EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/HMPC/669738/2013
Committee for Herbal Medicinal Products (HMPC)

Assessment report on *Passiflora incarnata* L., herba

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)	*Passiflora incarnata* L; herba
Herbal preparation(s)	a) Comminuted herbal substance b) Powdered herbal substance c) Liquid extract (DER 1:8) extraction solvent ethanol 25% V/V d) Liquid extract (DER 1:8) extraction solvent ethanol 45% V/V e) Liquid extract (DER 1:3.6) extraction solvent ethanol 60% V/V f) Liquid extract (DER 1:1) extraction solvent ethanol 25% V/V g) Liquid extract (DER 1:1) extraction solvent ethanol 70% V/V h) Liquid extract (DER 1:3.8-4.3) extraction solvent ethanol 54% m/m, glycerine 4% m/m, water 60% Dried extracts corresponding to the tea and liquid extracts above.
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in solid and liquid dosage forms for oral use.
Rapporteur	P. Claeson
Assessor(s)	P. Claeson and H. Green

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephon☐ +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@☐ma.europa.eu ☐☐**bsite** www.ema.☐uropa.eu

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1. Introduction

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

- **Herbal substance(s)**

- *Passiflora incarnata* L., herba is the fragmented or cut/dried aerial parts of *Passiflora incarnata* L. It may contain flowers and/or fruits. Content: minimum 1.5% of total flavonoids, expressed as vitexin (dried drug) (European Pharmacopoeia, 2012).

- *Passiflora incarnata* L., herba extract is the dry extract of *Passiflora incarnata* L., herba, prepared with ethanol (40% – 90% V/V) or methanol (60% V/V), or acetone (40% V/V), and containing a minimum of 2.0% flavonoids, expressed as vitexin (European Pharmacopoeia, 2012).

Constituents:
Flavonoids, mainly *C*-glycosides of apigenin and luteolin, *e.g.* isovitexin, isoorientin and their 2"-β-D-glucosides, schaftoside, isoschaftoside, vicenin-2 and swertisin, with considerable variation in qualitative and quantitative composition according to source (Hänsel *et al*., 1994; Bradley, 1992; Wichtl, 2004; Barnes *et al.*, 1996; 2007; ESCOP, 2003; PDR for herbal medicines, 1998; Weniger & Anton, 1996).

Maltol which, however, may be an artefact (Hänsel *et al*., 1994; Bradley, 1992; Barnes *et al.*, 1996 and 2007; ESCOP, 2003; Weniger & Anton, 1996).

Essential oil in trace amounts comprising more than 150 components (Hänsel *et al*., 1994; Bradley, 1992; Wichtl, 2004; Barnes *et al.*, 1996 and 2007; ESCOP, 2003; PDR for herbal medicines, 1998; Weniger & Anton, 1996).

Gynocardin (a cyanogenic glycoside) (Hänsel *et al*., 1994; Bradley, 1992; Wichtl, 2004; ESCOP, 2003; PDR for herbal medicines, 1998; Weniger & Anton, 1996).

β-carboline alkaloids (e.g. harman, harmol, harmalol) may be present in traces. However, these alkaloids are undetectable in most commercial materials (ESCOP, 2003).

A tri-substituted benzoflavone derivative (Dhawan *et al.*, 2004). The presence of this substance in *Passiflora incarnata* has later been questioned by Holbik *et al*.,2010, who were unable to repeat isolation of the substance from plant materials of three different geographical origins.

- **Herbal preparation(s)**
- Comminuted herbal substance
- Powdered herbal substance
- Liquid extract (DER 1:8) extraction solvent ethanol 25% V/V
- Liquid extract (DER 1:8) extraction solvent ethanol 45% V/V
- Liquid extract (DER 1:3.6) extraction solvent ethanol 60% V/V
- Liquid extract (DER 1:1) extraction solvent ethanol 25% V/V

- Liquid extract (DER 1:1) extraction solvent ethanol 70% V/V
- Liquid extract (DER 1:3.8-4.3) extraction solvent ethanol 54% m/m, glycerine 4% m/m, water 60%

  Dried extracts corresponding to the tea and liquid extracts above.

- **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.

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:	
Belgium	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combination products
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	HMPs on the market until 2004. Probably products marketed as food supplements
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Also authorised and registered combination products on the market
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combination products
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combination products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Only authorised

Member State	Regulatory Status				Comments
				Food supplements	combination products
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:	No products on the market
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	One combination product
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market. No information concerning food supplements.
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:	Also combination products.
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Two major electronic databases, PubMed and Toxline, were searched on 20 June 2006 with the search term “passiflora”. For the revision of the monograph the same databases were searched on 24 April 2013 (search term “passiflora incarnata”).

Results:
PubMed: 160 references obtained in 2006 and 41 additional references in 2013.
Toxline: 37 references obtained in Toxline Core on PubMed and 68 references in Toxline Special in 2006 and 11 additional references in 2013.

The abstracts of the references found were screened manually and all articles deemed relevant were accessed and included in the assessment report.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Traditional medicinal use of *Passiflora incarnata* L., herba in the form of powdered herbal substance, herbal tea or ethanol extracts, for the relief of mild symptoms of mental stress and to aid sleep has been documented continuously in recognised handbooks dating e.g. from 1938, 1958, 1977 and 2003 (Madaus, 1938; Hoppe, 1958; List & Hörhammer, 1977; ESCOP, 2003). It is often used in combinations with other sedative herbal substances.

The following information about products currently on the market was obtained from the Member states following a new request.

Austria

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1	Comminuted herbal substance	Registered in 2009	Tea bag (2 g comminuted herbal substance)	According to HMPC monograph	According to HMPC monograph
2	Liquid extract DER 1:3.6 extraction solvent ethanol 60% V/V	On the market since 1981	Oral liquid	0.89 g herbal preparation x3-5 = 1 ml herbal preparation x3-5	According to HMPC monograph
3	Dry extract DER 5-7:1, extraction solvent ethanol 50% V/V	Registered in 2007	Coated tablet (1 coated tablet contains 425 mg dry extract)	According to HMPC monograph	According to HMPC monograph
4	Liquid extract, DER 1:3.8-4.3, extraction solvent ethanol 54% m/m, glycerine 4% m/m, water 60%	On the market since 1963	Oral liquid	Adults: 0.3-0.4 ml herbal preparation x 3-5 Adolescents: 0.3-0.4 ml herbal preparation x 3	According to HMPC monograph

Belgium

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication

1	Dry extract, DER 3.5-5, extraction solvent ethanol 60% V/V	Registered in 2011	Coated tablet (200 mg dry extract per coated tablet)	Adults and children from 12 years: 1 to 2 tablets 2 times a day to alleviate mental stress (max 8 tablets a day) 1 to 2 tablets half an hour before going to sleep to aid sleep.	Traditional herbal medicinal product used to relieve the mild symptoms of mental stress, such as nervousness, worrying or irritability and to aid sleep.

France

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1	Dry extract, DER 4-6:1, extraction solvent ethanol 70% V/V	On the market since 1986	Hard capsule (1 capsule contains 200 mg of extract)	Adults and adolescents over 12 years of age: 1 to 2 hard capsules 2 times daily.	Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.
2	Dry extract, DER 4-7:1, extraction solvent ethanol 60% V/V	Registered in 2008	Coated tablet (One tablet contains 300 mg of extract)	Adults and adolescents over 12 years of age: 2 tablets daily	Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.
3	Powder	On the market since 1981	Hard capsule (1 capsule contains 300 mg of powdered drug)	Adults: 2 hard capsules 2 times daily Adolescents over 12 years of age: 1 hard capsule 2 times daily	Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.

Germany

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication

1	Dry extract, DER 5-7:1, extraction solvent ethanol 50% V/V	On the market since 2004	Coated tablet (425 mg extract per tablet)	Adolescents over 12 years of age, adults, elderly: 1 coated tablet 2-3 times daily	Herbal medicinal product for the relief of mild nervous tension
2	Liquid extract, DER 1:1, extraction solvent ethanol 70% V/V	At least since 1978	Oral liquid	Adolescents over 12 years of age, adults, elderly: 2 ml 3 times daily	Herbal medicinal product for the relief of mild nervous tension
3	Dry extract, DER 5-7:1. extraction solvent methanol 60% V/V	On the market since 1999	Hard capsule (260 mg extract per capsule)	Adolescents over 12 years of age, adults, elderly: 2 hard capsules 2 times daily	Herbal medicinal product for the relief of mild nervous tension
4	Dry extract, DER 5-7.5:1. extraction solvent ethanol 60% V/V	On the market since 1994	Coated tablet (175 mg extract per tablet)	Adolescents over 12 years of age, adults, elderly: 2 coated tablets 2-4 times daily	Herbal medicinal product for the relief of mild nervous tension
5	Liquid extract, DER 1:1. extraction solvent ethanol 37% V/V	On the market since 1993	Oral liquid	Adolescents over 12 years of age, adults, elderly: 1.9 ml 3 times daily	Herbal medicinal product for the relief of mild nervous tension
6	Dry extract, DER 5-7:1. extraction solvent methanol 60% V/V	On the market since 1992	Hard capsule (260 mg extract per capsule)	Adolescents over 12 years of age, adults, elderly: 1-2 hard capsules 3 times daily	Herbal medicinal product for the relief of mild nervous tension
7	Dry extract, DER 5-7:1. extraction solvent methanol 60% V/V	On the market since 2002	Coated tablet (360 mg extract per tablet)	Adolescents over 12 years of age, adults, elderly: 1 coated tablet 3 times daily	Herbal medicinal product for the relief of mild nervous tension
8	*Passiflorae herba*, cut	Registered in 2010 Herbal tea has been on the market since	Herbal tea (2g per tea sachet)	Adults and adolescents over 12 years: 1 cup of tea from 1 tea sachet 2-4 times daily	Traditional herbal medicinal product to improve general condition in mental stress and to aid sleep

		1986			
9	Dry extract, DER 5-8:1, extraction solvent ethanol 25% m/m	Registered in 2010	Film-coated tablet (108 mg extract per tablet)	Adults and adolescents over 12 years: ½-1 tablet 2-4 times daily	Traditional herbal medicinal product to improve general condition in mental stress and to aid sleep
10	Dry extract, DER 3-5:1, extraction solvent water	Registered in 2012	Instant herbal tea (1.2 g per measuring spoon contains 240 mg dry extract)	Adults and adolescents over 12 years: 1-2 measuring spoons instant herbal tea in 150 ml hot water 1-4 times daily	Traditional herbal medicinal product to improve general condition in mental stress and to aid sleep

Spain

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1	Dry extract, DER 5-7:1, extraction solvent ethanol 60% V/V	On the market since 2002	Film coated tablet (200 mg extract per tablet)	Adults and adolescents over 12 years of age: 400 mg (2 tablets per day)	For relief of mild symptoms of mental stress
2	Dry extract, DER 5:1, extraction solvent ethanol 50% V/V	Registered in 2007	Film coated tablet (425 mg extract per tablet)	Adults and adolescents over 12 years of age: 1275 mg (2-3 tablets per day)	Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep
3	*Passiflora incarnata* L., herba	Registered in 2009	Hard capsule (300 mg/capsule	Adults and adolescents over 12 years of age: 600 mg-1800 mg (2-6 capsules per day)	Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep
4	*Passiflora incarnata* L., herba	Registered in 2012	Hard capsule (250 mg/ capsule	Adults and adolescents over 12 years of age: 500 mg- 2 g (2-8 capsules per day)	Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep
5	*Passiflora incarnata* L.,	Registered in	Tablet	Adults and adolescents over	Traditional herbal medicinal product for

	herba	2012	(400 mg/tablet)	12 years of age: 400 mg – 2 g (1-4 tablets per day)	relief of mild symptoms of mental stress and to aid sleep

Sweden

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1	Dry extract, DER 5-7:1, extraction solvent ethanol 50% V/V	Registered in 2011	Coated tablet (425 mg dry extract per coated tablet)	Adults and children from 12 years: 2-3 tablets daily for the relief of mild anxiety. 1-2 tablets half an hour before bedtime to aid sleep (max 3 tablets a day)	Traditional herbal medicinal product used for the relief of mild anxiety and temporary difficulties in falling asleep.

UK

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1	Passion flower herb	Registered in 2011	Hard capsules (300mg/capsule)	Adults (over 18 years) and the elderly: For relief of symptoms of mild anxiety 1-2 capsules 3 times a day. To aid sleep, take 2 capsules 30 minutes before bedtime with an earlier dose of 2 capsules earlier in the evening if necessary. Maximum daily dose: 8 single doses	A traditional herbal medicinal product for the temporary relief of mild anxiety and to aid sleep, based on traditional use only.
2	Passion flower herb	Registered in 2010	Hard capsule (300 mg/capsule)	Adults (over 18 years) and the elderly: 2 capsules after evening meal and 2 capsules	A traditional herbal medicinal product used for the temporary relief of symptoms

				before going to sleep. Up to 6 capsules daily.	associated with stress such as mild anxiety and to aid sleep, based on traditional use only.
3	Dry extract, DER 7:1, extraction solvent ethanol 60% V/V	Registered in 2013	Film-coated tablet (71.4 mg of extract/tablet)	Adults (over 18 years)and elderly: One tablet to be taken three times a day with meals. If required a further tablet may be taken at bedtime.	A traditional herbal medicinal product used for the temporary relief of symptoms associated with stress such as mild anxiety, based on traditional use only.
4	Dry extract, extraction solvent methanol 80%	Registered in 2012	Tablet (36 mg of extract/tablet)	Adults (over 18 years) and elderly: Take 2 tablets early evening and 2 at bedtime.	A traditional herbal medicinal product used to aid to sleep, based on traditional use only.
5	Dry extract, DER 5-7:1, extraction solvent ethanol 50% V/V	Registered in 2009	Coated tablet (425 mg extract per tablet)	Adults (over 18 years) and the elderly: For the temporary relief of symptoms of mild anxiety take 1 tablet 2 to 3 times a day. To aid sleep take 1 to 2 tablets 30 min before bedtime. The maximum daily dose is 3 tablets.	A traditional herbal medicinal product used for temporary relief of mild anxiety and to aid sleep, based on traditional use only.
6	Dry extract, DER 5-7:1, extraction solvent ethanol 50% V/V	Registered in 2009	Coated tablet (425 mg of extract/tablet)	Adults (over 18 years) and the elderly: 1 tablet daily.	A traditional herbal medicinal product used for the temporary relief of symptoms associated with stress such as mild anxiety, based on traditional use only.

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

Medicinal use of *Passiflora incarnata* L., herba for the relief of mild symptoms of mental stress and to aid sleep has been recorded *e.g.* in the following handbooks:

Lehrbuch der Biologischen Heilmittel Daily dose: 30-50 drops or 0.250-0.375 g fresh plant material ("Teep"-tablets) before bedtime. Duration of use: No information. (Madaus, 1938)

Martindale Extra Pharmacopoeia Single dose: liquid extract (1 in 1): 0.5-1 ml; tincture (1 in 5): 0.5-2 ml. (Todd, 1967).

British Herbal Pharmacopoeia, 1976. Dosage (3 times daily): 0.25-1 g (by infusion); 0.5-1 ml liquid extract (1:1 in 25% alcohol); 0.5-2 ml tincture (1:8 in 45% alcohol).

Hagers Handbuch. Single dose: 2 gas infusion. (List & Hörhammer, 1977.

Hagers Handbuch. Daily oral dose: 4 – 8 g of the crude drug or the corresponding amount of the extract. For tea: 15 g crude drug in 150 ml of water. Used mostly in combinations with *Valeriana officinalis* L., root, *Humulus lupulus* L., cone or *Melissa officinalis* L., leaf. Also combinations with *Pimpinella anisum* L., fruit, *Lavandula angustifolia* Mill., flower, *Citrus aurantium* L., flower or *Mentha piperita* L., leaf are used. Duration of use: No information. (Hänsel *et al.*, 1994).

British Herbal Compendium Daily oral dose: crude drug: 2 – 8 g. Liquid extract (1:1, 25% ethanol) 2 – 8 ml. Tincture (1:8, 25% ethanol) 8 – 16 ml. Duration of use: No information. (Bradley, 1992).

Herbal Drugs and Phytopharmaceuticals. Daily oral dose: 6 g. Duration of use: No information. (Wichtl, 2004).

Herbal Medicines. Daily oral dose*:* crude drug: 1,25 – 8 g. Liquid extract (1:1, 25% ethanol) 1.5 – 3.0 ml. Tincture (1:8, 45% ethanol) 1.5 – 6.0 ml. Duration of use: No information.(Barnes *et al.*, 1996).

Commission E Monograph.For restlessness and resulting irritability and insomnia, and nervous tension 0.5-1 g of dried plant equivalent three times daily (Mills); 4-8 g herb daily . (Barnes *et al.,* 2007).
For tenseness, restlessness and irritability with difficulty falling asleep: 0.5-2 g of drug three to four times daily: 2.5 g of drug as an infusion three to four times daily; 1-4 mL of tincture (1:8) three to four times daily . Duration of use: No information. (ESCOP, 2003).

Handbook of Medicinal Herbs. Daily oral dose: 2 – 8 g. Duration of use: No information. (Duke, 2002).

Daily oral dose: crude drug: 2 – 8 g. As infusion: crude drug 10 g. Tincture (1:8) 4 – 16 ml. Duration of use: No restriction. (ESCOP, 2003).

PDR for Herbal Medicines,1998. Daily oral dose: 3 teaspoons (~ 6 g) for tea preparation. Duration of use: No information.

Acupuncture & Médicine traditionelle chinoise . Daily oral dose: 6 – 9 g for tea preparation. Powdered crude drug: 0.5 – 1 g. Duration of use: No information. (Weniger & Anton, 1996).

Drogenkunde. Daily oral dose: No information. Duration of use: No information. (Hoppe, 1958).

Précis de Matière Médicale. Daily oral dose: tincture or fluid extract 2 – 5 g (unclear if this amount relates to the crude drug). Duration of use: No information. (Paris & Moyse, 1981).

Phytothérapie. Les données de l´évaluation Daily oral dose: No information. Duration of use: No information.(Bruneton, 2002).

Commission E Monographs. Daily oral dose: 4 – 8 g. Equivalent amount of preparations. Duration of use: No information. (Blumenthal *et al.*, 1998).

Commission E monographs. Daily oral dose: 4 – 8 g. Equivalent amount of preparations. Duration of use: No information. (Blumenthal *et al.,* 2000).

WHO Monographs. Daily dose, adults: as a sedative: 0.5-2.0 g of aerial parts three to four times; 2.5 g of aerial parts as an infusion three to four times; 1.0-4.0 ml tincture (1:8) three to four times; other equivalent preparations accordingly.

Liquid extract (DER 1:3.6 extraction solvent ethanol 60%) has been on the Austrian market since 1981. Oral dose: 20 drops, 3-5 times daily. (Austria).

Liquid extract (DER 1:3.8-4.3; extraction solvent ethanol 54% m/m, glycerine 4% m/m, water 60%) has been on the Austrian market since 1963. Oral dose: 15-20 drops, 3-5 times daily; adolescents 3 times daily. (Austria).

No information on medicinal use of acetone extracts have been found in the literature or received from the Member States.

Extracts prepared with acetone are included in the European Pharmacopoeia but data on traditional use (30 years) of these extracts have neither been found in the literature, nor reported by Member States.

Methanol extracts are also included in the European Pharmacopoeia and have been authorised in Germany since 1992. As the required 30 years of medicinal use have not elapsed, acetone and methanol extracts cannot be included in a Community herbal monograph.

Medicinal and traditional use for the relief of mild symptoms of mental stress and to aid sleep is also described in a number of reviews (Bizet & Roubaudi, 1998; Brasseur & Angenot, 1984; Lutomski *et al*., 1981; Meier, 1995). Only one reference (Lutomski *et al*., 1981) contains information on dosage and quotes the information from Commission E and ESCOP. None of the reviews contains any information on the duration of use. An extensive review of the botany, chemistry, pharmacology and clinical use of plants of the genus *Passiflora*, including *Passiflora incarnata* has been published (Dhawan *et al*., 2004).

The herbal preparations included in the revised Community monograph have been in medicinal use for 30 years or more according to literature information or according to information on approved products obtained from the Member States.

As seen in section 2.1 above, several additional herbal medicinal products, containing herbal preparations considered corresponding to the ones in the monograph, have been registered in Member States. These herbal preparations have not been included in the revised monograph as the documentation showing that they are ‘corresponding products’ is not public (*i.e.* available only to the competent authorities concerned).

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

For relief of mild symptoms of mental stress and to aid sleep the following oral dosages have been recorded:

For herbal tea, a daily dosage of 1 – 8 g of herbal substance is used to make an infusion.

The daily dosage ranges from 0.5 – 8 g of herbal substance as powder.

For liquid extracts (DER 1:8, extraction solvent 25% ethanol), the dose range from 8 – 16 ml daily in divided doses.

For liquid extracts (DER 1:8, extraction solvent 45% ethanol), the dose range from 2 – 6 ml daily in divided doses.

For liquid extract (DER 1:3.6, extraction solvent ethanol 60%), the dose is 1 ml 3-5 times daily.

For liquid extracts (DER 1:1, extraction solvent 25% ethanol), a daily dose ranging between 0.5 and 8 ml.

For liquid extracts (DER 1:1, extraction solvent 70% ethanol), a daily dose of up to 3 times 2 ml.

For the liquid extract (DER 1:3.8-4.3, extraction solvent ethanol 54% m/m, glycerine 4% m/m, water 60%), the dose for adults is 0.3-0.4 ml 3-5 times daily and 0.3-0.4 ml 3 times daily for adolescents.

Doses of dried extracts corresponding to the posologies of tea and liquid extracts above.

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

In-vitro

In vitro studies indicated that pharmacological effects of *Passiflora incarnata* (dry extract DER 5-7:1; extraction solvent 50% ethanol (V/V), at concentrations of the extract up to 1000 µg/ml) are mediated via modulation of the GABA system including affinity to $GABA_A$ (IC_{50} 101µg/ml) and $GABA_B$ (IC_{50} 120 µg/ml) receptors and inhibiting effects (EC_{50} 95.7 µg/ml) on GABA uptake (Appel *et al*., 2011).

In-vivo

A number of early pharmacological studies have been reviewed by Hänsel *et al*., 1994, most of which are said to be of poor quality. Newer studies are reviewed in the ESCOP 2003 monograph, which indicate, a sedative effect in rodents of hydroethanolic extracts, including reduction of spontaneous locomotor activity and prolongation of pentobarbital-induced sleeping time at doses of 50 – 400 mg/kg administered intraperitoneally or *per os*. The authors conclude that the available pharmacodynamic studies generally support, with some conflicting results, the empirically acknowledged sedative and

anxiolytic effects of passion flower but it is not yet clear which constituents are responsible for these effects.

A tri-substituted benzoflavone derivative, comprising a benzene ring fused at positions 6, 7 of a flavone compound has been isolated and claimed to be the main bioactive phyto-constituent of *Passiflora incarnata*. It exhibits significant anxiolytic activity at an oral dose of 10 mg/kg in mice. It also causes reversal of morphine tolerance in mice (dose 10 – 100 mg/kg), prevention of nicotine addiction in mice (10 – 20 mg/kg), prevention of Δ9-THC dependence and tolerance in mice (10 – 20 mg/kg) and prevention of ethanol dependence in mice (10 – 50 mg/kg). The compound was also found to counteract dependence on benzodiazepines in mice and to increase libido in aged rats and to prevent loss of libido induced by ethanol, Δ9-THC or nicotine. The authors postulate that the mechanism for all these effects is inhibition of the enzyme aromatase (a member of the cytochrome P-450 family), resulting in inhibition of the metabolic conversion of androgens to oestrogens thereby increasing free testosterone and decreasing free oestrogen (Dhawan *et al*., 2004).

The validity of these findings was questioned by Holbik *et al.*, 2010. These authors could not find the benzoflavone moiety in *Passiflora incarnata* cultivated in India and France and only trace amounts in an Italian material.

The anxiolytic properties of a commercial extract of *Passiflora incarnata* (dry extract DER 5-7:1; extraction solvent 50% ethanol (V/V)) was investigated in the elevated plus maze test in mice. Using an HPLC method the flavonoids homoorientin, orientin, vitexin and isovitexin were identified as major compounds in the extract. Following oral administration, the extract exerted an anxiolytic effect that was comparable to diazepam (1.5 mg/kg) at a dose of 375 mg/kg. Neither a lower (150 mg/kg) nor a higher (600 mg/kg) dose showed any anxiolytic activity, indicating a U-shaped dose-response according to the authors. In addition, antagonism studies using the $GABA_A$/benzodiazepine receptor antagonist flumazenil and the 5-HT_{1A}-receptor antagonist WAY-100635 were conducted. The anxiolytic effect observed at a dose of 375 mg/kg was effectively antagonised by flumazenil, but not by WAY-100635. This implies that the anxiolytic effects are mediated via the GABAergic system (Grundmann *et al*., 2008).

Whole Passiflora extract induced dose-dependent direct $GABA_A$ currents in hippocampal slices, but the expected modulation of synaptic $GABA_A$ currents was not seen. GABA was found to be a prominent ingredient in Passiflora extract, and GABA currents were absent when amino acids were removed from the extract. Five different extracts, prepared from a single batch of *Passiflora incarnata* (hot and cold extraction methods with water or ethanol 65%: fresh or dried herb), were administered to CF-1 mice for 1 week in their drinking water prior to evaluation of their behavioural effects. Anticonvulsant effects against PTZ-induced seizures were seen in mice that received 2 of the 5 Passiflora extracts. Instead of the anxiolytic effects described by others, anxiogenic effects in the elevated plus maze were seen in mice receiving any of the 5 passiflora extracts (Elsas *et al*., 2010).

Secondary Pharmacodynamics

In -vivo

The anticonvulsant effect of a hydroethanolic extract from the aerial parts of *Passiflora incarnata* was investigated in mice using the pentylentetrazole model. The flavonoid content was 4% (w/w) including vitexin and rutin. Passiflora extract, diazepam and normal saline were administered intraperitoneally at the doses 0.05-0.4 mg/kg, 0.5-1 mg/kg and 10 ml/kg respectively 30 minutes before PTZ (90 mg/kg, i.p.). Flumazenil and naloxone were also injected 5 minutes before the extract to groups of mice. At the dose of 0.4 mg/kg the Passiflora extract prolonged the onset time of seizure and decreased the duration of seizures compared to the saline group. The selective benzodiazepine receptor antagonist flumazenil and the opioid receptor antagonist naloxone could suppress anticonvulsant effects of the Passiflora extract (Nassiri-Asl *et al*., 2007).

The anticonvulsant effects of a commercially available preparation of a hydro-alcoholic extract of *Passiflora incarnata* (total flavonoid content 4%) was investigated in rats after intracerebroventricular injections of 0.125-1.5 µg Pasipay. The extract could dose-dependently and significantly affect minimal clonic seizures and generalised tonic-clonic seizures induced by pentylenetetrazole. Additionally, pretreatment with flumazenil could abolish the anticonvulsant effects. The authors concluded that the results indicate that this passiflora extract has anticonculsant effects in the brain, possibly through modulation of the $GABA_A$ receptor complex via interaction at the benzodiazepine site (Nassiri-Asl *et al.*, 2008).

In a study designed to investigate the protective effect of a hydroethanolic extract of *Passiflora incarnata* in pentylenetetrazol (PTZ)-induced seizure and associated post-ictal depression in mice, different groups of mice were administered repeated sub-convulsive doses of PTZ (50 mg/kg; i.p.) at an interval of 5 days for 15 days. From 5^{th} to 15^{th} day the animals in different groups were given daily varying doses of the hydroethanolic extract of *Passiflora incarnata* (150, 300 and 600 mg/kg; i.p), diazepam (2 mg/kg; i.p.) and vehicle. Treatment with the extract significantly reduced the seizure severity and immobility period as compared to vehicle control, in a dose and time-dependent manner. At a dose of 600 mg/kg, the extract showed similar anticonvulsant effects as that of diazepam. However, diazepam treatment worsened the depressive condition, indicated by increased immobility period. Moreover, the extract treatment retained the serotonin and noradrenaline levels of the brain (Singh *et al.*, 2012).

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

No data available.

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

Acute toxicity:

Dry hydroalcoholic extract (not further specified): mice, *i.p.*, 900 mg/kg. LD_{50}: oral: >15 g/kg (mice and rats), *i.p.*: 3510 mg/kg (rats), 3140 mg/kg (mice), *s.c.*: >10 g/kg (rats), 8300 mg/kg (mice) (Committee of experts on cosmetic products, 2001).
Maltol: LD_{50} *s.c.*, mice 820 mg/kg (Hänsel *et al.*, 1994), *i.p.*, mice 820 mg/kg, (Committee of experts on cosmetic products, 2001).
Ethylmaltol: LD_{50} *i.p.*, mice 910 mg/kg (Committee of experts on cosmetic products, 2001).

Repeated dose toxicity:

Hydroethanolic extract (not further specified): male rats, oral, 10 ml/kg body weight = 5 g/kg dried herb, 21 days, no change in weight, rectal temperature and motor coordination (ESCOP, 2003). An oral daily dose of 600 mg/kg for 4 weeks did not give any toxic symptoms in rats (Weniger & Anton, 1996).

Genotoxicity:

No genotoxic effects in the diploid strain *Aspergillus nidulans* D-30 of 1.30 mg/ml of a fluid extract (16.2% dry matter, 0.32% ethanol) (ESCOP, 2003).

Carcinogenicity, reproductive and developmental toxicity:

No studies concerning carcinogenicity, reproductive and developmental toxicity are available.

3.4. Overall conclusions on non-clinical data

Published data on the pharmacodynamics of *Passiflora* extracts and its constituents, particularly the tri-substituted benzoflavone derivative, give some support to the traditional use of *Passiflora* for the relief of mild symptoms of mental stress and to aid sleep. The chemical structure of the benzoflavone derivative does not appear to be known and the amounts of substance present in the herbal substance/preparations have not been reported in the literature. Subsequently, the validity of these findings has been questioned by Holbik *et al*.,2010. These authors could not find the benzoflavone derivative in plant materials of *Passiflora incarnata* cultivated in India and France, and only in trace amounts in an Italian plant material.

In summary, the doses employed in the animal experiments seem high compared to the doses of *Passiflora* extracts that humans are exposed to during use of herbal medicinal products containing *Passiflora*. The mechanism of action cannot, at present, be regarded as clarified although more recent studies imply that the anxiolytic effects may be mediated via modulation of the GABA system.

The non-clinical information indicates that the acute and repeated dose toxicity is low. As there is no information on reproductive and developmental toxicity the use during pregnancy and lactation cannot be recommended. Minimum required data on mutagenicity (Ames test) are not available.

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

No data available.

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

No data available.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

In order to evaluate the efficacy and safety of Passiflamin (*Passiflora* extract) a multicentre, double-blind study in comparison with mexazolam was carried out in 28 institutions in Japan. The administration period was 4 weeks and the initial dose was 3 tablets/per day (90 mg of Passifamin or 1.5 mg of mexazolam), which was increased to 6 tablets/day after 1 week. Sixty-three patients received Passiflamin and 71 received mexazolam. With efficacy on the major neurotic symptoms as assessed with PNR-D, passiflamin showed a significant effect on 4 items (including anxiety, tenseness, irritation) of the 8 items, and mexazolam showed in all 8 items (Mori *et al*., 1993).

In one small pharmacological screening study (12 healthy female volunteers), the effect of a passion flower extract (1.2 g) was compared with that of placebo and diazepam (10 mg). Alertness was rated by the subjects on a VAS scale after receiving the medication and after challenge with 100 mg of caffeine. Diazepam and, to an apparent lesser degree, placebo and passion flower extract, all decreased mental alertness. The effects of the passion flower extract on qualitative EEG signals could not be distinguished from placebo (Schulz *et al.*, 1998).

The effect of an extract (45 drops/day) of passion flower on patients with general anxiety was compared with the effect of oxazepam (30 mg/day) in a study during 28 days. Eighteen patients were treated with passion flower extract and 18 with oxazepam. Patients were assessed by a psychiatrist at baseline and days 4, 7, 17, 21 and 28 after the medication started. The score on the Hamilton anxiety rating scale was the same for both groups on days 0, 21 and 28. The authors concluded that the extract was equally effective as oxazepam (Akhondzadeh *et al*., 2001a).

Another study by Akhondzadeh *et al*., 2001b comprised 65 opiate addicts undergoing withdrawal. Treatment was 60 drops of an extract of passion flower + 0.8 mg of clonidine or placebo + the same dose of clonidine for 14 days. Both treatments were equally effective with regard to the physical symptoms of withdrawal. However, the combination of passion flower and clonidine was superior to clonidine alone with respect to psychological symptoms.

Sixty patients (25-45 years) were randomised into two groups to receive either oral *Passiflora incarnata* (500 mg tablet containing 1.01 mg benzoflavone) or placebo as premedication, 90 min before surgery. A numerical rating scale (NRS) was used to assess anxiety and sedation before and 10, 30, 60 and 90 min after premedication. Psychomotor function was assessed with the Trieger Dot test and Digit-Symbol Substitution test at arrival in the operating room. The NRS anxiety scores were significantly lower in the passiflora group than in the control group. The authors concluded that oral premedication with *Passiflora incarnata* 500 mg reduces preoperative anxiety without inducing sedation or changing psychomotor function (Movafegh *et al*., 2008).

In a Cochrane review of *Passiflora incarnata* for anxiety disorder, two studies with a total of 198 participants were eligible for inclusion in the review (Mori *et al.,* 1993 ; Akhondzadeh *et al.,* 2001a). The author concluded that relevant randomised clinical trials examining the effectiveness of passiflora for anxiety are too few in number to permit any conclusions to be drawn. Clinical trials with larger samples that compare the effectiveness of passiflora with placebo and other types of medication, including antidepressants, are needed (Miyasaka *et al.,* 2009).

In a double-blind, placebo-controlled study in 41 healthy volunteers (18-35 years) the effects of *Passiflora incarnata* on sleep quality was investigated. Treatment was passionflower tea (teabags containing 2 g of dried *Passiflora incarnata* leaves, stems, seed and flowers in 250 ml boiling water for 10 min). Placebo teabags contained 2 g of dried parsley. The participants were exposed to each treatment for a week and consumed a cup of tea one hour before bedtime and filled out a sleep diary for 7 days and completed Spielberger´s state-trait anxiety inventory on the seventh morning. Ten participants also underwent overnight polysomnography (PSG) on the last night of each treatment period. *Passiflora incarnata* produced no significant changes in any of the PSG parameters (EEG, EOG,EMG). Amongst the PSG and subjective sleep parameters analysed, only subjective sleep quality,was found to be significantly better than placebo (mean increase of 5.2% relative to placebo). Significant positive correlations between the subjective and PSG measures of quantitative sleep were found for sleep-onset latency and sleep efficiency, but not for total sleep time and nocturnal awakenings (Ngan & Conduit, 2011).

The effect of preoperative oral administration of *Passiflora incarnata* on anxiety, psychomotor functions, sedation and hemodynamics in 60 patients (25-55 years) undergoing spinal anesthesia was investigated in a prospective, randomised, double-blind and placebo-controlled study. An aqueous extract of *Passiflora incarnata* containing 2.8 mg benzoflavone per 5 ml extract was given to the patients 30 min before spinal anaesthesia at a dose of 700 mg/5ml. The same volume (5 ml) of mineral water was given to the placebo-group. There was a statistically significant, but small, difference between the two groups for the increase in State Anxiety Inventory (STAI-S) score obtained just before spinal anesthesia when compared to the baseline. There was no significant difference between the two groups in psychomotor function, sedation score, hemodynamics and side effects. The authors concluded that oral preoperative administration of *Passiflora incarnata* suppresses the increase in anxiety before spinal anesthesia without changing psychomotor function test results, sedation level or hemodynamics (Aslanargun *et al*., 2012).

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

In a randomised, double-blind study in 34 children (between 6 and 13 years of age) recently diagnosed with ADHD, the efficacy of passion flower tablets was compared with methylphenidate (Akhondzadeh *et al*., 2005). Seventeen children were treated with passion flower tablets (0.04 mg/kg/day) for 8 weeks. A control group of 17 children received methylphenidate (1 mg/kg/day). The primary efficacy parameter was outcome on a parent and teacher ADHD rating scale that has been extensively used in Iran in school-age children. Both groups improved significantly over the 8 weeks trial compared to the baseline value. There was no statistically significant difference in treatment result between the two groups. No placebo group was employed.

4.3. Overall conclusions on clinical pharmacology and efficacy

In the study in 12 healthy volunteers (Schulz *et al*., 1998), the effect of passion flower could not be distinguished from that of placebo. No statistical evaluation of the results was performed.

In the study by Akhondzadeh *et al*., 2001a, major deficiencies in methodology include that the type of herbal preparation and details of the posology are unclear. Concerning the design of the study, the number of patients involved (18 treated with passion flower) is too small to provide robust information. No placebo group was used, but the patients visited a psychiatrist 6 times during the 28 days trial. It appears very reasonable to assume that this extensive contact with a doctor may in itself have a beneficial effect on patients with general anxiety. In the absence of a placebo group, the intrinsic effect of the medication cannot be assessed. The trial has been discussed in the literature, and it has been pointed out that the study was not designed as an equivalence study and conclusions about efficacy cannot be drawn (Ernst, 2006). This study does not give conclusive evidence of efficacy of passion flower extract for treatment of anxiety, but as a pilot study it may be seen as supportive of the traditional use to relieve mild symptoms of mental stress.

The study by Akhondzadeh *et al*., 2001b is a report of the use of passion flower as an adjuvant to clonidine in the treatment of opiate withdrawal symptoms in opiate addicts. The type of herbal preparation was not reported. The indication and study population used in this study cannot be considered relevant for evaluation of the traditional use of passion flower. This is the first report of the use of passion flower in the treatment of opiate withdrawal symptoms. Medicinal use of passion flower in this indication cannot be recognised as well-established nor as traditional in the Community.

In the study where the effect of preoperative oral administration of *Passiflora incarnata* was investigated (Movafegh *et al*., 2008) the type of herbal extract in the tablet was not reported. In the second study by Aslanargun *et al*.,2012 there was small differences in the STAI scores but also difficulties in producing a placebo with the same taste and colour as Passiflora. The trials must be considered pilot studies. Medicinal use of passion flower in this indication cannot be recognised as well-established/traditional in the Community.

In the study where sleep quality was investigated (Ngan & Conduit, 2011) the sample size was too small and participants with sleep disorders were excluded.

In the Cochrane review (Miyasaka *et al.,* 2009) the author concluded that relevant randomised clinical trials examining the effectiveness of passiflora for anxiety are too few in number to permit any conclusions to be drawn. Clinical trials with larger samples that compare the effectiveness of passiflora with placebo and other types of medication, including antidepressants, are needed.

In a study by Akhondzadeh *et al*., 2005 in children with ADHD, the efficacy of passion flower was compared to metylphenidate. The type of herbal preparation was not reported, but apparently the dose (0.04 mg/kg/day) is several orders of magnitude lower than the doses used in traditional European phytotherapy (approximately 10 - 100 mg/kg/day; 70 kg body weight assumed). There are a number of limitations of the study, which the authors themselves point out. These include e.g. the lack of placebo group and the small number of patients involved. The trial must be considered as a pilot study. This is the first report of the use of passion flower in the treatment of ADHD. Medicinal use of passion flower in this indication cannot be recognised as well-established/traditional in the Community.

All clinical studies retrieved from literature suffer from serious deficiencies from the efficacy point of view such as too small number of patients involved, lack of adequate statistical design/treatment of the results, undefined testing medication or therapeutic indications of doubtful relevance to the traditional medicinal use. Clinical data have recently been reviewed by Miroddi *et al*., 2013. They concluded that published clinical studies revealed crucial weaknesses such as limited patient samples, no description of blinding and randomisation procedures and little information regarding the extract used. To conclude, the clinical data cannot be considered to fulfil the criteria required for "well-established medicinal use" according to Directive 2001/83/EC as amended.

5. Clinical Safety/Pharmacovigilance

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

No signals of safety concern were identified in the published clinical trials reported under 4.2.2 and 4.2.3.

5.2. Patient exposure

Products containing *Passiflora incarnata* L., herba are currently available in most Member States. The products have various regulatory statuses. A considerable patient/consumer exposure must be assumed although no exact figures can be given.

5.3. Adverse events and serious adverse events and deaths

Hypersensitivity is possible in very rare cases (ESCOP, 2003). One case of hypersensitivity vasculitis has been reported (Smith *et al*., 1993).

One case of ventricular tachycardia accompanied by severe nausea, vomiting, drowsiness and prolonged QT interval required hospital admission for cardiac monitoring and intravenous fluid therapy (Fisher *et al.*, 2000). The daily ingested dose corresponded to 1.5 g respectively 2 g crude drug during 2 days. Causality cannot be assessed with certainty due to incomplete data.

For unregistered products containing *Passiflora incarnata* as single active ingredient, nausea and thrombocytopeniea have been reported. The following adverse reactions were also reported for *Passiflora incarnata* as single active ingredient, however, concomitant drug uses were noted: tachycardia, vomiting, abnormal nausea, left ventricular failure, ventricular fibrillation, hepatic function abnormal, arrhythmia, tremor, agitation and withdrawal syndrome. A causality of these reported serious adverse events and Passiflora intake has not been established. (Ireland).

No adverse events appear to have been reported for registered products in the EU. According to recent decisions and scope of the revision, the MLWP agreed not to include references to single cases in the revised version of the Community monograph.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Drug interactions

One case of a possible interaction of *Valeriana officinalis* and *Passiflora incarnata* in a patient treated with lorazepam was reported. The patient reported hand tremor, dizziness, throbbing and muscular fatigue within 32 h before clinical diagnosis. The symptoms disappeared after stopping consuming valerian and passionflower (lorazepam medication continued). An additive or synergistic effect is suspected to have produced these symptoms (Carrasco *et al*., 2009).

Although no clinical data are available on *Passiflora incarnata* as a single active ingredient concerning interactions with synthetic sedatives (such as benzodiazepines), concomitant use is not recommended.

Use in pregnancy and lactation, influence on fertility

Safety during pregnancy and lactation has not been established. No adverse effects have been reported from the use of *Passiflora incarnata* during pregnancy and lactation. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

Fertility data are not available.

Contraindications

Hypersensitivity to the active substance.

Effects on ability to drive or operate machinery

Theoretically, products containing *Passiflora incarnata* L., herba may cause drowsiness. The ability to drive a car or to operate machinery may be reduced. If affected, patients should not drive nor operate machinery (ESCOP, 2003). Excessive doses may cause sedation (Barnes *et al.*, 1996).

5.6. Overall conclusions on clinical safety

Conventional clinical safety data are virtually absent. However, longstanding medicinal use and experience of *Passiflora incarnata* L., herba has been documented within the Community. During this time, no clear clinical signals that *Passiflora incarnata* L., herba is harmful under normal conditions of use have been identified. As no data on use in children are available, products containing *Passiflora incarnata* L., herba cannot be recommended for use in children below the age of 12 years. No data to recommend a specific limit of duration of use of Passiflora products is available, but as a general precaution the patient is recommended to consult a doctor or a qualified health care practitioner if the symptoms persist longer than 2 weeks during the use of the product.

6. Overall conclusions

The information available is still insufficient to establish that *Passiflora incarnata* L., herba has a recognised efficacy and a ´well-established´ medicinal use as defined in article 10a of Directive 2001/83/EC.

However, traditional medicinal use of *Passiflora incarnata* L., herba for the relief of mild symptoms of mental stress and to aid sleep is well documented in a number of recognised handbooks. The pharmacodynamic studies in animals and the clinical studies may be seen as supportive to the plausibility of the traditional use of *Passiflora incarnata* L, herba.

Products containing *Passiflora incarnata* L., herba have been registered as THMPs in many Member States. A lot of the products commercially available are combination products with other herbal substances/preparations.

The requirement of medicinal use for at least 30 years (15 years within the Community) according to Directive 2004/24/EC as amended is considered fulfilled for the following herbal preparations:

a) Comminuted herbal substance

b) Powdered herbal substance

c) Liquid extract (DER 1:8) extraction solvent ethanol 25% V/V

d) Liquid extract (DER 1:8) extraction solvent ethanol 45% V/V

e) Liquid extract (DER 1:3.6) extraction solvent ethanol 60% V/V

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

g) Liquid extract (DER 1:1) extraction solvent ethanol 70% V/V

h) Liquid extract (DER 1:3.8-4.3) extraction solvent ethanol 54% m/m, glycerine 4% m/m, water 60%

Dried extracts corresponding to the tea and liquid extracts above.

There is very little information on toxicity. Information on genotoxicity, carcinogenicity, reproductive and developmental toxicity is lacking. Use during pregnancy and lactation thus can not be recommended.

Conventional clinical safety data are virtually absent, however, longstanding medicinal use and experience of *Passiflora incarnata* L., herba have been documented within the Community. No clinical signals that *Passiflora incarnata* L., herba is harmful under normal conditions of use have been identified.

Insufficient data on use in children are available therefore products containing *Passiflora incarnata* L., herba are not recommended for use in children below the age of 12 years.

In view of the empirically acknowledged sedative properties of *Passiflora incarnata* L., herba a warning for use in connection with driving of cars and operation of machinery is advisable.

Sufficient data for a Community herbal monograph on the traditional use of *Passiflora incarnata* L., herba are available. As the minimum required data on mutagenicity (Ames test) are still not available, an inclusion to the Community list of traditional herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products is not recommended.

Annex

List of references