European Medicines Agency
Evaluation of Medicines for Human Use

London, 15 November 2008
Doc. Ref.: EMEA/HMPC/383450/2007

OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *PASSIFLORA INCARNATA* L., HERBA' (EMEA/HMPC/230962/2006)

Table 1: Organisations providing comments on the draft 'Community herbal monograph on *Passiflora incarnata* L., herba' as released for consultation on 8 March 2007 until 15 June 2007.

	Organisation
1.	The Association of the European Self-Medication Industry (AESGP)
2.	Europlant PhytoPharm Sp. z o. o., Poland
3.	Kooperation Phytopharmaka, Germany
4.	Bayer Santé Familiale, France

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Table 2: Discussion of comments

GENERAL COMMENTS TO DRAFT DOCUMENT	
Comment and Rationale	**Outcome**
<u>Section 2 : Quantitative and Qualitative Composition - Traditional Use of the monographs</u> From a general point of view, we propose the HMPC monographs (traditional use section) to be consistent with the current general Eur. Ph. Monographs, meaning that the herbal preparations described in the monograph should be consistent with those already existing in the Eur.Ph. Indeed, most of the herbal preparations described in the Eur.Ph. have been used for years in herbal medicinal products and fulfill the provisions for traditional use listed in Articles 16a(1) and 16c(1)(c) of the European Parliament and Council Directive 2001/83/EC (amended by Directive 2004/24/EC) related to traditional herbal medicinal products, where the period of traditional use is defined as follows "*a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community*". This is particularly true for Valerian dry extract (hydroalcolic – 60% Ethanol / Eur.Ph. n° 1898) and Passion Flower dry extract (hydroalcolic – 60% Ethanol / Eur.Ph. n° 1882) used in several herbal medicinal products currently on the market in France, for example in Euphytose that has been marketed in France for more than 30 years. **Therefore, we think that it would be fully justified to have the following Eur. Ph. herbal preparations listed in all the HMPC monographs:** **Herbal Preparations:** - **Tincture (when applicable) acc. to Eur. Ph. n°xxx** - **Dry extracts (when applicable) acc. to Eur. Ph. n°xxx** - **Liquid extracts (when applicable) acc. to Eur. Ph. n°xxx** **Herbal substance for tea preparation (when applicable) acc. to Eur. Ph. n°xxx**	We try to achieve consistency between the HMPC monographs and Ph. Eur. monographs as far as possible, but the criteria for inclusion of a herbal substance/preparation in a HMPC monograph and a Ph. Eur. monograph are different. Some discrepancies cannot be avoided. No changes. HMPC has taken note of the need for a monograph for hawthorn.

<u>Hawthorn in the HMPC monographs list</u> Hawthorn currently is not included in the prioritary monographs list of HMPC to be established, under review or already published. There is currently a Eur Ph monograph relating to Hawthorn herbal preparation, and there is many herbal medicinal products containing hawthorn herbal substances or herbal preparations currently on the market. Therefore, Hawthorn should be added to the current list of prioritary monographs.		
SPECIFIC COMMENTS ON TEXT		
SECTION TITLE		
Paragraph no.	**Comment and Rationale**	**Outcome**
2. Qualitative and quantitative composition	<u>Well-established use</u> ***Passiflora incarnata* L., herba (Passiflora) as a single substance or in combination with other herbal preparations, i.e. valerian root, lemon balm leaf or hop strobiles** **Dry extract (50-70% ethanol)** **Dry extract (60% methanol)** **Liquid extract (1:1 in 25 to 90% ethanol)**	Published clinical data are insufficient to support a well-established use. References mentioned rather reinforce the plausibility of the traditional use. No change.
2. Qualitative and quantitative composition	<u>Traditional use</u> ii) Herbal preparations ~~Powdered herbal substance for tea preparation~~ **Powdered herbal substance** **Herbal substance for tea preparation** Liquid extract/ **Tincture** (1:8 in 25% ethanol) Liquid extract / **Tincture** (1:8 in 45% ethanol) ~~Liquid extract (1:1 in 25% ethanol)~~ ~~Liquid extract (1:1 in 70% ethanol)~~ **Liquid extract (1:1 in 25 to 90% ethanol)** ~~iii) Corresponding dry extracts~~ **Dry extract (25-90% ethanol)**	Herbal substance for tea preparation is not limited to “powder”. It can be cut or otherwise fragmented. Amendment endorsed. The term liquid extract is only used to describe the physical properties of the extract. No change. 30 years of medicinal use of extracts made with 60% methanol and 40-90 % ethanol (Ph. Eur.) have not been documented, and thus cannot be included in the HMPC monograph. No changes.

	Dry extract (60% methanol) Reasons: According to the British Pharmacopoeia, "liquid extract (1:8 in 25% ethanol) and "liquid extract (1:8 in 45% ethanol)" should be read as "tincture (1:8 in 25% ethanol)" and "tincture (1:8 in 45% ethanol)". According to the European Pharmacopoeia monograph #1882 – Passsion flower dry extract, the extract for passiflora is described as an 'hydroalcoholic dry extract produced from herbal drug and ethanol (40% to 90% (V/V)). We therefore strongly recommend that the herbal preparations listed in the monograph cover those listed in the European Pharmacopoeia. The German *Rote Liste* currently lists the following phytomedicines under the item "Passiflora". All extracts are dry extracts unless otherwise stated. TABLE enclosed. Analogous ethanolic and methanolic extracts were also listed in the "Rote Liste" of 1989 (e.g., Moradorm S, Passiorin, Seda-Pasc N, Somnium, Somnuvis, Valobonin, Visinal). The requirement of '15 years of medical use in Europe' is thus also fulfilled.	
2. Qualitative and quantitative composition	Traditional use ii) Herbal preparations 1. Liquid extract (2:1 in 60% ethanol) should be added to the list of herbal preparations. 2. Dry extract (5-7:1 in 60% ethanol) should be added to the list of herbal preparations. Rationale: Extraction solvent ethanol (40 per cent V/V to 90 per cent V/V) is allowed for extracts produced from Passion flower according to European Pharmacopoeia 01/2006:1882 (monograph *Passion flower dry extract*). Native dry extract 5:0-6:0:1 (w/w) is recommended according to Herbal Medicine Expanded Commission E Monographs 2000.	See response to comment above.

	In addition to our comments already submitted we would like to inform you that from our point of view the scope of the monograph, i.e. the qualitative and quantitative composition, should be described in a more precise manner. Particularly for the so-called "other herbal preparations" information on the drug extract ratio and on the extraction solvent is of utmost importance as well as - if possible - a reference to the respective pharmacopoeia. We would like to recommend to add such information in accordance with the Note for Guidance on the declaration of herbal substances and herbal preparations in medicinal products/traditional products in the SPC. Thus dosage information can be interpreted unambiguously. The HMPC Draft Monograph on Melissa leaf contains a "liquid extract 1:1 in 45% ethanol" and a dosage of 2-4 ml up to 3 times per day. We are wondering whether there is a Pharmacopoeia available describing the production of this extract and particularly of the corresponding dry extracts. Furthermore it is not clear whether "in 45% ethanol" means the concentration of ethanol in the herbal medicinal product or the concentration of the extraction solvent. We would be very happy if you could take these comments into account. The same applies to the draft monograph on Passiflora herb.	We agree that the requested detailed information on the quantitative and qualitative composition would be desirable. Unfortunately it is not available. No changes. No reference to an official Pharmacopoeia is available. Information in the monograph stems from the British Herbal Pharmacopoeia (1976). “in 45% ethanol” is interpreted as “use 45% ethanol/water (v/v or W/W) as extraction solvent”. Reference is now made to ‘extraction solvent 45% ethanol’.
2. Qualitative and Quantitative composition (p2/5)	**We propose to change *§2 – Qualitative and Quantitative composition of* the monograph into the following:** <u>Traditional Use</u>: With regard to the registration application of Article 16d(1) of Directive 2001-83-EC as amended Passiflora incarnate L., herba (passion flower) i) Herbal Substance Fragmented or cut, dried aerial parts ii) Herbal Preparations o Powdered herbal substance for tea preparation	30 years of medicinal use of extracts made with 60% methanol and 40-90 % ethanol (Ph. Eur.) have not been documented, and thus cannot be included in the HMPC monograph. If other extraction solvents are preferred by a certain manufacturer, it is up to that manufacturer to show that the product in question is “a corresponding product”. This must be assessed for each product, on a case-by-case basis, and is not addressed in the monograph. No changes.

	o Liquid extracts prepared with ethanol / water (ethanol 25 – 90 % (V/V)) o Dry extracts prepared with ethanol / water (ethanol 25 – 90 % (V/V)) Or: o Powdered herbal substance for tea preparation o Liquid extracts according to Eur. Ph. monographs o Dry extracts according to Eur. Ph. monographs **Comment and Rationale** From a general point of view, the herbal preparations described in § 2 of the proposed monograph do not cover the diversity of extracts traditionally used in Herbal Medicinal Products, i.e. Eur.Ph. standard extracts, currently marketed in France. For instance, Euphytose tablets contains 4 plant extracts, including Passion Flower dry extract prepared with 60 % ethanol. This extract is compliant with the current European Pharmacopoeia monograph n° 1882 – Passion Flower dry extract, where the extract is described as an "*hydroalcoholic dry extract produced from herbal drug and ethanol (40 to 90 % (V/V))* […]". This extract is not included in the proposed monograph for Passion Flower, whereas it is fully compliant with the Eur.Ph. monograph currently in force. The extracts described in 2-ii) as "*liquid extracts 1:8"* do not correspond to any of the Eur.Ph. n° 0765 definitions, were: - liquid extracts = 1:1 (herbal drug : solvent) in appropriate % ethanol or water - tinctures = 1:10 or 1:5 (herbal drug : solvent) in appropriate % ethanol Therefore, to be consistent with the definitions of the monograph n°0765, **we propose to suppress the ratio *"1:1"* and *"1:8",* and to refer only to the terms "liquid extract", "dry extract" and** **appropriate % of solvent.** Dry extracts are also considered as herbal preparations (ref. general Eur.Ph. monograph for herbal preparations n° 1434), therefore dry extracts should be included in *ii) Herbal preparation*.	

	We propose to delete *2-iii) Corresponding dry extracts, and include dry extracts in 2-ii) Herbal preparation with corresponding Eur. Ph. definitions.*	
3. Pharmaceu-tical form	Well-established use **Herbal substance or herbal preparations in solid or liquid dosage forms for oral use (Extraction solvent and drug-extract ratios should be indicated)** Reasons: Herbal substances or herbal preparations in solid or liquid dosage forms for oral use, as mentioned under traditional use are also used in well-established preparations. The reference to Ph. European pharmacopoeia is not necessary for well-established use, as the extract needs to be specified in more details (i.e. extraction solvent and drug-extract ratio).	Published clinical data are insufficient to support a well-established use. References mentioned rather reinforce the plausibility of the traditional use. No changes.
4.1. Therapeutic indications	Well-established use **Tenseness, restlessness and irritability with difficulty falling asleep.** Reasons: The indication added under the heading well-established use corresponds to the one attributed to Passiflora herba in monographs (1-3), and granted in a German standard authorisation. The indication is also compatible with the finding of anxiolytic effects in pharmacological studies and clinical trials. Tenseness, restlessness and irritability are symptoms occurring in anxiety disorders. An effective treatment against anxiety will automatically have a positive impact on these symptoms	Published clinical data are insufficient to support a well-established use. References mentioned rather reinforce the plausibility of the traditional use. No changes.
4.1.	*We propose to include the well-established medicinal use for Passiflorae herba in accordance with the monographs published by ESCOP and Commission E.*	Published clinical data are insufficient to support a well-established use. References mentioned rather reinforce the plausibility of the traditional use. No changes.

4.2. Posology and method of administra-tion	Well-established use **Posology** **Adolescents over 12 years of age, adults** **3-4 times daily** • **0.5-2 g of the drug** • **2.5 g of the drug as an infusion** • **1-4 ml of tincture (1:8)** • **equivalent doses of dry or liquid extracts.** **Children from 3 to 12 years under medical supervision:** **Proportion of adult dose according to body weight.** **Duration of use** **No restriction. Neither dependence nor withdrawal symptoms have been reported.** **Method of administration** **Oral use** Reasons: The additions made in the section "Well-established use" correspond to those of the ESCOP monograph "Passiflorae herba" (1). Traditional use Posology Adolescents over 12 years of age, adults ~~1-2 g~~ **0,5-2g** of herbal substance as powder ~~1-4~~ **2-4** times daily. To make an infusion, pour 150 ml of boiling water over 1-2 g of herbal substance. Steep for 10 minutes. To be taken 1-4 times daily.	Published clinical data are insufficient to support a well-established use. References mentioned rather reinforce the plausibility of the traditional use. No changes.

	2-4 ml of liquid extract/ **tincture** (1:8 in 25% ethanol) up to 4 times daily. 2 ml of liquid extract/ **tincture** (1:8 in 45% ethanol) up to 3 times daily. 0.5-2 ml of liquid extract (1:1 in 25% ethanol) up to 4 times daily. 2 ml of liquid extract (1:1 in 70% ethanol) up to 3 times daily. Corresponding doses of dry extracts. ~~The use in children under 12 years of age is not recommended (see section 4.4 Special warnings and precautions for use)~~. Dosage recommendations of the literature for the herbal substance as powder include: Reasons: • 0.25-1 g (thrice daily) [1, 2] • 0.5-2 g (up to four times daily) [3] • 0.5-1 g daily [4] • 0.5-2 g (three to four times daily) [5] Initially, the draft proposal for a core data for Passiflora (EMEA/HMPWP/18/00) suggested 0.5-2 g (2-4 times daily) instead of 1-2 g (1-4 times daily). Such dosage for powdered herbal substance is in line with proposed posology for other preparations (liquid extract and tincture) starting with lower dosage unit (see EMEA/HMPC/230962/2006). [References (all cited in "list of references for assessment of Passiflora herba, EMEA/HMPC/111180/2007"): [1] British Herbal Pharmacopoeia. British Herbal Medicine Association, London 1976. [2] Newal A.C., Anderson, L.A., Phillipson, J.D. Herbal Medicines. A guide for healthcare professionals. 1st Ed. Pharmaceutical Press, London, Chicago 1996.	

	[3] Bradley, P.R. (ed). British Herbal Medicine Association, Dorset 1992. [4] Weniger B. and Anton R. Monographies de plantes: Passiflore Passiflora incarnata L. (Passifloraceae) in Cornillot P. Acupuncture & Médecine traditionnelle chinoise. Phytothérapie & aromathérapie, Homéopathie. Frison-Roche, Paris. P. 123-7. 1996. [5] ESCOP Monographs. 2nd Ed. European Scientific Cooperative on Phytotherapy, Exeter 2003.] In addition, a disclaimer for use in children in the traditional section is not appropriate, because Passiflora is known to have a very good tolerability. No dependency or withdrawal symptoms are known. The German commission E monograph on Passiflora did not make restrictions for the use in children. Neither do monographs on this herb (1;4). In addition, Passiflora preparationshave explicitly been tested in children in a clinical study (see section 4.4) (5).	
4.2. Posology and method of administra-tion	<u>Traditional use</u> Posology 1-2 g of herbal substance as powder 1-4 times daily should be changed into 0.5-2 g of herbal substance as powder 1-4 times daily. Rationale: "Dosage: adult single dose, three to four times daily: 0.5-2 g of the drug" is recommended in ESCOP Monographs 2nd Ed., Exeter 2003; and the same dose "Dosage: unless otherwise prescribed, up to four times daily: dried herb, 0.5-2 g" is recommended in British Herbal Compendium Volume 1, 1992.	To include a lower posology starting with a daily dose of 0.5 g of herbal substance as a powder is not connected with any safety concerns and it appears well documented for at least the last 15 years. A lower starting posology is also documented in British Herbal Pharmacopoeia (1976). Amendment accepted.

4.2. Posology and method of administra-tion (p3/5)	**Proposed change:** Single dose: - 1 to 2 g of powdered herbal substance for tea preparation - Dry extracts corresponding to *x – y g* of the herbal substance *(range to be defined)* - Liquid extracts corresponding to *x – y g* of the herbal substance *(range to be defined)* Maximum daily dose: x single doses (quantity to be defined Rationale: The writing of this section seems unclear regarding the maximum daily dose allowed. It would be more appropriate to refer to quantity of herbal substance instead of volume or quantity of herbal preparation. Indeed, this way of expression was used for the valerian monograph (ref EMEA/HMPC/340719/2005) already published.	We agree that the requested detailed information on the dry and liquid extracts would be desirable. Unfortunately such information is not available. No changes.
4.3. Contraindi-cations	Well-established use **Hypersensitivity to *Passiflora* species.** Background: No contraindications are known for Passiflora (1;3). As one single case of allergy related to the intake of Passiflora has, however, been reported in the literature (6), a corresponding disclaimer is acceptable.	The text is changed to the general statement: Hypersensitivity to the active substance.
4.4. Special warnings and precautions for use	Well-established use **Medical advice should be sought for use in children under 12 years of age.** **For liquid extracts, the appropriate labelling for ethanol, taken**	No indication for well-established use is accepted. No changes. Use in children under the age of 12 years is not recommended for a

	from the "Guideline on excipients in the label and package leaflet of medicinal products for human use" must be included. Traditional use ~~The use in children under 12 years of age is not recommended because data are not sufficient and medical advice should be sought~~. Medical advice should be sought for use in children under 12 years of age. For liquid extracts, the appropriate labelling for ethanol, taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use" must be included. Reasons: No special warnings or precautions can be derived from bibliographic sources (1;4). The recommendation against the use in children under 12 years of age was based on the assumed lack of clinical studies. However, traditional use is by definition is not supported by clinical evidence. Thus, clinical data in specific subgroups of the population are by definition absent, and the statement as proposed in the draft monograph is misleading. In addition, Passiflora extract was in fact specifically given to children in the scope of a clinical double-blind trial for the treatment of attention deficit hyperactivity syndrome (5). Typical sleeping aids for children were mostly liquid preparations containing, among other herbs, Passiflora. No case reports of adverse effects are known from this long-standing use. A warning against the use in children can only be justified based on therapeutic grounds i.e. a differential diagnosis should be sought in children having lasting restlessness and irritability for no obvious reason.	traditional herbal medicinal product, because mental stress and sleep disturbances in this group of patients requires medical supervision. No changes.

4.5. Interactions with other medicinal products and other forms of interactions	Well-established use **Although no data about interactions with synthetic sedatives are available, concomitant use with synthetic sedatives (such as benzodiazepines) is not recommended unless advised by a doctor.** Traditional use **Although no data about interactions with synthetic sedatives are available,** concomitant use with synthetic sedatives (such as benzodiazepines) is not recommended unless advised by a doctor. Reasons: No interactions with other drugs including synthetic sedatives are known (1,4) and this should be reflected in the monograph.	No indication for well-established use is accepted. No changes. Proposed amendment concerning traditional use is reasonable and accepted.
4.5. Interaction with other medicinal products and other forms of interactions (p4/5)	There are currently no supportive data not to recommend to intake Passion Flower and benzodiazepines at the same time. To date, none of the SmPcs of herbal medicinal products of traditional use currently on the market in France states that concomitant use of benzodiazepines and Passion Flower (alone or in combination) containing products is not recommended. Therefore, in order to be consistent with the currently registered traditional herbal medicinal products, **we propose to remove this warning.**	See response above.
4.6. Pregnancy and lactation	Well-established use **In accordance with general medical practice, the product should not be used during pregnancy and lactation without medical advice.** Reasons: The suggested statement for well-established use is derived from the ESCOP-monograph (1). No increase in frequency of	No indication for well-established use is accepted. No changes.

	malformation or other harmful effects on the foetus are known from human application and from animal studies (4). Passiflora is compatible with breast feeding (4).	
4.7. Effects on ability to drive and use machines	**Well-established use & Traditional use** **As with most sedatives, taking Passiflora incarnata L., Herba preparations immediately (up to 2 hours) before driving a car or operating hazardous machinery is not recommended.** Reasons: The suggestion corresponds to the statement in the ESCOP monograph (1). Other monographs suggest a complete lack of effects on the ability to drive or to use machinery (4).	No indication for well-established use is accepted. No changes.
4.8. Undesirable effects	Well-established use **Hypersensitivity has been reported in one case. Nausea, brachycardia and ventricular arrhythmia has been observed in one case. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.** Traditional use Hypersensitivity~~, vasculitis,~~ **(vasculitis),** nausea and tachycardia have been reported **in single case reports**. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted. Reasons: The adverse reactions mentioned in the draft monograph refer to one single case report of an immunologic reaction (vasculitis) (6), and a second single case report of cardiovascular adverse events (7). The special circumstances of this latter case report point, however,	No indication for well-established use is accepted. No changes. Traditional use: The proposed amendments are accepted.

	to a problem with the quality of the ingested product. There is no evidence of a more general occurrence of cardiovascular adverse events under intake of Passiflora preparations. The relevance of this adverse event is thus questionable.	
4.9. Overdose	Well-established use **No case of overdose has been reported.** Reasons: Corresponds to ESCOP monograph (1) and to other compilations (4).	No indication for well-established use is accepted. No changes.
5.1. Pharmaco-dynamic properties	Well-established use **Pharmacodynamic studies in animals support the application of hydroalcoholic extracts from *Passiflora* against anxiety and restlessness. Corresponding effects against anxiety, tenseness and irritation have also been confirmed in randomized clinical trials.** Reasons: Passiflora extract has sedative and anxiolytic effects in rodents. Della Loggia et al. (1981) found sedative and anxiolytic effects in rats without negative effects on motor coordination ability of EEG activity (8). Speroni et al. (1988) demonstrated a raise of the nociceptive threshold in the tail flick and hot plate test in rats on oral application of an extract prepared with 50% ethanol, and a prolongation of sleeping time on intraperitoneal application (9). Sopranzi et al. (1990) recorded tail flick, motor coordination and general activity in a one-arm radial maze in rats under oral treatment with *Passiflora*. Whereas no change was found in motor	No indication for well-established use is accepted. No changes.

	coordination, a diminished general activity and an anxiolytic effect was observed in the one-arm radial maze (10). Galliano et al. (1994) treated mice orally with a hydromethanolic extract, and found reduced exploratory and spontaneous motor activity, prolonged sleeping time induced by pentobarbital, and inhibition of aggressiveness and restlessness caused by amphetamine (11). Capasso and Pinto (1995) observed prolongation of pentobarbital-induced sleeping time on intraperitoneal application of a 70% ethanolic extract to mice, and reduced amphetamine-induced hypermotility on oral application (12). Speroni et al. (1996) observed dose-dependent reduction in spontaneous locomotor activity in mice on intraperitoneal and oral application of a hydromethanolic extract. Pentobarbital-induced sleeping time was significantly increased (13;14). Soulimani et al. (1997) assessed hydroalcoholic and aqueous extracts of *Passiflora incarnata* L. for behavioural effects in mice. The anxiolytic and sedative properties were confirmed in the staircase test (non-familiar environmental test), and in tests on locomotor activity. The aqueous extract induced sleep in mice after treatment with a sub-hypnotic dose of pentobarbital (15). Dhawan et al. (2001) found the most potent anxiolytic effects of Passiflora herb preparations in the hydromethanolic fraction on testing in the elevated plus-maze model for anxiety in mice (16-18). Petry et al. (2001) also tested in the elevated plus-maze model. They found anxiolytic activity for hydromethanolic extracts from the closely related species *Passiflora alata* and *Passiflora edulis*	

	(19). Capasso and Sorrentino (2005) examined the anxiolytic effect of an extract from Passiflora produced with 70% ethanol. *Passiflora* reduced amphetamine-induced hypermotility in rats at an oral dose of 250 mg/kg, and prolonged barbiturate-induced sleep duration in mice at the same dose (8). De Castro et al. (2007) found anxiolytic activity of a hydroalcoholic extract from *Passiflora quadrangularis* L. (a closely related species) in the elevated plus-maze-model in mice (20). The pharmacodynamic studies generally support the application of hydroalcoholic extracts from *Passiflora* against anxiety and restlessness (1). Sedative effects could not be confirmed in a clinical trial in healthy human volunteers (21). However, such effects would not be expected in healthy study participants not showing symptoms of restlessness. The results are therefore not suitable for the exclusion of efficacy of *Passiflora*, but rather demonstrate a safety feature of its application, inasmuch as indiscriminate and unwanted sedation as observed with benzodiazepines or barbiturates will not occur with the intake of preparations from Passiflora by patients with no impaired cognition. In contrast, the anxiolytic effect of a hydromethanolic Passiflora extract was demonstrated in a randomized, placebo- and oxazepam-controlled clinical double-blind trial (22). Further evidence of clinical efficacy was given in a placebo-controlled trial aimed on the alleviation of opiate withdrawal symptoms. Addition of Passiflora to the standard treatment clonidine gave significantly better results than clonidine alone (23). Finally, Passiflora extract was also clinically tested in both groups	

	of children and adolescents with hyperactivity syndrome (ADHA). In a reference-controlled, randomized double-blind trial no difference could be found between *Passiflora* and methylphenidate, except for a better tolerability of Passiflora (5). The patients of this study were children in the range of 6-13 years old. A Japanese double-blind trial was designed to provide clinical evidence for efficacy of Passiflora extract against neurotic symptoms. In this 4-week benzodiazepine-controlled parallel-group trial, positive action of Passiflora was found on the anxiety, tenseness and irritation paramaters, with better tolerability (less adverse effects) for the herbal group (24). In a pilot study in 10 patients with generalized anxiety disorder, Passiflora extract was tested against various benzodiazepines. Whereas the sedative component of the overall effect was shown to be only minor, a good anxiolytic effect without muscle relaxation was found (25). The practical applicability and safety of application was confirmed in a post-marketing surveillance study with a combination product (Passiflora herb, valerian roots and hop strobiles) (26).	
5.2. Pharmacokinetic properties	Well-established use **No pharmacokinetic data is available.** Background: Despite decades of phytochemical research the constituents responsible for the effect of Passiflora herb against nervous tension, restlessness and irritability are still not identified. Consequently, pharmacokinetic studies have not been performed.	No indication for well-established use is accepted. No changes.

5.3. Pre-clinical safety data	Well-established use **Acute toxicity, repeat-dose toxicity, genotoxicity and teratogenicity were tested and excluded in rats.** Traditional use Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended~~, unless necessary for the safe use of the product~~. ~~Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.~~ Background: Directive 2001/83/EC does not require pre-clinical safety data. Safety of traditionally applied products is sufficiently characterized by long-standing experience. Thus, the restriction "unless necessary for the safe use of the product" is misleading in the case of *Passiflora*, as there is no evidence of unsafe use. No acute toxicity was observed after intraperitoneal administration of Passiflora extracts to mice in doses up to 900 mg/kg body weight (9;27). No signs of toxicity were observed on repeat dose-administration to rats for 21 days with doses equivalent to 5 g/kg body weight (10). No genotoxic effects were detected in vitro with a fluid extract from Passiflora (28). No teratogenicity was observed in two studies in rats (cited in (4)).	No indication for well-established use is accepted. No changes. Traditional use: The proposal to omit the text "unless required for the safe use of the product" is agreed. Sufficient data on reproductive toxicity, genotoxicity and carcinogenicity are missing, and the text should remain "as is". No changes.