28 January 2014
EMA/HMPC/44209/2012 *Corr.*[1]
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Rubus idaeus* L., folium

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Rubus idaeus* L., folium
Herbal preparation(s)	Dry extract (DER 4:1), extraction solvent water Comminuted herbal substance
Pharmaceutical form(s)	Herbal preparations in solid dosage form for oral use. Comminuted herbal substance as herbal tea for oral use and for preparation of infusion for oromucosal use.
Rapporteur	G. Fossum
Assessor(s)	Hedvig Nordeng Mitra Saboni Anne Berit Samuelsen

[1] Added assessors' names.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Introduction

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

- Herbal substance(s)

The herbal substance consists of the dried leaf of *Rubus idaeus* L. (Fam. Rosaceae).

It is described in the French Pharmacopoeia (XI edition, 2012), in the monograph 'Rubus – Ronce' from 1991: it consists of the compound leaf or leaflet of *Rubus* sp. It contains a minimum of 5% tannins.

The British Herbal Pharmacopoeia also describes the herbal substance: *"Rubus* consists of the dried chopped leaves of *Rubus idaeus* L. (Fam. Rosaceae) which is a small shrub that is grown in most temperate countries" (British Herbal Pharmacopoeia 1983).

The herbal substance, *Rubus idaeus* L., folium is also described in Wichtl 2004:

"The cut drug consisting of leaf fragments with a sparsely pubescent, dark green to brownish green upper surface and a dense silver-grey tomentum on the lower surface. The fragments also show a pinnate venation and clump together due to the dense tomentum. Also characteristic is the presence of fragments with a sharply serrate margin and large green or reddish tinged, also petiole fragments and a few pieces of the stem. The petiole and lower part of the midrib occasionally bear very small thorns. Odour: Faint. Taste: Somewhat astringent and bitter."

In 'King's American Dispensatory' (1898), it is described that the leaves and fruits are the parts of the plant that are used for medicinal purposes. The leaves impart some of their constituents to water, giving to the infusion an odour and flavour somewhat similar to that of some kinds of black tea (according to the version of in 'King's American Dispensatory' scanned and published on Henriette's Herbal Homepage 2011).

- Herbal preparation(s)

Dry extract (DER 4:1), extraction solvent water

Comminuted herbal substance

Information on herbal preparations is described in section 2.2. 'Information on traditional/current indications and specified substances/preparations'.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

Constituents

Dried raspberry leaves contain polyphenolic secondary metabolites, mainly hydrolyzable tannins (2.6% to 6.9%) (Gudej 2004). Different types of hydrolysable tannins have been identified including gallotannins which are esters of gallic acid and D-glucose (Gudej 2004, Durgo 2012), dimeric and tetrameric ellagitannins have also been identified (Haslam *et al*. 1989). Other polyphenolic compounds

present are mainly flavonoids such as kaempferol, kaempferol glycosides, quercetin and quercetin glycosides (Gudej 2004, Gudej 2003). Dried leaves contain 0.46 -1.05 % flavonoids (Gudej 2004). Small quantities of volatile compounds have been identified (Czygan 1995), the amounts being dependent on the stage of plant growth (Patel 2004). In addition, terpenes, Vitamin C and E, and minerals such as calcium, magnesium and zinc have been identified. Raspberry leaf also contains very small amounts of phenolic acids such as caffeic and chlorogenic acid (Durgo 2012). Constituents of raspberry leaf are presented in Table 1.

Table 1: Constituents of raspberry leaf

Constituents			**Amounts**	**References**
POLYPHENOLS **Tannins**			*Total*: 2.6 up to 6.9 % w/w in dried leaf	Gudej 2004
	Ellagitannins			
	Monomer	Ellagic acids	*2,1-4,1 %* w/w in dried leaf	Gudej 2004
			3.79 mg/g (0.0038 %) w/w in dried leaf	Durgo 2012
	Dimer	Sanguiin H-6		**Haslam 1989**
	Trimer	Lambertianin D		
		Lambertianin C		** Tanaka 1993** cited by Patel 2004
	Methyl gallate		0.045 % w/w in dried leaf	Gudej 2003, Gudje 1966
	Gallotannins	1.2.6- Trigalloylglucose		**Haddock 1982** cited by Bradley 2006
		Pentagallolyl- D-glucose		
FLAVONOIDS			*Total*: 0.46 -1.05 % w/w in dried leaf	Gudej 2004
	Kaempferol glycosides	Kaempferol - 3-Oβ-D galactopyranoside	0.013 % w/w in dried leaf	Gudej 2003, **Gudej 1996** as cited by Bradley 2006
		Kaempferol-3-O-β-L Arabinopyranoside	0.036 % w/w in dried leaf	

		Kaempferol-3-O-β-D glucoside	0.04 % w/w in dried leaf	
	Kaempferol		*0.17 -0.31 %* w/w in dried leaf	Gudej 2004
	Quercetinglycosides	Quercetin 3-O-β-D glucopyranoside	0.04 % w/w in dried leaf	Gudej 2003, Gudej 1966,
		Quercetin 3-O-β-D galactopyranoside	0.13 % w/w in dried leaf	
		Quercetin 3- rutinoside (rutin)	No information	**Khabibullaeva 1975**, as cited by Bradley 2006
	Quercetin		*0.10-0.32 %* w/w in dried leaf	Gudej 2004
	Hyperoside		*0.5-0.8 %* w/w in dried leaf	Gudej 2004
OTHER CONSTITUENTS	*Phenolic acids*	Caffeic acid	0.55 mg/g w/w in dried leaf	Durgo 2012
		Chlorogenic acid	0.70 mg/g w/w in dried leaf	
		p- coumaric acid		**Krzaczek 1984** as cited by Bradley 2006
		Ferulic acid		
		Protocatechuic acid		
		Gentisic acid		
		p–hydroxybenzoic acid		
		Vanillic acid		
	Minerals	Magnesium		**Hughes 1979**as cited by Bradley 2006
		Zinc		
	Vitamins	C (Ascorbic acid)	0.39-0.43% w/w in dried leaf	**Fejer 1970**
		δ,Tocopherol, α-Tocopherol γ-Tocopherol		**Shepherd 1999** as cited by Patel 2004
	Alcohols	Octanol		Czygan 1995
		n-Butanol		
		3- Hexen		
	Aldehydes	Benzaldehyde		**Maga 1992** as cited by Patel 2004
		Phenylacetaldehyde		
		Decanal		
		Hexanal		
		2 –hexenal		
		Tetradecanal		

	Terpenoids	***Monoterpenoids***		
		Terpinolene		**Maga 1992**
		Nerol		**Kirsi 1990**, **Hans-Ulrich 1991** as cited by Patel 2004
		Pulegone		**Kirsi 1990**
		α-Terpineol		
		Citral		
		Sesquiterpenoids		
		3-Oxo-α-ionol		**Hans-Ulrich 1991** as cited by Patel 2004
		4- Oxo-β-ionol		**Pabst 1992**
		4-Hydroxy-β-ionone		**Pabst 1992** as cited by Patel 2004
		Triterpenes		
		α-Amyrin		**Shepherd 1999**
		β-Amyrin		
		Squalene		
		Cycloartenol		

*Note*The specified amounts in the table above were found in different species of raspberry leaves.
Note These references are not available to the Rapporteur. They have not been included in the List of references.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Croatia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination and food supplements.
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

Member State	Regulatory Status				Comments
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐MA	☐TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
United Kingdom	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Both combination and single products on general sales list. See below.
Serbia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products

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

Information on marketed products in the United Kingdom (MHRA 1968)

Product: Potters Raspberry Leaf Tablets G44® (on the market as a licensed medicine since 1968)
Active ingredients: Dried aqueous extract (4:1), raspberry leaf 113 mg. Equivalent to 452 mg raspberry leaf
Indication: A herbal remedy traditionally used for the symptomatic relief of painful menstrual cramps.
Posology: Adults: 1-2 tablets to be taken after meals whilst discomfort lasts. Not recommended for use in the elderly or in children under 12 years of age.

1.3. Search and assessment methodology

The following electronic databases were searched on various dates from August 2011 to September 2012 with the search terms "*Rubus idaeus* L.", "*Rubi idaei* L., folium" and "Raspberry leaf".

Results:

Rubus idaeus L:

PubMed: 39 references (No case report of safety concern)

Toxline: 27 references

Scifinder: 205 (Both chemical abstracts and Medline)

The Cochrane Library: No references were obtained.

Rubi idaei L., folium:

PubMed: 0 reference (No case report of safety concern)

Toxline: 20 references

Scifinder: 9 references (Both chemical abstracts and Medline)

The Cochrane Library: No references were obtained.

Raspberry leaf:

PubMed: 57 references (No case report of safety concern)

Toxline: 44 references

Scifinder: 95 references (Both chemical abstracts and Medline)

The Cochrane Library: 3 references.

Each database was searched from its start to the search dates. All languages were included.
Key text books were also searched for relevant studies. All references from the extracted papers were searched for citations not retrieved in the literature search.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Raspberry leaf has been used in Europe for centuries, certainly as early as the sixth century. It is native to Europe, North America and temperate Asia. The material of commerce is collected in central and eastern Europe especially Bulgaria, Macedonia and Romania and is cultivated to some extent (Wichtl 2004). The traditional use of raspberry leaf has been continuously documented in handbooks, pharmacopoeias and scientific literature. The traditional medicinal use of raspberry leaf has been recommended for treating various disorders most commonly related to menstruation, parturition, and ailments of the gastrointestinal tract and other purposes. They have been documented in handbooks and scientific articles such as Burn and Withell 1941, British Pharmaceutical Codex 1949, Becket *et al*. 1954, British Herbal Pharmacopoeia 1983, Wichtl 1984, Reynolds 1989, Gruenwald 1998, Johnson 1999, McFarlin *et al*. 1999, Duke *et al*. 2002, Wichtl 2004, Tiran 2003 and Hall *et al*. 2011.

Use of teas made from the dried raspberry leaves as an antidiarrhoeic and as an astringent gargle for inflammation of the mouth and throat, less often for chronic skin conditions in folk medicine is reported in handbooks (British Herbal Pharmacopoeia 1983, Tyler 1994, Bisset and Wichtl 2001). According to Grieve (1931) experience has shown that raspberry leaf has been used in cases of severe dysmenorrhea. It is also reported that hot tea made from raspberry leaves taken before birth, stimulates and facilitates labour and shortens its duration. Tea is also listed in newer literature on herbal medicines such as the British Herbal Pharmacopoeia (1983, 1996). Newer studies have found a prevalence of use during pregnancy ranging from 6 to 58% (Nordeng *et al*. 2011, Holst *et al*. 2009, Hepner *et al*. 2002 and Byrne *et al*. 2002). Raspberry leaf is evidently a commonly used herb during pregnancy today.

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

The indications most frequently described in traditional herbal literature include facilitating parturition, to relieve menstrual cramps, diarrhoea, as an astringent mouthwash and as a treatment of

conjunctivitis (Table 2). Barnes *et al*. (2007) states that "Modern interest is focused on the use of raspberry leaf to stimulate and facilitate labour and to shorten duration".

Table 2: The following traditional uses have been reported for raspberry leaf

Traditional uses	**References**
To facilitate parturition	Burn and Withell 1941
	British Herbal Pharmacopoeia 1983
	Reynolds 1989
	Tyler 1994
	British Herbal Pharmacopoeia 1996
	Newall *et al*. 1996
	Chevallier 1996
	Parsons *et al*. 1999
	Gruenwald *et al*. 2000
	Barnes *et al*. 2007
A remedy for painful menstruation	Whitehouse 1941
	British Pharmaceutical Codex 1949
	Beckett 1954
	Blumenthal *et al*. 1998
	Reynolds 1989
	Tyler 1994
	Chevallier 1996
	Blumenthal *et al*. 1998
	Duke *et al*. 2002
As a mouthwash/ astringent gargle	Grieve 1931
	British Herbal Pharmacopoeia 1983
	Blumenthal *et al*. 1998
	Reynolds 1989
	Haslam *et al*. 1989
	Czygan 1995
	Chevallier 1996
	Blumenthal *et al*. 1998
	Tyler 1981
	Tyler and Robbers 1999
A remedy for diarrhoea	Grieve 1931
	British Herbal Pharmacopoeia1983
	Blumenthal *et al*. 1998
	Tyler 1994
	Czygan 1995
	Newall *et al*. 1996
	Barnes *et al*. 2007
A treatment of conjunctivitis	British Herbal Pharmacopoeia 1983
	Newall *et al*. 1996
	Duke *et al*. 2002

For disorders of the gastrointestinal tract the respiratory tract and the cardiovascular system	Blumenthal *et al*. 1998

Table 3: Evidence regarding the traditional use and posology from handbooks

Traditional use	**Oral dose**	**Mode of administration**	**References**
For treatment of painful menstruation, and before and during confinement to make parturition easier and speedier. As an astringent gargle.	284-568 ml of 5% infusion of the dried leaves in hot water taken in wineglassful 2-3 times daily	As a tea	British Pharmaceutical Codex 1949
To facilitate parturition, Pregnancy, diarrhoea, stomatitis, Tonsillitis as mouth wash, Conjunctivitis as eye lotion. Specific indication: To facilitate parturition	4-8 g dried leaves, 3 times daily Liquid Extract 1:1 in 25% alcohol. 4-8 ml , 3 times daily		British Herbal Pharmacopoeia 1983
For disorders of the gastrointestinal tract, the respiratory tract, the cardiovascular system and the mouth and throat	1.5 g finely cut drug, steep for 5 minutes and then strain (1 teaspoonful = 0.8 g drug)	As a tea	Gruenwald *et al*. 2000, Wichtl 1984, Wichtl 2004
For the symptomatic treatment of inflammation in the mouth or throat	Posology: 1.5 g of the comminuted herbal substance in 150 ml of boiling water	Astringent gargle	Wichtl 1984 with reference to Hagers Handbuch der Pharmazeu-tischen Praxis, 1979
Treatment of diarrhoea	Posology: 1.5 g of the comminuted herbal substance in 150 ml of boiling water	As a tea	Wichtl 1984 with reference to Hagers Handbuch der Pharmazeu-tischen Praxis, 1979
Nausea, and parturition and cramp	Fresh leaf: 0.25-0.5 cup Dry leaf: 6-12 g	oral	Pedersen 1998, (cited by Duke *et al*. 2002)
Pregnancy, cramp, diarrhoea, cold, sore throat, wound, bleeding	1-2 teaspoons crushed leaf/ cup water up to 6 times daily	As a tea	Lininger *et al*. 1998, Peirce 1999 (cited by Duke *et al*. 2002)
Cramp, conjunctivitis, virus infection, pregnancy, sore	4-8 ml liquid Leaf extract	oral	Newall *et al*. 1996, Lininger *et al*. 1998

throat, diarrhoea	(1:1 in 25% ethanol) 3 times daily		(cited by Duke *et al*. 2002)
Bleeding, conjunctivitis, diarrhoea, morning sickness, sore throat and ulcer	1 (384 mg dried leaves) - 3 capsules 3 times daily	As capsules	Peirce 1999 (cited by Duke *et al*. 2002)
For facilitating labour	Steeping 2 g dried leaf in 240 ml of boiling water for 5 minutes and then straining.	As a tea	McFarlin *et al*. 1999
A herbal remedy traditionally used for the symptomatic relief of painful menstrual cramps	113 mg dry extract in tablets: 1-2 tablets (113-226 mg) after meals while discomfort lasts	Dry aqueous extract in tablets	MHRA 1968

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

Based on the available information, the following information is suggested for inclusion in the monograph:

Table 4: Indications suggested for inclusion in the monograph

Indication(s)	**Reference(s)**
Indication 1: Traditional herbal medicine for the symptomatic relief of minor spasm associated with menstrual periods. Posology: Dry extract: 113-226 mg, up to 3 to 4 times daily. Oral use If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.	MHRA 1968
Indication 2: Traditional herbal medicine for the symptomatic treatment of inflammation in the mouth or throat. Posology: 1.5 -8 g of the comminuted herbal substance in 150 ml of boiling water, 3 times daily. Oromucosal use If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.	British Pharmaceutical Codex 1949, British Herbal Pharmacopoeia 1983 Wichtl 1984 with reference toHagers Handbuch der Pharmazeutischen Praxis, 1979
Indication 3: Traditional herbal medicine for the symptomatic treatment of diarrhoea. Posology: 1.5-8 g of the comminuted herbal substance in 150 ml of water as a decoction, 3 times daily. Oral use	British Herbal Pharmacopoeia 1983 Wichtl 1984 with reference to Hagers Handbuch der Pharmazeutischen Praxis, 1979

If the symptoms persist longer than 3 days during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.	

Assessor's comment:
The information documented by a marketing authorisation from 1968 in UK for the symptomatic relief of painful menstrual cramps is also found in the literature (traditional use to relieve menstrual cramps). The documented phytotherapeutic traditional use related to menstruation is considered a plausible indication based on documented long-standing use and experience. Restriction to the duration of use to one week is recommended based on the nature of the indication, in line with similar monographs with the same indication.

For the other herbal preparations with similar indications shown in Table 3, information related to posology fulfilling the criteria for 30 years of use is available. Use as an astringent gargle and anti-diarrhoea activity of raspberry leaf are comprehensively documented in literature (Grieve 1931, British Pharmaceutical Codex 1949, British Herbal Pharmacopoeia 1983, Wichtl 1984, Tyler 1994, Newall *et al.* 1996 and Barnes *et al.* 2007).
Therefore, requirements to show 30 years of medicinal use for defined herbal preparations with a specified posology for these three traditional indications are fulfilled according to guidelines and the indications can be recommended in the monograph.

According to literature and handbooks, traditional use of raspberry leaf to facilitate parturition seems to be most widespread. This tradition is extensively documented in the literature (Burn and Withell 1941, British Herbal Pharmacopoeia 1983, Reynolds 1989, Tyler 1994, Newall *et al*. 1996, Chevallier 1996, Parsons *et al.* 1999, Gruenwald *et al*. 2000, Barnes et al. 2007 and Hall *et al.* 2011).
Requirements to show 30 years of medicinal use for a defined herbal preparation with a specified posology for a traditional indication are fulfilled, but information on safety regarding the use of raspberry leaf during pregnancy and lactation is insufficient. Lack of safety data is the reason why the tradition for use to facilitate parturition is not recommended as a possible indication in the monograph.

3. Non-Clinical Data

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

Primary pharmacodynamics (related to the indication "symptomatic relief of minor spasms associated with menstrual periods")

In vitro

Aqueous extracts

Saline infusion of dried raspberry leaves (1 g/15 ml saline infused for 10 min) tested in the uterine strips of both non-pregnant rats and pregnant rats had different outcomes. Little or no effect was seen in uteri from non-pregnant rats. Contractions of uteri from pregnant rats were inhibited for 3-4 min. Contact with the extract of 20 min caused a more regular rhythm in pregnant uteri and less frequent contractions (Bamford *et al*. 1970).

Effect of three commercial forms of raspberry leaf (tea, capsules [no further information] and an extract with 35-40% ethanol) were tested on uterine contractility in non- pregnant and late pregnant rats. Red raspberry leaf tea and an aqueous extract of the raspberry leaf capsule were prepared by removing the contents of either the tea bag or the capsule and adding each into boiling deionized

water (dH2O) to a concentration of 0.2 g/ml. Uterine contractility was assessed under different conditions. Since uterine contractility is dependent on the levels of oestrogen and progesterone, not-pregnant rats were subcutaneously injected with 0.8 mg/kg diethylstilbestrol (DES) 2 days prior to sacrifice to produce an oestrogen dominant state. Cumulative additions of the aqueous extract of the tea (1.0-4.6 mg/ml), the aqueous extract of the capsule content (1.0-4.6 mg/ml) and the ethanolic extract (2.2 -10.1 mg/ml) on naive DES-treated NP uterine strips was examined. Based on the results of the experiments with the DES-treated NP uterine preparations, only the aqueous extract of the tea (1.0-4.6 mg/ml) was used in the pregnant uterine preparations. Furthermore non-pregnant (DES-treated) rats were given both the aqueous extracts of the raspberry leaf and capsule. Results showed that neither preparation affected the ability of oxytocin to initiate contractions, but both partially inhibited the pre-existing oxytocin-driven contraction at the highest concentration. Raspberry leaf tea had varying effects on pre-existing oxytocin-induced contractions. It was shown that aqueous extracts of raspberry leaf can trigger contractions of uterine strips from pregnant and non-pregnant rat, while ethanol extract had no effect on contractility which may depend on the type of solvent and the solvent polarity (Zheng *et al*. 2010).

The extract of red raspberry leaves and several purified extracts thereof (see Table 5) were tested for their actions on isolated uterus of cats, dogs, rabbits and guinea pigs (no further details on concentrations given). Two actions of the extracts were seen in the isolated preparation. The uterus of the dog or cat when first suspended usually remained for some time tonically contracted. If the extract of raspberry leaf was added to the bath, the uterus relaxed. If however the uterus had been suspended for some time the muscle gradually relaxed, and when extract was added to the bath a contraction occurred. If the tone was restored in a cat uterus by the addition of pituitary (posterior lobe) extract to the bath, raspberry-leaf extract then once more caused relaxation. The uterus of a rabbit had little tone when suspended in a bath and was stimulated by the addition of raspberry leaf extract, but if a tone was produced by the addition of adrenaline, raspberry-leaf extract relaxed the tone. The only effect observed to be produced on the isolated guinea pig uterus was that of contraction (Burn and Withell 1941).

In a preliminary study, fractions of an aqueous raspberry leaf extract activated isolated guinea pig uterus. The effect remained after boiling with sodium bicarbonate. The extract did not potentiate the action of acetylcholine added to the uterus, but the effect was blocked by a dose of atropine which was just sufficient to eliminate the effect of acetylcholine. Attempts to elucidate the specific underlying mechanisms of these responses were inadequate (Beckett *et al*. 1954).

Organic extracts, powders

An *in vitro* study showed that raspberry leaf methanol extract was able to provide a smooth muscle relaxant activity on isolated guinea pig ileum. Extracts prepared from 2 g samples of the leaves of *Rubus idaeus* with n-hexane, ethyl acetate, chloroform and methanol for preliminary investigation showed that the methanol extract consistently produced a strong relaxant effect (>80%) on transmurally stimulated guinea pig ileum *in vitro*. In contrast, extracts prepared with less polar solvents (n-hexane and ethyl acetate) produced no response. The chloroform extract produced a small relaxant response (<15%). Furthermore the herbal substance was extracted with n-hexane, to remove non-polar substances, followed by extraction with methanol.

The methanolic extract (previously extracted with n-hexane) produced a strong relaxant activity and was then fractionated on a silica gel column. The fractions were also tested. Methanol blanks were tested before starting the pharmacological assays and these were devoid of activity. Two of the fractions of the methanolic extract showed a relaxing effect, dose response relationships were established for the most active of the fractions for which the IC_{50} responses were obtained with doses

of 2.70 mg and 0.76 mg, respectively. The components of the fractions were not identified, and the mechanism of action is unclear (Rojas-Vera *et al*. 2002).

Chromatographically separated fractions from a chloroform extract of raspberry leaf produced relaxant effects on isolated guinea pig ileum (concentration unknown), but active constituents were not identified (Patel *et al*. 1995).

In vivo

In vivo studies have been summarised in the review from 2009 by Holst *et al*. Two studies have investigated the effect on uterine muscle as well as uterine tissues.

Aqueous extracts

Table 5: Extraction methods (Burn and Withell 1941)

Extraction methods	
a) Infusion: 10 g of dried leaves in 100 ml boiling water. Standing in 1/2 hour and then squeezed through muslin. The infusion was concentrated by evaporation at 40°C up to 2 g of leaf was present in 1 ml. (c) By preparing an infusion as in (a) (before concentration), and adding basic lead acetate in amount just insufficient to throw down all precipitable matter. The filtrate was evaporated to dryness.	b) An infusion prepared as in (a) evaporated to dryness and was given 1 g of residue of 10 g. 1 g of residue was taken up in 5 ml of distilled water and 5 ml of absolute alcohol. This gave a precipitate and inactive material was removed by filtration. The filtrate was taken to dryness; 1 g of residue corresponds to 20 g of leaf. (d) By treating an infusion prepared as in (a) (before concentration) with Norit charcoal, filtering and evaporating to dryness.

The extract of red raspberry leaves and several purified extracts thereof (see Table 5) were tested for their actions on the uterus, both in situ of cats and rabbits. The injection of an amount of extract equivalent to 2 g leaf into the external jugular vein produced a three phasic effect in the uteri of cats: relaxation followed by contraction, and further relaxation. However, sometimes only the first or the two first phases were seen. These effects were often not obtained with the first injection but after successive injections. The 5th injection led to complete arrest of all uterine movements, the muscle being fully relaxed. In the rabbits relaxation was not observed following the injection of raspberry leaf extract. Instead a contraction of short duration was seen. This was explained by the fact that the uteri of the parous rabbits used were thicker than those of the cat, and so it may be that a much larger amount of raspberry leaf extract is needed to produce relaxation in the rabbit. The active constituent was not identified (Burn and Withell 1941).

Primary pharmacodynamics (related to the indications "symptomatic treatment of inflammation in mouth and throat" and "symptomatic treatment of mild diarrhoea")

No information available.

Secondary pharmacodynamics

Antioxidant activity

A combined 70% ethanol extract of air dried leaves of four varieties of raspberries and two varieties of blackberries were tested for antioxidant activity *in vitro.* Identification of the components showed high levels of flavonoids (rutin, quercetin, isoquercetin, and kaempferol) in raspberry and blackberry leaves. Antioxidant activity was measured in relation to the degree of absorption of oxygen during the initiated oxidation of isopropyl benzene (coumol). Blackberry leaves showed higher levels of inhibitory components than the raspberry leaves (Nikitina *et al*. 2000).

In a second study, the total antioxidant capacity of leaves from four different varieties of blackberries (*Rubus* sp.), red raspberry (*Rubus idaeus* L.), black raspberry (*Rubus occidentalis* L.) and strawberry (*Fragaria ananassa* D.) plants was determined by the oxygen radical absorbance capacity (ORAC) method. The total phenolic content of leaves examined ranged from 10.5-32.3 mg/g fresh leaves. Results indicate that when the leaves get older, the ORAC values are reduced, and so is the total phenolic content and thus antioxidant activities. A positive and highly significant correlation between total phenolic and antioxidant activity was found and may indicate that the antioxidant capacity can be highly specific for tissue type (Wang and Lin 2000).

Durgo *et al*. examined the polyphenolic profile and cytotoxic and antioxidative activity of red raspberry leaf extract. Aqueous raspberry leaf extracts were tested on human cancer cells, both laryngeal carcinoma (HEp2) and colon adenocarcinoma (SW 480). The cells were exposed to four different extract concentrations (25 mg, 37.5 mg, 50 mg and 125 mg /ml water) for various time intervals and tested for cytotoxicity by the neutral red assay. Reactive oxygen species (ROS) formation in cells after treatment with raspberry leaf extract was determined by dichlorohydrofluorescein (DCF) assay using a microplate reader. Intracellular glutathione (GSH) content was examined by Spectrophotometric method, and measurements were performed in triplicates for each treated Petri dish and the total amount of proteins was determined in supernatants after reaction with 2-nitrobenzoic acid. The results showed that SW 480 cells are more susceptible to raspberry leaf extract compared with HEp2 cells. After an hour of exposure, no cytotoxicity was observed, but after 2 hours of incubation (37.5, 50 and 125 mg/ml) cytotoxic effects were observed in SW 480 cells. However, after one or two hour treatment with extract followed by a 24 hours recovery period cytotoxic effects were observed. The authors suggested that “irreversible events” take place during extract incubation, and cytotoxic effects are obvious after a period of one cell cycle. Raspberry leaf extract induced ROS formation in SW 480 cells, suggesting that the level of glutathione in these cells was reduced after long exposure (24 h). The opposite was observed in HEp2 cell lines after incubation with 50 mg/ml and 125 mg/ml of extract, suggesting that the active constituents of raspberry leaf extract increased glutathione levels and thereby reduce ROS that leads to anti-oxidative activity in cells. This effect was enhanced after 24 h of recovery, indicating that induction was caused by the products formed during cellular metabolism of compounds present in the extract. The antioxidant properties of raspberry leaf extract is considered to be associated with polyphenolic compounds (quercetin derivatives, ellagic acid derivatives, caffeic and chlorogenic acids), which is mainly due to its ability to scavenge free radicals and ROS and to form complexes with metal ions, thus preventing oxidation of metals with oxygen (Durgo *et al*. 2012).

Safety Pharmacology

No information available.

Pharmacodynamic interactions

No information available.

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

Pharmacokinetic interactions with other medicinal products

Six commercially available herbal products (black elderberry, cranberry, fennel, ginger, horsetail, and raspberry leaves) showed a significant but variable inhibition of drug marker substrates for human cytochrome P-450 isoforms (CYP2D6) *in vitro.* Possible clinical significance was associated with recommended doses of the various herbal products. Extracts of teas were made with water and raspberry leaves showed the highest potencies for a possible clinically relevant inhibition of CYP2D6 with a IC_{50} of 47 µg/ml (Langhammer and Nilsen 2012).

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

Toxicology

Acute toxicity

The toxicity of raspberry leaf extracts has been tested in mice both orally and intravenously. An extract prepared by method (b) (see Table 5) was dissolved in distilled water so that 1 ml = 4 g raspberry leaf. An oral dose (0.5 ml= 2 g raspberry leaf) had no deleterious effect on mice. However, intravenous injection of the same dose was lethal. The average lethal dose for such a solution was 5 ml/kg, which corresponds to 20 g leaf/kg. Mice injected with this lethal dose had convulsions and died. Similar seizures were also observed by intravenous injection of extracts prepared by method (a) in cats (Burn and Withell 1941).

Repeated dose toxicity

There are no reports available for a possible repeated dose toxicity of raspberry leaf preparations.

Genotoxicity

No data have been found.

Carcinogenicity studies

No data have been found.

Reproductive toxicity

Administration of raspberry leaf extract to female rats injected s.c. with aqueous Pregnant Mares´Serum (PMS) gonadotrophin at 300 IU/mg PMS had a reducing effect on ovarian weight gain. Some of the extracts were made from fresh green leaves, and others from the dried plant. All the extracts that were made from dried plants were found to be active on 10-18 mg dried herbal substance per dose (~230 mg/kg b.w.) dose level and the activity was seasonally variable and fell after storage of the dried leaves for 15 months (Graham and Noble 1955).

An animal study consisting of 40 nulliparous Wistar rats were randomly assigned to one of four different oral treatments, from the first day of pregnancy until birth. The pregnancy length, litter size, litter weight, birth weight, sex, and stillbirths were recorded. Female offspring (F1) were followed up to their first birth and their offspring (F2) to weaning. The same factors were recorded. The only statistically significant difference detected was an increased gestational length with intake of raspberry leaf (10 mg/kg/day). A trend towards lower pregnancy success rate which is the percentage of attempts resulting in pregnancy (100% for controls and kaempferol group, 90% for quercetin group, but only 78% of the raspberry leaf group) were also seen. The female offspring (F1 generation) in this

group showed precocious puberty measured as significantly lower age at vaginal opening. They concluded that foetal exposure to raspberry leaf has previously unidentified transgenic rational effects, and further safety assessment is strongly recommended (Johnson *et al*. 2009).

The safety of raspberry leaf during pregnancy and lactation has not been established.

3.4. Overall conclusions on non-clinical data

Pharmacology

Pharmacodynamics

In vitro and *in vivo* experiments have shown variable effects of raspberry leaf extracts on smooth muscle. Results from relevant experimental studies on raspberry leaf to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

Pharmacokinetics

Raspberry leaf has, in a preliminary study, shown to inhibit CYP2D6 enzyme activity *in vitro*.

Toxicology

Toxicological data on raspberry leaf are limited. In mice an oral dose of extract equivalent to 10% of body weight of dried raspberry leaves was considered nontoxic, but these data are not transferrable to humans. Nonetheless, neither the chemical composition nor the long-term widespread use in the European Union suggests that there is a high risk associated with the use of raspberry leaf preparations. Adequate tests on reproductive toxicity and tests on genotoxicity and carcinogenicity have not been performed. Therefore, a Community list entry cannot be recommended from a non-clinical point of view.

4. Clinical Data

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Due to lack of data, no conclusions can be drawn.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Due to lack of data, no conclusions can be drawn.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data have been found.

4.2.2. Clinical studies (case studies and clinical trials)

A total of 156 women were included in three studies to assess the efficacy and safety of raspberry leaf during pregnancy (Parsons *et al*. 1999, Simpson *et al*. 2001, Whitehouse 1941). Table 7 summarises the findings from these studies.

Table 7: Clinical trials and other human studies of raspberry leaf during pregnancy

Dose and duration	**Number of participants (test: control)**	**Conclusions regarding safety and efficacy**	**Reference**
Three ''case'' reports on purified extract from raspberry leaf inserted as an intrauterine bag one week after delivery.*	3: No controls	Efficacy: The main effect on non-pregnant uterus was relaxation. Weaker contractions, lower frequency, regular, secondary contractions eliminated.	Whitehouse 1941
Various doses (range: 1–8 tablets/cups of tea daily), 1–32 weeks	57:51	Safety: No identified adverse effects. No clinically significant differences in maternal blood loss, babies' Apgar score at 5 min of age, maternal diastolic blood pressure pre labour or transfer of baby to special care unit. Efficacy: No difference in length of gestation period, likelihood of medical augmentation of labour, occurrence of meconium liquor or need for an epidural block. No statistically significant difference in likelihood of artificial rupture of membranes (greater likelihood in the control group). No statistically significant difference in time of the three stages of labour but shorter first stage in the raspberry leaf group.	Parsons *et al*. 1999
Tablets (2×1.2 g) a day, from 32 weeks until labour. Each raspberry leaf tablet contained 1.2 g (400 mg of 3:1 extract) of raspberry leaf extract. *	96:96	Safety: No adverse effects. No significant differences in maternal blood loss, maternal diastolic blood pressure, meconium stained fluid, Apgar score at 5 min of age, birth weight or transfer of baby to special care. Efficacy: No significant difference with respect to length of gestation, medical augmentation of labour, need for pain relief during labour or time of the three stages of labour (shorter second stage in the raspberry leaf group). Slightly more women in the placebo group had forceps or vacuum assisted birth but this was not statistically significant either. No difference in emergency caesarean rate.	Simpson *et al*. 2001 **Parsons *et al*. 2000**

*No further information was available on the extracts used.

In a retrospective observational study at hospitals in Sydney, Australia, in 1998 safety data from the raspberry leaf herb for women and their babies during pregnancy were registered. A total of 108 patients were included in this study. Women received different doses for different periods (1-32 weeks). The groups were comparable with respect to age, weight, parity, ethnicity and level of obstetric care. No adverse effects were identified. No clinically significant differences were found in maternal blood loss, babies Apgar score at 5min of age, maternal diastolic blood pressure pre labour or transfer to special care baby unit. With regard to the effect no difference in length of gestation, the likelihood of medical augmentation of labour, incidence of meconium liquor or the need for an epidural block was seen. No statistically significant difference in risk for artificial rupture of membranes or in the time of the three stages of labour was found (Parsons *et al*.1999, Mills *et al*. 2006).

A double-blind, randomized, placebo-controlled study conducted at a hospital in Sydney, Australia studied the efficacy and safety of raspberry leaf tablets taken by nulliparous women from 32 weeks gestation until the beginning of labour. Experimental group (96) had raspberry leaf tablets, 2 × 1.2 g / day from 32 weeks to labour and the control group (96) who received placebo tablets. No further information on the extract in these tablets was available. Compliance was good, 89% of tablets consumed per woman. No adverse effects to mother or infants were reported. No significant differences were observed between the groups. As for the effect of treatment, there was no significant difference seen in the length of pregnancy, medical augmentation of labour, need for pain relief during labour or the time of the three stages of labour (Simpson *et al*. 2001, Mills *et al*. 2006).

In 1941, three cases were reported for women a week after birth. They all had an intrauterine bag to get an overview of the effect on uterine contractions. Various doses and regimens of raspberry leaf extract were administered orally. The results suggested that the main effect of non-pregnant uterus is relaxation. The extract caused weaker contractions, lower frequency, more regular contractions and eliminated secondary contractions (Whitehouse 1941).

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

No information is available.

4.3. Overall conclusions on clinical pharmacology and efficacy

Raspberry leaf is often recommended in various sources to be taken during pregnancy to stimulate and facilitate labour and to shorten the duration of labour, however the scientific documentation of effects is sparse and of questionable quality. Further investigations to assess the effects of well-characterised preparations in well-designed randomised controlled studies involving sufficient numbers of participants are required. No clinical studies were found on the effects of raspberry leaf for dysmenorrhea, diarrhoea, used as an astringent agent or any of the other listed traditions.

Overall, the existing data cannot be considered to meet the criteria for "well-established medicinal use" in accordance with Directive 2001/83/EC. However, sufficient data is available to develop a Community herbal monograph on the traditional uses of raspberry leaf.

5. Clinical Safety/Pharmacovigilance

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

Safety data of raspberry leaf herb of the foetus was assessed and recorded in two of the clinical studies examined at a hospital in Sydney, Australia. The meconium-stained fluid, Apgar score at 5 min of age, birth weight and the transfer of the baby to special care were evaluated and no adverse effects were identified and no clinically significant differences were observed between the groups (Simpson *et al*. 2001, Parsons *et al*. 1999).

5.2. Patient exposure

Products containing raspberry leaf are available on the market (tea, capsules and tablets) for both menstrual pain and for use in pregnancy. A significant patient/consumer exposure can be expected by both pregnant and non-pregnant women as women continue to use herbal medicines during pregnancy because they perceive them to be safer than conventional medications (Holst *et al*. 2009). In a study among 600 Norwegian women, raspberry leaves were the fifth most commonly used herbal preparations during pregnancy (5.7% of pregnant women). The most commonly reported reason for use was to "prepare the uterus for labour" (Nordeng *et al*. 2011).

5.3. Adverse events and serious adverse events and deaths

The World Health Organization's Uppsala Monitoring Centre (WHO-UMC) received two reports from the national pharmacovigilance centre of United Kingdom according to a search performed on 27.09.2011. In one of the two reports, a total of six different herbal preparations were used in therapeutic doses. In the other report, raspberry leaf as a single ingredient is the only preparation listed. Raspberry leaf had been used orally for two months to "precipitate labour", first one dose per week for one month and then one dose daily for 30 days. The reaction in a new-born boy (2 days) was convulsions.

The incidences of adverse events were recorded in two studies. In the retrospective study, participants reported a case of diarrhoea and an increased frequency of Braxton Hicks contractions (normal contractions of pregnancy). These adverse reactions attributed to raspberry leaf could have been avoided by lower doses (Parsons *et al*. 1999).

In a double-blind, randomised, placebo-controlled study of raspberry leaves among pregnant women; no serious side effects were reported. The side effects reported were most likely related to common pregnancy ailments, mainly nausea, vomiting, diarrhoea, constipation and changes in blood pressure (Simpson *et al*. 2001). There has also been a case report of petechiae and ecchymoses in a new-born infant whose mother drank raspberry leaf tea and took 6.5 g of primrose oil (as 500 mg capsules, vaginally and orally) one week before giving birth (Wedig and Whitsett 2008).

5.4. Laboratory findings

No information available.

5.5. Safety in special populations and situations

Use in pregnancy and lactation

A retrospective and a randomized double-blind -placebo-controlled clinical trial investigated the efficacy and safety of raspberry leaf during pregnancy. Total 153 pregnancies exposed to raspberry leaf and 147 controls were included. Two types of raspberry leaf preparations were used; tea and tablets. There were no statistical differences in outcomes (maternal blood loss, babies Apgar score, maternal diastolic blood pressure pre labour or transfer two special care baby units) between the raspberry group and control group. Adverse effects on pregnancies were observed in the randomized study. The side effects reported were most likely related to common pregnancy ailments, mainly nausea, vomiting, diarrhoea, constipation and changes in blood pressure but with no significant differences between groups. According to Mills *et al*. (2006) raspberry leaf is most likely not to be harmful to an unborn child, but administration should be limited to the last two trimesters since safety data on organogenesis are sparse. For safety reasons, it seems appropriate that pregnant women should preferably avoid using raspberry leaf during pregnancy. However, if used it should be under the supervision of medical personnel, and not as self-medication.

Guidelines on the use of herbal remedies during pregnancy have been published, classifying raspberry infusions as a tonic that can be used during the last two trimesters of pregnancy (Belew 1999).

Assessor's comments:

A moderate amount of data on pregnant women (n = 153) revealed no malformations or foeto/neonatal toxicity of raspberry leaf. Clinical studies have not showed a higher incidence of adverse pregnancy outcomes. However, it must be stressed that the duration of treatment has been short, and only a small number of patients have been included in clinical trials. In the absence of sufficient data, the use in pregnancy is not recommended.

There is a lack of basic knowledge on the use of raspberry leaf during lactation; use during lactation is therefore not recommended.

Overdose

None reported.

Drug abuse

None reported.

Withdrawal and rebound

None reported.

Effects on ability to drive or operate machinery or impairment of mental ability

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

5.6. Overall conclusions on clinical safety

Raspberry leaf has traditionally been used by pregnant women. Three small studies did not find a significantly higher incidence of adverse pregnancy outcomes after use of raspberry leaf during pregnancy. However, considering the short duration of treatment and small number of patients

included in the clinical studies, these data cannot be used to confirm a safe traditional use of raspberry leaf preparations during pregnancy. There is also a lack of data on the use of raspberry leaf during lactation; on this basis use by breast-feeding women cannot be recommended.

The data from clinical trials with defined herbal preparations from raspberry leaf indicate reasonable safety in non-pregnant individuals.

Raspberry leaf is not recommended in adolescents and children below 18 years due to insufficient data on safety and efficacy. No serious side effects have been reported.

6. Overall conclusions

Raspberry leaf is a well-known herb that has traditionally been used for decades against various ailments according to handbooks and articles. Raspberry leaf preparations are generally recognised as safe. However, the evidence regarding efficacy is weak and the identification of active constituents is lacking. The available clinical studies cannot be considered to meet the criteria for "well-established medicinal use" in accordance with Directive 2001/83/EC.

Clinical studies have not found a higher incidence of adverse pregnancy outcomes with raspberry leaf treatment, but treatment durations have generally been short, and only a small number of exposed pregnant women (n = 153) has been included in clinical trials.

Although the available data do not seem to suggest any definitive concerns with regard to reproductive and developmental safety, the use of raspberry leaf in pregnancy is not recommended. The possible negative consequences for foetal development, together with the minor clinical benefit, do not support a positive benefit-risk balance in favour of traditional use of raspberry leaf to facilitate parturition.

Use in symptomatic relief of dysmenorrhea, use of dried raspberry leaf as an astringent gargle and the anti-diarrhoea activity of raspberry leaf have been continuously documented in handbooks. Traditional medicinal use of raspberry leaf for the indications below fulfils the requirement for medicinal use for at least 30 years (including at least 15 years in the EU) under Directive 2004/24/EC. Traditional use has shown that raspberry leaf can be recognised as safe when used at the specified dosages under the conditions outlined in the monograph.

The following indications are accepted:

Indication 1: Traditional herbal medicinal product for the symptomatic relief of minor spasm associated with menstrual periods.

Indication 2: Traditional herbal medicinal product for the symptomatic treatment of mild inflammation in the *mouth or throat.*

Indication 3: Traditional herbal medicinal product for the symptomatic treatment of mild diarrhoea.

The evidence regarding efficacy and safety during pregnancy and lactation is lacking. Raspberry leaf cannot be recommended during pregnancy and lactation or in children and adolescents under 18 years.

There are insufficient data on the genotoxicity, carcinogenicity, reproductive and developmental toxicity of raspberry leaf. As minimum required data on mutagenicity (Ames' test) are not available, an inclusion in the Community list of herbal substances, herbal preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.