii radix	-	22%	-	22%	22%	-	-	-	22%
Gentianae radix	10-30%	10-33%	33%	-	33%	10-30%	10-15%	10-30%	10-33%
Marrubii herba	33%	22%	22%	22%	-	-	-	-	22-33%
Menyanthis folium	10-15%	10-50%	-	10-15%	-	33%	-	-	10-50%
Millefolii herba	10-54%	10-35%	-	10-35%	-	-	33%	-	10-54%
Taraxaci radix cum herba	-	10-35%	-	10-35%	-	-	-	-	10-35%

According to the data included in tables 1 and 2, the number of active substances in a herbal tea combination varies from 2 to 4, therefore in the monograph the number of active substances is limited to a maximum of 4.

### How to use the information on traditional medicinal use of these combinations?

Evidence for combination: the grey shaded fields in table 11 indicate combinations with evidence of traditional medicinal use. Example: Millefolii herba has evidence of combination with Absinthii herba, Centaurii herba, Gentianae radix and Menyanthidis folium. Out of these documented combinations the combination partners for an application for a traditional herbal medicinal product may be chosen

Number of combination partners: The number of active substances in a herbal tea combination should be limited to a maximum of 4 based on the corresponding products and the references used for assessment. Further herbal substances may be added as excipients, their number, amount and function should be justified.

Amount of each herbal substance in the combination: The very right column indicates the traditional percentages of the herbal substance in the combinations. The calculation is based on those combination partners only, which are mentioned in the table. The amount in a traditional herbal medicinal product should be within this range. The sum of active ingredients should end up with 100%. Excipients are not considered in this range.

Example: Combination of Absinthii herba + Centaurii herba + Gentianae radix. The combination should contain 10-50% Absinthii herba, 10–50% Centaurii herba and 10–33% Gentianae radix. Therefore a combination of 30% Absinthii herba, 40% Centaurii herba and 30% Gentianae radix is covered by this assessment and by the European Union monograph.

### Information from published European Union herbal monographs

#### Indication:

Millefolii herba Marrubii herba	Traditional herbal medicinal product used for temporary loss of appetite
Menyanthidis folium	Traditional herbal medicinal product used in temporary loss of appetite
Absinthii herba	Traditional herbal medicinal product for temporary loss of appetite
Centaurii herba	Traditional herbal medicinal product used in mild dyspeptic/gastrointestinal disorders and in temporary loss of appetite
Cichorii radix Taraxaci radix cum herba	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
Gentianae radix	Traditional herbal medicinal product for temporary loss of appetite

*Assessment for combinations: According to the indications of medicinal products on the market and according to the terminology of the herbal tea combinations in pharmacopoeias and text books the first indication appears suitable to all combinations.*

#### Posology:

Based on the information from marketed products the single dose of herbal tea combinations is in the range between 1-4 g, with one combination up to 6 g. The single dose for these combinations was considered to 2 g.



The mean dosage frequency is 2-3 times daily. Many references do report a "several times daily" frequency. It can be assumed that the traditional use of herbal teas in general is linked to a '3 times daily' dosage frequency, since are taken before each main meal of the day.

*Assessment for combinations:*

**Table 11:** Comparison of the daily dose in the combinations with the upper limit according to the HMPC monographs

	<b>Range in a combination (excl. excipients)</b>	<b>Daily dose (2 g combination, 3 times daily)</b>	<b>Maximum daily dose HMPC monograph</b>
Absinthii herba	10-50%	0.6-3.0 g	Up to 3 g
Centaurii herba	10-50%	0.6- 3.0 g	Up to 16 g
Cichorii radix	22%	1.32 g	Up to 4 g
Gentianae radix	10-33%	0.6-1.98 g	Up to 6 g
Marrubii herba	22-33%	1.32-1.98 g	Up to 6 g
Menyanthidis folium	10-50%	0.6-3 g	Up to 4.8 g
Millefolii herba	10-54%	0.6- 3.24 g	Up to 16 g
Taraxaci radix cum herba	10-35%	0.6- 2.1 g	Up to 30 g

Age limits:

Millefolii herba Cichorii radix Taraxaci radix cum herba Menyanthidis folium	Adolescents, adults and elderly
Absinthii herba Centaurii herba Gentianae radix	Adults and elderly
Marrubii herba	Adolescents over 12 years of age, adults and elderly

*Assessment for combinations:*

Tea combinations containing Absinthii herba, Centaurii herba or Gentianae radix are restricted to the use in adults and elderly. Other combinations may be used in adolescents.

Duration of use:

Millefolii herba Absinthii herba Gentianae radix Marrubii herba Menyanthidis folium	2 weeks; To be taken 30 minutes before meals.
Centaurii herba Cichorii radix Taraxaci radix cum herba	2 weeks

*Assessment for combinations:*

The restriction to 2 weeks for all combinations is justified by the indication.

Contraindications:

Millefolii herba Cichorii radix	Hypersensitivity to the active substance and to other plants of the Asteraceae (Compositae) family.
Taraxaci radix cum herba	Hypersensitivity to the active substance and to other plants of the Asteraceae (Compositae) family. Obstructions of bile ducts, cholangitis, liver diseases, gallstones, active peptic ulcer and any other biliary diseases.
Absinthii herba	Hypersensitivity to the active substance(s) and to other plants of the Asteraceae (Compositae) family. Obstruction of the bile duct, cholangitis or liver disease
Centaurii herba	Hypersensitivity to the active substance(s). Peptic ulcer.
Gentianae radix	Hypersensitivity to the active substance
Marrubii herba	Hypersensitivity to the active substance and to other plants of the Lamiaceae (Labiatae) family. Obstruction of the bile duct, cholangitis, liver disease, ileus
Menyanthis folium	Hypersensitivity to the active substance. Patients with active gastric or duodenal ulcer.

*Assessment for combinations:*

All combinations have to include the contraindication:

- Hypersensitivity to the active substance.

*Combinations including Millefolii herba or Cichorii radix:*

Additionally: Hypersensitivity to other plants of the Asteraceae (Compositae) family.

*Combinations including Taraxaci radix cum herba:*

Additionally: Hypersensitivity to other plants of the Asteraceae (Compositae) family. Obstructions of bile ducts, cholangitis, liver diseases, gallstones, active peptic ulcer and any other biliary diseases.

*Combinations including Absinthii herba:*

Additionally: Hypersensitivity to other plants of the Asteraceae (Compositae) family. Obstruction of the bile duct, cholangitis or liver disease.

*Combinations containing Centaurii herba:*

Additionally: Peptic ulcer.

*Combinations containing Marrubii herba:*

Additionally: Hypersensitivity to other plants of the Lamiaceae (Labiatae) family. Obstruction of the bile duct, cholangitis, liver disease, ileus

Menyanthis folium: Patients with active gastric or duodenal ulcer.

Special warnings and precautions for use:

Millefolii herba	The use in children under 12 years of age has not been established due to lack of adequate data.
Absinthii herba	Patients with gallstones and any other biliary disorders should consult a doctor before using Absinthii herba preparations. The use in children and adolescents under 18 years of age has not been established due to lack of adequate data.

Centaurei herba Gentianae radix	The use in children and adolescents under 18 years of age has not been established due to lack of adequate data.
Cichorii radix	The use in children under 12 years of age has not been established due to lack of adequate data.
Marrubii herba	Patients with active peptic ulcer, gallstones and any other biliary disorders should consult a doctor before using Marrubii herba preparations. The use in children under 12 years of age has not been established due to lack of adequate data.
Menyanthis folium	The use in children under 12 years of age has not been established due to lack of adequate data.
Taraxaci radix cum herba	The use in children under 12 years of age has not been established due to lack of adequate data.

*Assessment for combinations:*

Based on the age limit specified above the respective warning has to be given: "The use in children and adolescents under 18 years of age has not been established due to lack of adequate data" or "The use in children under 12 years of age has not been established due to lack of adequate data".

Combinations containing Absinthii herba:

Additionally: Patients with gallstones and any other biliary disorders should consult a doctor before using Absinthii herba preparations.

Combinations containing Marrubii herba:

Additionally: Patients with active peptic ulcer, gallstones and any other biliary disorders should consult a doctor before using Marrubii herba preparations.

Interactions:

Millefolii herba Absinthii herba Centaurei herba Cichorii radix Gentianae radix Marrubii herba Menyanthis folium Taraxaci radix cum herba	None reported
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*Assessment for combinations:*

All combinations have to include the statement: None reported

Fertility, pregnancy and lactation:

Millefolii herba Taraxaci radix cum herba	Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.
Absinthii herba	There are no or limited data from use during pregnancy and lactation. The use is not recommended during pregnancy and lactation. No fertility data available.
Centaurei herba Cichorii radix Gentianae radix Marrubii herba	Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. No fertility data available

Menyanthidis folium	
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*Assessment for combinations:*

All combinations have to include the statement:

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. No fertility data available.

Effects on ability to drive and use machines

Absinthii herba Centaurii herba Cichorii radix Gentianae radix Marrubii herba Millefolii herba Menyanthidis folium Taraxaci radix cum herba	No studies on the effect on the ability to drive and use machines have been performed.
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*Assessment for combinations:*

All combinations have to include the statement:

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

Undesirable effects:

Millefolii herba	Hypersensitivity reactions of the skin have been reported. The frequency is not known.
Absinthii herba Centaurii herba Cichorii radix Gentianae radix Marrubii herba Menyanthidis folium	None known
Taraxaci radix cum herba	Epigastric pain and hyperacidity may occur. The frequency is not known. Allergic reactions may occur. The frequency is not known.

*Assessment for combinations:*

The section 'Undesirable effects' should contain the combined information taken from the European Union herbal monographs for the single ingredients.

For all combinations: The frequency is not known.

Overdose:

Millefolii herba Absinthii herba Cichorii radix Gentianae radix Marrubii herba Menyanthidis folium Taraxaci radix cum herba	No case of overdose has been reported.
Centaurii herba	Stomach disturbances and nausea have been reported.

*Assessment for combinations:*

All combinations without Centaurii herba should include the statement:

No case of overdose has been reported.

*Combinations containing Centaurii herba:*

Stomach disturbances and nausea have been reported.

Preclinical safety data:

Millefolii herba	Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.
Absinthii herba	Thujone is reported to be neurotoxic and chemotypes with low content of thujone should be preferred. Tests on reproductive toxicity have been performed with a dry ethanolic extract of Absinthii herba administered orally to pregnant rats. Results showed reduced sites of implantations and a reduced rate of born pups. Thujone is known for its uterus stimulating activity Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed with the preparations of Absinthii herba covered by HMPC monograph
Centaurii herba Cichorii radix Marrubii herba Menyanthidis folium	Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.
Gentianae radix	Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.  For some xanthenes which are among the constituents of Gentiana lutea, positive results were found in the AMES test (pre-incubation method).
Taraxaci radix cum herba	Adequate tests on genotoxicity have not been performed. Tests on reproductive toxicity and carcinogenicity have not been performed.

*Assessment for combinations:*

All combinations without *Absinthii herba* have to include the statement: Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

*Combinations containing Absinthii herba:*

As *Absinthii herba* may be contained in herbal tea combinations up to 50% the additionally wording of the European Union herbal monograph on *Absinthii herba* should be used:

Thujone is reported to be neurotoxic and chemotypes with low content of thujone should be preferred. Tests on reproductive toxicity have been performed with a dry ethanolic extract of *Absinthii herba* administered orally to pregnant rats. Results showed reduced sites of implantations and a reduced rate of born pups. Thujone is known for its uterus stimulating activity.

*Combinations containing Gentianae radix:*

Additionally: For some xanthenes which are among the constituents of *Gentiana lutea*, positive results were found in the AMES test (pre-incubation method).

### 3. Non-Clinical Data

Please refer to the assessment reports of the individual herbal substances.

## 4. Clinical Data

Please refer to the assessment reports of the individual herbal substances.

## 5. Clinical Safety/Pharmacovigilance

Please refer to the assessment reports of the individual herbal substances.

## 6. Overall conclusions (benefit-risk assessment)

The herbal substances *Millefolii herba*, *Absinthii herba*, *Centaurii herba*, *Cichorii radix*, *Gentianae radix*, *Marrubii herba*, *Menyanthidis folium* and *Taraxaci radix cum herba* for which a EU herbal monograph has been established, are traditionally used in herbal tea combinations with the indication 'Traditional herbal medicinal product used for temporary loss of appetite'.

The evidence on traditional medicinal use of the single herbal substances is discussed and justified in the assessment reports.

The evidence on traditional medicinal use of the combinations is based on marketed products in the member states, on monographs in national pharmacopoeias, on standard marketing authorisations and on publications.

Based on the composition of traditionally used combinations a matrix is developed indicating what herbal substances are traditionally combined and in what percentage they are traditionally combined.

This matrix can be used as basis for evidence of traditional medicinal use for individual applications for registration as traditional herbal medicinal product.

The traditional medicinal use is plausible due to the long-standing medicinal use in the proposed indication.

The safety of the individual herbal substances has been assessed in the assessment reports published together with the respective European Union monographs.

Potential risks and undesirable effects are properly addressed in the proposed European Union monograph for the combinations.

Based on the long-standing medicinal use no potentiation of undesirable effects due to the combination is to be expected.

Depending on the safety data of the individual herbal substances the medicinal use of the combinations is restricted to adults or adolescents and adults.

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

## Annex

### ***List of references***