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SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Species amarae*

Final

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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Table of contents

Table of contents	2
1. Introduction	3
1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof ..	3
1.2. Search and assessment methodology	4
2. Data on medicinal use	4
2.1. Information about products on the market	4
2.1.1. Information about products on the market in the EU/EEA Member States	4
2.1.2. Information on products on the market outside the EU/EEA	10
2.2. Information on documented medicinal use and historical data from literature	10
2.3. Overall conclusions on medicinal use	13
3. Non-Clinical Data	31
4. Clinical Data	31
5. Clinical Safety/Pharmacovigilance	31
6. Overall conclusions (benefit-risk assessment)	31
Annex	32

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.

EU herbal monographs on herbal tea combinations are based on combinations which have been shown to fulfil the applicable criteria according to 2001/83/EC. In addition, the specific herbal preparations included have a documented traditional use on a specific indication already established in previous HMPC assessments for the single substance use. There are data showing their use in combinations in certain ranges that can be considered safe and plausible.

The legislation does not impose any limitation to the number/percentage of combination partners in herbal teas. However, the scientific opinion of the HMPC is:

- *Usually not more than 4 herbal substances should be used in a herbal tea as active substance and each substance should represent not less than 10% of the total weight. More combination partners at lower proportions imply technical obstacles in terms of quality testing and raise questions about the plausible contribution and the need/justification. These may be better considered excipients.*
- *More than 4 substances or less than 10% of the total weight in a herbal tea would in principle not raise concerns from a public health viewpoint provided that the marketing authorisation holder/traditional use registration holder can control the quality of the product and that appropriate justification on the need and the plausibility as active substance as well as the safety for a specific indication, strength and posology is provided.*

According to data from marketed products, pharmacopoeias, textbooks and literature, traditional herbal tea combinations in the EU member states contain mostly 3-4 main herbal substances with a well-documented single and combined use and plausibility in a specific indication. Accordingly, HMPC agreed and cover a large proportion of traditional combinations. Such limitation allows also a reasonable reference to previous single substance assessments and appropriate complexity of the monograph for use by applicants and assessors.

Tea combinations in EU herbal monographs can be considered plausible and safe in a certain indication and thus facilitate national registration procedures providing some flexibility for applicants. However, it is not supposed to be exhaustive or exclude other individual combinations. It is always possible to obtain registration/authorisation for a specific combination product provided that all requirements are met - even if not covered by the EU herbal combination monographs. Reference can be made to the established herbal tea monographs with an adequate justification of the deviation (e.g. inclusion of a preparation without an EU monograph or different number of combination partners).

It is further referred to Q&A [EMA/HMPC/345132/2010](https://www.ema.europa.eu/en/qa/hmhc/345132/2010) questions R1 and R8 as well as general HMPC guidance in this respect:

- *Guideline on the clinical assessment of fixed combinations of herbal substances / herbal preparations ([EMA/HMPC/166326/2005](https://www.ema.europa.eu/en/qa/hmhc/166326/2005))*
- *Quality of combination herbal medicinal products/traditional herbal medicinal products ([EMA/HMPC/CHMP/CVMP/214869/2006](https://www.ema.europa.eu/en/qa/hmhc/chmp/cvmp/214869/2006))*

This assessment report refers to herbal tea combinations used in the therapeutic area 'loss of appetite'. Herbal substances contained in such combinations for which previously an assessment by the HMPC has been performed for the use as single substance are Millefolii herba, Absinthii herba, Centaurii herba, Cichorii radix, Gentianae radix, Menyanthidis folium, Marrubii herba and Taraxaci radix cum herba¹.

Other herbal substances that are linked to the therapeutic area are found occasionally in historic tea combinations but are not yet assessed by the HMPC leading to a EU herbal monograph for the single substance (e.g. Aurantii amari epicarpium et mesocarpium). These are not considered in this assessment report for inclusion into the combination monograph. Also Cinnamomi cortex was not considered because the indication 'loss of appetite' is not included in the European Union herbal monograph on Cinnamomi cortex alone (EMA/HMPC/246774/2009).

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

Table 1: Overview of data obtained from marketed medicinal products

For preparations 1-7: Herbal substances mentioned in brackets are considered as excipient (no plausible contribution to the traditional indication as typical bitter drug).

¹ 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)

	Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
1	Magentee I 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 (approximately 4 g) of herbal tea (steeping time 5-10 min.) ½ hour before meals several times daily	1987, WEU, DE, Standard Marketing Authorisation
2	Magentee II* 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 (approximately 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	Magentee III* 100 g herbal tea combination contain: (10-35 g Melissa folium), 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 (approximately 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	Magentee IV* 100 g herbal tea contain: 10-30 g Gentianae radix,	To stimulate appetite	Herbal tea 1 cup of a fresh warm infusion prepared from 2 teaspoonful (approximately	1988, WEU, DE, Standard Marketing Authorisation

	Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	10-35 g Taraxaci herba cum radice, 10-35 g Centaurii herba		4 g) of herbal tea (steeping time 10-15 min.) ½ hour before meals several times daily	
5	Magentee V* 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 (approximately 4 g) of herbal tea (steeping time 10-15 min.) ½ hour before meals several times daily	1988, WEU, DE, Standard Marketing Authorisation
6	Magentee VI* 100 g herbal tea combination contain: 10-15 g Gentianae radix, 15-25 g Aurantii amari epicarpium et mesocarpium, 10-25 g Centaurii herba, 10-20 g Absinthii herba	To stimulate appetite	Herbal tea 1 cup of a fresh warm infusion prepared from 2 teaspoonful (approximately 4 g) of herbal tea (steeping time 10-15 min.) ½ hour before meals several times daily	1988, WEU, DE, Standard Marketing Authorisation
7	2 g of herbal tea contain: (0.30 g Matricariae flos, comminuted), (0.28 g Foeniculi amari fructus, comminuted),	Traditional herbal medicinal product to stimulate appetite in adults	Herbal tea Adults: 1 cup of an infusion prepared from 1 tablespoonful (approximately 2 g) herbal tea (steeping time 5-10 min.) 2-3 times daily No longer than 2 weeks	1976, DE, TUR in 2013

	Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	(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			
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 min. Do not allow the tea to boil. Drink warm and unsweetened 3 times a day after meals. Always prepare fresh.	SK, 1998*** 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 min. 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:	For relief of mild gastrointestinal	Herbal tea	SK, 1971

	Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	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 75 mg	disorders-stomachicum, carminativum, the product has mild spasmolytic, antiphlogistic and choleric effect.	Tea bag: pour one cup (¼ l) of boiling water over one infusion bag and allow to steep for 15 min. in a covered cup or teapot. Drink warm 2-3 times per day, ½ hour before meals. Always prepare a fresh serving, just before use.	CZ, 1971
11* *	Angelicae radix 15 g Calami radix 15 g Matricariae flos 15 g Agrimoniae herba 10 g Centaurii herba 10 g Hyperici herba 10 g Menthae piperitae herba 10 g Rubi fruticosi folium 10 g Foeniculi amari fructus 5 g	For relief of mild gastrointestinal disorders stomachicum, carminativum, the product has mild spasmolytic, antiphlogistic and choleric effect.	Herbal tea Loose tea: pour one cup (¼ 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 per day, ½ 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	Used for support of bile excretion in temporary loss of appetite and in mild bile disorders, flatulence. The product has mild	Herbal tea Pour ¼ l of boiling water over 1 teabag, cover and steep for 10 min. Do not allow the tea to boil. Drink warm and unsweetened 3	SK, 1998*** CZ, 1995, TUR since 2011

	Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	Hyperici herba 150 mg Levistici radix 150 mg Liquiritiae radix 150 mg Foeniculi dulcis fructus 150 mg	spasmolytic, antiphlogistic and choleric effect.	times a day after meals. Always prepare fresh.	
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 ¼ l of boiling water over 1 teabag, cover and steep for 5 min. 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*** 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/gastro-intestinal disorders	Herbal tea 1 tea bag per 250 ml of boiling water 3 times daily	CZ, 1995*** switched to TUR 2011

*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 taken into account and included in Species digestivae (stomachicae) monograph.

*** Less than 30 years of marketing authorisation/registration at time of first market overview/ first assessment

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 per 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 tablespoon) 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 gr. It was accepted that one coffee spoon contains 2 g herbal tea.

Table 2: Overview of historical data

Herbal substances mentioned in brackets are not considered as typical bitter drug active partners in tea combinations*

	Active substance	Indication	Pharmaceutical form Strength Posology	Reference
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 per 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 per 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 per cup, as an infusion, 2 cups daily, ½ hour before meals	Czechoslovak Pharmacopoeia, II. Edition, 1954 Karmazín <i>et al.</i> , 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 2 g per cup, as an infusion, 2-3 cups daily, ½ hour before meals	Karmazín <i>et al.</i> , 1984
20	(Juniperi pseudo-fructus): Menyanthidis folium: (Sennae folium) 1:1:1.	Species amarae	Herbal tea One tablespoon 3 g per 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 per ¼ 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 ¼ l boiling water; 1 cup of tea 250 ml before each meal	Romania Produse Farmaceutice Romanesti, 1970

* Menthae folium or/and herba are used for the symptomatic relief of digestive disorders, therefore can be considered active partners in *Species stomachicae*. In *Species amarae*, they have no clear contribution to the traditional indication as typical bitter drug.

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	28% 10- 20% 22% 20%	1.12 g / 3.36 g, 3 times daily 0.4-0.8 g / 1.2-2.4 g, 3 times daily 0.33 g / - 0.8 g / 1.6 g, 2 times daily	1 6 15 18
Calami rhizoma	22%	0.33 g / -	15

Combination partner	Amount Absinthii herba in combination (excl. excipients)	Single dose Absinthii herba/daily dose Frequency	Reference (# in tables 1 and 2)
	20%	0.8 g / 1.6 g, 2 times daily	18
	15%	0.3 g / 0.6-0.9 g, 2-3 times daily	19
Centaurii herba	28%	1.12 g / 3.36 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
	10-20%	0.4-0.8 g / 1.2-2.4 g, 3 times daily	6
	22%	0.33 g / -	15
	20%	0.8 g / 1.6 g, 2 times daily	18
	15%	0.3 g / 0.6-0.9 g, 2-3 times daily	19
Gentianae radix	28%	1.12 g / 3.36 g, 3 times daily	1
	10-25%	0.4-1 g / 1.2-3 g, 3 times daily	5
	10-20%	0.4-0.8g / 1.2-2.4 g, 3 times daily	6
	22%	0.33 g / -	15
	20%	0.8 g / 1.6 g, 2 times daily	18
	15%	0.3 g / 0.6-0.9 g, 2-3 times daily	19
Marrubii herba	33%	1 g / 3 g, 3 times daily	23
Millefolii herba	10-25%	0.3-1 g / 0.9-3 g, 3 times daily	2
	33-77%	0.66-2.31 g / 1.98-6.93 g, 3 times daily	3
	10-25%	0.4-1 g / 1.2-3 g, 3 times daily	5
	20%		17
Menyanthis folium	22%	0.33 g / -	15
	20%	0.8 g / 1.6 g, 2 times daily	18
	15%	0.3 g / 0.6-0.9 g, 2-3 times daily	19
Summary	10-77%	Single dose 0.3-2.31 g Daily dose 0.6-6.93 g Frequency: 2-3 times daily Monograph: Single dose: 1-1.5 g Daily dose: 2-3 g	

Combination partner	Amount Absinthii herba in combination (excl. excipients)	Single dose Absinthii herba/daily dose Frequency	Reference (# in tables 1 and 2)
		Frequency: -	

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

Comments on Reference 3: Absinthii herba 46-77%; single dose: 0.92-2.31 g per daily dose: 2.76-6.03 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	28%	1.12 g / 3.36 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
	22%	0.33 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	28%	1.12 g / 3.36 g, 3 times daily	1
	10- 25%	0.4- 1 g / 1.2-3 g, 3 times daily	6
	22%	0.33 g / -	15
	20%	0.8 g / 1.6 g, 2 times	18
Calami rhizoma	22%	0.33 g / -	15
	20%	0.8 g / 1.6 g, 2 times daily	18

Combination partner	Amount Centaurii herba in combination (excl. excipients)	Single dose Centaurii herba/daily dose Frequency	Reference (# in tables 1 and 2)
	30%	0.6 g / 1.2–1.8 g, 2-3 times daily	19
	32%	-	22
Cardui Benedicti herba	32%	-	22
Cichorii radix	22%	0.66-1.32 g / 2-4 g, 3 times daily	24
Gentianae radix	28%	1.12 g / 3.36 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
	22%	0.33 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
	10-25%	0.4-1 g / 1.2-3 g, 3 times daily	5
Menyanthidis folium	50%	0.06 g / 0.12-0.18 g, 2-3 times daily	7
	22%	0.33 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
Taraxaci radix cum herba	10-35%	0.4-1.4 g / 1.2-4.2 g, 3 times daily	4
Summary	10-50%	Single dose 0.06–1.4 g Daily dose 0.12–4.2 g Frequency: 2-3 times daily Monograph: Single dose 1-4 g Daily dose: 4-16 g	

Combination partner	Amount Centaurii herba in combination (excl. excipients)	Single dose Centaurii herba/daily dose Frequency	Reference (# in tables 1 and 2)
		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
Summary	22%	Single dose 0.66-1.32 g Daily dose 2-4 g Frequency: 3 times daily 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	22%	0.88 g / 2.64 g, 3 times daily	1
	10-30%	0.4-1.2 g / 1.2-3.6 g, 3 times daily	5
	10-15%	0.4- 0.6 g / 1.2-1.8 g, 3 times daily	6
	11%	0.165 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

Combination partner	Amount Gentianae radix in combination (excl. excipients)	Single dose Gentianae radix/daily dose Frequency	Reference (# in tables 1 and 2)
Aurantii amari epicarpium et mesocarpium	22%	0.88 g / 2.64 g, 3 times daily	1
	10- 15%	0.4- 0.6 g / 1.2-1.8 g, 3 times daily	6
	11%	0.165 g / -	15
	10%	0.4 g / 0.8 g, 2 times daily	18
Centaurii herba	22%	0.88 g / 2.64 g, 3 times daily	1
	10-30%	0.4-1.2 g / 1.2-3.6 g, 3 times daily	4
	10-30%	0.4-1.2 g / 1.2-3.6 g, 3 times daily	5
	10-15%	0.4-0,6 g / 1.2-1.8 g, 3 times daily	6
	11%	0.165 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
33%	1-2 g / 3-6 g, 3 times daily	24	
Cichorii radix	33%	1-2 g / 3-6 g, 3 times daily	24
Calami rhizoma	11%	0.165 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
Carduii Benedicti Herba	32%	-	22
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
Menyanthidis folium	11%	0.165 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
Summary	10-33%	Single dose 0.165–2 g Daily dose 0.6–6 g	

Combination partner	Amount Gentianae radix in combination (excl. excipients)	Single dose Gentianae radix/daily dose Frequency	Reference (# in tables 1 and 2)
		Frequency: 2-3 times daily 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
Summary	22-33%	Single dose 0.3–1.32 g Daily dose 0.9–4 g Frequency: 3 times daily 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)
Absinthii herba	11%	0.165 g / -	15
	15%	0.6 g / 1.2 g, 2 times daily	18
	15%	0.3 g / 0.6-0.9 g, 2-3 times daily	19
Cardui Benedicti herba	33%	-	21
Centaurii herba	50%	0.06 g / 0.12-0.18 g, 2-3 times daily	7
	11%	0.165 g / -	15
	15%	0.6 g / 1.2 g, 2 times daily	18
	15%	0.3 g / 0.6-0.9 g, 2-3 times daily	19
Gentianae radix	11%	0.165 g / -	15
	15%	0.6 g / 1.2 g, 2 times daily	18
	15%	0.3 g / 0.6-0.9 g, 2-3 times daily	19
Millefolii herba	33%	-	21
Summary	11-50%	Single dose 0.06–0.6 g Daily dose 0.12–1.2 g Frequency: 2-3 times daily Monograph: Single dose 0.4-1.6 g Daily dose: 0.8-4.8 g Frequency: 2-4 times daily	

Table 9: Millefolii herba in combinations

Combination partner	Amount Millefolii herba in combination (excl. excipients)	Single dose Millefolii herba/daily dose Frequency	Reference (# in tables 1 and 2)
Angelicae radix*	15-30%	0.45-1.2 g / 1.35-3.6 g, 3 times daily	2
Absinthii herba	15-30%	0.45-1.2 g / 1.35-3.6 g, 3 times daily	2
	11-54 %	0.22-1.62g / 0.66-4.86 g, 3 times daily	3

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

Combination partner	Amount Taraxaci radix cum herba in combination (excl. excipients)	Single dose Taraxaci radix cum herba/daily dose Frequency	Reference (# in tables 1 and 2)
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
Summary	10-35%	Single dose 0.4–1.4 g Daily dose 1.2–4.2 g Frequency: 3 times daily Monograph: Single dose 4-10 g	

Combination partner	Amount Taraxaci radix cum herba in combination (excl. excipients)	Single dose Taraxaci radix cum herba/daily dose Frequency	Reference (# in tables 1 and 2)
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
		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	-	10-28%	-	10-28%	33%	10-50%	15-22%	-	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	11-15%	11-50%	-	11-15%	-	33%			11-50%
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 bitter substances in a herbal tea combination varies mostly from 3 to 4. HMPC agreed to follow the majority of traditional tea combinations to cover a reasonable proportion of the traditional combinations in a specific indication. In the case of bitter combinations, a limit of 4 partners was considered appropriate.

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 following indication appears suitable to all combinations: Traditional herbal medicinal product used for temporary loss of appetite.

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

	Range in a combination (excl. excipients)	Daily dose (2 g combination, 3 times daily)	Maximum daily dose HMPC monograph
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	11-50%	0.66-3 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	Adolescents, adults and elderly
Absinthii herba Centaurii herba Gentianae radix Menyanthidis folium	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
Menyanthidis 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.
Centaurii 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 18 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	None reported
Absinthii herba	
Centaurii herba	
Cichorii radix	
Gentianae radix	
Marrubii herba	
Menyanthidis folium	
Taraxaci radix cum herba	

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.
Centaurii herba Cichorii radix Gentianae radix Marrubii herba Menyanthidis folium	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

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	No case of overdose has been reported.
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Taraxaci radix cum herba	
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 <i>Absinthii herba</i> 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 <i>Absinthii herba</i> 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 <i>Gentiana lutea</i> , 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 xanthones 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