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Evaluation of Medicines for Human Use

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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT ASSESSMENT REPORT ON *VITEX AGNUS-CASTUS* L., FRUCTUS

Note: This Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Vitex agnus-castus* L., fructus. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed, on an exceptional basis, to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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I. REGULATORY STATUS OVERVIEW[1]

MA: Marketing Authorisation;
TRAD: Traditional Use Registration;
Other TRAD: Other national Traditional systems of registration;
Other: If known, it should be specified or otherwise add 'Not Known'

Member State	Regulatory Status				Comments[2]
Austria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	six products dry extracts and tincture
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products
Bulgaria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	one product dry extract
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Czech Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	two products dry extracts
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	one product dry extract
Estonia	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	four products dry extracts
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products
France	☐ MA	☒TRAD	☐ Other TRAD	☐ Other Specify:	one product
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	36 products dry extracts and tincture
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Hungary	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	four products dry extract
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products

[1] This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.
[2] Not mandatory field.

Member State	Regulatory Status				Comments[2]
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products
Poland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	one product
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products
Romania	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	one product dry extract
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	two products dry extract
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products
Spain	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	three products dry extract
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	three products dry extracts
United Kingdom	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	one product tincture one product dry extract

II. ASSESSMENT REPORT

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

(TRADITIONAL USE)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Vitex agnus-castus* L. Whole, ripe, dried fruit of *Vitex agnus-castus* L.
Herbal preparation(s)	1) tincture (1:5), extraction solvent: ethanol 58-60% m/m 2) tincture (1:5), extraction solvent: ethanol 70% (v/v) (manufacture under addition of calcium carbonate) 3) dry extract (7-13:1), extraction solvent: ethanol 60% m/m 4) dry extract (10-18.5:1), extraction solvent: ethanol 50-52% m/m
Pharmaceutical forms	Solid or liquid dosage forms for oral use
Rapporteur	Germany

II.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. Sources for this assessment report include DIMDI (Deutsches Institut für Medizinische Dokumentation und Information)-database (including MEDLINE), the database of the division for Complementary and Alternative Medicines of the Federal Institute for Drugs and Medical Devices (BfArM) and information received from other countries.

Vitex agnus castus , located in the region of the Mediterranean Sea, is a shrub which belongs to the Verbenaceae plant family. The medicinal plant was already mentioned by Dioskurides, a famous pharmacologist of the antiquity. "Agnós" as well as "castus" means "chaste". The plant respectively its seeds, ingested as a potion, were believed to reduce libido (Schulz & Hänsel 1999).

Attention has to be paid to the fact that a lot of research concerning *Vitex agnus castus* has been performed with Mastodynon®. Mastodynon® is a homoeopathic preparation with several homoeopathic active substances, *Vitex agnus castus* being one of them. These studies have not been evaluated for this assessment report.

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

- Herbal substance(s):

Agni casti fructus

Synonymes: Baccae agni casti, Fructus agni casti, Semen agni casti, Monks pepper chasteberry, poire sauvage

Other names: English: Fruits of *Vitex agnus castus*, French: Fruit de gattilier, Italian: Frutto di Agnocasto, Spanish: fruto de agnocasto, German: Mönchspfefferfrüchte

Agnus castus fruit is oval to almost globular, with a diameter of up to 5 mm. The persistent calyx is greenish-grey, finely pubescent, ends in 4-5 short teeth and envelops 2/3 to 3/4 of the surface of the fruit. The blackish-brown fruit consists of a pericarp that becomes progressively sclerous up to the endocarp. The style scar is often visible. Some of the fruits may retain a stalk, about 1 mm long. A transverse section of the fruit shows 4 locules, each containing an elongated seed (European Pharmacopoeia).

Constituents: (HagerROM 2006, Wichtl 2002, Barnes et al. 2007, Ganapaty & Vidyadhar 2005, Hajdu et al. 2007)

Iridoidglycosids (about 1%) including agnuside and aucubin, agnucastosides A-C.

Flavonoide such as casticin (lipophilic) with a content of 0.02 – 2.0%, small amounts of penduletin, chrysoplenole-D, vitexin and eupatorin; hydrophilic flavonoids of O or C- glycosidic types as orientin, luteolin-7-glycoside and isovitexin.

Essential oil with the main components (15%-25%) such as 1.8 cineole, limonene, α and β pinene. In smaller contents (2-5%) are contained bornylacetate, campher, p-cymol and sabinene.

Triglycerides with α-linolenic, palmitic, oleic, stearic and linolenic acid.

Diterpenes such as rotundifuran (0.04-0.3%), vitexilactone (0.02-0.17%), vitetrifolines B and C.

No constituents with therapeutic activity are known.

- Herbal preparation(s):

The herbal preparations are in liquid forms as an ethanolic tincture and in solid forms as dry extracts with different concentrations of ethanolic solvent (50% -70% (v/v)) and different DER.

II.1.2 Information on period of medicinal use in the Community regarding the specified indication

Different medicinal products have been marketed in Europe as well under well established use as as under traditional use. According to the market overview there are herbal preparations in Germany and in Austria for a period of over 30 years on the market.

The following data are derived from the overview of marketed products in Europe.

Information on products under well-established use

Austria
1) 3.85 mg dry extract (9.58-11.5:1); extraction solvent: ethanol 60% m/m
2) 100 g contain 9 g tincture (1:5), extraction solvent: ethanol 68% (v/v)
3) tincture (1:5), extraction solvent: ethanol 58% m/m
4) 1 film tablet contains 4.0 mg dry extract (8:3-12.5:1), extraction solvent: ethanol 70% (v/v)
5) 100 g solution contain 0.240 g dry extract (8.3-12.5:1), extraction solvent: ethanol 70% (v/v)
6) 1 film tablet contains 4.0 mg dry extract (7-13:1), extraction solvent: 60% m/m

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
1) 2000	capsule	1 x 1
2) 2000	oral drops, solution	1 x 40 drops
3) 1968	oral drops, solution	1 x 40 drops
4) 1999	film tablets	1 x 1
5) 1999	oral drops	1 x 40 drops
6) 2007	film tablets	1 x 1

Indications:
anomalies in the frequency of menstruation, premenstrual disorders, mastodynia

Bulgaria
agni casti extractum siccum (6-12:1), extraction solvent: ethanol 60% m/m

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
14.04.2004	film-coated tablets	1 x 1

Indication:
For the treatment of premenstrual syndrome which may include physical and psychical problems causing everyday activities to be more complicated, such as headaches, skin problems, breast swelling, subabdominal problems, nervousness, irritability, mood lability, fatigue and sleeping disorders.

Czech Republic
1) agni casti fructus extractum siccum 2:1 (contains 16-24% of the native extract and 84-76% of povidone), extracted with ethanol 70% (v/v) – 20 mg/tbl

2) agni casti fructus extractum siccum 2:1 (contains 16-24% of the native extract and 84-76% of povidone), extracted with ethanol 70% (v/v) – 1.2 g/100 ml (1 ml = 24 gtt)

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
1) 1997	por tbl flm (film-coated tablets)	1 x 1
2) 1997	por gtt sol (oral drops, solution)	1 x 40 drops

Indications:
Menstruation cycle disorders, mastodynia, premenstrual syndrome

Denmark
1 tablet contains 20 mg dry extract (6-12:1) of chaste tree fruit (agni casti fructus), corresponding to 120-240 mg fruit, extraction solvent: ethanol 60% m/m

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
July 2005	coated tablets	1 x 1

Indication:
Herbal medicinal product for the relief of minor disorders in the days before menstruation (premenstrual symptoms). ATC GO2CB

Germany

1, 3)	dry extract (7-11:1), extraction solvent: ethanol 70% (v/v)
2, 4, 5, 6, 8, 11, 12, 13, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26, 28, 30, 31, 32, 34)	**dry extract (7-13:1), extraction solvent : ethanol 60% m/m**
7, 37)	**dry extract (15-18.5:1), extraction solvent: ethanol 50% m/m**
9, 21, 35, 38)	**tincture (1:5), extraction solvent: ethanol 70% (v/v); (manufacture under addition of 72 mg calcium carbonate)**
10, 27, 29)	**tincture (1:5), extraction solvent: ethanol 68% (v/v)**
14)	extract (1-22.5 m/m), extraction solvent: ethanol 60% (v/v)
20)	tincture (1:5), extraction solvent: ethanol 70% (v/v)
33)	tincture (1:5), extraction solvent: ethanol 60% (v/v)
36)	**dry extract (10-16:1), extraction solvent: ethanol 60% (v/v)**

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
1, 3) 1995		
2, 4, 6, 8, 10-13, 15, 16, 17-19, 22, 24-27, 30-32, 34) 1999		
5, 7, 28, 29, 35-38) at least since 1976		
9, 14) 1992		
20) 1993		
21, 23) 1998		
33) 2005		
	1, 10, 14, 20, 27, 29)	

	oral drops, solution	
	2, 3, 4, 5, 12, 16, 17, 19, 22, 24, 30, 36) film-coated tablet	
	6, 8, 11, 13, 15, 18, 23, 25, 26, 28, 31, 32, 34) capsule, hard	
	7, 37) capsule, soft	
	9, 21, 33, 35, 38) oral liquid	
		1) 1 x 40 drops (= 1.7 ml = 1.67 g) 100 g contain 0.24 g dry extract
		2-6, 8, 11-13, 15-19, 22-26, 28, 30-32, 34) 1 x 1 containing 4 mg dry extract
		7, 37) 1 x 1 containing 2.4 mg dry extract
		9, 21, 35, 38) 1 x 30 drops (= 1 ml) 100 g (= 108.7 ml) oral liquid contain 18 g tincture
		10, 27, 29) 1 x 40 drops (= 1.83 g) 100 g contain 9 g tincture
		14) 2 x 10 drops (= 0.5 ml) 100 g contain 100 g extract
		20) 1 x 35-45 drops (40 drops = 1 ml) 100 g (= 109 ml) contain 20 g tincture
		33) 2 x 15 ml 1 g (= 0.96 ml) contains 6.3 mg tincture
		36) 1 x 1 containing 3 mg dry extract

Indications:

1-34, 36, 37)	irregular menstruation, premenstrual syndrome, mastodynia
35, 38)	premenstrual syndrome; mastodynia

Hungary

1) 1.92-2.88 mg/1g solution agni casti fructus dry extract (8.3-12.5:1), extraction solvent: ethanol 70% (v/v)
2) 3.2-4.8 mg/tabl agni casti fructus dry extract (8.3-12.5:1), extraction solvent: ethanol 70% (v/v)
3) 4.00 mg agni casti fructus dry extract (7-13:1), extraction solvent: ethanol 60% m/m
4) 20 mg agni casti fructus dry extract (6-12:1), extraction solvent: ethanol 60% m/m

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
1) 01.02.2002	oral drops, solution	1 x 40 drops
2) 01.03.2002	film-coated tablet	1 x 1
3) 04.07.2002	capsule, hard	1 x 1
4) 19.02.2001	film-coated tablet	1 x 1

Indications
1 and 2) menstrual cycle disorders and mastodynia, premenstrual syndrome
3 and 4) for the treatment of premenstrual syndrome.

Poland
agni casti fructus, extractum siccum (7.0-13.0:1); extraction solvent: ethanol 60% (m/m), 4 mg

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
since 2004	capsule, hard	1 x 1

Indication
Premenstrual syndrome (PMS) including symptoms such as mastodynia, menstrual cycle disorder such as polymenorrhoea, oligomenorrhoea or amenorrhoea

Romania
40 mg dry extract (native extract: colloidal silica dioxide = 1:1) standardized to 0.3% casticin (6:1), extraction solvent: ethanol 60% (v/v)

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
no answer	film-coated tablet	1 x 1

Indication
Add-on therapy in premenstrual syndrome

Slovakia
1) agni casti fructus extractum siccum (6-12:1) standardized to min. 0.6% of casticin, extraction solvent: ethanol 60% w/w
2) agni casti fructus extractum siccum (8.3-12.5:1), extraction solvent: ethanol 70% (v/v)

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
1) IX/2006	film-coated tablet	1 x 1
2) IX/2006	film-coated tablet	1 x 1

Indication

1) treatment of premenstrual syndrome
2) treatment of premenstrual syndrome, menstruation disorders, mastodynia

Spain
1) Dry extract (7-13:1), extraction solvent: ethanol 60% (v/v)
2) Dry extract (4-5.6:1), extraction solvent: ethanol 70% (v/v)
3) Dry extract (5-7:1), extraction solvent: ethanol 70% (v/v)

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
1) 27/10/2003	capsules	1 x 1
2) 08/08/2006	capsules	1 x 1
3) 15/09/2006	capsules	1 x 1

Indication
Relieve of premenstrual breast tension

United Kingdom
5 ml of solution contain: 0.411 g tincture of *Vitex agnus castus* fruits (agni casti fructus) (1:5), extraction solvent: ethanol 58% (v/v)

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
no answer	solution	1 x 40 drops

Indications
A traditional herbal remedy to help restore normal fluid balance and relieve occasional bloatedness in women. If symptoms persist or worsen patients should consult a physician.

Information on products under traditional use

Estonia
1) extract of agni casti fructus 4,0mg (*agni casti fruct. Spir. Sicc*.) (8.3-12.5:1), extraction solvent: ethanol 70%
2) extract of agni casti fructus 20mg (6-12:1), extraction solvent: ethanol 60% m/m
3) 100g of Agnucaston oral drops contain 0.240 g extract of agni casti fructus (8.3-12.5:1), extraction solvent: ethanol 70% (v/v)
4) extract of agni casti fructus 20mg (6-12:1), extraction solvent: ethanol 60% m/m

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
1) 17.12.1999	film-coated tablet	1 x 1
2) 13.08.2004	film-coated tablet	1 x 1
3) 17.12.1999	oral drops, solution	1 x 40 drops
4) 17.06.2005	film-coated tablet	1 x 1

Indications
Premenstrual syndrome

France
dry extract (4:1), extraction solvent: ethanol 30% (v/v)

Since when are the preparations on the market?	Pharmaceutical form	Posology/daily dosage
2005	hard capsules	1 to 2 (10 mg extract/cap)

Indication
Traditionally used in painful periods

Sweden
1) extract (8.3-12.5:1), extraction solvent: ethanol 70% 4.0 mg. 1 tablet corresponds to 40 mg dried fruit.
2) extract (7-13:1), extraction solvent: ethanol 60% 4 mg. 1 capsule corresponds to 40 mg dried fruit.
3) extract (3-6:1), extraction solvent: ethanol 60% 40 mg. 1 tablet corresponds to 180 mg dried fruit.

Since when are the preparations on the market?	Pharmaceutical form	Posology / daily dosage
1) before 1997	film-coated tablet	1 x 1
2) 2005	capsule, hard	1 x 1
3) 2005	film-coated tablet	1 x 1

Indication
Traditionally used to relive symptoms of PMS (premenstrual syndrome), such as tender breasts, bloating, irritability, anxiety and sudden dejection that appear during the week before menstruation and usually disappear when the menstruation starts.

United Kingdom
Each film-coated tablet contains: 4.0 mg dry extract (7-13:1) (equivalent to 28-52 mg of agnus castus), extraction solvent: ethanol 60% m/m

Since when are the preparations on the market?	Pharmaceutical form	Posology / daily dosage
no answer	film-coated tablet	1 x 1

Indication
A traditional herbal medicinal product that has been used to help relieve the symptoms associated with premenstrual syndrome, based on traditional use only.

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

II.2.1.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

In-vitro:

Several publications are available which describe for extracts of fruits of *Vitex agnus castus* effects on prolactin secretion and dopaminergic effects *in vitro* and *in vivo* (Jarry et al. 1991; Becker 1991; Sliutz *et al*. 1993, Jarry *et al*. 1994 and Wuttke *et al*. 1995). 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 ethanolic extract (60% EtOH) of fruits of *Vitex agnus castus* as spissum or siccum extract. The ethanolic extract inhibited the binding of ^{3}H-spiroperidole with an IC_{50} of 40-70 µg/ml. After separation the ethanolic 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 ethanolic 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 methanolic extract (Meier *et al*. 2000).

Using rat pituitary cells it could be demonstrated that an ethanolic 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 ethanolic 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).

In binding studies using ^{3}H-naloxone as ligand to the µ- and κ-opiate receptor and the ethanolic extract of *Vitex agnus castus* as inhibitor IC_{50}-values of ~30 and 20 µg/ml respectively were found while 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*. 2009).
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).

In a receptor binding assay performed with recombinant human estrogen receptor an ethanolic extract of *Vitex agnus castus* showed a preferential binding to estrogen receptor β over estrogen receptor α (Christoffel *et al*. 2002). The estrogenic compounds of this extract were identified as the flavonoids penduletin and apigenin (Jarry *et al*. 2006).
A methanolic extract (not further characterised) showed significant competitive binding to estrogen receptor α (IC_{50} = 46 µg/ml) and estrogen receptor β (IC_{50} = 64 µg/ml). Furthermore the extract stimulated the expression of the progesterone receptor but estrogen-dependent alkaline phosphatase activity was induced (Liu *et al*. 2001). Bioassay-guided isolation resulted in the isolation of linoleic acid as possible estrogenic component of the extract (Liu *et al*. 2004).
Oerter Klein *et al*. (2003) could not find any estrogen bioactivity using an estrogen receptor binding assay in a genetically engineered yeast system with a methanolic extract from *Vitex agnus castus*.

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 test on cytotoxicity and apoptosis inducing effects of *Vitex agnus castus* fruits (ethanolic extract, not further described). Test on cytotoxicity were done 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 ethanolic extract (60% EtOH) on antiproliferative effects on different human prostate epithelial cell lines. Proliferation of these cells was inhibited and apoptosis induced in a concentration dependent manner with IC_{50} values below 10 µg/ml.

In-vivo:

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 per oral 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.

II.2.1.2 Overall conclusions on pharmacology

Most pharmacological data were raised using ethanolic or methanolic extracts. Inhibitory influence on the prolactin release and dopaminergic (dopamine-agonistic) effects were seen by different working groups.
From the data seen there are opposite results concerning binding to estrogen 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).

II.2.2 Pharmacokinetics

II.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No data available.

II.2.2.2 Overall conclusions on pharmacokinetics

For the herbal substance or the herbal preparation no data are available and therefore no conclusion can be drawn.

II.2.3 Toxicology

II.2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Single dose toxicity:

A tincture from *Vitex agnus castus* was given to male and female rats and mice (2000 mg/kg) in acute toxicity studies. Behaviour and body weight gain remained unaffected throughout the study (observation time 14 days). The necropsy revealed no macroscopical lesion (Mengs 1992a, b).

Repeat dose toxicity:

A tincture from *Vitex agnus castus* was given to male and female rats (0, 10, 100, 1000 mg/kg) in a subacute toxicity study (4 weeks). All parameter (behaviour, general condition, body weight, food consumption, haematological, blood biochemical and urin analytical parameters) remained unaffected. Gross pathology, organ weight analysis and histopathology showed no findings which were attributable to dosing (Mengs 1993).

Reproductive and developmental studies:

In adult male mice an ethanolic extract of *Vitex agnus castus* (80% EtOH) was injected intraperitoneally in concentrations of 65, 165, 265, 365 and 465 m/kg bw for 30 days. Luteneizing 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 bw 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. Coadministration 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 post partum with 2 x 5 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 post partum. 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 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).

II.2.3.2 Overall conclusions on toxicology

There are only limited preclinical safety data for *Vitex agnus castus* fruits or preparations thereof. The data from reproductive studies suggest that extracts of the fruits might influence lactation.

Due to the lack of data on mutagenicity, carcinogenicity and reproductive and developmental toxicity, a list entry for *Vitex agnus castus* fruits can not be recommended.

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

II.3.1.1 Pharmacodynamics

II.3.1.1.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

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 *Vitex agnus castus* on prolactin.

Merz et al. (1995, 1996) describe an open placebo-controlled clinical study with an intra-individual comparison in which the effects of three doses of the agnus castus extract BP1095E1 (extracts from 120 mg, 240 mg and 480 mg of drug per day) on prolactin secretion and tolerance were examined in 20 healthy male subjects during a period of 14 days. With the lowest dose a significant increase in the 24-hour prolactin secretion profile was registered in comparison to placebo, the opposite being the case with the higher doses but not at a significant level. The 1-hour AUC after TRH-stimulation resulted in a significant increase with the lowest dose and a significant reduction with the highest dose. Nine out of ten participants whose $AUC_{0\text{-}24h}$ value was below the median showed an increase in the $AUC_{0\text{-}24h}$ value after the lowest dose. While no uniform effect was registered after dose A, nine of ten participants with $AUC_{0\text{-}24h}$ values above the median showed a reduction in the $AUC_{0\text{-}24h}$ value after dose B. The reported 26 adverse events consisted mostly of slight feeling of ill-health, skin reactions, vegetative disorders and gastrointestinal disorders. Respectively one case was reported of disturbed perception, slight confusion, slight activated state, headache, itching in the mouth and in the nose. No dose-dependency was seen. In the majority of cases a causation by the test medication was evaluated as uncertain. No changes concerning the following parameters were observed: blood pressure, heart rate, serum levels of FSH, LH or testosterone, clinical chemistry values. 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 *Vitex agnus castus*. 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 and with higher doses the agonistic effects strengthen the inhibitive effect of dopamine. As other possible explanations the following are mentioned: with dose-increasing a competitive displacement of the opposite components occurs due to the differently formed receptor affinities, a subpopulation of lactotrophs sensitive to the stimulatory effects of dopamine are affected by low dopamine agonistic concentrations of the extract similarily stimulating prolactin secretion. The authors draw the conclusion that the ability to reproduce such findings would have to be examined using randomisation and double-blind conditions.

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 exrtract 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 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 extract is in contrast to results of other trials. Vogel discusses possible reasons for this: low number of probands, physiological counterregulation, 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 (70% ethanolic extract, 120-480 mg/die) 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.

II.3.1.1.2 Overall conclusions on pharmacodynamics

There are inconsistent results concerning the influence of *Vitex agnus castus* on prolactin levels. But if taking into account the preclinical studies mentioned above and the clinical studies mentioned below, in which prolactin levels were evaluated in patients, overall there are more studies in favour for a prolactin decreasing effect of *Vitex agnus castus*, especially considering that the study of Vogel was not carried out under steady state conditions.

II.3.1.2 Pharmacokinetics

II.3.1.2.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

There are no studies concerning pharmacokinetics.

II.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

Not applicable.

II.3.2 Clinical Efficacy[3]

There are several indications for which the use of preparations of agni casti fructus is described: Premenstrual syndrome (PMS), abnormal oestrous cycle, mastodynia, acne, and others. In the German monograph of the Commission E the following indications are mentioned: Anomalies of the length of menstruation. Premenstrual disorders, 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 drug.

II.3.2.1 Dose response studies

Dose response studies were not found.

II.3.2.2 Clinical studies (case studies and clinical trials)

<u>Premenstrual syndrome (PMS)</u>

[3] In case of traditional use the long-standing use and experience should be assessed.

The premenstrual syndrome is diagnosed when the patient prospectively documents at least one of the following affective or somatic symptoms during the five days before menses for three menstrual cycles (Rapkin 2006):

Affective Symptoms	**Somatic Symptoms**
Depression	Breast tenderness
Angry outbursts	Abdominal bloating
Irritability	Headache
Anxiety	Swelling of extremities
Confusion	
Social withdrawal	

Adapted from ACOG Practice Bulletin 2000; 15: 1-9

Symptoms have to be of significant severity to impact social or economic performance and have to abate during the first four days of the menstrual cycle and do not recur until at least cycle day 13. There may be no concomitant pharmacologic therapy, hormone ingestion, or drug or alcohol abuse. The aetiology is unknown.

In the ACOG (American College of Obstetricians and Gynecologists) Practice Bulletin the most commonly used instruments for research purposes are mentioned: Calendar of Premenstrual Experiences (COPE), Prospective Record of the Impact and Severity of Menstruation (PRISM) and the Visual Analogue Scales (VAS).

The premenstrual dysphoric disorder (PMDD) is a sub-group of PMS. 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." The criteria for diagnosing PMDD are the following (Rapkin 2006):

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* • 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.
3.	Documents absence of symptoms during the week following menses
4.	Demonstrates marked interfering of symptoms with work, school, or usual social activities and relationships
5.	Symptoms are not an exacerbation of another disorder
6.	Prospective daily ratings confirm three of the above criteria during at least two consecutive symptomatic menstrual cycles.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Washington, D.C.: American Psychiatric Association; 1994, 715-718

Selective serotonin reuptake inhibitors (SSRIs) are considered the treatment of choice for severe PMS or PMDD in the adult population (Steiner et al. 2006).

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

Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. BMJ 2001, 322: 134-137

Title	Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study
Author	Schellenberg R
Source	BMJ 2001, 322:134-137
Funding	Zeller AG, Switzerland
Setting	General medicine community clinics
Study design	multicentre, randomised, double-blind, placebo controlled, parallel group comparison
Study objective	to compare the efficacy and tolerability of agnus castus fruit (*Vitex agnus castus* L. extract Ze 440) with placebo for women with premenstrual syndrome
Methodology	baseline assessment → facultative visit at the start of the second cycle → mandatory visit at the end of the third cycle
Patients	178 screened and randomised → 170 had at least one baseline and one post-baseline value recorded (active: 86, placebo: 84)
Criteria for inclusion	• women aged ≥ 18 years • premenstrual syndrome diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R) • written informed consent

Exclusion criteria	• participation in other trials • concomitant psychotherapy • pregnancy or breastfeeding • inadequate contraception • dementia • alcohol or drug dependence • concomitant serious medical condition • hypersensitivity to agnus castus • fever • pituitary disease • concomitant use of sex hormones except oral contraceptives for which the doses were unchanged
Concomitant medication	data are not sufficient.
Test product / Dose	*Vitex agnus castus* L. extract Ze 440, extract ratio 6-12:1, extraction solvent: 60% ethanol m/m; one 20 mg tablet per day corresponding to 180 mg drug per day on average
Study period / Duration of treatment	April to December 1998 / three menstrual cycles
Main efficacy parameter	Change from baseline to end of third cycle in women's self assessment of irritability, mood alteration, anger, headache, breast fullness, and other menstrual symptoms including bloating (Women rated each item using a visual analogue scale ranging from "0 = no symptoms" to "10 = unbearable".)
Secondary efficacy parameters	• changes in clinical global impression • responder rate (50% reduction in symptoms)
Statistical evaluation	A difference in mean values of 12 points and 2.5-fold SD was calculated as clinically meaningful. The expected withdrawal rate was 10%. It was calculated that a sample size of 80 per group would give a statistical power of 80%.
Results	Improvement concerning the main variable was more pronounced in the active group compared to the placebo group ($P<0.001$): Active (n=86): -128.5, Placebo (n=84): -78.1; difference in mean reduction: -50.5 (95% CI: -23.5 to -77.5). The secondary variables showed significant superiority of active treatment in five (irritability, mood alteration, anger, headache, breast fullness) of the six self-assessment items ("other symptoms including bloating" being unaffected), each of three global impression items and responder rates (≥ 50% reduction in self assessed symptoms) were 52% and 24% for active and placebo (no statistical analysis presented).
Tolerance	Seven women reported mild adverse events, four of them had received the active treatment: Acne, multiple abscesses, intermenstrual bleeding, urticaria.

The inclusion criterion "Premenstrual syndrome diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R)" is very similar to the above mentioned criteria for PMDD.

A biostatistical evaluation was done by BfArM-statisticians. Based on the publication no serious concerns were raised.

Atmaca M, Kumru S, Tezcan E. Fluoxetine versus *Vitex agnus castus* extract in the treatment of premenstrual dysphoric disorder. Hum Psychopharmacol Clin Exp 2003, 18: 191-195

Type of study: randomized, 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 but fluoxetine was more effective for psychological symptoms while the extract was more effective for physical symptoms.
A definite assessment of this publication was not undertaken because a specification of the *Vitex agnus castus* extract is lacking.

Berger D. *Vitex agnus castus*: Unbedenklichkeit und Wirksamkeit beim prämenstruellen Syndrom, Wirkprinzipien und Wirkmechanismen eines neu entwickelten Extraktes. Ph.D.-Thesis, University of Basel 1998

and

Berger D, Aebi S, Samochowiec E, Schaffner W. Klinisch kontrollierte Anwendungsbeobachtung beim prämenstruellen Syndrom. Zs. f. Phytotherapie 1999, 20: 155-158

and

Berger D, Schaffner W, Schrader E, Meier B, Brattström A. Efficacy of *Vitex agnus castus* L. extract Ze 440 in patients with pre-menstrual syndrome (PMS). Arch Gynecol Obstet 2000, 264: 150-153

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 corresponding to 180 mg drug per day on average
The thesis includes data of a prospective observational study with 50 women suffering from PMS. The two 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 a day over a period of three menstrual cycles. This corresponds to 180 mg drug per day on average. The extract is described as "standardized" for casticin but according to current criteria and an internet research the preparation is not "standardized". There is only mentioned a minimum content of 0.6% of casticin. Overall the observation spanned eight menstrual cycles: two baseline, three 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 analog 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 but 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).

Coeugniet E, Elek E, Kühnast R. Das prämenstruelle Syndrom (PMS) und seine Behandlung. Ärztezeitschr. f. Naturheilverf. 1986, 27(9): 619-622

Type of study: open study
Specification and daily dose of the extract: "Agnolyt®"
Thirty-six women with PMS were treated with Agnolyt® 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.
Lacking data and dosage do not allow a sufficient evaluation of this publication.

Di Lorenzo C, Goppola G, Pierelli F, Ambrosini A. The use of vitex – agnus castus in migrainous women with premenstrual syndrome. Cephalgia 2007, 27: 747 (Poster-Abstract!)

Type of study: not mentioned
Specification and daily dose of the extract: "40 mg/day"
In a population with 36 women with 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 FW, Böhnert K-J, Peeters M, Albrecht M, Lamertz M, Schmidt U. Prämenstruelles Syndrom. Behandlung mit einem Phytopharmakon. TW Gynäkologie 1982, 5: 60-68

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 corresponding to 33 mg drug (according to BfArM-data)
1542 patients with PMS were treated with Agnolyt®. The average dose rate was 42 ± 9.3 drops per day. The duration of intake varied between 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).

Falch BS, Bitzer J, Polasek W. Die Behandlung des prämenstruellen Syndroms (PMS) mit dem *Vitex agnus castus*-Extrakt Ze 440: Eine Therapiebeobachtung. Therapiewoche 2003, 19: 287-288

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 dragée 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".

Feldmann HU, Albrecht M, Lamertz M, Böhnert K-J. Therapie bei Gelbkörperschwäche bzw. prämenstruellem Syndrom mit *Vitex agnus castus*-Tinktur. Gyne 1990, 12: 421-425

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 corresponding to 33 mg drug (according to BfArM-data)

1571 patients were treated with Agnolyt®, 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).

Lauritzen C, Reuter HD, Repges R, Böhnert KJ, Schmidt U. Treatment of premenstrual tension syndrome with *Vitex agnus castus.* Controlled, double-blind study versus pyridoxine. Phytomedicine 1997, 4(3): 183-189

Type of study: randomized, double-blind, reference-controlled

Specification and daily dose of the extract: 3.5-4.2 mg dried extract (drug-extract ration 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 randomized, controlled trial versus pyridoxine (100 mg pyridoxine-HCL twice daily on days 16 to 35 of the menstrual cycle) the efficacy and tolerability of Agnolyt® 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; modified from Moos, 1968) 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) 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 probably would lead to alleviation.

Assessor's comment: Summing up data of the study cannot be classified as prove of efficacy because of the lacking placebo control. And treatment with pyridoxine cannot be classified as standard treatment. Furthermore it is not explained if the PMTS scale according to Steiner is a sufficiently validated tool.

Loch EG, Selle H, Boblitz N. Treatment of Premenstrual Syndrome with a Phytopharmaceutical Formulation Containing *Vitex agnus castus.* Journal of Women's Health & Gender-based Medicine 2000, 9(3): 315-320

Type of study: noninterventional 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 multicentric noninterventional trial covers data of 1634 patients suffering from PMS who were treated with Femicur® capsules 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 for determining the effect on psychic and somatic symptoms was used. 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. Fourty-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).

Peters-Welte C, Albrecht M. Regeltempostörungen und PMS. *Vitex agnus castus* in einer Anwendungsbeobachtung. TW Gynäkologie 1994, 7 (1): 49-52

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 corresponding to 33 mg drug (according to BfArM-data)
Efficacy and tolerance of Agnolyt® 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).

Priplepskaya VN, Ledina AV, Tagiyeva AV, Revazova FS. *Vitex agnus castus:* Successful treatment of moderate to severe premenstrual syndrome. Maturitas 2006, 55S: 55-63

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 using the PMS-Diary primarily consistently decreased during treatment, on average from 22.8 score points to 10.2 (mean decrease 12.6 points, $p < 0.0001$, 95% CI: 10.9-14.4). The following adverse events were judged at least possibly 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), allergic dermatitis (2).

Regnani G, Gasparetto A, Facchinetti F. *Vitex agnus castus* and Premenstrual Syndrome. 14th International Conference of Psychosomatic Obstetrics and Gynaecology, Edinburgh, Scotland, May 16-19, 2004

Type of study: prospective, cross-over
Specification and daily dose of the extract: "4 mg/die"
In this pilot prospective cross-over trial after one cycle of run-in 20 patients with PMS were randomised to receive either low dose magnesium oxide alone (Magnesium-OK Donna, 145 mg/die; Wassen International Ltd., England) or high dose magnesium oxide and a *Vitex agnus castus* preparation (Sindrogin, 300 mg/die Mg oxide plus 4 mg/die *Vitex agnus castus*; Euroderm R.D.C., Italy) 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.
From this publication there cannot be drawn any conclusions concerning the efficacy of *Vitex agnus castus* 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 S, Mills S. A double-blind clinical trial on a herbal remedy for premenstrual syndrome: a case study. Complementary Therapies in Medicine 1993, 1: 73-77

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. 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.

Widmer R, Baez Y, Kreuter U, Terreaux C. Mönchspfeffer beim Prämenstruellen Syndrom. Ein Praxiserfahrungsbericht PEB zur Wirksamkeit und Verträglichkeit eines standardisierten Extraktes aus den Früchten von *Vitex agnus castus* L. Schweiz. Zschr. GanzheitsMedizin 2005, 17: 351-354

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 Opran® in treating women with PMS. 462 patients were included. Data of 409 patients could be analysed after three cycles. 432 women took one dragée per day corresponding to 180 mg drug per day on average. The single PMS-symptoms changed for the better significantly ($P<0.0001$). Eleven adverse events are described (only those with more than one mentioning are listed here): night sweat (2), pruritus (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 randomized to receive a 3-month course of either bromocriptine (Parlodel® 2.5 mg twice daily, Novartis, Turkey) or fructus agni casti (Agnucaston® 40 mg daily, Biomeks, Germany). 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 hyper-prolactinemia.
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.

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 A, Gejdel E, Sworen H, Sienkiewicz K, Jedrzejak J, Teucher T, Schmitz H. *Vitex agnus castus*-Extrakt zur Behandlung von Regeltempoanomalien infolge latenter Hyperprolaktinämie. Ergebnisse einer randomisierten Plazebo-kontrollierten Doppelblindstudie. Arzneim.-Forsch./Drug Res. 1993, 43(II)(7): 752-756

Type of study: Randomized, 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 ca 20 mg drug daily)
In this randomized, placebo-controlled, double-blind study the efficacy of Strotan® capsules 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 be normalized. Blood samples were taken at days 5-8 and 20 of the menstrual cycle before and after three months of therapy. Latent hyperprolactinaemia was analyzed 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 D, Katzorke T. Treatment of Corpus Luteum Insufficiency. Zeitschrift für Allgemeinmedizin 1987, 63: 932-933

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 corresponding to 33 mg drug (according to BfArM-data)
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 Agnolyt 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 patients, two women became pregnant. In seven patients the progesterone level in the luteal phase increased above12 ng/ml and in four cases there was an obvious trend towards normalization. Before treatment the basal body temperature curve showed a shortened hyperthermic phase in ten patients and after treatment in four women.

Propping D, Katzorke T, Belkien L. Diagnostik und Therapie der Gelbkörperschwäche in der Praxis. Therapiewoche 1988, 38(41): 2992-3001

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 corresponding to 33 mg drug (according to BfArM-data)
Fourty-eight patients were treated with Agnolyt. Inclusion criteria were a decreased progesterone level (7-12 ng/ml) and a shortened hyperthermic phase of the basal temperature curve. After taking Agnolyt for three months in a dosage of 40 drops daily in 25 of 45 patients a normalization of the serum progesterone level was observed, in seven patients a trend towards normalization was seen. Seven patients became pregnant.

Menstrual bleeding disorders

Loch E-G, Böhnert K-J, Peeters M, Schmidt U, Lamertz M. Die Behandlung von Blutungsstörungen mit *Vitex agnus castus*-Tinktur. Sonderdruck aus DER FRAUENARZT 1991, 32(8): 1-4

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 corresponding to 33 mg drug (according to BfArM-data)
In two observational studies 2447 women with menstrual bleeding disorders were treated with Agnolyt®. 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).

- **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 et Roth (1954) mention six patients with secondary amenorrhoea whose menstruation recurred after the intake of Agnolyt®.
Amann (1982) reports on three women with amenorrhoea whose menstruation also recurred after the intake of Agnolyt®.

Loch E-G, Kaiser E. Diagnostik und Therapie dyshormonaler Blutungen in der Praxis. gynäkol. prax. 1990, 14: 489-495

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 corresponding to 33 mg drug (according to BfArM-data)
Twenty patients with secondary amenorrhoea were treated with Agnolyt. At the end of the study there were data of 15 patients covering a period of at least six months. In ten of these women cyclic bleeding reappeared.

- **Oligomenorrhoea**

In cases of oligomenorrhoea menstruation occurs at intervals greater than 35 days.
Probst et Roth (1954) report on six of nine patients with oligo- and hypomenorrhoea whose menstruation recurred in time after the intake of Agnolyt®.
Bleier (1959) describes the cases of 35 women with oligomenorrhoea who took 15 drops of Agnolyt® three times daily. The menstruation interval changed from 39 days (±2.64) to 31.14 (±2.82).

- **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 Agnolyt® three times daily. The interval of menstruation changed from 20.143 days (±2.35) to 26.27 (±2.304).

- **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 Agnolyt® three times daily. According to the author a statistically relevant shortening of the intervals could be achieved.

Acne vulgaris

Amann (1967) reports on an individual case of Acne vulgaris with improvement under therapy with Agnolyt®.

Improvement of breastfeeding

Bautze (1953) performed a non-controlled investigation with two preparations of 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 Agnolyt® (15 drops three times daily) on lactation was tested in patients of a postnatal ward. Half of all patients

received vitamin B1 und afterwards half of the patients received Agnolyt®. 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 Agnolyt® and of the patients without treatment only those were evaluated who stayed in hospital for 12 days or longer (Agnolyt®: 62(?), no treatment: 79(?)). For the patients who had received Agnolyt® 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 Agnolyt®: pruritic exanthema (15), early restart of menses.

Amann and Kerres (1966) report on a women with an improvement of breastfeeding after the intake of agnus castus (Agnolyt 40 drops three times daily).

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 standardized 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 of lotion. 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.

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 a 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 Agnolyt® daily.

II.3.2.3 Clinical studies in special populations (e.g. elderly and children)

None.

II.3.2.4 Overall conclusions on clinical efficacy

PMS:
According to the "Final Concept Paper on the Implementation of Different Levels of Scientific Evidence in Core-Data for Herbal Drugs" (EMEA/CPMP/HMPWP/1156/03) and to the "Updated Draft Points to Consider on the Evidence of Safety and Efficacy for Well-established Herbal Medicinal Products in Bibliographic Applications" (EMEA/HMPWP/23/99) 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. Only 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, extract ratio 6-12:1, extraction solvent: 60% ethanol m/m / 20 mg per day corresponding to 180 mg drug per day on average. The indication is supported by the observational studies of Berger (1998, 1999, 2000) and Widmer (2005). According to an information of the manufacturer (Zeller AG, Switzerland) 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 Sweden it is launched (2006) with traditional status but a CTD dossier was submitted for reclassification (well-established use). In Poland there is a marketing authorization in well-established use (2004) but the medicinal product is not launched yet. 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. 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 Poland and Estonia there are no indications translated in English.

Concerning the traditional use of *Vitex agnus castus* preparations the MLWP was in favour of a traditional use indication. There are two countries, Austria and Germany, in which preparations have been on the market for 30 years or more in this indication. The ma**j**ority of 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. Because the indication should differ from a possible WEU-indication and because serious symptoms should be excluded from treatment the following indication was chosen: "Traditional herbal medicinal product for the relief of minor symptoms in the days before menstruation (premenstrual syndrome)."

Mastodynia / Mastalgia:

Data of the above mentioned 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. 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 and 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.

II.3.3 Clinical Safety/Pharmacovigilance

II.3.3.1 Patient exposure

Aside from their market presence and data from studies there are no concrete data concerning patient exposure.

II.3.3.2 Adverse events

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

In the studies listed above the following adverse reactions were noticed in more than one study and more than once relating to the 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 fertilization 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 women 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 between the authors and Dr Propping 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.

II.3.3.3 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) puts up for disussion whether there are oestrogenic effects like an elevated risk for thromboembolic complicatins in smoking women.

II.3.3.4 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 analyzed: 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. 13 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), 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 and doses of 240 mg and more decreased it.

II.3.3.5 Safety in special populations and situations

Publications concerning safety in special populations and situations were not found**.**

II.3.3.5.1 Intrinsic (including elderly and children)/extrinsic factors

In Germany tumours of the pituitary gland are labelled as an absolute contraindication. Because of the probable prolactin decreasing effect of *Vitex agnus castus* a special warning seems to be the adequate way to inform doctors and patients: "Agnus castus is thought to act on the pituitary-hypothalamic axis and therefore patients with a history of a pituitary disorder should consult with a doctor before using this product. In cases of prolactin secreting tumours of the pituitary gland the intake of /…/ can mask symptoms of the tumour."

Furthermore in Germany breast cancer is labelled as an absolute contraindication. Since there are differing data concerning the effect of *Vitex agnus castus* on the oestrogen level a warning is justified for all patients with a history of estrogen-sensitive cancer.

II.3.3.5.2 Drug interactions

Because of the possible dopaminergic and oestrogenic effects of *Vitex agnus castus* interactions with dopamineagonists, dopamineantagonists, oestrogens and antioestrogens cannot be excluded.

II.3.3.5.3 Use in pregnancy and lactation

The indication excludes the use during pregnancy.

Data from reproductive studies suggest that extracts of the fruits influence lactation. Therefore it should be avoided during lactation.

II.3.3.5.4 Overdose

No case of overdose has been reported.

II.3.3.5.5 Drug abuse

No case of drug abuse has been reported.

II.3.3.5.6 Withdrawal and rebound

Based on our state of knowledge there is no evidence for symptoms of withdrawal. But after cessation of the intake a recurrence of symptoms is possible.

II.3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

To our knowledge no studies on the effect on the ability to drive and use machines have been performed.

II.3.3.6 Overall conclusions on clinical safety

The following adverse events should be labelled: Severe allergic reactions with face swelling, dyspnoea and swallowing difficulties. (Allergic) skin reactions (rash and urticaria), headache, dizziness, gastrointestinal disorders (such as nausea, abdominal pain), acne, menstrual disorders. The adverse events are not allocated to frequency categories because data are not sufficient for that.

The use during lactation is not recommended. The risks associated with possible oestrogenic effects for patients with oestrogen-sensitive cancer are addressed in the special warnings section.

II.4 OVERALL CONCLUSIONS

There is one publication proving efficacy for the indication “Premenstrual syndrome” for an extract specified as follows: *Vitex agnus castus* L. dry extract (6-12:1), extraction solvent: 60% ethanol m/m / 20 mg per day corresponding to 180 mg drug per day on average but the WEU cannot be favoured because until today the extract is only launched for eight years in the EU.

Based on the argumentation of the MLWP for a traditional use indication the following one was chosen: “Traditional herbal medicinal product for the relief of minor symptoms in the days before menstruation (premenstrual syndrome)."

Except for severe allergic reactions there are no documented severe adverse events. Therefore the application of the mentioned extracts - in combination with an adequate labelling resulting from the discussion in the MLWP - can be favoured.

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPH ON *VITEX AGNUS-CASTUS* L., FRUCTUS

III.2 LITERATURE REFERENCES