EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 March 2018
EMA/HMPC/606741/2018
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Vitex agnus-castus* L., fructus

Final

Based on Article 10a of Directive 2001/83/EC (well-established use)

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Vitex agnus-castus* L., fructus
Herbal preparation(s)	**Well-established use**: Dry extract (6-12:1), extraction solvent: ethanol 60% (m/m) **Traditional use**: Powdered herbal substance Tincture (1:5), extraction solvent: ethanol 68-70% V/V Dry extract (7-13:1), extraction solvent: ethanol 60% m/m Dry extract (10-18.5:1), extraction solvent: ethanol 50-52% m/m
Pharmaceutical form(s)	**Well-established use**: Herbal preparation in solid dosage form for oral use. **Traditional use**: Herbal preparation in solid or liquid dosage forms for oral use
Rapporteur(s)	Susanne Flemisch, Jacqueline Wiesner (first version)

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Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Vitex agnus-castus* L., fructus
Peer-reviewer	Olga María Palomino

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1. Introduction

The assessment report at hand refers to the use of the mellowed and dried fruits of *Vitex agnus-castus* in phytomedicine and gives a review of scientific data*. Vitex agnus-castus* (VAC) is a shrub or small tree native to Mediterranean Europe, central Asia and parts of India. It belongs to the Lamiaceae (former Verbenaceae) plant family (Blaschek *et al*. 2016).

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

- Herbal substance(s)

There is a monograph with the title 'Agnus Castus Fruit (Agni casti fructus)' published in the European Pharmacopeia (01/2015: 2147).

Definition according to Ph.Eur.:

Whole, ripe, dried fruit of *Vitex agnus-castus* L.

Content: minimum 0.08% of casticin (C19H18O8; Mr 374.3) (dried drug)

- Herbal preparation(s)

The herbal preparations appear in liquid forms as an ethanol tincture, in solid forms as dry extracts using solvents with different concentrations of ethanol (50-70% V/V) and different DER, or as powdered herbal substance.

Another monograph is available for 'Agnus Castus Fruit Dry Extract (Agni casti fructus extractum siccum) also published in the European Pharmacopeia (01/2015: 2309).

Definition according to Ph.Eur.:

Dry extract produced from Agnus castus fruit (2147).

Content: minimum 0.10% of casticin (C19H18O8; Mr 374.3) (dried extract).

The extract is produced from the herbal drug by a suitable procedure using ethanol (40-80% V/V).

Herbal preparations used as active substances should be declared conform to the guideline EMEA/ HMPC/CHMP/CVMP/287539/05 Rev. 1.

- 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. Search and assessment methodology

This assessment report revised the first HMPC assessment report on *Vitex agnus-castus* L., fructus (EMA/HMPC/144003/2009) and is based on the literature on VAC available at the Federal Institute for Drugs and Medicinal Devices in Germany and the publications provided by the AESGP (Association of the European Self-Medication Industry) in response to the EMA HMPC call for data on 14 October 2015. Additionally a literature search in the DIMDI database was performed in July 2017 using the following terms: VAC included in the title, humans, clinical, preclinical, safety, year of publication between 2010 and 2017, language in English or German. A separate literature research was performed for the therapeutic use of VAC in the indication premenstrual syndrome in the database XMEDALL (terms used: Premenstrual syndrome, VAC).

Only the articles considered as relevant for the establishment of this assessment report on a well-established and traditional use of VAC were included in the reference list.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

The following data are derived from the request for information concerning the marketed products of VAC preparations (dated 1 July 2008) and the request for updated market overviews for VAC preparations (September 2017).

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form Strength (where relevant) Posology Duration of use**	**Regulatory Status**
Tincture (1:5), ethanol 68% V/V	Irregular menstruation, premenstrual syndrome, mastodynia	Oral liquid, 9 g tincture/100 g oral liquid, 1 x daily 40 drops	WEU (1968, AT)
Tincture (1:5), ethanol 58% m/m	Irregular menstruation, premenstrual syndrome, mastodynia	Oral liquid, 100 g tincture/100 g oral liquid, 1 x daily 40 drops	WEU (1986, formerly 1968,-2008, AT)
Dry extract, DER 8.3-12.5:1, ethanol 58% m/m	Irregular menstruation, premenstrual syndrome, mastodynia	Film-coated tablet, 4.0 mg dry extract per tablet, 1 tablet per day	WEU (1999, AT)
Dry extract, DER 7-13:1, ethanol 60% m/m	Irregular menstruation, premenstrual	Film-coated tablet, 4.0 mg dry extract per tablet, 1 tablet per day	WEU (2007, AT)

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status
	syndrome, mastodynia		
Dry extract, DER 6-12:1, ethanol 60% m/m	Premenstrual syndrome	Film-coated tablet, 20 mg dry extract per tablet, 1 tablet per day	WEU (2011, AT)
Dry extract, DER 6-12:1, ethanol 60% m/m	Premenstrual syndrome	Film-coated tablet, 20 mg dry extract per tablet, 1 tablet per day, up to 6 months	WEU (2013, BE)
Dry extract, DER 7-13:1, ethanol 60% m/m	Relief of minor symptoms in the days before menstruation	Film-coated tablet, 4 mg dry extract per tablet, 1 tablet per day, up to 6 months	TU (2015, BE)
Dry extract, DER 6-12:1, ethanol 60% m/m	Premenstrual syndrome	Film-coated tablet, 20 mg dry extract per tablet, 1 tablet per day	WEU (2004, BG)
Dry extract, DER 7-11:1, ethanol 70% V/V	Premenstrual syndrome	Film-coated tablet, 4 mg dry extract per tablet, 1 tablet per day	WEU (1997, CZ)
Dry extract, DER 7-13:1, ethanol 60% m/m	for the relief of minor symptoms in the days before menstruation (premenstrual syndrome)	Film coated tablet, 4 mg dry extract per tablet, 1 tablet per day	TU (2015, CZ)
Dry extract, DER 7-11:1, ethanol 62% m/m	Premenstrual syndrome	Film-coated tablet, 10 mg dry extract per tablet, 1 tablet per day, 3 months	WEU (2017,DCP, CZ=CMS)
Tincture (1:5), ethanol 68% V/V	Irregular menstruation, premenstrual syndrome, mastodynia	Oral liquid, 9 g tincture/100 g oral liquid, 1xdaily 40 drops (=1.83 mg finished product)	WEU (1976, DE)
Dry extract, DER 7-13:1, ethanol 60% m/m	Irregular menstruation, premenstrual syndrome, mastodynia	Capsule, hard, 4 mg dry extract per capsule, 1 capsule per day, at least 3 months	WEU (1976, DE)
Tincture (1:5), ethanol 70% V/V	Irregular menstruation, premenstrual syndrome, mastodynia	Oral liquid, 18 g tincture/100 g (=108.7 ml) oral liquid, 1xdaily 30 drops (=1ml), 3 months	WEU (1976, DE)
Liquid extract preparation,	Irregular menstruation,	Oral liquid, 100 g medicinal product/100 g	WEU

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status
DER 7.9-8.8:1, ethanol 60% V/V	premenstrual syndrome, mastodynia	liquid extract preparation, 2xdaily 10 drops (=0.5 ml), several months	(1992, DE)
Tincture (1:5), ethanol 70% V/V	Irregular menstruation, premenstrual syndrome, mastodynia	Oral liquid, 20 g tincture/100 g (=109 ml) oral liquid, 1xdaily 35-45 drops (40 drops =1 ml), 3 months	WEU (1993, DE)
Dry extract, DER 7-11:1, ethanol 70% V/V	Irregular menstruation, premenstrual syndrome, mastodynia	Oral liquid, 0.24 g dry extract/ 100 g oral liquid, 1xdaily 40 drops (=1.7 ml=1.67 g), several months	WEU (1995, DE)
Dry extract, DER 7-11:1, ethanol 70% V/V	Irregular menstruation, premenstrual syndrome, mastodynia	Film-coated tablet, 4 mg dry extract per tablet, 1 tablet per day, several months	WEU (2 authorised medicinal products since 1995, DE)
Dry extract, DER 7-13:1, ethanol 60% m/m	Irregular menstruation, premenstrual syndrome, mastodynia	Capsule, hard, 4 mg dry extract per capsule, 1 capsule per day, at least 3 months	WEU (1998, DE)
Dry extract, DER 7-13:1, ethanol 60% m/m	Irregular menstruation, premenstrual syndrome, mastodynia	Capsule, hard, 4 mg dry extract per capsule, 1 capsule per day, at least 3 months	WEU (7 authorised medicinal products since 1999, DE)
Dry extract, DER 7-13:1, ethanol 60% m/m	Irregular menstruation, premenstrual syndrome, mastodynia	Film-coated tablet, 4 mg dry extract per tablet, 1 tablet per day, at least 3 months	WEU (7 authorised medicinal products since 1999, DE)
Dry extract, DER 7-11:1, ethanol 72% m/m	Premenstrual syndrome	Film-coated tablet, 10 mg dry extract per tablet, 2 tablets per day, 3 months	WEU (2017, DCP, DE=RMS)
Dry extract, DER 6-12:1, ethanol 60% m/m	Premenstrual syndrome	Film-coated tablet, 20 mg dry extract per tablet, 1 tablet per day	WEU (2005, DK)
Dry extract, DER 8.3-12.5:1, ethanol 70% V/V	Premenstrual syndrome	Film-coated tablet, 4 mg dry extract per tablet, 1 tablet per day	TU (1999, EE)

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status
Dry extract, DER 6-12:1, ethanol 60% m/m	Premenstrual syndrome	Film-coated tablet, 20 mg dry extract per tablet, 1 tablet per day	TU (2004, EE)
Dry extract, DER 8.3-12.5:1, ethanol 70% V/V	Premenstrual syndrome	Oral liquid, 0.240 g dry extract/ 100 g oral solution, 1xdaily 40 drops	TU (1999, EE)
Dry extract, DER 6-12:1, ethanol 60% m/m	Premenstrual syndrome	Film-coated tablet, 20 mg dry extract per tablet, 1 tablet per day	TU (2005, EE)
Dry extract, DER 7-13:1, ethanol 60% V/V	Relief of premenstrual breast tension	Capsule, 1 capsule per day	WEU (2003, ES)
Dry extract, DER 4-5.6:1, ethanol 70% V/V	Relief of premenstrual breast tension	Capsule, 1 capsule per day	WEU (2006, ES)
Dry extract, DER 5-7:1, ethanol 70% V/V	Relief of premenstrual breast tension	Capsule, 1 capsule per day	WEU (2006, ES)
Dry extract, DER 4:1, ethanol 30% V/V	Traditionally used in painful periods	Capsule, hard, 10 mg dry extract per capsule, 1 to 2 capsules per day	TU (2005, FR)
Dry extract, DER 8.3-12.5:1, ethanol 70% V/V	Irregular menstruation, premenstrual syndrome, mastodynia	Oral liquid, 1.92-2.88 mg dry extract/1 g solution, 1xdaily 40 drops	WEU (2002, HU)
Dry extract, DER 8.3-12.5:1, ethanol 70% V/V	Irregular menstruation, premenstrual syndrome, mastodynia	Film-coated tablet, 3.2-4.8 mg dry extract per tablet, 1 tablet per day	WEU (2002, HU)
Dry extract, DER 7-13:1, ethanol 60% m/m	Premenstrual syndrome	Capsule, hard, 4 mg dry extract per capsule, 1 capsule per day	WEU (2002-2016, HU)
Tincture (1:5), ethanol 70% V/V	Premenstrual syndrome	Oral liquid, 20 g tincture/100 g (=109 ml) oral liquid, 1xdaily 35-45 drops (40 drops =1 ml)	WEU (2002-2004, HU)
Dry extract,	Premenstrual	Film-coated tablet,	WEU

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status
DER 6-12:1, ethanol 60% m/m	syndrome	20 mg dry extract per tablet, 1 tablet per day	(2001, HU)
Dry extract, DER 6-8:1, ethanol 75% V/V	Relief of minor symptoms of premenstrual syndrome	Film-coated tablet, 3.9 mg dry extract per tablet (equivalent to 23.4-31.2 mg herbal substance), 1 tablet per day, 3 months	TU (IE)
Tincture (1:10), ethanol 69.5% V/V	Relief of minor symptoms of premenstrual syndrome	Oral liquid, 407-542 mg tincture/15-20 drops, 2xdaily 15-20 drops, 3 months	TU (IE)
Dry extract, DER 7-11:1, ethanol 70% V/V	Irregular menstruation, premenstrual syndrome, mastodynia	Film-coated tablet, 4 mg dry extract per tablet, 1 tablet per day	WEU (1999, LV)
Dry extract, DER 7-13:1, ethanol 60% m/m	Irregular menstruation, premenstrual syndrome, mastodynia	Capsule, hard, 4 mg dry extract per capsule, 1 capsule per day	WEU (2004, PL)
Dry extract, DER 6:1, ethanol 60% V/V	Add-on therapy in premenstrual syndrome	Film-coated tablet, 40 mg dry extract (native extract : colloidal silica dioxide = 1:1) standardized to 0.3 % casticin per tablet, 1 tablet per day	WEU (RO)
Tincture (1:5), ethanol 58% V/V	A traditional herbal remedy to help restore normal fluid balance and relieve occasional bloatedness in women	Oral liquid, 0.411 g tincture/5 ml, 1xdaily 40 drops	WEU (UK)
Dry extract, DER 7-13:1, ethanol 60% m/m	A traditional herbal medicinal product that has been used to help relieve the symptoms associated with premenstrual syndrome, based on traditional use only	Film-coated tablet, 4 mg dry extract per tablet, 1 tablet per day	TU (UK)
Powdered herbal substance	A traditional herbal medicinal product that has been used to help	Tablet or capsule, 300-2000 mg per day	TU (1979, UK)

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status
	relieve the symptoms associated with premenstrual syndrome, based on traditional use only		

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

In the market overviews the posology of tinctures is related to the finished products. In order to establish a posology for the herbal preparations the following table is included.

Table 2: Posology of tinctures

Herbal preparation	Composition of medicinal product	Daily dose of medicinal product	Daily dose of herbal preparation
Tincture (1:5), ethanol 68% V/V, AT 1968, DE 1976	100 g oral liquid contain 9 g tincture	1xdaily 40 drops (≈1.83 g)	165 mg
Tincture (1:5), ethanol 70% V/V, DE 1976	100 g (=108.7 ml) oral liquid contain 18 g tincture	1xdaily 30 drops (=1 ml), 1 ml≈920 mg	165 mg
Tincture (1:5), ethanol 70% V/V, DE 1993 (not included in the monograph)	100 g (=109 ml) oral liquid contain 20 g tincture	1xdaily 35-45 drops (40 drops=1 ml), 1 ml≈917 mg	183 mg
Tincture (1:5), ethanol 58% m/m, AT 1986-2008 (not included in the monograph)	100 g oral liquid contain 100 g tincture	1xdaily 40 drops, 40 drops = 2 g	2000 mg

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

Not applicable

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

Not applicable

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

Not applicable

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

The medicinal plant was already mentioned by Dioscurides, a famous pharmacologist of the antiquity. “Agnós” as well as “castus” mean “chaste”. The plants, respectively its seeds, ingested as a potion, were believed to reduce libido (Schulz & Hänsel 1999). The fruit (agnus castus fruit) has been used for centuries for a variety of gynaecological complaints such as premenstrual syndrome (PMS).

The German Commission E had established a monograph (Blumenthal *et al*. 1998). In the monograph the following indications are mentioned: Irregular menstruation, premenstrual syndrome, mastodynia. This monograph refers to preparations with liquid or dried extracts with ethanol as extraction solvent (50-70% V/V) and in a daily dosage of 30 to 40 mg herbal substance.

Table 3: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form Strength (where relevant) Posology Duration of use**	**Reference**
Agni casti fructus, ethanolic liquid or dry extracts, 50-70% V/V	Irregular menstruation, premenstrual syndrome, mastodynia	Herbal preparations for oral use, daily dose corresponding to 30-40 mg herbal substance	Monograph of the Commission E (Blumenthal *et al.* 1998)

2.3. Overall conclusions on medicinal use

Different medicinal products have been marketed in Europe under well-established use or under traditional use. According to the market overview there are herbal preparations in Germany and Austria for a period of over 30 years on the market. The following herbal preparations (Table 4) were included in the monograph.

For an extract specified as follows: Dry extract (DER 6-12:1), extraction solvent 60% ethanol m/m, with the posology 20 mg per day the well-established use indication “Premenstrual syndrome” was accepted.

For the traditional use, the HMPC majority agreed on following indication: “Traditional herbal medicinal product for the relief of minor symptoms in the days before menstruation (premenstrual syndrome)” (for assessment of the clinical data see chapter 4).

Table 4: Overview of evidence on period of medicinal use

Herbal preparation **Pharmaceutical form**	**Indication**	**Strength** **Posology**	**Period of medicinal use**
Dry extract (DER 6-12:1), extraction solvent ethanol 60% m/m Herbal preparation in solid dosage form for oral use	Treatment of premenstrual syndrome	Once daily 20 mg dry extract	Since 2001
Powdered herbal substance Herbal preparation in solid dosage form for oral use	Traditional herbal medicinal product that has been used to help relieve the symptoms associated with PMS, based on traditional use only	300-2000 mg powdered herbal substance (Because of safety concerns the dosage is limited to two times 400 mg daily in the monograph. See also 4.4.)	Since 1979
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 68% V/V Herbal preparation in liquid dosage form for oral use	Irregular menstruation, premenstrual syndrome, mastodynia	Once daily 165 mg tincture	Since 1968
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 70% V/V Herbal preparation in liquid dosage form for oral use	PMS, mastodynia	Once daily 165 mg tincture	Since 1976
Dry extract (DER 7-13:1), extraction solvent ethanol 60% m/m Herbal preparation in solid dosage form for oral use	Irregular menstruation, PMS, mastodynia	Once daily 4 mg dry extract	Since 1976
Dry extract (DER 15-18.5:1), extraction solvent ethanol 50% m/m Herbal preparation in solid dosage form for oral use	Irregular menstruation, PMS, mastodynia	Once daily 2.4 mg dry extract	Since 1976

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Dry extract (DER 10-16:1), extraction solvent ethanol 60% V/V = 52% m/m Herbal preparation in solid dosage form for oral use	Irregular menstruation, PMS, mastodynia	Once daily 3 mg dry extract	Since 1976

The monograph presented to the HMPC in November 2010 contained a tincture with extraction solvent ethanol 58-60% m/m which was later-by mistake-published as 58-60% V/V. 60% m/m correspond to app. 68% V/V. Therefore, tincture (1:5) with extraction solvent ethanol 68% V/V (AT 1968, DE 1976) is included in the monograph.

The tincture (1:5) with extraction solvent ethanol 58% m/m (AT 1986-2008) does not fulfil the criteria for traditional use.

3. Non-Clinical Data

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

The mode of action of agnus castus fruit is not yet completely understood. Non-clinical studies suggest that agnus castus fruit acts on the hypothalamus and pituitary gland, interacting with the dopaminergic receptors in the anterior pituitary gland and leading to a reduction of prolactin secretion *in vitro* and *in vivo* (Jarry *et al.* 1994, Sliutz *et al*. 1993, Wuttke *et al.* 1995).

3.1.1. Primary pharmacodynamics

In vitro tests

Dopamine receptor activity and prolactin

Dopaminergic receptor binding activity (D_2-receptor) was evaluated in the membrane fraction of the stratium of calf brains using ^{3}H-spiroperidole as positive ligand. Investigations were done with an ethanol extract (60% EtOH) of fruits of *Vitex agnus-castus* as spissum or siccum extract. The ethanol extract inhibited the binding of ^{3}H-spiroperidole with an IC_{50} of 40-70 µg/ml. After separation the ethanol extract in hydro- and lipophilic fractions the inhibitory activity was found in the latter. The diterpens rotundifurane and 6β, 7β-diacetoxy-13-hydroxy-labda-8,14-dien showed inhibitory activity (IC_{50}=45 and 79 µg/ml, respectively) while aucubin or flavonoids as isoorientin and castricin had no effects on the binding of ^{3}H-spiroperidole to the receptor. In a second assay the release of acetylcholine was inhibited by the extract. This was interpreted as dopamin-agonistic effect of the ethanol extract. Furthermore it was postulated that the extract has also cholinergic activity (Berger *et al*. 1999, Meier *et al*. 2000). Similar results were found for the aqueous fraction of a methanol extract (Meier *et al*. 2000).

Using rat pituitary cells it could be demonstrated that an ethanol extract of *Vitex agnus-castus* contains constituents which inhibit prolactin release via interaction with D_2-subtype of the dopamine receptor expressed in lactotrope cells. Bioassay-guided fractionation yielded a group of compounds with the skeleton of bicyclic diterpenes of the clerodane typ which exerted this activity (Wuttke *et al*. 2003, Christoffel *et al*. 2005, Jarry *et al*. 2006).

The ethanol extract did not significantly inhibit the binding, neither to the histamine H_1, benzodiazepine and OFQ receptor, nor the binding site of the serotonin (5-HT) transporter (Meier *et al*. 2000).

Opioid receptor activity

In binding studies using ^{3}H-naloxone as ligand to the μ- and κ-opiate receptor and the ethanol extract of *Vitex agnus-castus* as inhibitor, IC_{50}-values of ~30 and 20 μg/ml, respectively, were found. The binding of δ-receptor (using ^{3}H-naltrinole as ligand) was only slightly influenced (IC_{50} = 190 μg/ml). Especially the lipophilic fraction seems to be responsible for the activity on the μ- and κ-opiate receptor while the aqueous soluble fraction revealed a strong activity to the δ-receptor (Brugisser *et al*. 1999, Meier *et al*. 2000).

Fruits and defatted fruits of *Vitex agnus-castus* were extracted with methanol. Both extracts showed significant affinities to the μ-opiate receptor. It could be shown that the affinity of the extract from defatted fruits was higher (Webster *et al*. 2006). Normal human melanocytes (R6-NHEM-2) were incubated with different concentrations of an extract of *Vitex agnus-castus* (0.06, 0.13 and 0.25%) for 10 days. Melanin production of melanocytes was increased by 0, 12 and 47%, respectively. Because β-endorphin is linked to the regulation of pigmentation this was seen as β-endorphin-like activity (Schmid *et al*. 2006).

Oestrogen receptors

In a receptor binding assay performed with recombinant human oestrogen receptor, an ethanol extract of *Vitex agnus-castus* showed a preferential binding to oestrogen receptor β over oestrogen receptor α (Christoffel *et al*. 2002). The oestrogenic compounds of this extract were identified as the flavonoids penduletin and apigenin (Jarry *et al*. 2006).

A methanol extract (not further characterised) showed significant competitive binding to oestrogen receptor α (IC_{50} = 46 μg/ml) and oestrogen receptor β (IC_{50} = 64 μg/ml). Furthermore the extract stimulated the expression of the progesterone receptor but oestrogen-dependent alkaline phosphatase activity was induced (Liu *et al*. 2001). Bioassay-guided isolation resulted in the isolation of linoleic acid as possible oestrogenic component of the extract (Liu *et al*. 2004).

Oerter Klein *et al*. (2003) could not find any oestrogen bioactivity using an oestrogen receptor binding assay in a genetically engineered yeast system with a methanol extract from *Vitex agnus-castus*.

In vivo tests

The influence of *Vitex agnus-castus* on β-endorphin content in the blood of female rats was examined by Samochowiec *et al*. (1998). The content on β-endorphin was measured in blood on day 1. After this the rats received on three consecutive days orally an extract of *Vitex agnus-castus* (20, 30 and 60 mg/kg, respectively). On day 4 the content of β-endorphin was measured again. In the lowest dosage group, the content of β-endorphin was increased by ~50%; while in the two other groups the content was increased by~100%. This was seen as an explanation for the analgesic properties of the extract.

3.1.2. Secondary pharmacodynamics

Anti-inflammatory activity

Anti-inflammatory effects were reported for several agnus castus fruit components. Choudhary *et al.* (2009) could demonstrate lipoxygenase enzyme-inhibiting activity of casticin *in vitro*. In an experimental *in vivo* inflammation model the flavonoid vitexin inhibited pro-inflammatory cytokine production and proved to be an inhibitor of inflammation-induced pain (Borghi *et al*. 2013).

Anti-proliferative activity

Breast carcinoma (MCF-7), gastric signet ring (KATO III), cervical carcinoma (SKG-3a), colon carcinoma (COLO 201), ovarian cancer (SKOV-3) and small cell lung carcinoma (Lu-134-A-H) cell lines as well as fetal fibroblasts (HE-21) were used for tests on cytotoxicity and apoptosis inducing effects of agnus castus fruit (ethanol extract, not further described). Test on cytotoxicity were performed in logarithmic growth-phase cells and in stationary-phase cells. Final concentrations of the extract were between 1 and 100 µg/ml. The extract was not cytotoxic against HE-21 cells. For all the other cells, the cytotoxic effect was depending on the cell growth rate. While during the logarithmic growth-phase a concentration depending effect was seen, this did not occur in the stationary-phase cells. In this phase even cytotoxicity was not as significant as in the logarithmic growth-phase. For SKOV-3, KATO III, COLO 201 and Lu-134-A-H cells an apoptosis inducing effect of the extract could be shown (Ohyama *et al*. 2003). Using the KATO III cell line for further investigations, it was demonstrated that intracellular oxidative stress and mitochondrial membrane damage are responsible for the Vitex-induced apoptosis (Ohyama *et al*. 2005). Weisskopf *et al.* (2005) examined an ethanol extract (60% EtOH) on anti-proliferative effects on different human prostate epithelial cell lines. Proliferation of these cells was inhibited and apoptosis induced in a concentration dependent manner with IC50 values below 10 µg/ml.

3.1.3. Safety pharmacology

No *in vivo* safety pharmacological studies are available with agnus castus fruit preparations. The available toxicological studies do not yield any data that would require further safety pharmacology evaluation regarding the well-established and traditional use. No safety concerns are documented for the usage of agnus castus fruit with respect to safety for e.g. the central nervous system, the respiratory tract, or the cardiovascular system.

3.1.4. Pharmacodynamic interactions

No drug interactions with agnus castus fruit have been reported. Because of the possible dopaminergic and oestrogenic effects of agnus castus fruit however, interactions with dopamine agonists, dopamine antagonists, oestrogens and anti-oestrogens cannot be completely excluded.

3.1.5. Conclusions

The mode of action of agnus castus fruit is not completely elucidated yet. Inhibitory influences on the prolactin release and dopaminergic (dopamine-agonistic) effects were seen by different working groups.

There are contradictory results concerning binding to oestrogen receptor in general and the preferential binding to β-or α-receptors. Furthermore there are some references concerning β-endorphin-like activity (possibly via µ-opiate receptor binding).

Because of the possible dopaminergic and oestrogenic effects of agnus castus fruit, interactions with dopamine agonists, dopamine antagonists, oestrogens and anti-oestrogens cannot be completely excluded.

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

There is no specific information on pharmacokinetics of agnus castus fruit.

Ho *et al*. (2011) studied the potential of a hydroethanolic extract of *Vitex agnus-castus* to inhibit *in vitro* the major human drug metabolizing enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP1A1. The VAC extract did not affect CYP1A1 and CYP2C9 at concentrations up to 3.3 µg/ml and 6 µg/ml, respectively. The CYPs 1A2, 2C19, 2D6 and 3A4 were inhibited with IC50 values of 3.5 µg/ml (CYP1A2), 0.22 µg/ml (CYP2C19), 2.9 µg/ml (CYP2D6) and 0.3 µg/ml (CYP3A4).

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

3.3.1. Single dose toxicity

Studies on single dose toxicity have not been published.

3.3.2. Repeat dose toxicity

Toxicological data on *Vitex agnus-castus* (VAC) extracts, including repeat-dose toxicity studies, were received by a competent authority. In two repeat-dose toxicity studies (4 weeks, 26 weeks), signs of liver toxicity have been observed in rats. In the 26 weeks study, effects were observed at all doses tested. Since the product is indicated for a treatment of at least three months and not limited in time, the data have to be taken into consideration.

The HMPC considered these toxicological data as a signal. However, because there have been no corresponding observations from clinical studies or case reports, it was decided not to introduce a labelling into the monograph. Since no recently published data are available, the monograph remains unchanged in this regard.

3.3.3. Genotoxicity

Tests on genotoxicity have not been performed.

3.3.4. Carcinogenicity

No studies on the carcinogenic potential of VAC are available.

3.3.5. Reproductive and developmental toxicity

In adult male mice, an ethanol extract of *Vitex agnus-castus* (80% EtOH) was injected intraperitoneally in concentrations of 65, 165, 265, 365 and 465 m/kg body weight for 30 days. Luteinizing hormone (LH) and testosterone were measured in the serum after 30 days. Haloperidol (dopamine receptor antagonist) and bromocriptine (dopamine receptor agonist) were used to compare the effects. The extract decreased in concentrations of 165, 265 and 365 mg/kg body weight LH and testosterone levels of male mice significantly comparing to the control group. The same effects were seen with bromocriptine while haloperidol increased the levels of LH and testosterone. Co-administration of the extract with haloperidol and of the extract with bromocriptine decreased LH and testosterone levels (Nasri *et al*. 2007).

Pregnant female Wistar rats (selected on the base of the formerly stable oestrus cycle) were treated after giving natural birth from day 5 of lactation until day 8 *postpartum* with 2x5 ml/kg of a preparation of *Vitex agnus-castus* (1:20 diluted mother tincture). Control groups received NaCl-solution (0.9%) or bromocriptine (5 mg/kg) once daily. The animals were monitored until day 14 *postpartum*. Dams and pups were weighted on a daily base. The number of pups with and without noticeable milk in the stomach and mortality of pups were recorded. The body weight of the dams did

not change during observational period. After the second day of treatment, the number of pups without noticeable milk in the stomach increased in the Vitex and the bromocriptine group. The highest number of pups without noticeable milk in the stomach was seen on day 9 and 10 after birth (first and second day after treatment). Mortality increased in these two groups to the same extent. After treatment, the surviving pups of the Vitex group did show an accelerated increase of body weight. The effects of the Vitex group were seen as lactation inhibiting effect (decrease of prolactin) comparable to effect of the dopaminergic substance bromocriptine (Winterhoff *et al*. 1991).

Powdered seeds of *Vitex agnus-castus* provoked a slight reduction of the mean number of foetuses in uterine horns when given to female rats with established pregnancy in concentrations of 1 or 2 mg/kg from D1 to D10 of pregnancy as compared to the control group. Furthermore the water extract of this seeds inhibited the spontaneous uterine activity of the isolated rat uterus. Partial inhibition was seen at doses of 2.4 mg/ml while complete inhibition was noted at 8 mg/ml (Lal *et al*. 1985).

3.3.6. Local tolerance

No studies are available.

3.3.7. Other special studies

Not applicable

3.3.8. Conclusions

There are only limited preclinical safety data for agnus castus fruit or preparations thereof. The data from reproductive studies suggest that extracts of the fruits might influence lactation. Data indicated a signal of hepatotoxicity in animal models. In two repeat-dose toxicity studies in rats (4 weeks, 26 weeks) signs of liver toxicity have been observed.

Tests on mutagenicity and carcinogenicity have not been performed. Adequate tests on reproductive toxicity have not been performed.

3.4. Overall conclusions on non-clinical data

Overall conclusions on pharmacology

Most pharmacological data were raised using ethanol or methanol extracts. Inhibitory influence on the prolactin release and dopaminergic (dopamine-agonistic) effects was seen by different working groups.

From the data seen there are opposite results concerning binding to oestrogen receptor (more preferential binding to β-or α-receptor) or not. Furthermore there are some references concerning β-endorphin-like activity (via μ-opiate receptor binding).

Overall conclusions on pharmacokinetics

There is no specific information on pharmacokinetics of VAC.

An *in vitro* study by Ho *et al.* (2011) has identified the potential for some herbal preparations, including VAC, to inhibit human drug metabolizing enzymes. It is, however, doubtful, whether or not this potential could eventually translate into clinically significant herb drug interactions.

Overall conclusions on toxicology

There are only limited preclinical safety data on agnus castus fruit or preparations thereof.

The data from reproductive studies suggest that extracts of the fruits influence lactation.

In two repeat-dose toxicity studies in rats (4 weeks, 26 weeks) signs of liver toxicity have been observed.

Due to the lack of data on mutagenicity a list entry for agnus castus fruit cannot be recommended.

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

The mode of action of agnus castus fruit is not completely understood, but it is assumed that it has dopaminergic effects resulting in changes of prolactin secretion.

Prolactin is a hormone of the adenohypophysis. Foremost it stimulates growth of the mammarian gland during pregnancy and is responsible for lactation. The release of prolactin is regulated by the hypothalamus. Dopamine inhibits the release. Amongst others in women an increased prolactin level can cause amenorrhoea and infertility. Besides it is discussed as a cause of the premenstrual syndrome.

There are several studies dealing with the influence of VAC on prolactin. Non-clinical studies are available, describing the effects of extracts of fruits of VAC on prolactin secretion and dopaminergic effects *in vitro* and *in vivo*. Inhibitory influence on the prolactin release and dopaminergic (dopamine-agonistic) effects were seen by different working groups (see section 3.1.). In human pharmacology, however, a reduction of elevated prolactin levels by VAC has not yet been conclusively proven. The prolactin inhibiting effect seems to be dependent on the dose administered and the initial level of prolactin concentration.

An open, placebo-controlled cross-over study conducted according to GCP assessed high daily doses of the VAC extract BP 1095E1 (120, 240, 480 mg) given for 14 days to 20 healthy male subjects with a basal prolactin level$\geqslant$80 µIU/ml. During each study phase the 24-hour prolactin secretion profile was measured from the penultimate to the final day and the amount of prolactin release was monitored an hour after TRH stimulation on the last day. A significant increase in the 24-hour profile was registered with the lowest dose in comparison to placebo; a decrease of prolactin secretion was seen with higher doses. During this study, 18 subjects experienced 26 adverse drug reactions (ADRs) during active treatment. Among them, vegetative disorders such as dry mouth, disturbed perception, slight confusion, and slight activated states as well as itching in the roof of the mouth and in the nose were experienced. These are reactions to be expected by dopaminergic compounds and indirectly confirm the dopaminergic effects of VAC (Merz *et al*. 1995, 1996). The authors interpret the reduction in prolactin release stimulated by TRH for the highest dose as a possible explanation for the therapeutic effects of medications containing VAC. From their point of view it can be assumed that the extract contains agonistic and antagonistic components or qualities with possibly different sites of action. According to the authors, the antagonistic effects are predominant at the lower dose range. With higher doses, the agonistic effects strengthen the inhibitive effect of dopamine.

In her thesis, Vogel (2001) reports on a randomised, double-blind, reference-(bromocriptine 2.5 mg) and placebo-controlled cross-over-study, in which the influence of four different doses (1.5, 15, 30, 60 mg) of an agnus castus extract on the nocturnal prolactin secretion in six healthy male probands was examined. Besides the influence on LH, FSH, testosterone and oestradiol was analysed. The tested agnus castus extract is described as a dry extract of the dried fruits of *Vitex agnus-castus* L.

(extraction solvent: ethanol 60% (m/m), DER: 33:1). The preparation was composed of 70% native extract and 30% glucose syrup. After the one-time intake of bromocriptine there was a significant decrease of prolactin in all probands. The one-time intake of all doses of agnus castus fruit showed no effect on the nocturnal secretion of prolactin, LH, testosterone or oestradiol. The missing decrease of prolactin after the intake of the agnus castus fruit extract is in contrast to results of other trials. Vogel discusses possible reasons for this: low number of probands, physiological counter regulation, too few ingredients with dopaminergic effect in the extract, poor bioavailability, no steady state.

Dericks-Tan *et al.* (2003) report on the measurement of melatonin secretion in 20 healthy male subjects after intake of placebo or various doses of an extract of agnus castus fruit (70% ethanol extract, 120-480 mg/day) for 14 days. A significant dose-dependent increase of the area under the melatonin secretion curve (AUC) is described. The pattern of circadian rhythm of melatonin secretion was not influenced. According to the authors it remains to be elucidated whether the increase of melatonin secretion is suitable for treatment of sleep disorders.

Overall conclusions on pharmacodynamics

The mode of action is not known. Inhibitory influences on the prolactin release and dopaminergic (dopamine-agonistic) effects were seen in preclinical studies by different working groups. In human pharmacology, however, a reduction of elevated prolactin levels by agnus castus fruit has not yet been conclusively proven.

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

There are no studies concerning pharmacokinetics.

4.2. Clinical efficacy

There are several indications for which the use of preparations of agnus castus fruit is described: Premenstrual syndrome (PMS), abnormal oestrous cycle, mastodynia, acne, and others. In the German monograph of the Commission E (Blumenthal *et al.* 1998) the following indications are mentioned: Anomalies of the length of menstruation. Premenstrual disorders, mastodynia. The Commission E monograph refers to preparations with liquid or dried extracts with ethanol as extraction solvent (50-70% V/V) and in a daily dosage of 30 to 40 mg drug.

4.2.1. Dose response studies

Clinical studies have been performed with several VAC extracts and different posologies. The dose studied is usually 4 mg of different ethanolic extracts, corresponding to approximately 40 mg herbal substance daily, as recommended in the German monograph of the Commission E (1992) and in the ESCOP monograph (2003). One study (Schellenberg 2001) however, has been carried out with a daily dose of 20 mg VAC dry extract (DER 6-12:1), extraction solvent ethanol 60% m/m, equivalent to 180 mg herbal substance (see section 4.2.2.). This study was the scientific basis for the well-established use indication “Premenstrual syndrome” included in the European Union herbal monograph.

A dose-response study (Schellenberg *et al.* 2012) is also available to support this posology. The results of this dose-response, multicentre, randomised, double-blind, placebo controlled, parallel group trial in 162 women suffering from PMS according to the DSM III-R (Diagnostic and Statistical Manual of Mental Disorders, third edition, revised criteria) and randomised to three different dosages (8, 20, or 30 mg) of the VAC extract Ze 440 (DER 6-12:1, extraction solvent ethanol 60% m/m) or placebo were reported; it evaluated the changes of PMS symptoms over three menstrual cycles. This study revealed

that the VAC extract Ze 440 was effective in relieving symptoms of PMS when used at a dose of 20 mg once daily. A daily dose of 8 mg did not show an overall effectiveness, although the symptom breast fullness showed borderline improvement. The higher dose of 30 mg did not significantly decrease symptom severity compared to the 20 mg treatment providing a rationale for the usage of 20 mg.

There are no data for other herbal preparations available.

4.2.2. Clinical studies (case studies and clinical trials)

4.2.2.1. Premenstrual syndrome (PMS)

Premenstrual syndrome (PMS) is characterized by the cyclic occurrence of physical, behavioural, and psychological symptoms during the luteal phase of the menstrual cycle disappearing within a few days of the onset of menstruation (O'Brien *et al.* 2011). According to the ISPMD (International Society for Premenstrual Disorders) not a number of specific symptoms is required to be present, but a single symptom causing negative influence on the daily functioning and levels of distress suffices to meet the criteria for diagnosing PMS. Nevertheless, some symptoms are considered key or characteristic symptoms (Kadian and O'Brien 2012):

Table 5: Key or characteristic PMS symptoms (Kadian and O'Brien 2012)

Physical Symptoms	**Psychological Symptoms**
Breast tenderness	Angry outbursts
Abdominal bloating	Irritability
Headache	Anxiety
Swelling of extremities	Confusion
	Social withdrawal

Theories about the causes of PMS suggest increased sensitivity to hormonal imbalances such as hyperprolactinemia or fluctuations in the levels of circulating oestradiol and progesterone. Other hypotheses include neurotransmitters involvement, e.g. serotonin and g-aminobutyric acid (GABA). None of these hypotheses has been scientifically proven (Yonkers *et al*. 2008). One fact is clear however, that without ovarian activity there is no PMS, e.g. in prepubertal or menopausal females, after bilateral ovariectomy or treatment with gonadotropin-releasing hormone (GnRH) analogues. Recent guidelines such as the RCOG (Royal College of Obstetricians and Gynaecologists) Green-top Guideline No. 48 on the management of PMS (RCOG Green-top Guideline No. 48, 2016) advise a step-by-step approach to the treatment, starting with lifestyle and diet changes, the use of dietary supplements, and cognitive behavioural therapy. Pharmacologic treatment includes symptomatic treatment, e.g. nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal treatment, e.g. ovulation inhibitors. Many patients turn to therapeutic approaches outside of conventional medicine. There is an increasing interest in the use of herbal medicine treatment, e.g. agnus castus fruit.

In the absence of any objective parameter to measure or diagnose PMS, clinicians and researchers rely largely on validated scales in which patients self-rate their symptoms. The following validated instruments are used to quantify PMS (Dhingra and O'Brien 2007):

Table 6: Instruments to quantify PMS according to Dhingra and O'Brien 2007 (modified)

HDRS	Hamilton Depression Rating	Observer-rated instrument to assess items in

	Scale	(premenstrual) mood disturbance; originally designed for diagnoses other than PMS
MMDQ	Moos Menstrual Distress Questionnaire	47 symptoms rated on a six-point scale
VAS PMI	Visual analog scale: Premenstrual Mood Index	100 mm line at either end of which are opposing adjectives representing the symptoms
CGIS	Clinical Global Impression Scale	Developed for use in clinical trials to provide a brief assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication; originally designed for diagnoses other than PMS
PMTS-O	Premenstrual Tension Syndrome-Observer	Assess symptoms in 10 different domains, 36 symptoms with severity ranging from 0 to 4
PMTS-SR	Premenstrual Tension Syndrome-Self-Rating	Assess symptoms in 10 different domains, 36 symptoms with severity ranging from 0 to 4 (Steiner *et al*. 1980)
PAF	Premenstrual Assessment Form	Retrospective questionnaire based on psychological and behavioural symptoms
PRISM	Prospective record of the Impact and Severity of Menstrual Symptoms	Daily chart records a large number of symptoms rated 1-3
COPE	Calendar of Premenstrual Experiences	Prospective inventory including physical and behavioral symptoms, summation of scores across 7 cycle days
DRSP	Daily Record of Severity of Problems	22-item rated 0-6
PSST	Premenstrual Screening Tool	Retrospective 0-3 scale

The premenstrual dysphoric disorder (PMDD) is a sub-group of premenstrual disorders. The women involved suffer from an extreme dysphoric-depressive mood. According to Pearlstein (2004) “PMDD” can be considered the “severe” end of the spectrum of women with premenstrual symptoms. Fulfilment of strict criteria as defined by the American Psychiatric Association is required. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, published in May 2013), established 4 research criteria (A through D) for the diagnosis of PMDD:

PMDD is diagnosed when, for most of the preceding twelve cycles, the following criteria are met:
1. Experiences five or more symptoms, including at least one core symptom
• Markedly depressed mood, hopelessness, self-deprecating thoughts* • Marked anxiety, tension* • Marked affective lability* • Persistent and marked anger or irritability*

PMDD is diagnosed when, for most of the preceding twelve cycles, the following criteria are met:
• Decreased interest in usual activities • Subjective sense of difficulty in concentrating • Subjective sense of being out of control • Lethargy, easy fatigability • Marked change in appetite • Hypersomnia or insomnia • Other physical symptoms, such as breast tenderness, headache, bloating * core symptom
2. Reports symptoms during the last week of the luteal phase, with remission within a few days of onset of menses (Criterion A)
3. Documents absence of symptoms during the week following menses (1.+2.+3.=Criterion A)
4. Demonstrates marked interfering of symptoms with work, school, or usual social activities and relationships (Criterion B)
5. Symptoms are not an exacerbation of another disorder (Criterion C)
6. Prospective daily ratings confirm three of the above criteria during at least two consecutive symptomatic menstrual cycles (Criterion D)

Based on theories regarding the underlying causes of PMS and PMDD, two main treatment options for severe PMS or PMDD in the adult population have been developed: (1) targeting the hypothalamus-pituitary-ovary axis by abolishing fluctuations in gonadal hormone levels (e.g. GnRH analogues, oestradiol, combined oral contraceptives) and (2) targeting brain serotonergic synapses by increasing central serotonergic transmission (e.g. SSRI) (RCOG Green-top Guideline No. 48, 2016).

In the following, the published clinical studies are listed in alphabetical order. Because of its fundamental relevance the publication by Schellenberg (2001) has been evaluated in detail and is – out of the alphabetical order-mentioned at the beginning in Table 7:

Table 7: Clinical study in PMS by Schellenberg 2001

Type	Study	Test Product(s)	Number of subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
Schellenberg 2001	Multicentre, randomised double-blind, placebo controlled, parallel group comparison April-December 1998	20 mg dry extract Ze 440 (DER 6-12:1, 60% ethanol m/m) per tablet, one tablet per day over 3 menstrual cycles	178 women aged ≥ 18 years, 170 with at least one baseline and one post-baseline value recorded (active: 86, placebo: 84)	PMS diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R)	VAS total score and on 6 symptoms (irritability, mood alteration, anger, head-ache, breast fullness, and other menstrual symptoms including bloating) ranging from 0=no symptoms to 10=unbearable: significantly greater decrease in VAC group compared to placebo (P<0.001) except for symptom 'bloating' CGIS: VAC superior in global impression items, responder rates (≥50% reduction in self assessed symptoms): 52% in VAC vs. 24% placebo	No statistical analysis is presented in the publication. A bio-statistical evaluation was done by BfArM-statisticians.	Well-conducted clinical trial with significant results to prove efficacy of the studied VAC extract for treat-ment of PMS; clinical indication is clearly defined and a sufficient specification of the used extract is provided.

Ambrosini *et al*. (2013)

Title: Use of *Vitex agnus-castus* in migrainous women with premenstrual syndrome: an open-label clinical observation.

Type of study: open, uncontrolled, single centre study.

Specification and daily dose of the extract: Vitex agnus-castus L. extract BNO 1095 (1 film-coated tablet containing 4.0 mg of dried ethanol (70%) extract of VAC, DER 7-11:1) orally once daily throughout three months

This open, uncontrolled, single centre study aimed at investigating the effect of VAC on patients with PMS and migraine attacks. It included 107 women, mean age 35.6±8.4 years with severe PMS since>1 year and migraine without aura. They were prescribed BNO 1095 VAC in a dosage of 4 mg native extract per tablet once daily over a period of three menstrual cycles. The primary endpoint was improvement of headache as self-assessed in a diary. At the end of the study the participants were asked to rate subjectively their PMS symptoms on a 3-point rating scale (no effect, mild reduction of intensity and duration, dramatic reduction or total absence).

100 women, mean age 35.3±8.6 years (range 18–50), completed the trial. 66 reported a dramatic, 26 a mild, 8 no improvement of PMS symptoms. 72 reported a reduction, 8 no modification and 10 a worsening of the migraine attacks per months. Similarly, a reduction of migraine duration was experienced. Reduction of monthly attacks and monthly days with headache were statistically significantly reduced ($p<0.0001$; t-test). 42% of the women responded to reduction of monthly attacks (reduction by≥50%), 57% to reduction of headache duration. No major side effects were seen. Seven patients concluded the study prematurely, 4 because of adverse events (head pruritus, mild gastralgia, worsening of PMS, worsening of dysmenorrhoea), three because not compliant to the protocol (study drug intake).

Assessor's comment:

As this study was not aimed to show the effects of VAC in PMS, no specific and validated PMS tools were used.

Atmaca *et al.* (2003):

Type of study: randomised, double-blind, reference-controlled.

Specification and daily dose of the extract: "20-40 mg/day".

Aim of this study was to compare the efficacy of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), with that of a *Vitex agnus-castus* extract in the treatment of PMDD. According to the authors, there was no statistically significant difference between the groups with respect to the rate of responders. Fluoxetine was more effective for psychological symptoms, while the extract was more effective for physical symptoms.

Assessor's comment:

A definite assessment of this publication was not undertaken because a specification of the Vitex agnus-castus extract is lacking.

Berger (1998), Berger *et al.* (1999 a, b; 2000):

Type of study: prospective observational study

Specification and daily dose of the extract: 20 mg native extract (drug-extract ratio 6-12:1, extraction solvent: ethanol 60% m/m) per tablet once a day.

The thesis includes data of a prospective observational study with 50 women suffering from PMS. The three articles seem to describe the same study. The women were treated with the *Vitex agnus-castus* extract V23/95/Ze 440 in a dosage of 20 mg native extract per tablet once daily over a period of three menstrual cycles. The extract is described as "standardised" for casticin but according to current criteria and an internet research the preparation is not "standardised". There is only mentioned a minimum content of 0.6% of casticin. Overall the observation covered eight menstrual cycles: two at baseline, three during treatment and three post-treatment. Criteria for inclusion were the following: Diagnosis of "late luteal phase dysphoric disorder" according to DMS-III-R, "appropriate" premenstrual score of a visual analogue scale (VAS) with 12 symptoms of the late phase dysphoric disorder according to DSM-III-R, "appropriate" premenstrual score of "Moos' menstrual distress questionnaire (MMDQ score >90%), intermittent therapy of the symptoms. Seven patients dropped out of the study, one of them because of an adverse event (fatigue and headache). All evaluated patients took at least 85% of the medication. The main effect parameter was the MMDQ, which is–according to the authors– a validated tool. Secondary parameters were the VAS and a global impression scale. A significant score reduction (42.5%) of the MMDQ is described ($p<0.001$). However, symptoms returned after treatment cessation. A difference of 20% from baseline remained ($p<0.001$) up to three cycles after cessation of treatment. 20 patients were considered responders (reduction by at least 50% relative to baseline). The results for the VAS were alike. On average, the influence on psychic symptoms was more pronounced than on physical symptoms. The following adverse events were mentioned for more than one patient: increased acne (7), headache/ migraine (6), spotting (5), gastrointestinal complaints (5), fatigue (3), dizziness (3), rash (2). An objective proof of efficacy cannot be derived due to study design.

Assessor's comment:

Study results support the use of 20 mg VAC dry extract (DER 6-12:1), ethanol 60% m/m, daily for treatment of PMS.

Ciotta *et al.* (2011)

Title: Psychic aspects of the premenstrual dysphoric disorders. New therapeutic strategies: our experience with *Vitex agnus-castus*

Type of study: randomised, double blind, active controlled study.

Specification and daily dose of the extract: 31 to 40 mg once a day of a not further characterised VAC preparation to be taken during 2 months.

This randomised, double blind, active controlled, single centre study investigated the effect of VAC on PMDD in women with PMS. It included 57 women, mean age 30.5±2.3 years, suffering since 7–8 years from PMDD. 26 were randomised to receive 20–40 mg fluoxetine once a day, 31 to 40 mg once a day of a not further characterised VAC preparation to be taken during 2 months. The primary endpoint was the change of the four items "depressed humour", "work and interests", "psychic anxiety", and "general somatic symptoms" of the Hamilton depression rating scale (HDRS) with weekly assessments. In both study groups the pre-and post-treatment dysphoric symptoms improved statistically significantly ($p<0.001$ in fluoxetine, $p<0.04$ in VAC).

Assessor's comment:

A specification of the VAC extract and a placebo control group is lacking. Study results have only supportive character.

Coeugniet *et al.* (1986):

Type of study: open study

Specification and daily dose of the extract: 100 g of dilution contain 9 g tincture (1:5), extraction solvent: ethanol 68% V/V; normal daily dosage: 40 drops corresponding to 33 mg drug (according to BfArM-data).

Thirty-six women with PMS were treated with the VAC dilution for three menstruation cycles. Statistically significant changes for affective and somatic symptoms in the used score between the beginning and after three cycles are described.

Assessor's comment:

Lacking data and missing dosage information do not allow a sufficient evaluation of this publication. An objective proof of efficacy cannot be derived due to study design.

Di Lorenzo *et al.* (2007):

Type of study: not mentioned.

Specification and daily dose of the extract: "40 mg/day".

In a population of 36 women with PMS and migraine the influence of a treatment with *Vitex agnus-castus* was evaluated ("40 mg/day"). The mean number of headache attacks was 4.28 (±1.9); the mean number of headache days per month was 7.55 (±3.8). After the treatment, the mean headache attack/month was 2.83 (±1.71, p=0.000003); the mean headache days/month was 4.08 (±2.62, p=0.000000005). It is mentioned that a headache reduction was observed also in non-menstrual attacks. Author's conclusion: "*Vitex* appears to be effective as headache treatment, in women with PMS. The effectiveness could be due to biological action of *Vitex*, that is a dopaminergic, oestrogenic, and opiatergic agonist. Placebo-controlled trials on larger number of patients are necessary to confirm our findings."

Assessor's comment:

Data from this poster/abstract and specification of the preparation are not sufficient for an evaluation.

Dittmar *et al.* (1982):

Type of study: observational study.

Specification and daily dose of the extract: 100 g of dilution contain 9 g tincture (1:5), extraction solvent: ethanol 68% V/V; normal daily dosage: 40 drops.

1542 patients with PMS were treated with the VAC dilution. The average dose rate was 42±9.3 drops per day. The duration of intake varied between seven days und 16 years. Only 4.5% of the patients and 4.4% of the physicians were not satisfied with the treatment. On average the improvement of symptoms began after 25.3±27 days (n = 1355). Thirty-two women reported adverse events (only those with more than one mentioning are listed here): not specified (7), nausea (5), diarrhoea (2), stomach trouble (3), anomalies of the length of menstruation (2), acne (3), erythema (2).

Assessor's comment:

An objective proof of efficacy cannot be derived due to study design.

Falch *et al.* (2003):

Type of study: prospective observational study.

Specification and daily dose of the extract: 40 mg extract (drug-extract ratio 6-12:1, extraction solvent: ethanol 60% m/m) per tablet once a day corresponding to 360 mg drug per day on average.

In this observational study in Switzerland 428 women with PMS were treated by 104 practice physicians. During three months the patients received Ze 440-extract in a dose of one tablet per day corresponding to 360 mg drug per day on average. Asked whether the three symptoms from which the women suffered most were treated successfully, 63.3% of the physicians answered with “yes”, 22.9% with “in parts” and 13.8% with “no”.

Assessor’s comment:

An objective proof of efficacy cannot be derived due to study design. The daily dose is questionable. An explanation for 40 mg daily dose instead of 20 mg (regular daily dose for this extract) is not given.

Feldmann *et al.* (1990):

Type of study: observational study.

Specification and daily dose of the extract: 100 g of dilution contain 9 g tincture (1:5), extraction solvent: ethanol 68% V/V; normal daily dosage: 40 drops.

1571 patients were treated with the VAC dilution, 867 of them suffering from PMS. There is no evaluation based on the different diagnoses. Thirty women reported adverse events (only those with more than one mentioning are listed here): gastrointestinal symptoms (12), not specified complaints (13).

Assessor’s comment:

An objective proof of efficacy cannot be derived due to study design.

He *et al.* (2009):

Type of study: randomised, prospective, double-blind, placebo controlled, multi-centre.

Specification and daily dose of the extract: VAC BNO 1095 (film-coated tablets containing 4.0 mg of dried ethanol (70%) extract of VAC corresponding to 40 mg of herbal drug) orally once daily throughout three cycles.

217 Chinese women suffering from moderate to severe premenstrual syndrome (PMS) were treated with either VAC BNO 1095 in a once daily dosage of 40 mg herbal drug or with placebo for three cycles. As primary efficacy variable the “Premenstrual Syndrome Diary” (PMSD) total score was used (changes in the mean PMSD total score during seven days before menses from the cycle zero to the cycle 3). In the full analysis set (FAS), the mean total PMSD score decreased from 29.23 at baseline to 6.41 at the termination for the treatment group and from 28.14 to 12.64 for the placebo group (inter group $p<0.0001$). “In order to eliminate the influence of subjects in difference centres, Cochran-Mantel-Haenszel analysis was used to calculate the decreasing level from baseline to the 3rd cycle. A significant difference was found.” The “Premenstrual Tension Syndrome Self-Rating Scale” (PMTS) score decreased from 26.17±4.79 to 9.92±9.01 for the treatment group, and from 27.10±4.76 to 14.59±10.59 for the placebo group (inter-group $p<0.05$). According to the publication no serious adverse event occurred in either group. 19 adverse events were reported (treatment group 9). 3 of the adverse events in the treatment group were judged at least possibly related to study medication (headache: 2).

Assessor’s comment:

A study conducted in Chinese women cannot serve as the only proof of efficacy for the treatment of European women. In this context it is referred to the Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU-population (EMEA/CHMP/EWP/692702/2008).

Information about the screening questionnaire and its appropriateness is missing. Furthermore information on the appropriateness of the PMTS rating scale and the PMSD and their validation in Chinese are not sufficient.

The same results were observed in the following two publications by Ma et al., both published in 2010. The study population appears to be a subset of the study population by He et al. (2009).

Ma *et al.* (2010 a, b)

Titles: a) Treatment of moderate to severe premenstrual syndrome with *Vitex agnus-castus* (BNO 1095) in Chinese women *and* b) Evaluating therapeutic effect in symptoms of moderate-to-severe premenstrual syndrome with *Vitex agnus-castus* (BNO 1095) in Chinese women.

Type of study: prospective, randomized, double-blind, placebo-controlled.

Specification and daily dose of the extract: VAC BNO 1095 (one film-coated tablet containing 4.0 mg of dried ethanol (70%) extract of VAC, DER 7-11:1) orally once daily throughout three cycles.

Sixty-seven patients were enrolled and randomly assigned to receive one tablet of VAC or placebo once a day.

Ma *et a*l 2010 a): The premenstrual syndrome diary (PMSD) sum score decreased from 29.38 score points at baseline to 4.28 at the 3rd cycle in the treatment group, while it decreased from 28.76 to 11.79 in the placebo group. There was a significant difference in PMSD sum score, score of negative affect and water retention between two groups at cycle 3 ($p<0.05$), but not for pain or food cravings.

Ma *et al* 2010 b): 16 out of 17 symptoms of PMS diary (PMSD), a daily rating scale with 17 items, showed a significantly greater improvement with VAC than placebo ($p<0.05$) except lower abdominal cramping ($p>0.05$) in the same cohort.

The side-effect experienced by one patient in the treatment group was prolonged period, and there were no other notable adverse events occurring during the treatment phase.

Assessor's comment:

See above (He et al. 2009). The response to placebo was found to be higher than in other publications.

Lauritzen *et al.* (1997):

Type of study: randomised, double-blind, reference-controlled.

Specification and daily dose of the extract: 3.5-4.2 mg dried extract (drug-extract ratio 9.58 - 11.5:1, extraction solvent: 60% ethanol m/m) per capsule once a day corresponding to 40 mg drug per day on average.

In this randomised, controlled trial versus pyridoxine (100 mg pyridoxine-HCL, twice daily on days 16 to 35 of the menstrual cycle) the efficacy and tolerability of VAC dry extract in a dosage of one capsule per day–corresponding to 40 mg drug per day on average-were investigated in 127 women (ITT) with "premenstrual tension syndrome". The authors mention that a placebo-controlled design was rejected for ethical reasons since the level of suffering would be considerable in at least a third of all PMTS patients. The primary endpoint was the rating of symptoms on the PMTS scale according to Steiner *et al.* (1980) for the self-assessment. As inclusion criteria PMTS symptoms had to correlate with the luteal phase of the menstrual cycle, recur with every cycle and be sufficiently severe to affect the patient's quality of life. The initial score data for the PMTS scale differed in both groups: *Vitex agnus-castus* (VAC) group 15.2, pyridoxine group 11.9. The mean absolute changes of the PMTS scores are described as 10.1 points for the VAC group and 6.8 for the pyridoxine group ($p=0.0377$) and the 95% confidence interval was -0.4261 to -0.1670 excluding a treatment difference of 0. At the end of

treatment the mean scores were 5.1 and the standard deviations 6.6 in both groups and therefore–taking into account the higher starting scores in the VAC group–the authors declared that it is statistically valid to conclude that VAC is at least as effective as pyridoxine. There occurred five adverse events in the agnus castus-group: persistent gastroenteritis, nausea, allergic rashes (2), acneiform inflammation.

In Germany, there are no pyridoxine-preparations licensed for the treatment of PMS. According to an evaluation of the German Institute for Quality and Efficiency in Health Care (IQWiG 2008), studies concerning PMS-treatment with pyridoxine include more than 1600 women and the pyridoxine preparations caused an alleviation of symptoms. The scientists presumed that a daily dosage of around 50 to 100 mg per day would probably lead to an alleviation of symptoms.

Assessor's comment:

The summarised data of the study cannot be classified as proof of efficacy, because of the lacking placebo control. Also, treatment with pyridoxine cannot be classified as standard treatment. Furthermore it is not explained, whether the PMTS scale according to Steiner is a sufficiently validated tool.

Loch *et al.* (2000):

Type of study: non-interventional trial.

Specification and daily dose of the extract: 1.6-3.0 mg dried extract (drug-extract ratio: 6.7-12.5:1, extraction solvent–according to BfArM-database: ethanol 60% m/m) per capsule twice a day corresponding to 40 mg drug per day on average.

This multi-centre non-interventional trial covers data of 1634 patients suffering from PMS, who were treated with VAC dry extract in a dosage of one capsule twice a day – corresponding to 40 mg drug per day on average by 857 gynaecologists in Germany. A newly developed questionnaire was used for determining the effect on psychic and somatic symptoms. After a treatment period of three menstrual cycles, 42% of patients reported that they were no longer suffering from PMS, 51% showed a decrease in symptoms, and 1% an increase. Forty-five adverse events were documented in 37 patients. For 23 of these adverse events a correlation with the intake of the *Vitex agnus-castus* preparation was assumed (only those with more than one mentioning are listed here): symptoms of skin, mucosa and integumentary appendage (13), symptoms of gastrointestinal tract (6).

Assessor's comment:

An objective proof of efficacy cannot be derived due to study design.

Momoeda *et al*. (2014)

Title: Efficacy and safety of *Vitex agnus-castus* extract for treatment of premenstrual syndrome in Japanese patients: a prospective, open-label study.

Type of study: a prospective, open-label study.

Specification and daily dose of the extract: Vitex agnus-castus L. extract Ze 440, extract ratio 6-12:1, extraction solvent 60% ethanol m/m; one 20 mg tablet per day for three months.

This open, uncontrolled, multicentre, phase III study aimed at investigating the effect of VAC on PMS symptoms in Japanese women. 83 patients were screened and 69 were enrolled. They were given VAC Ze 440 20 mg orally, once a day., for three months. The primary endpoint was the reduction of ten PMS symptoms assessed on a validated 100 mm VAS after each cycle. All symptoms (irritability, depressed mood, anger, headache, bloating, breast fullness, skin disorder, fatigue, drowsiness, sleeplessness) were statistically significantly decreased already after the first cycle ($p<0.001$, paired t-

test). The variations in the total VAS score of the 6 symptoms (irritability, depressed mood, anger, headache, bloating, breast fullness), assessed also in studies in Caucasian populations, diminished from 200 at baseline to 33.5 at the 3rd cycle ($p<0.05$). The responder rates increased with the duration of the treatment and were 64.2% (43/67), 80.6% (54/67), and 91.0% (61/67) at the 3rd menstrual cycle after the start of the intervention. This was in good agreement with the physician's global assessment scores, as after the 3rd cycle 9 women had no, 48 mild, 9 moderate, 1 very severe symptoms compared to baseline when 53 indicated severe, 14 very severe symptoms.

Assessor's comment:

The study suggests that the VAC extract may show efficacy also in Asian populations, although the same considerations expressed for the He et al. (2009) trial are equally valid in this case. An objective proof of efficacy cannot be derived due to study design.

Peters-Welte & Albrecht (1994):

Type of study: observational study.

Specification and daily dose of the extract: 100 g of dilution contain 9 g tincture (1:5), extraction solvent: ethanol 68% V/V; normal daily dosage: 40 drops.

Efficacy and tolerance of VAC dilution in 551 patients with different indications (such as menstrual time anomalies and other bleeding disorders, PMS, wish for children) was documented over several cycles. There is no evaluation based on the different diagnoses. Twenty-eight women reported adverse events (only those with more than one mentioning are listed here): gastrointestinal symptoms (11), menstrual bleeding disorder (4), headache (3), pruritus (3).

Assessor's comment:

An objective proof of efficacy cannot be derived due to study design.

Prilepskaya *et al.* (2006):

Type of study: prospective, non-comparative.

Specification and daily dose of the extract: 4.0 mg dried extract (drug-extract ratio: 7-11:1, extraction solvent: ethanol 70% V/V) per tablet once daily corresponding to 40 mg drug per day on average.

In this prospective, open, non-comparative, monocentre study 121 women suffering from moderate to severe PMS were treated for up to three cycles with the above mentioned *Vitex agnus-castus* extract in a dosage of 40 mg drug per day. According to the article, the severity of the PMS symptoms (primarily by using the PMS-Diary) consistently decreased during treatment, from 22.8 score points to 10.2 on average (mean decrease 12.6 points, $p<0.0001$, 95% CI: 10.9-14.4). The following adverse events were judged to be the least possible related to study medication (only those with more than one mentioning are listed here): pruritus (4), erythema (3), headache (2), diarrhoea (2), dyspepsia (2), breast pain (2), and allergic dermatitis (2).

Assessor's comment:

Study results have supportive character due to study design.

Regnani *et al.* (2004):

Type of study: prospective, cross-over.

Specification and daily dose of the extract: "4 mg/day".

In this pilot prospective cross-over trial 20 run-in patients with PMS were randomised after one cycle to receive either low dose magnesium oxide alone (145 mg/day) or high dose magnesium oxide and a

Vitex agnus-castus preparation (300 mg Mg oxide plus 4 mg *Vitex agnus-castus*) for two cycles. Treatment lasted from day 15 of the menstrual cycle to the first day of menses. After the first two cycles both treatments significantly reduced the "Calendar of Premenstrual Experiences (COPE) score". When the women were shifted to the other treatment for the next two months, those receiving Mg oxide alone returned to baseline values whereas in those receiving Mg oxide plus *Vitex agnus-castus* the COPE score remained significantly lower.

Assessor's comment:

From this publication, no conclusions concerning the efficacy of Vitex agnus-castus can be drawn because the medicinal product did not only contain Vitex agnus-castus but also a higher dose of magnesium oxide. Therefore it cannot be excluded that the higher dose of magnesium alone caused the treatment effect.

Turner & Mills (1993):

Type of study: randomised, double-blind, placebo-controlled.

Specification and daily dose of the extract: 300 mg tablets of powdered *Vitex agnus-castus*, 2 tablets 3 times per day.

The trial was conducted on a volunteer sample of 600 women with self-diagnosed PMS. A questionnaire based on the Moos Menstrual Distress Questionnaire was used as instrument for evaluating efficacy. At the end of the trial period 217 women completed the full three months of treatment, 105 on VAC and 112 on the soya-based placebo. After a three cycle period in one reported symptom ("feel jittery or restless") a statistically significant difference is described in favour of *Vitex agnus-castus*. For the other main symptoms there was no significant result.

Assessor's comment:

High drop-out rate. Choice of placebo on basis of soy is questionable.

Widmer *et al.* (2005):

Type of study: observational study.

Specification and daily dose of the extract: 20 mg dried extract (drug-extract ratio: 6-12:1, extraction solvent: ethanol 60% m/m) per tablet corresponding to 180 mg drug per day on average.

The authors give an account of their practical experiences concerning the efficacy and tolerability of VAC dry extract in treating women with PMS. 462 patients were included. Data of 409 patients could be analysed after three cycles. 432 women took one sugar coated tablet per day corresponding to 180 mg drug per day on average. The single PMS-symptoms changed significantly for the better ($p<0.0001$). Eleven adverse events are described (only those with more than one mentioning are listed here): night sweat (2), pruritus (2).

Assessor's comment:

Study results support the use of 20 mg VAC dry extract (DER 6-12:1), ethanol 60% m/m, daily for treatment of PMS.

Zamani *et al*. (2012)

Title: Therapeutic effect of Vitex agnus castus in patients with premenstrual syndrome.

Type of study: randomised, double-blind, placebo-controlled.

Specification and daily dose of the extract: 40 drops once per day of a not further characterised VAC preparation.

This randomised, double-blind, placebo-controlled, single centre study (University hospital, Hamedan, Iran) investigated the therapeutic effect of VAC in women with PMS. It included 128 women suffering from PMS. 62, mean age 31±4 years, were randomised to receiving 40 drops once per day of a not further characterised VAC preparation and 66, mean age 31±4 years, received matching placebo starting 6 days before menses for 6 cycles. The primary endpoint was improvement of PMS symptoms self-assessed on the VAS of a PMS questionnaire about headache, anger, irritability, depression, breast fullness and bloating and tympani during the premenstrual period. PMS VAS scores decreased in both groups, but more significantly in the VAC group ($p<0.0001$). Mean rank of differences of all six items was significantly different at study beginning and end, in both and between groups ($p<0.0001$).

Assessor's comment:

No information is available on the study's GCP adherence or on the VAC extract used. The quality of the product and of the clinical trial cannot be assessed conclusively.

4.2.2.2. Mastodynia / Mastalgia

The terms mastodynia and mastalgia stand for pain in the breast. It can appear cyclical – sometimes as one of the physical symptoms of PMS–or noncyclical.

Mastodynia as a symptom of PMS has been examined in the above mentioned studies.

In a brief communication **Kilicdag *et al.* (2004)** describe a study which was conducted with the aim to investigate fructus agni casti as treatment for mild hyperprolactinemia and for mastalgia, and to compare its efficacy with that of bromocriptine (dopamine agonist) therapy. 40 women with cyclic mastalgia and 40 with mild hyperprolactinemia were included. In each of the two groups the patients were randomised to receive a 3-month course of either bromocriptine (2.5 mg twice daily) or fructus agni casti (40 mg daily). The efficacy was evaluated by comparing pre- and post-treatment findings for serum prolactin on days 5-8 of the menstrual cycle and breast pain (assessed by visual analogue scale). Both groups showed significantly lower prolactin levels after treatment ($p<0.0001$ for both). There was no significant difference between the two groups with respect to the size of the drop. Concerning the mastalgia cases both groups had significantly less breast pain after treatment ($P<0.0001$ for both) with no significant difference between the two groups. There were no adverse events concerning the intake of fructus agni casti, but 12.5% of the patients treated with bromocriptine suffered nausea and vomiting. The authors recommend fructus agni casti as a first-line therapy option for cyclic mastalgia and mild hyperprolactinemia.

Assessor's comment:

In Germany, bromocriptine-preparations are licensed for the treatment of "conditions and diseases in which a decrease of the prolactin level is indicated, such as …". Mastodynia and/or mastalgia are not mentioned in the listing. Summing up data of the study cannot be classified as prove of efficacy because of the lacking placebo control and because treatment with bromocriptine cannot be classified as standard treatment.

Dinç and Coşkun (2014)

Title: Comparison of fructus agni casti and flurbiprofen in the treatment of cyclic mastalgia in premenopausal women.

Type of study: Open, prospective, comparator-controlled.

Specification and daily dose of the extract: 40 mg VAC extract as tablet once daily for three months.

114 premenopausal Turkish patients younger than 40 years with a complaint of cyclic mastalgia and without any clinical, family or ultrasonography findings were analysed prospectively. Fructus agni casti extract (Group 1) or flurbiprofen (Group 2) were administered to the patients. VAS scores were accepted as full recovery with a score of zero, as significant healing when the score improved more than 50%, as mild-moderate healing when the improvement was less than 50% and as no healing in case of no improvement. The mean age in group 1 was 28.29±5.81, and in group 2 was 29.09±4.49. The mean number of days with pain was 6.0±1.70 days in group 1, and was 6.3±1.63 in group 2. There was no significant difference in VAS scores between the two groups after treatment. The authors conclude that both medications significantly reduced the complaints and had acceptable side-effects. Confusion and rash were reported by two patients each in the VAC group. There is no proven superiority over each other. Further clinical and laboratory studies are necessary to determine the ideal medication for the treatment of cyclic mastalgia.

Assessor's comment:

Study data cannot be classified as prove of efficacy because of the lacking placebo control. No information on the VAC extract used is available. It is unclear, if the daily dose refers to the herbal substance or preparation.

Mirghafourvand *et al.* (2016)

Title: Effects of Vitex agnus and Flaxseed on cyclic mastalgia: A randomized controlled trial.

Type of study: randomized, controlled.

Specification and daily dose of the extract: 3.2-4.8 mg VAC extract once daily, two months.

This randomized controlled trial was conducted on 159 women referred to health centres of Tabriz, Iran. Subjects were allocated into three groups (n=53 per group) using block randomization. Group I received 25 g daily flaxseed powder and placebo of VAC; group II received daily 3.2-4.8 mg VAC tablet and placebo of flaxseed and control group received both placebo. Nominal day breast pain (NDBP) was applied at baseline, first, and second month after the intervention. Data were analysed using general linear model. There was no statistical significant difference between the three groups in terms of socio-demographic characteristics and baseline values. Breast pain intensity scores significantly decreased in all groups from baseline to the end of the study: flaxseed: 12.8±5.6 vs. 3.5±2.5, VAC: 12.0±3.7 vs. 3.9±2.8, and placebo: 12.5±4.5 vs. 10.4±4.2. At both 1 and 2 months, breast pain intensity scores in the flaxseed and VAC groups were significantly lower than the placebo group. Breast pain duration scores were also significantly lower at the end of the study for all. In addition, at 1 and 2 months, pain duration scores were significantly lower in the flaxseed and VAC groups as compared with the placebo group. There were some adverse effects that included dysentery symptoms and nausea that occurred in women taking flaxseed. No other adverse effects were reported.

Assessor's comment:

No further specification of the VAC extract used is available. Another weakness point is the short study duration.

4.2.2.3. Luteal insufficiency (syn. Corpus luteum insufficiency)

The term "luteal insufficiency" describes an endocrinal disorder of the menstrual cycle with a shortened progestational stage and a decreased progesterone level in blood. It is a possible cause for female sterility.

Milewicz *et al.* (1993):

Type of study: Randomised, placebo-controlled, double-blind.

Specification and daily dose of the extract: "20 mg extract" of *Vitex agnus-castus* L., extraction solvent: ethanol 50-70% V/V (according to BfArM-data: one capsule contained 0.6 mg dried extract of the fruits of *Vitex agnus-castus* (25-40:1), extraction solvent: ethanol 60% m/m corresponding to 20 mg drug daily).

In this randomised, placebo-controlled, double-blind study the efficacy of VAC dry extract in the treatment of luteal phase defects due to latent hyperprolactinaemia was investigated in 52 women. Aim of the study was to prove whether the elevated pituary prolactin reserve could be reduced and deficits in luteal phase length and progesterone synthesis could be normalised. Blood samples were taken at days 5-8 and 20 of the menstrual cycle before and after three months of therapy. Latent hyperprolactinaemia was analysed by monitoring the prolactin release 15 and 30 minutes after intravenous injection of 200 µg TRH. The results of 37 complete case reports (placebo: n=20, verum: n=17) demonstrate a reduced prolactin release after three months, normalised length of luteal phases (placebo: 3.4±5.1 days→3.4±5.0; verum: 5.5±5.2 days→10.5±4.3) and eliminated deficits in luteal progesterone synthesis (placebo: 1.99±0.65→2.34±0.59 ng/ml; verum: 2.46±0.70→9.69±6.34) in the verum group. The changes were significant. All other examined hormonal parameters did not change with the exception of 17ß-estradiol which increased significantly in the luteal phase in patients receiving verum (placebo: 119.5±26.0 pg/ml→131.1±33.2; verum: 131.6±25.0 pg/ml→151.6±25.4).

Assessor's comment:

Usually there is no fixed normal range for the prolactin release after injection of TRH. The prolactin value has to be interpreted individually in comparison with the basic value. The test is not considered as reliable.

Propping & Katzorke (1987):

Type of study: open, non-controlled.

Specification and daily dose of the extract: 100 g of dilution contain 0.2 g extract of *Vitex agnus-castus*; extraction solvent: ethanol 68% (V/V); 40 drops daily.

The treatment group consisted of 18 women who had been unable to conceive for a period of more than two years. Each of them received 40 drops of the VAC dilution daily for a period of three months. Inclusion criteria included a normal prolactin assay, normal prolactin and TRH-stimulation tests and an abnormally diminished serum progesterone level. Treatment was regarded as being successful if the progesterone levels were restored to normal or if there was a clear trend towards normal (an increase of two units above initial levels of < 9 ng/ml or one unit above initial levels of > 9 ng/ml). Treatment was successful in 13 of the 18 women, two women became pregnant. In seven patients the progesterone level in the luteal phase increased above 12 ng/ml and in four cases there was an obvious trend towards normalisation. Before treatment the basal body temperature curve showed a shortened hyperthermic phase in ten women and after treatment in four women.

Propping *et al.* (1988):

Type of study: Open, non-controlled.

Specification and daily dose of the extract: 100 g of dilution contain 9 g tincture (1:5), extraction solvent: ethanol 68% V/V; normal daily dosage: 40 drops.

Forty-eight patients were treated with VAC dilution. Inclusion criteria were a decreased progesterone level (7-12 ng/ml) and a shortened hyperthermic phase of the basal temperature curve. After taking

VAC for three months in a dosage of 40 drops daily, in 25 of 45 patients a normalisation of the serum progesterone level was observed; in seven patients a trend towards normalisation was seen. Seven patients became pregnant.

4.2.2.4. Menstrual bleeding disorders

Loch *et al.* (1991):

Type of study: observational study (with prospective and retrospective data).

Specification and daily dose of the extract: 100 g of dilution contain 9 g tincture (1:5), extraction solvent: ethanol 68% V/V; normal daily dosage: 40 drops.

In two observational studies 2447 women with menstrual bleeding disorders were treated with VAC dilution. There is no evaluation based on the different diagnoses. 56 women reported adverse events (only those with more than one mentioning are listed here): not specified (12), nausea (8), allergy (2), diarrhoea (3), weight gain (3), stomach trouble (4), anomalies of the length of menstruation (4), acne (2), exanthema (2), erythema (2), headache (3).

4.2.2.5. Amenorrhoea

The term “amenorrhoea” describes the absence of a menstrual period in a woman of reproductive age. Primary amenorrhoea means that menstruation cycles never started, secondary amenorrhoea means ceasing of menstruation cycles.

Probst and Roth (1954) mention six patients with secondary amenorrhoea whose menstruation recurred after the intake of a VAC dilution.

Amann (1982) reports on three women with amenorrhoea whose menstruation also recurred after the intake of a VAC dilution.

Loch & Kaiser (1990):

Type of study: open study.

Specification and daily dose of the extract: 100 g of dilution contain 9 g tincture (1:5), extraction solvent: ethanol 68% V/V; daily dosage: 40 drops.

Twenty women with secondary amenorrhoea were treated with VAC dilution. At the end of the study, there were data of 15 women covering a period of at least six months. In ten of these women cyclic bleeding reappeared.

4.2.2.6. Oligomenorrhoea

In cases of oligomenorrhoea menstruation occurs at intervals greater than 35 days.

Probst & Roth (1954) report on six of nine women with oligo-and hypomenorrhoea whose menstruation recurred in time after the intake of VAC dilution.

Bleier (1959) describes the cases of 35 women with oligomenorrhoea who took 15 drops of VAC dilution three times daily. The menstruation interval changed from 39 days (±2.64) to 31.14 (±2.82).

4.2.2.7. Polymenorrhoea

In cases of polymenorrhoea menstruation appears more frequently than every 21 to 25 days.

Bleier (1959) mentions the cases of 33 patients with polymenorrhoea who took 15 drops of VAC dilution three times daily. The interval of menstruation changed from 20.143 days (±2.35) to 26.27 (±2.304).

4.2.2.8. Menorrhagia

Menorrhagia means an abnormally heavy and prolonged menstrual bleeding.

Bleier (1959) describes the cases of 58 women with menorrhagia who took 15 drops of VAC dilution three times daily. According to the author, a statistically relevant shortening of the intervals could be achieved.

Eltbogen *et al.* (2015)

Title: Vitex Agnus-Castus Extract (Ze 440) Improves Symptoms in Women with Menstrual Cycle Irregularities.

Type of study: observational.

Specification and daily dose of the extract: Vitex agnus-castus L. extract Ze 440, extract ratio 6-12:1, extraction solvent: 60% ethanol m/m; one 20 mg tablet per day, 3 months.

This non interventional, observational study has been conducted by Swiss gynaecologists and general practitioners in primary medical routine care. The objective was to evaluate the efficacy and safety of VAC extract Ze 440 in women suffering from menstrual cycle irregularities, such as polymenorrhea, oligomenorrhea, or amenorrhea. A total of 211 patients were included and symptoms associated with menstrual cycle irregularities (MCIs) and menstrual bleeding were assessed at baseline visit (BV) and at a follow-up visit (FV) after treatment with VAC extract during 3 subsequent menstrual cycles. The proportion of patients with remission improvement of MCIs (all in all) and specific symptoms such as polymenorrhea, oligomenorrhea, and amenorrhea was 79–85% at the FV. The proportion of patients with remission or improvement of symptoms related to menstrual bleeding such as dysmenorrhea, intermenstrual bleeding, hypermenorrhea, menometrorrhagia, ovulation bleeding, premenstrual or postmenstrual bleeding was 60–88% at FV. Out of 53 patients who reported an unfulfilled desire to have children at BV, 12 women (23%) got pregnant during treatment with VAC extract. At the FV, 91% of the physicians and 92% of the patients were “satisfied” or “very satisfied” with the achieved treatment outcomes, and 80% of the patients confirmed their preference to continue treatment with VAC extract. 4 out of 211 patients (2%) reported adverse events (rash, erythema, nausea, and abdominal pain). All adverse events were mild and transient.

Assessor’s comment:

An objective proof of efficacy cannot be derived due to study design.

4.2.2.9. Acne vulgaris

Amann (1967) reports on an individual case of Acne vulgaris with improvement under therapy with a VAC dilution.

4.2.2.10. Improvement of breastfeeding

Bautze (1953) performed a non-controlled investigation with two preparations of *Vitex agnus castus*, which are not specified in the publication and which were not on market at the date of investigation. From the results the author deduces a supporting influence of the preparations on breastfeeding.

Mohr (1954) conducted a study in which the influence of vitamin B1 and VAC dilution (15 drops three times daily) on lactation was tested in patients of a postnatal ward. Half of all patients received vitamin

B1 and afterwards half of the patients received the VAC dilution. After three months the sides of the ward were changed. At the end of the trial the amounts of breast milk which the newborns had drunk were identified. The effect of vitamin B1 did not satisfy the investigators and therefore they did not analyse these cases anymore. Of the patients who had received VAC and of the patients without treatment only those were evaluated who stayed in hospital for 12 days or longer (VAC: 62 patients, no treatment: 79 patients). For the patients who had received VAC the milk amount was higher beginning at the second week after delivery than for patients without treatment except for those with severe puerperal complications or mastitis. Adverse events concerning treatment with VAC: pruritic exanthema (15), early restart of menses.

Amann & Kerres (1966) report on women with an improvement of breastfeeding after the intake of VAC dilution, 40 drops three times daily.

4.2.2.11. Menopausal symptoms

There are two publications concerning the use of essential oils derived from *Vitex agnus-castus* in treating menopausal symptoms. In the first Lucks *et al.* (2003) report on 23 perimenopausal or menopausal women who volunteered in a survey. They were asked to use one of two different essential oils of *Vitex agnus-castus* (berry oil and leaf oil) for three months. The only standardised matter in this investigation was the reporting form in which the women were asked to rate the impact of nine menopausal symptoms before and after the use of the oil. Additionally, the main author reports on her own experience. According to her, the vast majority of the women taking part in the survey reported that the essential oils (both leaf and berry) had relieved their symptoms to a sufficient degree. In the second publication Lucks (2003) reports on 52 women with “common menopausal and perimenopausal symptoms” (perimenopausal: 31, postmenopausal: 11, “hysterectomy”: 10 subjects) who were monitored by 12 health care practitioners. Results were again submitted in surveys. The women used a 1.5% solution of the essential oil (steam distilled from aerial parts) in a bland base cream. They were instructed to apply 2.5 ml of the cream dermally once daily, 5-7 days per week for 3 months. The following results are mentioned: 33% reported major improvement, 36% mild to moderate improvement, 7.5% reported no change and 23.5% worse symptoms.

4.2.2.12. Prolactinoma

A prolactinoma is a benign adenohypophysial tumour which produces prolactin. There are discussions about the application of *Vitex agnus-castus* in cases of prolactinoma.

Tamagno *et al.* (2007) report on women with hyperprolactinemia and a pituitary adenoma. This patient refused therapy with a conventional dopamine agonist and decided to take a “VAC compound (20 drops b.i.d.)”. After three months prolactin levels were slightly decreased but symptoms persisted and VAC therapy was withdrawn. Six months later a pituitary MRI documented an unchanged microadenoma. Nevertheless the authors think that VAC could become a non-surgical therapeutic alternative for hyperprolactinemia in patients that do not tolerate or refuse conventional dopamine agonists.

Gallagher *et al.* (2008) describe a case of a 18-year old patient who presented to a women’s health clinic with a 2-year history of oligomenorrhoea and a 9-month history of amenorrhoea. On examination she was noted to have galactorrhoea. The serum prolactin level was elevated at 2166 IU/l (normal range: 80-600 IU/l). FSH and oestrogen were low. Six months later she reported return of menstruation with a regular 28-day cycle and there was no evidence of galactorrhoea. The serum prolactin level had decreased to 1588 IU/l. A MRI was arranged and showed a pituitary microadenoma 2 mm in size. It was detected that a complementary health practitioner had recommended the intake

of *Vitex agnus-castus* for a skin condition three months prior to her first visit. She had been taking 15 drops of a VAC dilution, 100 g containing 9 g tincture (1:5), ethanol 68% V/V, daily.

Meta-analyses

van Die *et al.* (2013)

Title: VAC extracts for female reproductive disorders: A systematical review of clinical trials.

12 randomised, controlled trials were included in this review of which eight studies investigated PMS. For PMS, seven of eight trials found VAC to be superior to placebo (5 of 6 studies), pyridoxine (1), and magnesium oxide (1). Overall the results indicate that VAC may be beneficial in the treatment of PMS and has a good safety profile, with adverse events being mild and generally infrequent.

Verkaik *et al.* (2017)

Title: The treatment of premenstrual syndrome with preparations of *Vitex agnus-castus*: a systematic review and meta-analysis.

17 randomized controlled trials of VAC in the treatment of PMS were selected. Fourteen of these could be included in the quantitative analysis. Thirteen of 14 studies with placebo, dietary supplements, or herbal preparations as controls reported positive effects of VAC on total premenstrual syndrome symptoms. Adverse events were mild and did not differ from those occurring with placebo treatment. The authors state however, that most of the trials are associated with a high risk of bias.

Assessor's comment:

The recent reviews support efficacy of VAC in the indication PMS. Overall, attempts at meta-analyses of the clinical studies have been complicated by the use of different preparations or lack of extract specification and result parameters.

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

No studies are available.

4.4. Overall conclusions on clinical pharmacology and efficacy

PMS

According to the "Guideline on the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for well-established and traditional herbal medicinal products (EMEA/HMPC/104613/2005 Rev.1) for claims such as "Premenstrual syndrome" at least significant data of one well-conducted clinical trial are the minimum requirement. General requirements are a clearly defined clinical indication and a sufficient specification of the used extract. In case of indications such as the premenstrual syndrome-known for their high placebo-response rates-the studies have to be placebo-controlled. The publication of Schellenberg (2001) meets all these demands. Therefore this study could be the scientific basis for the well-established use indication "Premenstrual syndrome" for an extract specified as follows: *Vitex agnus-castus* L. extract, DER 6-12:1, extraction solvent 60% ethanol m/m, 20 mg per day. A dose-response study (Schellenberg *et al.* 2012) is also available to support this posology. The indication is supported by the observational studies of Berger (1998), Berger *et al*. (1999 a and b, 2000) and Widmer (2005). According to an information of the manufacturer the extract–as film-coated tablets–is launched with well-established use status in Switzerland (launch dates: 1999, 2000, 2003), Hungary (2001), Bulgaria (2006), Romania (2006), Latvia (2005), Estonia (2006), Lithuania (2006) and Slovakia (2006). In Switzerland, the indication is as follows: "The fruit of the monk's pepper tree alleviate premenstrual complaints (Premenstrual

Syndrome; PMS). These are complaints such as headaches, skin problems, a slight feeling of tension in the breasts, and abdominal complaints, as well as mood swings, irritability, nervous tension, a depressive mood, fatigue and trouble sleeping. It is also traditionally used to treat disturbances of the menstrual cycle (too frequent or too rare menstruations)". In Bulgaria, there is an indication similar to the Swiss one. In Hungary, Romania, Latvia, Lithuania and Slovakia the well-established use indication is as follows: "…is indicated for the treatment of the premenstrual syndrome." For Estonia there is no indication available that is translated into English.

For the traditional use, there are two member states, Austria and Germany, in which VAC preparations (tinctures and dry extracts) have been on the market for 30 years or more for this indication. The majority of experts from different Member States in the MLWP shared the opinion that an indication in the field of premenstrual syndrome is possible because there is a common understanding of the symptoms and there is no general need for supervision by a medical practitioner. Taking into account the demarcation of the TU indication vs. the WEU indication with regard to a pure self-medication character of the former with serious symptoms excluded from treatment, the HMPC majority agreed on following indication: "Traditional herbal medicinal product for the relief of minor symptoms in the days before menstruation (premenstrual syndrome)."

Taking into account the above mentioned daily drug dosages of 300 mg to 2000 mg daily of the powdered herbal substance, the maximal daily dose is about 10-fold higher than that of the other herbal preparations included in the monograph (including the extract for WEU). Because the safety is not adequately addressed, the dosage was limited to 800 mg daily (which is 4.4 fold higher than that of the WEU-extract). This posology is in line with the traditional use of a product in the United Kingdom.

Mastodynia/Mastalgia

Data of the above mentioned studies cannot be classified as prove of efficacy for different reasons. Placebo control is lacking, treatment with bromocriptine cannot be classified as standard treatment or specification of the VAC extract used is not provided.

A traditional use–indication is not possible, because in cases of mastodynia/mastalgia a physician has to be contacted for diagnosis.

Luteal insufficiency (syn. Corpus luteum insufficiency)

The trial described by Milewicz *et al*. (1993) cannot justify the indication of luteal insufficiency because the test method (TRH-test) appears to be questionable.

Menstrual bleeding disorders

Data are not sufficient for a WEU-indication because there are no controlled clinical trials.

A traditional use–indication is not an option because a physician has to be contacted for diagnosis. Because of the possible seriousness of some bleeding disorders a medical supervision of therapy can also be necessary.

Acne vulgaris

Data are not sufficient for a WEU-indication, because there are no controlled clinical trials.

Improvement of breastfeeding

Data are not sufficient for a WEU-indication, because there are no controlled clinical trials.

Menopausal symptoms

Data are not sufficient for a WEU-indication, because there are no controlled clinical trials.

Prolactinoma

Data are not sufficient for a WEU-indication, because there are no controlled clinical trials.

5. Clinical Safety/Pharmacovigilance

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

The clinical safety evaluation of agnus castus fruit is based on the considerable clinical experience and on the clinical studies in the investigated indications. Numerous clinical trials have shown that agnus castus fruit has a positive safety profile in female adults.

5.2. Patient exposure

The patient population in the prospective and retrospective trials consists of more than 6000 women, with the majority being of child-bearing age and having an average age in the early thirties (see section 4.1 and 4.2).

There are no concrete data concerning sales volume, but it must be assumed that numerous patients have used agnus castus fruit preparations due to the Europe wide market presence.

5.3. Adverse events, serious adverse events and deaths

In the monograph of the German Commission E pruritic exanthema are mentioned as adverse reactions.

Adverse events

In Germany currently the following adverse reactions are labelled: headache, pruritus, abdominal complaints (such as nausea, stomach pain or pain in the hypogastric region), allergic reactions with rash and urticaria, severe allergic reactions with face swelling, dyspnoea and swallowing difficulties.

The following adverse reactions were noticed in several of the above listed studies and with multiple mentions within single studies:

- (worsened) acne
- headache
- gastrointestinal complaints
- (allergic) skin reactions: rash, erythema, pruritus
- anomalies in length of menstruation

Referring to the BfArM-database for adverse events (and referring to reports from studies) menstrual disorders, dizziness and acne should also be labelled.

Cahill *et al.* (1994) report on a woman who–after three endocrinologically normal cycles while undergoing unstimulated *in vitro* fertilisation treatment–before and in the early follicular phase of her fourth cycle took a *Vitex agnus-castus* preparation. In this cycle her serum gonadotrophin and ovarian hormone measurements were disordered. Vaginal ultrasonography on day 6 revealed four developing follicles. One embryo resulted but a pregnancy did not ensue. The woman had symptoms suggestive of mild ovarian hyperstimulation syndrome in the luteal phase. Her mid-luteal phase serum progesterone

level was 110 nmol/l (normal range 30-53 nmol/l). In the two subsequent cycles without *Vitex agnus-castus* medication the serum concentrations of LH and 17ß-oestradiol were within the normal range. The authors conclude that there is no conclusive evidence that the unusual response was the result of the intake of the *Vitex agnus-castus* preparation. But from their point of view the normal pituitary gonadotrophin profile and normal, unifollicular ovarian response observed in five other ovarian cycles, "make a strong case for it being the causative agent, as no other medications were taken or dietary changes made during that time." They think that *Vitex agnus-castus* "may occasionally have potent effects on the ovarian cycle with possible increased risks of multiple pregnancy and ovarian hyperstimulation syndrome." In a following correspondence the authors explained that the patient had taken a formulation which contained two other herbal substances: *Viburnum opulus* and *Mitchella repens*. Therefore, even if being apted to see a causal relationship between the intake of the formulation and the ovarian hyperstimulation, there is no evidence for *Vitex agnus-castus* being the causative ingredient.

Daniele *et al.* (2005) present a systematic review of adverse events correlated with the intake of monopreparations of *Vitex agnus-castus*. They draw the conclusion that the following adverse events are the most frequent: nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritus and erythematous rash. In their opinion *Vitex agnus-castus* should be avoided during pregnancy or lactation und theoretically might interfere with dopaminergic antagonists.

Serious adverse events and deaths

In Germany, severe allergic reactions are labelled as possible adverse events because there are correspondent reports in the pharmacovigilance database of the BfArM. Ritzmann (2004) raised the awareness for the discussion whether there are oestrogenic effects like an elevated risk for thromboembolic complications in smoking women.

No new safety concern arose since the time of the adoption of the EU herbal monograph, as confirmed also by a recent review (van Die *et al*. 2013).

No serious adverse events were reported in any trial with agnus castus fruit.

5.4. Laboratory findings

Loew *et al*. (1996) reported on an open placebo-controlled study in 20 male subjects aiming on an intraindividual comparison for testing the subjective and objective tolerance of the extract BP1095E1 while taking it for 14 days respectively in rising doses (120, 240 and 480 mg drug). This extract (filled in gel capsules) is described as conform to the German pharmacopeia of 1996. Between the treatment intervals a week-long phase without medication was interposed. The following laboratory values were analysed: gamma glutamyl transpeptidase (GT), glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), alkaline phosphatase, lactate dehydrogenase, bilirubin, sodium, potassium, calcium, chloride, iron, anorganic phosphate, total protein, glucose, total cholesterol, triglyceride, thromboplastin time, uric acid, urea, creatinine, haemogram, basal prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. Adverse events were recorded days 7 and 14, laboratory values days 1 and 13. Blood pressure and heart rate were measured days 1, 7 and 14 of each cycle. An ECG was performed at the beginning and at the end of the study. Thirteen of the 20 probands reported on 27 adverse events (only those with more than one mentioning and an at least possible causality assessment are listed): slight confusion (2), eczema with pruritus (3), pruritus (2), gastrointestinal disorders (3), headache (3), increased activity (2) and fatigue (2). A connection with the rising dose rate could not be reproduced. Changes of blood pressure or heart rate or ECG parameters are not described. Concerning the laboratory parameters only the means with standard deviations are mentioned. Based on these values no influence is described except for the

thromboplastin time which was prolonged for 3 to 5% concerning the doses of 240 and 480 mg drug per day. No influence on FSH, LH and testosterone levels was observed. Doses of 120 mg drug increased the secretion of prolactin, while doses of 240 mg and more decreased it.

No laboratory parameters evaluations have been done in other clinical efficacy trials over time except for one randomised, double-blind, placebo controlled trial (Schellenberg *et al*. 2012) and two published uncontrolled trials (Berger 1998, Berger *et al.* 2000, Momoeda *et al*. 2014). In these studies laboratory parameters were not affected by treatment with the extract Ze 440.

There are no data available for other herbal preparations.

5.5. Safety in special populations and situations

Agnus castus fruit preparations are indicated in women in the reproductive phase of life without known organic causes for their complaints. Publications concerning safety in special populations and situations were not found.

5.5.1. Use in children and adolescents

There is no relevant indication in prepubertal children. The use in pubertal children and adolescents under 18 years of age has not been established due to lack of adequate data.

5.5.2. Contraindications

Hypersensitivity to the active substance.

5.5.3. Special warnings and precautions for use

Because of the probable prolactin decreasing effect of agnus castus fruit, a special warning seems to be the adequate way to inform doctors and patients: “Agnus castus fruit is thought to act on the pituitary-hypothalamic axis and therefore patients with a history of a pituitary disorder should consult a doctor before using this product. In cases of prolactin secreting tumours of the pituitary gland the intake of agnus castus fruit can mask symptoms of the tumour.”

Since there are differing data concerning the effect of agnus castus fruit on the oestrogen level, a warning is justified for all patients with a history of oestrogen-sensitive cancer.

5.5.4. Drug interactions and other forms of interaction

None reported. Because of the possible dopaminergic and oestrogenic effects of agnus castus fruit, interactions with dopamine agonists, dopamine antagonists, oestrogens and antioestrogens cannot be excluded.

5.5.5. Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of agnus castus fruit in pregnant women. Taking into account the indication “premenstrual syndrome” the use in pregnancy is excluded. Animal studies are insufficient with respect to reproductive toxicity. The use of agnus castus fruit is not recommended during pregnancy.

Lactation

It is unknown whether agnus castus fruit or metabolites thereof are excreted in human milk. Data from reproductive studies suggest that extracts of the fruits influence lactation. A risk to the suckling child cannot be excluded. Therefore agnus castus fruit should not be used during breastfeeding.

Fertility

No studies on fertility have been performed.

5.5.6. Overdose

No case of overdose has been reported.

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

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

5.5.8. Safety in other special situations

Not applicable

5.6. Overall conclusions on clinical safety

Data from clinical trials with defined herbal preparations from agnus castus fruit demonstrate a reasonable safety profile.

Immune system disorders (severe allergic reactions with face swelling, dyspnoea and swallowing difficulties), skin and subcutaneous tissue disorders (allergic skin reactions such as rash and urticaria, acne), nervous system disorders (headache, dizziness), gastrointestinal disorders (nausea, abdominal pain), reproductive system disorders (menstrual disorders) have been reported. The frequency is not known.

Patients with hypersensitivity to the active substance have to be excluded from the use.

Because of the probable prolactin decreasing effect of agnus castus fruit, a special warning seems to be the adequate way to inform doctors and patients: “Agnus castus fruit is thought to act on the pituitary-hypothalamic axis and therefore patients with a history of a pituitary disorder should consult a doctor before using this product. In cases of prolactin secreting tumours of the pituitary gland the intake of agnus castus fruit can mask symptoms of the tumour.”

Since there are differing data concerning the effect of agnus castus fruit on the oestrogen level, a warning is justified for all patients with a history of oestrogen-sensitive cancer.

Because of the possible dopaminergic and oestrogenic effects of agnus castus fruit, interactions with dopamine agonists, dopamine antagonists, oestrogens and antioestrogens cannot be excluded.

Except for severe allergic reactions, there are no documented severe adverse events. Therefore the use of the following herbal preparations: Dry extract (DER 7-12:1), extraction solvent: ethanol 60% m/m; Powdered herbal substance; Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 68-70% V/V; Dry extract (DER 7-13:1), extraction solvent: ethanol 60% m/m; Dry extract (DER 10-18.5:1), extraction solvent: ethanol 50-52% m/m-in combination with an adequate labelling as included in the monograph-can be supported.

Agnus castus fruit should not be taken for more than 3 months without medical advice.

In summary, the use of agnus castus fruit containing medicinal products can be considered a safe and well tolerated treatment under the conditions lined out in the EU herbal monograph.

6. Overall conclusions (benefit-risk assessment)

Vitex agnus-castus L., fructus (agnus castus fruit) preparations have been used for centuries to treat gynaecological problems and specifically premenstrual complaints. There is a large amount of clinical and traditional evidence that demonstrate the efficacy and safety of agnus castus fruit.

A specified preparation of *Vitex agnus-castus* L fulfils the requirements of well-established use. There is one trial (Schellenberg 2001) proving efficacy for the indication “Premenstrual syndrome” for the *Vitex agnus-castus* L., fructus, dry extract (DER 6-12:1), extraction solvent 60% ethanol m/m, 20 mg daily. The study by Schellenberg *et al.* in 2012 confirms the suitability of 20 mg of this VAC dry extract (DER 6-12:1), extraction solvent 60% ethanol m/m daily to treat PMS.

Proposed ATC code: G02CX03

Therapeutic area: Herbal medicinal product for the treatment of premenstrual syndrome

No constituent with known therapeutic activity or active marker can be recognised by the HMPC.Criteria for the traditional use are fulfilled by the preparations: Powdered herbal substance; Tincture (1:5), extraction solvent: ethanol 68-70% V/V; Dry extract (7-13:1), extraction solvent ethanol 60% m/m; and Dry extract (10-18.5:1), extraction solvent ethanol 50-52% m/m, which have been in the European market for more than 30 years. Based on the majority view of the MLWP on traditional use, the following indication was adopted by the HMPC for these preparations, as specified in the monograph: “Traditional herbal medicinal product for the relief of minor symptoms in the days before menstruation (premenstrual syndrome)."

Since the posology refers to specific herbal preparations (dry extracts with defined DER and extraction solvent, tincture with defined ratio of herbal substance to extraction solvent, and powdered herbal substance), references to the corresponding amount of herbal substance have been deleted in the revised version of the EU herbal monograph.

There is no relevant indication in prepubertal children. The use in pubertal children and adolescents under 18 years of age has not been established due to lack of adequate data.

Patients with hypersensitivity to the active substance have to be excluded from the use.

Agnus castus fruit is thought to act on the pituitary-hypothalamic axis and therefore patients with a history of a pituitary disorder should consult a doctor before use. In cases of prolactin secreting tumours of the pituitary gland the intake of agnus castus fruit can mask symptoms of the tumour.

Possible dopaminergic and oestrogenic effects of agnus castus fruit cannot be excluded. Patients who suffer or suffered from an oestrogen-sensitive cancer or are using dopamine agonists, dopamine antagonists, oestrogens and antioestrogens should consult a doctor before use.

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

Annex

List of references