European Medicines Agency
Evaluation of Medicines for Human Use

London, 17 September 2009
Doc. Ref.: EMEA/HMPC/3968/2008

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

ASSESSMENT REPORT ON *CIMICIFUGA RACEMOSA* (L.) NUTT., RHIZOMA

DISCUSSION IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST (MLWP)	January 2008 March 2008 January 2009 July 2009 September 2009
ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	17 September 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	15 February 2010
REDISCUSSION IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST (MLWP)	
ADOPTION BY HMPC	

Comments should be provided using this template to hmpc.secretariat@emea.europa.eu
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Note: This Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Cimicifuga racemosa* (L.) Nutt., rhizoma. 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.

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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:	6 authorised mp
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Bulgaria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	5 authorised mp
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Czech Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	2 authorised mp
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	2 authorised mp
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Finland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	1 authorised mp
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	37 authorised mp
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Hungary	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	6 authorised mp
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
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:	1 authorised mp
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Medicinal product
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	1 registered tmp

[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]
United Kingdom	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	1 registered tmp

II. ASSESSMENT REPORT

BASED ON ARTICLE 10A OF DIRECTIVE 2001/83/EC AS AMENDED

(WELL-ESTABLISHED USE)

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)	*Cimicifuga racemosa* (L.) Nutt., rhizoma (black cohosh)
Herbal preparation(s)	• Dry extract from Cimicifugae rhizoma (5-10:1) ethanol 58% V/V • Dry extract from Cimicifugae rhizoma (4.5-8.5:1) ethanol 60% V/V • Dry extract from Cimicifugae rhizoma (6-11:1) propan-2-ol 40% V/V
Pharmaceutical form	Herbal preparation in solid dosage forms for oral use.
Rapporteur	Germany

II.1 INTRODUCTION

Cimicifuga racemosa is a perennial plant of the Ranunculaceae (buttercup family). It is native to the eastern US and Canada, where normally all commercial stocks are derived from. Indian tribes used roots/rhizomes of this medicinal plant.

In some European countries a few specified herbal preparations of Cimicifuga racemosa are active substances of herbal medicinal products which are marketed with an indication for relief of menopausal symptoms, e.g. hot flushes. Additionally, in the United Kingdom there is a traditional product used for the symptomatic relief of rheumatic pain.

There is an ongoing discussion in literature on potential oestrogenic activity of some medicinal plants. One of these plants is Cimicifuga racemosa. Concepts have been suggested describing the effects as phytooestrogens or phyto-SERM (selective estrogen receptor modulators). The recently analysed data do not support a direct oestrogenic effect. Due to the problems caused by hormone replacement therapy (HRT) with chemical entities, products containing preparations of Cimicifuga racemosa are getting more and more into the focus of interest.

Chemically, an extract of the root and rhizome is known to contain at least three major natural product groups: cycloartenal-type triterpenes, phenolics and flavonoids (Al-Amier et al. 2005). Herbal preparations contain a complex mixture of triterpene glycoside amongst them actein, cimifugosid and cimiracemosids. The total amount of triterpene glycosides is about 40 to 70 mg/g herbal substance (calculated as 27-deoxyactein). There are controversial reports on the occurrence of the isoflavone formononetin. This natural product was discussed to be involved in oestrogenic effects. By means of methanolic extraction amounts up to 3.5 µg/g dry weight have been isolated from rhizomes. In contrast, formononetin could not be detected in other samples and in commercial products. Quinolizidine-type alkaloids especially cytisine and methylcytisine have been identified in minor amounts .

Common names in Germany are Cimicifuga-Wurzelstock, Frauenwurzel, Nordamerikanische Schlangenwurzel, Wanzenkrautwurzel. In English the plant is known as Black cohosh, other common names are black snakeroot, blackroot, rattleroot.

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

- Herbal substance(s) [3]:

  There is a draft-monograph of Cimicifugae racemosae rhizome published in Pharmeuropa.

- Herbal preparation(s):

  1.) dry extract from Cimicifugae rhizome (5-10:1) ethanol 58% V/V

  2.) dry extract from Cimicifugae rhizome (4.5-8.5:1) ethanol 60% V/V

  3.) dry extract from Cimicifugae rhizome (6-11:1) propan-2-ol 40% V/V

- Combinations of herbal substance(s) and/or herbal preparation(s)

  There are combinations with Hypericum.[4]
  This monograph refers exclusively to Cimicifuga racemosa.

3 According to the 'Procedure for the preparation of Community monographs for traditional herbal medicinal products' (EMEA/HMPC/182320/2005 Rev.2) and the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use (EMEA/HMPC/182352/2005 Rev.2)

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

- Cimicifuga was used in North America indigenous medicine since hundreds of years, in the treatment of different conditions, as a product for malaise, kidney disorders, rheumatism, snakebites, nervous disorders, including gynaecologic disorders, especially as a uterine stimulant and labour-inducing aid. Cimicifuga was first listed in the US pharmacopoeia in 1830 under the name "black snakeroot".
- In Germany Cimicifuga has been used since 1940 as a natural hormone agent for treating premenstrual, dysmenorrhoeal and menopausal caused neurovegetative symptoms. Nowadays only menopausal caused neurovegetative and emotional symptoms are accepted as indications. The dried rhizome of the plants is used according to the Monograph of the Commission E (BAnz Nr. 43, published 02.03.1989) for the relief of menopausal symptoms, e.g. hot flushes. There are two specified preparations for which clinical data are available.
- In several other member states products have obtained a marketing authorisation since 1999.

The following data are derived from the request (15 December 2006) for information concerning the marketed products of Cimicifuga preparations (these data are listed as reported by the member states):

4.) Austria: Well-established use

a.) Agnukliman drops (Gebro Pharma), liquid extract, 58% (M/M) ethanol , DER 1:5; 20 g root per 100 g preparation (since 1973); 3x30 drops (=corresp. 0,9 g root), later 3x20 drops.

Agnukliman tablets (Gebro Pharma), dry extract, 26.64 mg per tablet, corresponding 150 mg root. (since 1995); initially 3x2 tablets, (corresp. 0,9 g root), later 4 tablets daily.

b.) Linda tablets (Kwizda Pharma), dry extract, 50% (M/M) ethanol, DER 7-12:1, 1.66-2.86 mg extract per tablet corresponding app. 43 mg root per tablet; (since 2001) 1 tablet daily (corresp. 43 mg root).

c.) Klimadynon film coated tablets (Bionorica AG), dry extract, 58% (V/V) ethanol, DER 7-12:1, 1.66-2.86 mg extract per tablet, corresponding app. 21,5 mg root per tablet; (since 2002), 2x1 tablet corresponding 43 mg root).

d.) Remifemin tablets (Schaper & Brümmer), liquid extract in dry form, 40 (V/V) 2-propanol, DER 0.78-1.14:1, 0.018-0.026 ml extract per tablet corresponding 20 mg root; (since 1999), 2x1 tablet (corresponding 40 mg root).

e.) Sanvita Meno tablets (Sanamed), dry extract, 50% (M/M) ethanol, DER 7-12:1, 4.5 mg extract per tablet, corresponding app. 43 mg root per tablet; (since 2000), 1 tablet daily (corresponding 43 mg root).

Indications:

Ad a.) Dysfunctions of sex hormone balance, particularly in the prae- and post-menopausal climacterium.

Ad b.) Dysfunctions of sex hormone balance, particularly in the prae- and post-menopausal climacterium.

Ad c.) Perimenopausal complaints, PMS (premenstrual syndrome)

Ad d.) Neurovegetative and psychic climacteric disorders.

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[4] According to the 'Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations' (EMEA/HMPC/166326/2005)

Ad e.) Perimenopausal complaints, PMS (premenstrual syndrome)

Ad f.) Perimenopausal complaints, PMS (premenstrual syndrome)

Risks:

None reported.

5.) Bulgaria: Well-established use

a.) Remifemin oral drops, 50 ml, 100 ml, 150 ml; Extr. Cimicifugae racemosae fluidum (1:5); 60% ethanol V/V; 12 mg extract is equal to 2.4 mg of the drug. (31.10.2001), 2 x 20 drops daily.

b.) Remifemin tabl., x60, x100, x200; Extr, Cimicifugae racemosae siccum; 40% Isopropanol; 0.018-0.026 mg extract is equal to 20 mg of the drug. (31.10.2001), 2 x 1 tabl. daily.

c.) Cefakliman, oral drops, oral drops, 50 ml, 100 ml; Extr. Cimicifugae racemosae fluidum (1:10), 20 g/100 ml; 69.7% Ethanol V/V. (07.08.2002), 30-40-drops daily.

d.) Cefakliman, caps., x50, x100; Extr. Cimicifugae racemosae siccum (4:1) 5 mg / caps. (07.08.2002), 2 x 1 caps. daily.

e.) Klimadynon, tabl. Film. x60, x90; Extr. Cimicifugae racemosae siccum (5-10:1) 2.8 mg in a tabl.; 58% Ethanol V/V. (26.05.2005), 2 x 1 tabl. film daily.

f.) Indications for all products: Premenstrual syndrome, menopause associated with nervous disorders, painful menstruation.

6.) Croatia: Traditional use (registered as dietary supplements since 2002 and 2003).

a.) dry extract (DER = 3.5:1), capsule, 1 capsule (10 mg of extract) daily after meal during 2-3 months.

b.) dry extract (other data not available) → combination with other herbal preparations, capsule, 2-3 capsule after meal

c.) dry extract (other data not available), tablet, 1 tabl. (53.34 mg of extract) daily after meal during a month.

Indications:
Ad a.) PMS (pre-menstrual-syndrome) and menopause difficulties relief; support at menstrual disorder;
Ad b.) menopause difficulties removal;
Ad c.) menopause difficulties relief.
Risks:
Ad.a.) Contraindicated in pregnancy and lactation;
Ad b.) not mentioned
Ad c.) Contraindicated in pregnancy and lactation, in persons younger than age of 18 (warnings: do not expose to intensive sunlight, at hormone therapy consult your doctor).

7.) Czech Republic: Well-established use

a.) Cimicifuga dry extract (1:1), extracted with ethanol 60% (containing 15-20% of native extract 4.1-6.5:1, 40 mg/tbl. (since 1999), 1 tablet per day (after 6 months of use gynaecologist should be contacted)

b.) Cimicifuga dry extract (7-12:1), extracted with ethanol 58% (V/V), 1.66-2.86 mg/tbl. (corresponding to 20 mg of herbal drug), 1 tablet two times daily.

Indications:
Ad a.) Mild pre- and post-menopausal neurovegetative symptoms such as nervosity, mood swings, irritability, profuse sweating, hot flushes and sleep disorders.
Ad b.) Mild to moderate pre- and post-menopausal neurovegetative symptoms such as nervosity, mood swings, irritability, profuse sweating, hot flushes, sleep disorders and concentration disorders.

Risks:
Ad a.) Contraindications: known hypersensitivity to active substance, tumours of breast or uterus (even if suspected), pregnancy and lactation, risk of hepatotoxicity (see EMEA public statement).
Ad b.) Contraindications: known hypersensitivity to active substance, previous or existing oestrogen-dependent tumours, pregnancy and lactation. Warning: In case of long term or irregular vaginal bleeding gynaecologist should be contacted. Risk of hepatotoxicity (see EMEA public statement).

8.) Denmark: Well-established use

a.) Remifemin, 1 tabl. contains: 0.018-0.026 ml extract of Black Cohosh (Cimicifuga racemosa) rhizome, corresponding to 20 mg rhizome. Extraction solvent: Isopropanol 40% V/V. (09.03.1999), 1 tablet 2 times daily. Should not be used continuously for more than 6 months without medical advice.

b.) Menofem, 1 tab. contains: extract of Black Cohosh (Cimicifuga racemosa) rhizome, corresponding to 20 mg rhizome. Extraction solvent: ethanol 58% V/V. (25.08.2000), 1 tablet 2 times daily. Should not be used continuously for more than 6 months without medical advice.

Indications (both preparations): Herbal medicinal product for the relief of hot flushes and sweating in the menopause.

Risks (both preparations): Minor gastrointestinal reactions, such as nausea and diarrhoea, and allergic skin reactions is reported. Few reports of postmenopausal bleedings. Special warnings: Not to be used by women, who has or have had oestrogen sensitive tumours.
Patients should stop taking Cimicifugae racemosae rhizoma (Black Cohosh, root) and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine).
A few cases of weight gain and metrorrhagia has been reported.

Further information on existing standard marketing authorisations, combination products etc.:
Cimicifuga is not permitted as a food supplement in Denmark.

9.) Finland: Well-established use

a.) Cimicifuga racemosae rhiz. extr. sicc. (1:1) 20 mg. (25.10.2000), 1 tablet 2 times a day.

Indication: Herbal medicinal product for the relief of mild post-menopausal symptoms such as hot flushes, sweating and sleep disturbances.

Risks: Contraindicated: hormone depended breast cancer (past or known), hepatic insufficiency, hypersensitivity to actice ingredients or excipients. Not recommended if liver values have been / are unnormal. Adverse effects: vaginal bleeding, breast tension, liver injury.

10.) Germany: Well-established use

a.) 20 preparations (1,2,6,8,9,10,11,12,13,14,18,22,23,24,25,27,28,30,32,34) containing dry extract (4.5-8.5:1); extraction solvent: ethanol 60 (V/V); 2 preparations (3,35) containing liquid extract (1:1), extraction solvent : ethanol 60% (V/V); a tincture (4) (1:10), extraction solvent: ethanol 69.7% (V/V); a dry extract (5,33) (7-12:1), extraction solvent ethanol 50% (m/m); a dry extract (7) (4-9:1), extraction solvent ethanol 58% (V/V); a dry extract (15,16,17,19) (6-11:1)extraction solvent propan-2-ol 40% (V/V); tincture (20) from fresh Cimicifuga rhizoma (1:5), extraction solvent ethanol 60% (V/V); a dry extract (21,31) (4.1-6.5:1), extraction solvent ethanol 60% (V/V); tincture (26) (1:5), extraction solvent ethanol 50% (V/V); dry extract (29) special extract BNO 1055) 5-10:1), extraction solvent ethanol 58% (V/V); tincture (36) (1:5), extraction solvent ethanol 40% (V/V); dry extract (37)
(6.6-8.7:1), extraction solvent 60% (V/V).

a.) 10 preparations since 1998 (1,7,9,10,13,18,22,26,28,34); 12 preparations since 1997 (2,5,6,8,11,12,14,23,24,25,27,30); one (3) since 2001; 0ne (4) since 1993; 3 (15,16,17) since 2006; 4 (19,29,36,37) at least since 1976; 2 (20,33) since 2004; one (21) since 1999; one (31) since 1996; one (32) since 2000; one (35) since 1995.

b.) Pharmaceutical forms: capsules, hard; film-coated tablets; tablets; oral liquids, coated tablets.

c.) Posology: 1x daily 1 containing 6.5 mg dry extract (1,2,6,8,9,18,22,23,24,25,27,28,30,32,34); 1x daily 1 ml containing 40 mg liquid extract (= 25-30 drops) (3); 2 x daily 30-40 drops, 1 g (=1 ml) = 33 drops, 100 g (=100 ml) contain 20g tincture (4); 1 x daily 1 containing 4.5 mg dry extract (5,33); 1 x daily 1 containing 6 mg dry extract; (7); 2 x daily 1 containing 2.5 mg dry extract (15,16,17,19); daily 25 ml (1 x 15 ml + 1 x 10 ml), 100 ml (=104.4g) liquid contain 658 mg tincture (20); 1 x daily 1 containing 7 mg dry extract (21); 2 x daily 30 drops (2 x 0.9 ml), corresponding to 206.4 mg tincture per day) 100g liquid contain 12g tincture (26); 2 x daily 1 containing 2.8 mg dry extract (29); 1 x daily 1 containing 8 mg dry extract (31); 1 x daily 20 drops 100 ml liquid containing 4.5g liquid extract (35); 2 x daily 10 drops, 100 ml liquid containing 19.8 ml tincture (36); 2 x daily 1 containing 2.675 mg dry extract (37).

Indications:

1,2,3,5,6,7,8,9,10,11,12,13,14,17,18,20,21,22,24,25,26,27,28,29,30,32,33,34,37:
“Zur Besserung von psychischen und neurovegetativen Beschwerden bedingt durch die Wechseljahre”. (For improvement of psychological and neurovegetative complaints due to the menopause.)
4,31,35,36:
“Zur Besserung der durch die Wechseljahre bedingten psychischen und neurovegetativen Beschwerden”.(For improvement of psychological and neurovegetative complaints due to the menopause.)
15,16,19:
„Zur Besserung der durch die Wechseljahre bedingten psychischen und neurovegetativen Beschwerden wie z.B. Hitzewallungen, Schweißausbrüche, Schlafstörungen, Nervosität und depressive Verstimmungen“. (For improvement of psychological and neurovegetative

complaints due to the menopause such as hot flushes, sweating, sleep disorders, nervousness and depressive mood).
23:
"Zur symptomatischen Therapie von psychischen und neurovegetativen Beschwerden, bedingt durch die Wechseljahre". (For symptomatic treatment of psychological and neurovegetative complaints, due to the menopause)

Risks:
Since 9 June 2009 a pharmaco vigilance action is effective concerning the risks of hepatotoxicity and the consumption of Cimicifuga containing medicinal products.

11.)Hungary: Well-established use

a.) Remifemin tabl. (original or mixed), Cimicifugae rhizoma liquid extract. (0.78-1.14: 1) 0.018-0.026 ml/ tablet , Extract ant: 40% isopropanol (V/V) (Schaper & Brümmer) (corresponding to 20 mg herbal drug) (February 28, 2000), 1 tablet twice a day (1 in the morning and 1 in the evening) with liquid without chewing. The onset of action can not be expected at once, the treatment should be continued at least two months. The duration of application has been limited to 6 months without consulting doctors.

b.) Klimadynon film-coated tabl. (original or mixed applic.), Cimicifuga rhizome dry extract (7-12:1), 1.66-2.86 mg/filmtabl., ethanol 58% (V/V) (Bionorica); (April 26, 2004), unless otherwise prescribed, take 1 film-coated tablet twice daily (in the morning and in the evening). Tablets should be taken without chewing with enough liquid. The treatment should be continued at least two months, but the duration of application has been limited to 6 months without consulting doctors.

c.) Klimapur tabl. (Medico Uno/Kwizda, bibliographic), Cimicifuga racemosa rhiz. dry extract. (4-9:1) 4.5 mg/tabl., ethanol 50% (W/W) (Finzelberg); (April 20, 2004). The daily dosage of Klimapur is one tablet with liquid without chewing. The onset of action can not be expected at once the treatment should be continued at least two months. The duration of application has been limited to 6 months without consulting doctors.

d.) Cefakliman mono hard capsules (CEFAK bibliographic), Cimicifuga racemosa rootstock dry extract, native (6.6-8.7:1), extraction solvent: ethanol 60% (V/V) (Extract Chemie) 2.675 mg/caps.; (October 16, 2001). Unless otherwise prescribed, adults take 1 hard capsule twice daily. The onset of action can not be expected at once the treatment should be continued at least two months. The duration of application has been limited to 6 months without consulting doctors.

e.) Cimicin (Cimicifuga) Stada film-coated tablets (Stada bibliograph.). Dry extract of Cimicifuga rhizome, (4.5-8.5:1), 6.5 mg/tabl., extraction solvent: ethanol 60% (V/V) (Extract Chemie); (October 1, 2001 / June 1, 2007). Unless otherwise prescribed 1 Cimicin Stada film-coated tablet daily. Tablet should be taken with enough liquid. Preferable at the same time (in the morning or in the evening).

f.) Femitan capsules (Schwabe), Cimicifuga rhizome extract sicc. (4.5-8.5:1), 6.5 mg/caps., extraction solvent: ethanol 60% (V/V) (Extract Chemie); (April 29, 2004). Take one capsule daily. Femitan capsule should be taken at the same part of the day (in the morning or in the evening). The duration of treatment is generally 6 months, bur the application of Femitan capsule is not recommended more than 3 months without medical advice.

Indications:
Ad a.) Relief of menopausal (climacteric) neurovegetative complaints such as hot flushes, profuse sweating, sleeping problems, nervousness and depressive moods.

Ad b.) Relief of menopausal (climacteric) neurovegetative complaints.
Ad c.) Relief of menopausal (climacteric) neurovegetative complaints such as hot flushes, profuse sweating, sleeping problems, nervousness and depressive moods.
Ad d.) For improvement of psychical and neurovegetative disorders caused by the menopause.
Ad e.) Relief of the menopausal (climacteric) neurovegetative complaints such as hot flushes, profuse sweating, sleeping problems, nervousness and depressive moods.
Ad f.) Symptomatic treatment of menopausal (climacteric) complaints.

Risks:
Ad a.) Very rarely rash, pruritus, gastrointestinal complaints can occur. Very rare cases of liver injury have been reported in connection with the use of extract of Cimicifugae racemosae rhizome. A definite causal relationship with the intake of medicinal products containing this active substance has not been proven at the moment. In the case of feeling of tension and swelling in the breasts and in the case of menstrual disorders a doctor should be consulted.
Ad b.) In very rare cases gastrointestinal disorders (dyspepsia, diarrhoea) allergic skin reaction (urticaria, pruritus, rash) face oedema, peripheral oedema and weight increase may occur. In very rare cases of liver injury have been reported in connection with the use of medicinal products containing Cimicifugae racemosae rhizoma. A definite causal relationship with the intake of these medicinal products has not been proven for the moment.
Ad c.) Occasional gastrointestinal disturbances. In the case of feeling tension or swelling in the breasts a doctor should be consulted. In very rare cases of liver injury have been reported in connection with the use of medicinal products containing Cimicifugae racemosae rhizoma. A definite causal relationship with the intake of these medicinal products has not been proven for the moment.
Ad d.) Rarely (less than 1 of 1.000, but more than 1 of 10.000 patients treated) gastro-intestinal complaints (dyspeptic complaints, diarrhoea), allergic reactions of the skin (urticaria, pruritus, skin rash), facial oedema and peripheral oedema. Rarely there can be an increase in weight.
Ad e.) Rarely gastro-intestinal complaints can occur and an increase in weight is also possible. In very rare cases of liver injury have been reported in connection with the use of medicinal products containing Cimicifugae racemosae rhizoma. A definite causal relationship with the intake of these medicinal products has not been proven for the moment.
Ad f.) Rarely gastro-intestinal complaints can occur and an increase in weight is also possible.

12.) Iceland: No marketing authorisation and not on the market.

13.) Ireland: No authorised products on the Irish market containing Cimicifuga racemosa.

14.) Italy: There are no herbal or conventional medicinal products containing Cimicifuga racemosa rhizome or its preparation as an active substance currently authorised or registered in Italy. (12 September 2008)

15.) Lithunia: Well-established use

Extractum siccum (4:1), ethanolum; (2000-11-09). Oral + 5 mg 2 times daily.
Indications:
Climacteric complaints; premenstrual disorders; dysmenorrhoe disorders.

Risks: Not mentioned.

16.) Norway: Cimicifuga racemosa L. (NUTT.) is classified as medicinal product in Norway.

Not on the market.

17.) Portugal: No marketing authorisation and not on the market.

18.) Sweden: Traditional Use

Rhizome, liquid extract (0.78-1.14:1); 0.018-0.026 ml. 1 tablet corresponds to 20 mg Cimicifuga racemosa. (since 1992), 1 tablet twice daily. Treatment is recommended for 6 months at the most. Not to be used by children.

Indications:
Traditionally used in case of minor climacteric symptoms such as hot flushes, sweating, sleep disturbances and nervousness.
Warning and precautions (4.4):
Caution should be exercised when treating patients with previously known liver disease. The treatment should be stopped if patients develop signs and symptoms of liver reaction. See 4.8 'Adverse reactions'.

Adverse reactions (4.8):
Occasional cases of menstruation like bleedings during ongoing treatment of menopausal women have been reported. In case of bleeding a doctor should be consulted.
Very rare cases of serious liver influence and liver damage have been reported in treatment with products containing Cimicifuga racemosa.
Very rare cases of mild gastrointestinal disorders such as dyspepsia and diarrhoea and allergic skin reactions (urticaria, rash, redness) have been reported.

19.) United Kingdom: Traditional use

a.) Liquid extract of black cohosh or "Potters liquid extract Cimicifuga". 5 ml contains aqueous alcoholic extractive from Black cohosh 5 g. (Since before 1968). Adults and elderly (only) 0.2 ml (about eleven drops) three or four times a day. Not for children.

Indications:
A herbal remedy traditionally used for the symptomatic relief of rheumatic pain.

Risks:
Seek medical advice if condition persists or worsens. Keep medicines away from children. Avoid in pregnancy and lactation.

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 the 1980 years first investigations were performed to examine the-binding at oestrogen receptors and the influence on breast-cancer-cells and endometrium.

In vitro tests

Endocrine activity, binding at oestrogen receptor extracted from rats-uteri and rats-pituitary glands was tested. Binding could be demonstrated for a methanolic extract. A dose-dependent displacement of radioactively labelled estradiol from antibody could be shown for two ethanolic extracts (Jarry et al. 1985, a + b).

No proliferative virility was observed with the mamma-carcinoma-cell- MDA-MB 435 line in concentrations from 0.0025-0.25 µg/ml, dosages greater than 2.5 µg/ml led to an inhibition of proliferation (Neßelhut et al. 1993).

Zava et al. showed that a 50% hydroethanolic extract of Cimicifuga did not stimulate cell proliferation in T-47D cells in steroid-depleted serum (Zava D., et al. 1998).

Different ethanolic extracts in very low concentrations caused a significant increase in cell number of oestrogen dependent MCF-7-Cells (Löhning et al. 1999).

Dixon-Shanies and Shaikh showed that a 0,1% ethanolic extract of Cimicifuga had significant growth inhibitory effects on serum stimulated T-47D cells (Dixon-Shanies et al. 1999).

For one extract with isopropanol an inhibition of proliferations from MCF-7-cells could be shown for dilutions between 100 µg/ml and 1 ng/ml (Freudenstein et al. 1999).

Liu et al. observed oestrogen-like proliferation at low Cimicifuga concentrations but antioestrogen-like inhibition at high concentrations in human breast cancer MCF cells (Liu et al. 2001).

Amato et al. observed neither stimulation of MCF-/ cell proliferation in an oestrogen-depleted environment nor transactivation of ER-α or ER β in a cell reporter assay upon treatment with an alcoholic extract (Amato et al. 2002).

Cimigenol and 39 related compounds were screened as potential anti-tumour promoters by examining the inhibition of Epstein-Barr virus antigen (EBV-EA) activation in Raji cells (B-Lymphocyte; Burkitt's lymphoma). In this assay all compounds tested showed inhibitory effects on EBV-EA activation without cytotoxicity on Raji cells. The investigation suggested that certain cimigenol related compounds could be valuable as anti-tumour promoters or as lead compounds for new anti-cancer drug development (Sakurai et al. 2003).

A study performed to examine the effects of cancer therapy agents on breast cancer cells by Cimicifuga, using EMT6 mouse mammary tumour cells with liquid Cimicifuga extracts (1. Gaia herbs 50% ethanol/50% water, containing 3.0% triterpene glycosides, providing 1,2 mg per dose; 2. containing 2.5% triterpene glycosides, providing 1.0 mg per dose and 3. an extract containing 2 mg triterpene glycol deoxyactein and 1 mg isoflavenoids as formononetin).

(Sara Rockwell et al. 2005).

The interpretation of the results must rely on a thorough understanding of test system and the herbal preparations that were used in this study. Without further studies the data of this study are not useful to give valid information about the effects of cancer therapy agents on breast cancer cells by Cimicifuga.

In vivo tests

Serum levels of pituitary glands FSH, Prolactin and LH did not change after a 14 day treatment in ovariectomized rats with a 50% ethanolic Cimicifuga-extract. After a three day treatment LH level and Prolactin level were significantly reduced, after a one day treatment Prolactin levels were increased (Jarry, Harnischfeger 1985).

Three-days-treatment with a 50% ethanolic Cimicifuga-extract did not affect the weight of uteri of juvenile mice. There was also no effect on vaginal cytology (Einer-Jensen et al. 1996).

An in vivo investigation of a clinically tested isopropanolic extract showed that treatment with Cimicifuga extract did not stimulate cancerous growth, the hormone levels band organ weights and endometrial proliferation. Mammary tumours were induced in Sprague Dawley rats (n=75) by the application of dimethylbenz(a)anthracene. Five to nine weeks later the animals were ovariectomized, allowed to recover and administered daily doses of the extract (0.714, 7,14 or 71.4 mg/kg body weight per day) or control substances (oestrogen/positive control 450 µg/kg/day mestranol or extract vehicle/negative control. The animals were sacrificed 6 weeks later and tumour, number, size, plasma hormone levels and the weight of oestrogen sensitive organs were analysed. In contrast to the oestrogen treatment the Cimicifuga extract did not stimulate cancerous growth. The hormone levels, organ weights and endometrial proliferation were unaffected (Freudenstein et al. 2002).

A study with MMTV-neu transgenic mice was performed to investigate the effects of Cimicifuga on mammary tumour development and progression. In this model the female mice developed primary and metastatic mammary tumours by spontaneous activation of the proto-oncogen neu (erbB2, HER2) the most common oncogene in breast cancer. Cimicifuga was provided via diet to mimic the oral route of application in women. Cimicifuga did not alter the latency or incidence of mammary tumours compared to MMTV-neu females maintained under control diet. The lack of any effect on mammary tumour development in this experiment suggests that Cimicifuga would not beneficially or adversely modify women's risk of developing breast cancer. In contrast to its lack of effect on primary mammary tumour development, Cimicifuga negatively influenced progression of metastatic disease. In Cimicifuga-treated female mice, the percentage of mice with detectable lung tumours at necropsy was increased compared to those on the control diet (26.5% n =110, versus 10.7%, n = 116, of females with primary mammary tumours (Davis et al. 2003 and 2008).

An in vivo test in four groups of 5-6 female ovariectomised DA/Han rats was performed to examine whether concomitant administration of an isopropanolic extract of Cimicifuga and Tamoxifen in a tumour model of implanted RUCA-I rat endometrial adenocarcinoma cells. Ectopic growth of the primary tumour as well as the incidence and localisation of metastasis were analysed. Cimicifuga did not promote further growth or metastatic potential of the primary tumour. Pulmonary metastases were frequently found in all groups (Nißlein et al. 2004).

The purpose of another study was to determine whether the triterpene glycosides present in Cimicifuga enhance the growth inhibitory effects of specific breast cancer chemotherapy agents in the MDA-MB-453 cells. Actein enhanced the growth inhibitory effects of both the anthracycline doxorubicin and the antimetabolite 5-florouracil; the EtOAc (Ethyl Acetate) fraction enhanced doxorubicin (Einbond et al. 2006).

II.2.1.2 Overall conclusions on pharmacology

It is still an open question whether Cimicifuga has oestrogenic properties or not. The data on oestrogenic effects of Cimicifuga are conflicting. Data derived from studies in vivo and in vitro are not sufficient to prove that the efficacy of Cimicifuga is based on a direct, oestrogenic mechanism of action.

There is an ongoing discussion on the mode of action concerning the possible oestrogen receptor affinity and the consequences for treatment of patients with oestrogen dependent tumours like breast- or endometric cancer.

II.2.2 Pharmacokinetics

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

II.2.2.2 Overall conclusions on pharmacokinetics

There is no specific information on pharmacokinetics of Cimicifuga. There are only some data concerning interactions (see below).

II.2.3 Toxicology

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

Chronic toxicity:

There is a 6 month oral toxicity study with the isopropanolic extract followed by an 8 week recovery period in Wistar rats. The daily doses were 2.925, 21.06 and 58.5 mg/kg b.w. (equals 250, 1800 and 5000 mg granulate/kg b.w.).Animals in the extract test group were found to consume slightly more food. In the high dose several effects were noted: increased relative liver weight, increased ovary weight and significant changes in the heart. These observed values returned to normal after 8 weeks of recovery. The NOEL was therefore defined with 21.06 mg/kg b.w. (Korn W-D. 1991 and Freudenstein Addendum to the 6 month toxicity study 1997).

Genotoxicity:

The mutagenicity of the isopropanolic extract was studied in an Ames test. . The Test was conducted with the S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538. The highest concentration was 1000 µg /plate. In this setting no evidence for genetic mutation was found (Hillmann 1990).

Carcinogenicity:

The in-vitro studies using human cancer cell lines and in vivo studies using animal tumour models suggested that Cimicifuga has no effects, but data are not sufficient for a final conclusion (Neßelhut et al. 1993; Zava D., et al. 1998; Dixon-Shanies et al. 1999; Freudenstein et al. 1999; Liu et al.

2001; Amato et al. 2002; Sara Rockwell et al. 2005; Einer-Jensen et al. 1996; Freudenstein et al. 2002; Nißlein et al. 2004; Einbond et al. 2006). In a study with MMTV-neu transgenic mice Cimicifuga accelerated progression of metastatic disease. In Cimicifuga-treated female mice, the percentage of mice with detectable lung tumours at necropsy was increased compared to those on the control diet (26.5% n =110, versus 10.7%, n = 116, of females with primary mammary tumours (Davis et al. 2008).

Hepatotoxicity:
An ethanolic Cimicifuga extract was administered orally to rats. Liver sections were analyzed by electron microscopy. Tests for cytotoxicity, mitochondrial toxicity and apoptosis/necrosis were performed using HepG2 cells. Mitochondrial toxicity was studied using isolated rat liver mitochondria. Microvesicular steatosis was found in rats treated with > 500 µg/kg body weight Cimicifuga extract.

In vitro, cytotoxicity was apparent at concentrations > or =75 µg/mL, and mitochondrial beta-oxidation was impaired at concentrations > or =10 µg/mL The mitochondrial membrane potential was decreased at concentrations > or =100 µg/mL, and oxidative phosphorylation was impaired at concentrations > or =300 µg/mL. The mechanism of cell death was predominantly apoptosis. These findings might be compatible with an idiosyncratic hepatotoxicity as observed in patients treated with Cimicifuga extracts. The authors conclude, that the ethanolic Cimicifuga extract is associated with hepatic mitochondrial toxicity both in vivo in rats and in vitro using cell cultures and isolated rat liver mitochondria. This toxicity is not clinically relevant for most patients (toxic concentrations can most probably not be reached in humans treated with the recommended doses) but may become important in patients with underlying risk factors. (Lüde et al. 2007).

The in vivo study (high dose) and in vitro studies with Cimicifuga-extracts demonstrate the potential mechanism of Cimicifuga for hepatotoxicity, but no reliable extrapolation concerning the risk to humans can be performed.

Reproductive toxicity:
There are no studies on reproductive toxicity.

II.2.3.2 Overall conclusions on toxicology

There are some studies which address toxicology of herbal preparations from Cimicifuga. With a 6-month study in rodents a NOEL of 21.06 mg/kg b.w. for the isopropanolic extract could be found (human equivalent dose of 3.23 mg/kg b.w.). The daily dosage of the isopropanolic extract = 0.08 mg/kg b.w. (for a 60 kg adult).

For this isopropanolic extract an AMES-Test was performed, which does not completely fulfil the requirements of the current guidelines with regard to the used Salmonella strains. No mutagenic properties could be found up to a concentration of 1000 µg/plate, whereas it is not clear, if the given concentration refers to the native extract or the extract preparation. Because of this fact and the lacking pharmacokinetic data an evaluation of the appropriateness of the highest concentration tested is not possible.

Known risks are especially associated with hepatotoxicity. In an in vivo study in rats microvesicular steatosis was found in animals treated with > 0.5 mg ethanolic extract/kg bodyweight. This can be calculated to a human equivalent dosage of ~ 0.1 mg/kg b.w. The therapeutic dose in humans is ~ 0.08 mg/kg. In all clinical studies and in the preclinical study with the isopropanolic extract microvesicular steatosis was not detected in humans, even taking the same amount.

The mode of action of Cimicifuga extracts are discussed to be related to effects on oestrogenic receptors. According to the pharmacological studies no final conclusion about the mode of action

can be drawn. In the 6-month study with the isopropanolic extract no oestrogen-like morphological changes in tissues or organs were noted.

Studies on carcinogenicity and reproductive toxicity were not performed (for both extracts). Furthermore, there are no genotoxicity studies for the ethanolic extract and the AMES test of the isopropanolic extract is not conclusive because of the indicated deficiencies.

The study with MMTV-neu transgenic mice (Davis et al. 2008) can not be used as a sole evidence basis of restricting the use of Cimicifuga because of the model (animal) and because the mechanism of action is currently hypothetical and therefore not plausible. Further studies in humans and animals are warranted (discussion in MLWP and HMPC).

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.

- *Climacteric complaints include neurovegetative symptoms (hot flushes, fits of perspiration, night sweats, sleep disorders), psychological symptoms (nervousness, mood swings, depressed mood, physical and mental fatigue), disturbances of the menstrual cycle and urogenital symptoms (dyspareunia, vaginal dryness and itching). (Palacio et al. 2009)*
- *Hot flushes affect two thirds of postmenopausal women, and 10%-20% of all postmenopausal women find them nearly intolerable (Boekhout et al. 2006)*

There are numerous publications discussing the mode of action of Cimicifuga preparations especially addressing the relevance of oestrogen receptor binding. This is of special importance for usage of patients with breast cancer and the influence on other oestrogen dependent tissues has to be observed carefully as well.

Furthermore dopaminergic effects and serotonin-binding properties could be responsible for reduction of vasomotor and psychological symptoms under treatment with Cimicifuga preparations.

Nevertheless, an overview article (Piersen 2003) summarises the existing knowledge concluding that the mode of action of Cimicifuga still remains unknown.

An overview article about Cimicifuga (Walji et al. 2007) reported 5 studies with patients with breast cancer and treatment with Cimicifuga. (In order of quality, highest to lowest):

Jacobsen 2001 - A randomized, placebo controlled, double blind trial; Medication: either Tamoxifen® plus Cimicifuga, Tamoxifen® plus placebo, Cimicifuga alone or placebo in 85 Patients (43 placebo and 42 treatment). 59 were on Tamoxifen®; the extract of Black Cohosh is not identified. Duration of the study was only 60 days. Both, the treatment group and the placebo group experienced a benefit in terms of reduced number and intensity of hot flushes. No significant improvement in other menopausal symptoms, except sweating was observed.

Pockaj 2006 - A randomized, crossover, double-blinded, with 2 4-week crossover periods in 132 patients with a history of breast cancer or perceived increased risk of breast cancer, 4 weeks therapy with Black Cohosh or placebo , then crossover without wash-out period. Treatment: 20 mg extract of Cimicifuga, standardised to 1 mg triterpene glycosides twice per day or

an identical appearing placebo. No significant difference for hot flushes or quality of life, no adverse event.

Munoz et al. 2003 -136 young (35 - 52 years) premenopausal breast cancer survivors were involved in an open label randomly assigned study to examine the effect of Cimicifuga racemosa on hot flushes caused by Tamoxifen® adjuvant therapy. The treatment presents an off-label use of an ethanol/water extract of Cimicifuga (Menofem/Klimadynon®) corresponding to 20 mg of herbal drug and 20 mg Tamoxifen®. The duration of treatment for Tamoxifen® was 5 years and for Menofem®/Klimadynon® 12 months. The combined administration of Tamoxifen® plus Menofem®/Klimadynon® for a period of 12 months allowed satisfactory reduction in the number of hot flushes. No statement is given about the influence on breast cancer.

Pockaj 2004 - A pilot study open-label, nonrandomized, nonblinded, 23 patients (21 evaluable), 13 of them had a history of breast cancer, 4 week treatment with standardized extract of Cimicifuga 20 mg (Remifemin®). Results: significant reduction of hot flushes, one report of joint pain; lack of placebo group, small sample size, short treatment period.

Rebbeck 2007 - A retrospective case-control study; in 949 cases of women with breast cancer, 1524 controls without breast cancer, interviews were performed about use of any hormone-related supplements, including Cimicifuga. The reported use of Cimicifuga was found to have a significant protective effect for breast cancer. There is only poor information concerning the use of Cimicifuga in the patient-group. Due to the design of the study, we could not follow the conclusion.

II.3.1.1.2 Overall conclusions on pharmacodynamics

To date the most widely accepted explanation for climacteric or menopausal complaints still is a decrease of oestrogens. Therefore, special interest has to be focused on symptoms or diseases caused by lack of the hormone or substitution of the hormone.

Tamoxifen is established as adjuvant therapy for breast cancer patients. It induces an artificial menopause, named “chemopause” by some authors. Effects of a co-medication with Cimicifuga preparations can support an oestrogenic or oestrogen like effect of Cimicifuga preparations. In this regards, results of clinical studies were inconsistent as shown above. Data from clinical studies on pharmacodynamics are not consistent to establish a single model on the mode of action of Cimicifuga. A possible effect on oestrogenic receptors has still to be taken into account. In some pharmacological experiments Cimicifuga extracts exhibited organ specific effects, which resemble effects caused by oestrogen. Knowledge and experimental data are not consistent enough to characterise Cimicifuga as so-called selective estrogen-receptor-modulator (SERM). There are no randomised, controlled trials assessing the efficacy of Cimicifuga as a treatment for breast cancer.

The evidence for the ability of Cimicifuga to relieve hot flushes associated with the menopause also in women with breast cancer remains inconclusive.

Effects on other oestrogen-sensitive tissues have been investigated in clinical trials to prove efficacy and safety; these are assessed under II.3.2.2.

To date there are no clinical studies in humans concerning the influence of Cimicifuga preparations on CNS located receptors, neurotransmitters or hormones.

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.

Cimicifuga weakly inhibited CYP2D6. Clinically relevant interactions with drugs metabolised by the CYP P450 enzymes are not found (Gurley et al. 2005).

Cimicifuga is not a potent modulator of P-gp activity in vivo and therefore do not pose a significant interaction risk with digoxin (Gurley et al. 2006).

Cimicifuga does not seem to have a clinically relevant effect on CYP3A activity in vivo. Whether the effect is a function of dose, solubility, bioavailability or a combination of factors remains to be investigated (Gurley et al. 2006).

Patel et al. in 2007 reported about a possible increase in liver enzymes secondary to combined Atorvastatin and Cimicifuga administration. A 53 years old woman with a past history for atypical chest pain, family history of coronary artery disease and menopause discontinued oral HRT, started Cimicifuga. The patient also took atorvastatin, aspirin, glucosamin/chondroitin and vaginal oestradiol. Routine laboratory results revealed an acute elevation of liver enzymes. After discontinuing Cimicifuga, her liver enzymes decreased within 1 month. The use of Cimicifuga concomitantly with atorvastatin may potentially have led to a drug-/herbal preparation-interaction resulting in an elevation of liver enzymes.

II.3.1.2.2 Overall conclusions on pharmacokinetics

There is only poor information on pharmacokinetics of Cimicifuga. There are some data concerning interactions, but they are not of clinical relevance, with the exception of the concomitant intake of Cimicifuga and atorvastatin.

II.3.2 Clinical Efficacy[5]

II.3.2.1 Dose response studies

Information on posology is derived from clinical studies and includes the long-standing use as well as recommendations contained in the German Commission E monograph (daily dose: 40 mg drug).

One study was performed comparing a daily dosage of 39 mg Cimicifuga (40% isopropanol) with 127 mg per day (Liske et al., 2000); duration of this was up to 6 months). One study was performed with a preparation of Cimicifuga standardised to 27 deoxyactin, 160 mg daily (Newton et al. 2006).

The investigation conducted by Liske et al. showed same effects in both treatment groups; Kupperman Index decreased from 31.0 (high dose) to 7.0 (high dose) after 3 months of treatment compared to 31.5 to 8.0 in the low dose group.

In the Newton et al. study the high dose group is comparable with the placebo treated group. As in both groups no reduction of postmenopausal vasomotor symptoms could be observed, there is no rationale for a high dose treatment.

As in both investigations no benefit of high dose treatment could be demonstrated, the results support the recommended daily dose of 40 mg drug.

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

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

For assessment of efficacy in the clinical studies predominantly the validated Kupperman Index (KI) or the Menopause Rating Scale I (physician) or II (patient) were used.

Kupperman-Index (modified)						
Symptoms	None (0)	mild (1)	moderate (2)	severe (3)	multiplicator (factor)	numerical conversion = factor x severity
Vasomotor					4	
Paresthesia					2	
Insomnia					2	
Nervousness					1	
Melancholia					1	
Vertigo					1	
Weakness					1	
Arthralgia & Myalgia					1	
Headache					1	
Palpitation					1	
Formication					1	
Assessment: < 20 = mild; 20 – 35 = moderate; > 35 = severe					Index →	

(Kupperman HS, Blatt MHG et al. 1953)

Menopause Rating Scale I (performed by physician) (10 items)

Menopause Rating Scale II (performed by patient) (11 items [additionally anxiety])

Menopause Rating Scale II					
Symptoms score	none 0	mild 1	moderate 2	severe 3	very severe 4
1.) Hot flushes, sweating (episodes of sweating)					
2.) Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)					

3.) Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early)					
4.) Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)					
5.) Irritability (feeling nervous, inner tension, feeling aggressive)					
6.) Anxiety [MRS II] (inner restlessness, feeling panicky)					
7.) Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)					
8.) Sexual problems (change in sexual desire, in sexual activity and satisfaction)					
9.) Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)					
10.) Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)					
11.) Joint and muscular discomfort (pain in the joints, rheumatoid complaints)					

(Heinemann et al. 2004, International versions of the menopause rating scale (MRS)

Menopausal complaints (symptoms)

Menopausal complaints are caused by a decrease in oestrogen production and are characterised by neurovegetative, somatic and emotional complaints. Hot flushes represent the leading symptom. The theory of the cause of hot flushes is that there is a dysfunction in the central thermoregulatory set point in the hypothalamus as a result of decreased oestrogen or decreased gonadal steroid levels. Norepinephrine is the primary neurotransmitter responsible for lowering the thermoregulatory set point. Serotonin might also have an important role. Thermoregulation seems to be dependent on the balance of these factors, and a disbalance might trigger hot flushes (Boekhout et al. 2006) In addition e.g. excitability, irritability and sleep disturbances are reported. These complaints are usually treated with oestrogens, but extracts of Cimicifuga racemosa are used for this indication, too.

The term “climacteric complaints” is frequently used for symptoms occurring in women before the actual menopause. However, this term may be inaccurate since not all of those symptoms are in fact caused by low oestrogen. Therefore, the most suitable expression is “oestrogen deficiency symptoms”. The most important oestrogen deficiency symptoms are vasomotor symptoms (hot flushes). The severity of hot flushes is defined clinically as follows:

- mild: sensation of heat without sweating
- moderate: sensation of heat with sweating, able to continue activity
- severe: sensation of heat with sweating, causing cessation of activity.

(EMEA/CHMP/021/97 Rev. 1: Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women. London, 13 October 2005).

Clinical studies indicated an efficacy of Cimicifuga extracts in patients with menopausal symptoms though none of them completely showed a significant improvement of the total Kupperman Score or the total Menopause Rating Scale Score.

In the following chapter those studies of higher quality conducted with defined Cimicifuga herbal preparations are mentioned first [in chronological order] (1 – 3), the others in chronological order.

(1) Wuttke et al. 2003 and Wuttke et al. 2006. A double-blind, randomized, placebo controlled multicentre, GCP conform study, n = 62 (20/22/20) postmenopausal patients, age 40-60 with a minimum of three hot flushes per day, postmenopausal hormone values (17 β-estradiol ≤ 40 pg/ml, FSH ≥ 25 mU/ml), the menopausal symptoms were assessed with the Menopause Rating Scale (MRS) and a diary., Furthermore, levels of CrossLaps (marker of bone formation) and the bone-specific alkaline phosphatase were examined at baseline and after 12 weeks. Endometrial thickness was measured via transvaginal ultrasound, vaginal cytology was also examined, duration of study was 12 weeks. The aim of the study was to examine whether Cimicifuga tablets(Klimadynon® 58% V/V ethanolic extract; 1 tablet corresponding to 20 mg of herbal drug) in comparison to a standard hormone replacement therapy and placebo, improve menopausal complaints and has positive oestrogenic effects in the vagina and on bone metabolism, without showing uterotrophic activity.

Medication used: Klimadynon 58% ethanol tablets, equivalent to 40 mg drug per day; conjugated oestrogen (CE) 0.6 mg /day; placebo.

The results only show a significant predominance of Cimicifuga and CE vs. placebo in the MRS regarding the subscore “atrophy” defined as decrease in sexual desire, sexual activity and satisfaction, complaints on urination, frequency to urinate, involuntary urination, feeling of dryness in the vagina, difficulties with sexual intercourse, and pain mainly in the finger joints, rheumatic-like pains, tingling. This subscore for Cimicifuga was better than placebo. The subscore “hot flushes” for CE was significantly better than placebo whereas this subscore for Cimicifuga did not reach the level of significance though showing a marked difference to placebo. Also in the subscore “psyche” the improvement of symptoms did not reach the level of significance.

Patients treated with Cimicifuga showed significantly increased serum levels of alkaline phosphatase, which is indicative for an effect of osteoblast activity. Cimicifuga appears to have osteoprotective effects in bones by increasing osteoblast activity. Cimicifuga did not show effects on endometrium, in contrast to CE (conjugated oestrogen), but had a mild oestrogenic activity in the vagina, interpreted as SERM activities. The normal clinical laboratory data including liver enzymes showed no difference and remained unaffected; no serious adverse events were reported. This study is fitting the predominance of Cimicifuga and the equivalence to CE compared to placebo regarding the subscores “atrophy”. Improvements concerning the subscores “hot flushes” and “atrophy” were not significant compared to placebo. In this study only 20 patients were treated with the Cimicifuga preparation. All results, including the demonstrated effects on osteoblast activity and oestrogenic (SERM) activities, have to be interpreted taking account of the small sample size.

(2) Frei-Kleiner et al. 2005. A multicentre, randomised, placebo-controlled double-blind, parallel group study in 122 menopausal women (including 43 perimenopausal women) with

≥ 3 hot flushes per day, treated over 12 weeks, with either Cimicifuga (6.5 mg dried extract (4,5-8,5:1), average of 42 mg crude drug, extraction solvent 60% ethanol) or placebo.

The primary analysis showed no superiority of the tested Cimicifuga extract compared to placebo. Regarding the subgroup of patients with a Kupperman Index ≥ 20, a significant superiority could be demonstrated. The results indicate a superiority of the tested Cimicifuga extract compared to placebo in patients with menopausal disorders of at least moderate intensity according to a Kupperman Index ≥ 20, but not in the whole population.

The weekly weighted score of hot flushes decreased 37% in Black cohosh group and 30% in Placebo group; the Kupperman index decreased 26% in Black cohosh and 17% in Placebo group. Data for the claimed significant improvement of MRS-score (decrease of score values 48% (verum) versus 14% (placebo) were not shown in this publication. A multivariate analysis resulted in a superiority of the plant nearly reaching significance. In a subgroup of perimenopausale patients (n=28 verum, 15 placebo) the active preparation showed superiority with trend to significance (p=0.052).

The study is fitting the predominance of Cimicifuga compared to placebo with approached significance regarding patients with moderate menopausal symptoms, as laid down in the Kupperman Index.

(3) Osmers 2005. A double-blind, randomised, placebo controlled, multicentre, GCP conform study in: n = 304 postmenopausal women, (e.g.≥ 12 months since last regular menstruation or ≥6 months plus FSH ≥ 50 U/L; age at least 45 years old, climacteric complaints as defined by Menopause Rating Scale (MRS) ≥ 0.4 in at least 3 items; (verum 153, placebo 151), duration of treatment 3 months. Medication: Dry extract from Cimicifuga rootstock 2.5 mg, DER 6 – 11:1, extraction solvent: Isopropanol (40% V/V). Remifemin® (2 x 1 tablet) equivalent to 40 mg herbal substance per day. Efficacy measure was the decrease in MRS score after treatment compared to baseline. The total score of the MRS improved 0.03 – 0.05 [Menopause rating scale units] (p=0.01); data are not shown in publication; 3 subscores (hot flushes, atrophy and psyche) improved, the subscore "soma" did not show a difference to placebo. The efficacy of the extract was better in the early menopause. Good tolerance of the medication was described. Concerning the subscores hot flushes, atrophy and psyche the study is fitting the predominance of Cimicifuga compared to placebo. The claimed improvement of the subscores "hot flushes" (p=0.007), "atrophy" (p=0.012) and "psyche" (p=0.019) can not be deduced from the available data.

There are numerous clinical studies, which can support the efficacy and safety of Cimicifuga preparations. Most of them are lacking a placebo group:

(4) Stolze 1982. A non-interventional study, multicentre, n = 629, on average 51 years old, 6-8 weeks treatment. Improvement of menopausal symptoms was shown in 80% of women; no severe, only gastrointestinal adverse events. Medication used: Remifemin® 60% ethanol 2 x 40 drops, lack of placebo group, no validated scales. Descriptive improvement of symptoms (%) were shown in detail. Neurovegetative complaints → Hot flushes: 86.6%, sweating: 88.8%, headache: 81.9%, dizziness 86.6%, palpitations: 90.4%, tinnitus: 92.9%. Emotional complaints → nervousness: 85.6%, sleep-disorders: 76.8%, depressive disorders: 82.5%.

(5) Daiber 1983. An open, uncontrolled, n = 36, 45-62 years old, 3 month duration. Significant decrease of menopausal-index (Kupperman) from moderate (19) to light (11) after 12 weeks; decrease in hot flushes, sweating, nervousness, depressive disorders and sleep disorders (graphically shown without details); also significant decrease in CGI (Clinical Global Impression), good tolerance; Medication used: Remifemin® 60% ethanol 2 x 40 drops, lack of placebo group.

(6) Vorberg 1984. An open uncontrolled, n = 50, 38 postmenopausal women with contraindication for Hormone replacement therapies, 45-60 years old, 3 months treatment. Significant decrease of menopausal-index (Kupperman) from moderate to light, significant improvement of mood profile, no serious adverse events only mild gastrointestinal adverse events. Medication used: Remifemin® 60% ethanol 2 x 40 drops, lack of placebo group.

(7) Warnecke 1985. An open, controlled, randomized, n = 60 (20/20/20 treated with Remifemin® 60% ethanol 2 x 40 drops, or conjugated Oestrogen 0.625 mg/day or 2 mg diazepam, 3 months, under Cimicifuga treatment significant decrease of menopausal-index (Kupperman) and in HAMA (anxiety-scale), somatic disease under diazepam not influenced, tendentious increased proliferation of the vaginal epithelia under oestrogen as well as under Cimicifuga. Changes in vaginal cytology could hint at oestrogenic activity of Cimicifuga. Withdrawal from the study in 5 cases because of non amelioration of emotional symptoms; lack of placebo group.

(8) Pethö 1987. An open study, n =50, change in therapy (Pre-treatment: oestrogen), age on average 49 years , 6 months treatment, significant decrease of menopausal-index from 17.6 to 9.2 after 6 months (Kupperman), no adverse events, medication used: Remifemin® 40% isopropanol 2 x 2 tablets, lack of placebo group.

(9) Stoll 1987. A double-blind, randomized, placebo and reference controlled, n = 80 (30/30/20) treated with Remifemin® (40% isopropanolic extract) 2 x 2 tablets, conjugated oestrogen or placebo, 46-58 years old, 3 month, predominance of Cimicifuga, compared to placebo, decrease of menopausal-index (Kupperman) below 15 ($p<0.001$) and HAMA, vaginal cytology, all three parameters had significantly improved,, 13 withdrawals because of ineffectiveness in the oestrogen group. The administered oestrogen dose proved to be too low and yielded no effect compared to placebo. Changes in vaginal cytology could hint at oestrogenic activity of Cimicifuga. Three adverse effects of weight gain were reported without details.

(10) Lehmann-Willenbrock 1988. An open, controlled, randomized, n = 60 hysterectomized women. 4 treatment groups: Remifemin® (40% isopropanolic extract) 2 x 2 tablets, conjugated oestrogen 1.25 mg/day, estriol 1 mg/day, oestrogen/gestagen combination, 6 months treatment. In all groups significant decrease of menopausal-index (modified Kupperman index), no influence of LH, FSH, no adverse events, lack of placebo group.

(11) Georgiev & Lordanova 1997. An open uncontrolled, n = 50 postmenopausal women, 6 months treatment , decrease of menopausal-index (Kupperman) and HAMA, no change in endometrium thickness. Changes in vaginal cytology could hint at oestrogenic activity of Cimicifuga. No data on medication and adverse events. Very poor data available.

(12) Mielnik 1997. An open uncontrolled, n = 34 postmenopausal women, 6 months treatment, after 1 month clinically relevant decrease of menopausal-index from >20 to <10 (Kupperman), 4 drop outs, no more information on medication. Only very poor data available.

(13) Neßelhut & Liske 1999. A non-interventional study, n = 28, postmenopausal women, age on average 56.4 years, 3 months treatment, after 1 month clinically relevant decrease of menopausal-index (Kupperman), no influence to LH, FSH and Prolactin, no hormonal effects (or oestrogen agonistic activities) could be verified; no ovarian stimulation could be shown. Good efficacy in

neurovegetative symptoms, no adverse events. Medication: Remifemin® 40% isopropanol tablets 136 mg drug per day, which is approximately the threefold recommended daily dose, lack of placebo group.

(14) Liske et al. 2000. A double-blind, randomized, GCP-conform , n = 152 (76/76 Remifemin® (40% isopropanolic extract) tablets, equivalent to 39 mg drug per day or 127.3 mg drug per day, age 42-60 years, 3/6 months therapy duration, significant decrease of menopausal-index (Kupperman) in both groups from moderate to normal range. Also in SDS (self depression scale, CGI (clinical global impression scale) and in vaginal cytology no differences in the treatment groups were observed.19 mild to moderate adverse events without definite causal relationship to the investigational product, no serious adverse events in both groups, lack of placebo group.

(15) Nappi et al. 2005. A randomized clinical study to examine the efficacy of an isopropanolic extract (40 mg Remifemin®) compared with low dose transdermal estradiol. Hormonal parameters as FSH, LH, Prolactin, 17β-estradiol, cortisol, lipid profile, liver function and endometrial thickness were measured as well. 64 postmenopausal women were enrolled in the study (32 on Cimicifuga), duration was 3 months, both therapies significantly reduced the number of the hot flushes per day ($p<0.001$), no changes in laboratory parameters and thickness of the endometrium were observed. Significant improvement in anxiety and depression symptom rating tests. Lack of placebo group.

(16) Briese et al. 2007. A non-interventional study, n = 6141, 3027 treated with Remifemin® (40% isopropanolic extract) 2 tablets, equivalent to 40 mg drug per day (n=2798 received tablets, n=229 received medication as solution) and 3114 patients treated with Remifemin®plus hypericum, age on average 52 years, 6 months duration, after 3 months an interims analysis was made; a significant decrease in Menopause-Rating-Scale (MRS I) was claimed in both groups in all items (MRS total score and sub-scores soma, psyche, atrophy and hot flushes) ; results for the pre-defined primary effectiveness variable was the change in the MRS subscore PSYCHE from baseline to month 3 in the ITT-population; the choice of covariates and their influence on statistical results remain unclear and the claimed results could not be accepted. Theses results might have been observed under placebo treatment as well; good tolerance on the medication. Lack of placebo group.

(17) von Schoultz et al. 2005.(also published as Hirschberg Al et al. 2005) An open uncontrolled, n = 74 (age 50-70), 6 months, normal change in thickness of endometrium, no change on breast density, no adverse events, Remifemin® (40% isopropanolic extract) 2 x 1 tablets, equivalent to 40 mg drug per day. On breast epithelial cell proliferation and mammographic breast density in postmenopausal women, no proliferation of breast density and no increase of KI-67 positive cells (a marker of proliferation of breast tissue) was observed. There is only limited information; due to the design, we could not follow the conclusion of the study. Lack of placebo group, small sample size.

(18) Bai Wenpei 2005. A double-blind, parallel-controlled study, efficacy and tolerability of 40% isopropanol 2 x 1 tablets, equivalent to 40 mg active substance per day vs. Tibolone in 240 patients with menopausal symptoms, age 40 to 60 years, 84 days treatment. Cimicifuga can improve the menopausal complaints effectively and safely. Its efficacy-safety balance is non-inferior and even superior to Tibolone in Chinese women with peri- and postmenopausal menopausal complaints. Comparability and acceptability of results derived from an Asian study population to those of other ethnicities were not discussed.

(19) Newton et al. 2006. An one year lasting randomized, double-blind, placebo controlled trial with 351 women aged 45 to 55 with 2 or more vasomotor symptoms per day, 52% of the women were in menopausal transition and 48 % were postmenopausal; Medication was:

1. Cimicifuga standardised to 27 deoxyactin, 160 mg daily,
2. multibotanical with Cimicifuga 200 mg daily and 9 other ingredients,
3. multibotanical plus soy diet counselling,
4. conjugated equine oestrogen 0.625 mg daily, with or without medroxyprogesteron acetate 2.5 mg daily,
5. Placebo;

Vasomotor symptoms per day did not differ between the herbal interventions and placebo at 3, 6, 12 months or for the average over all the follow-up time points. The author gives independently from this results the conclusion, that Cimicifuga used in isolation or as part of a multibotanical regimen, shows no potential as an important therapy for relief of vasomotor symptoms.

(20) Raus et al. 2006. this study had the objective to investigate endometrial safety by endometrial biopsy samples and the tolerability and efficacy of Cimicifuga (corresponding to 40 mg of herbal drug, Klimadynon® 58% V/V), it is an open label, noncomparative, prospective, multicentre and multinational study in 400 postmenopausal women with symptoms related to oestrogen deficiency. The duration was 52 weeks. Investigated items: Endometrial biopsy, endovaginal sonography, bleeding.episodes diary, mammography, hormone blood samples; Menopause rating scale II, record of frequency and intensity of hot flushes per day in diary. Primary outcome: Occurrence of endometrial hyperplasia after 52 weeks of treatment. Endometrial safety has been proven as no cases of hyperplasia occurred (measured by endovaginal ultrasonography), the number of hot flushes was markedly decreased. This study supports the thesis that the investigated product has no oestrogenic or oestrogen like effects on the endometrium within a 12 months treatment period. There was no influence on breast density. No clinically relevant changes in hormone levels were observed. Lack of placebo.

(21) Oktem (Öktem) et al. 2007. a prospective, randomised study which compared the efficacy of Cimicifuga and Fluoxetine on 120 postmenopausal Turkish women with menopausal complaints. 3 months treatment plus 6 month follow-up visit. Modified Kupperman-Index, diary for intensity and quantity of hot flushes and night-sweats, Beck's depressions-scale and Rand-36 Quality of life questionnaire were carried out. High drop-out rate (33% in both treatment groups), no valid information on the tested Cimicifuga preparation (Remixin). The design, conduction and reporting could not be accepted.

(22) Ruhlen et al. 2007. A randomized, 2-armed study without placebo to evaluate the oestrogenic properties of Cimicifuga on the breast. The study goals were to determine at first the triterpene contents of two (0.5 mg of Remifemin® or CimiPure, each 40 mg capsule contains 1 mg 23-epi-25deoxyactein) Cimicifuga extracts. Furthermore, the effect of Cimicifuga on circulating and breast-specific oestrogenic markers should be demonstrated. 61 postmenopausal women took Cimicifuga for 12 weeks followed by a 12 week wash-out period. The Blatt-Kupperman menopause index was used to collect data of menopausal symptoms. The aspirated breast fluid was analyzed for estradiol and cytology was performed. The biological activity of Cimicifuga triterpens includes cytotoxicity to tumour cells, inhibition of MCF-7 cell proliferation, antioxidant activity, serotonin receptor binding. Cimicifuga has some effects similar to oestrogen. In this study Cimicifuga did not alter serum LH, FSH, estradiol, suggesting that Cimicifuga has no systemic or breast specific

oestrogenic effects. The menopausal symptoms were reduced by at least 1 point in the Blatt-Kupperman menopause index.

Menopausal symptoms in patients with breast-cancer

(23) Jacobsen et al. 2001. A double-blind, randomised, placebo controlled study in 85 patients with breast cancer, 59 under Tamoxifen®- therapy, age 50-60, 8 weeks treatment, no significant decrease in hot flushes, but in sweating, compared to placebo, no significant change in LH and FSH level, significant lower values compared to the groups with Tamoxifen, 3 severe adverse events and 10 others, medication used was: Remifemin® (40% isopropanolic extract) 2 tablets, equivalent to 40 mg drug per day.

(24) Munoz & Pluchino 2003. An open controlled, randomised, n = 136 (90/46) premenopausal breast cancer patients with primary therapy, aged 35-52 years old, 12 months treatment, significant reduction of number and intensity of hot flushes, 11 not serious adverse events, medication used was: Klimadynon® (58% ethanolic extract), 2 tablets, equivalent to 40 mg drug per day, Tamoxifen® 20 mg per day.

(25) Look , Morris et al. 2001. A double-blind, randomized, crossover study, n = 21 patients with breast cancer, 60 days treatment with a wash-out period of 7 days, medication used was: Cimicifuga extract (not defined), equivalent to 80 mg drug per day, venlafaxin 24 mg per day; under both medications reduction of number and severity of hot flushes, no data on adverse events. Poor information, not performed by physicians or medical staff.

(26) Bartsch & Fischer et al. 2006. non-interventional study, 50 patients with mamma carcinoma and menopausal symptoms under the therapy of Tamoxifen, six months, Remifemin (40% isopropanolic extract) 2 tablets per day, equivalent to 40 mg drug, dosage changed partially in a number of patients due to their needs, lack of placebo group, small sample size. Drop out rate about 25%. MRS II and three subscores (vegetative-somatic, psychologic, urologic symptoms); MRS II sum-score decreased from 17.6 to 13.6, subscores vegetative and psychologic also decreased. Urogenital symptoms remained unchanged.

(27) Becher et al. 2007. A pharmaco-epidemiological cohort study in patients with mamma carcinoma, including hormone-receptor-positive tumours, examined were 18861 patients with breast cancer, 1102 of them were treated with Remifemin®/Remifemin® plus. There are no clear results for efficacy and safety of Remifemin®. A minimised risk of 17% for a relapse is claimed for patients under treatment with Remifemin or Remifemin plus compared with the control group.

9 more overview articles covering the same studies have been published:

Moyad 2002 reported about the study Jacobsen 2001, he found that more studies relating to safety and mechanism of action are necessary.

Chlebowski 2003 also reported about the study Jacobsen 2001.

Simpson 2004 also reported about the study Jacobsen 2001 and the study Morris 2001.

Hickey 2005 reported about the study Jacobsen 2001, and the study Munoz & Pluchino 2003, she found that there are no convincing data to show a benefit greater than placebo.

Carpenter 2005 reported also about the study Jacobsen 2001, he found that Cimicifuga has been shown to act as a mixed competitive ligand and partial agonist of the 5-HT-7 receptor.

Boeckhout 2006 also reported about the study Jacobsen 2001, the study Munoz & Pluchino 2003 and the study Pockaj 2004, she found that the data on the effect of Cimicifuga in the treatment of hot flushes are conflicting.

Bruno 2006 reported also about the study Jacobsen 2001, the study Osmers 2005 and the study **Rockwell 2005**, she found that Cimicifuga can be used in an attempt to control menopausal symptoms, provided that patients are vigilant about possible hepatotoxicity and their use during the active antineoplastic treatment is avoided.

Bordeleau 2007 reported also about the study Jacobsen 2001 and the study Pockaj 2006.

Antoine 2007 found that very few data are available about the safety of Cimicifuga in breast cancer patients.

There are only two randomised, controlled trials in patients with breast cancer, one of them showed no statistically significance for the ability of Cimicifuga to relieve hot flushes associated with menopause in women with breast cancer. The other study showed a reduction of symptoms of menopause, whether it was statistically significant or not was not reported.

The data on the effect of Cimicifuga in the treatment of hot flushes in patients with breast cancer are conflicting.

There are no randomised, controlled trials assessing the efficacy of Cimicifuga for breast cancer.

Instruments (tests) used in clinical trials:

Kupperman Index: Rating-scale asking for several symptoms of menopausal discomfort

Menopause Rating Scale MRS: Rating-scale asking for several symptoms of menopausal discomfort

HAMD: Hamilton Depression Scale

HAMA: Hamilton Anxiety (rating) Scale

CGI: Clinical Global Impression

SDS: Self Rating Depression Scale

BDI: Beck's Depression Inventory

Vaginal cytology

Endovaginal ultrasonography

Mammography

Diary

Rand-36 Quality of life questionnaire

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

No data available in children, due to the indication menopausal symptoms children are excluded and studies are not necessary. In some of the studies the examined women had an age up to 70 years, but no special studies for elderly have been performed.

II.3.2.4 Overall conclusions on clinical efficacy

A total of 27 clinical trials with approximately 5300 patients treated with Cimicifuga in menopausal symptoms can be taken to support the efficacy in the proposed indication "Herbal medicinal product for the relief of minor symptoms of menopausal complaints."

Not one of the GCP conform conducted studies showed unambiguous results for the predefined improvement of menopausal complaints regarding the validated scores (Kupperman or Menopause Rating Scale).

The reasons for the vast variety of results are multifactorial:

a.) The complaints which are intended for treatment are not precisely defined.
b.) The groups of patients to be treated are not precisely defined.
c.) Instruments used for measurement of treatment benefits might be insufficient.

Ad a.) Lists of complaints composed of 10 or more single symptoms do not reflect the symptoms of an individual. The symptoms of the individual depend on many factors, most of them are not known. In case of menopausal complaints, e.g. age, hormonal status, ethnicity (Heinemann et al. The menopause rating scale, 2004), coincidences of diseases have to be taken into consideration.

Regarding the "Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1, 13 October 2005)" which defines the vasomotor symptoms as main criteria, it seems to be beneficial to investigate these symptoms as primary efficacy endpoint.

Ad b.) The only group of women with menopausal complaints that is defined precisely is represented by the postmenopausal women (last regular menstruation >12 months ago, FSH level > 40 U/L). In this defined group valid study results could be expected.

Especially for herbal medicinal products the group of perimenopausal women is the preferred target group for treatment of menopausal complaints. There are no other sufficient therapeutic options for this group, as hormone replacement therapy is obsolete. Therefore, the whole transition period has to be investigated carefully for Cimicifuga preparations to grant efficacy and safety for this age group. The term climacteric refers to the period of menopausal transition and this period between fertility and sterility is defined by: subfertility, accelerated loss of follicles after 38 years of age, increasingly anovulatory with luteal phase defects, initial shortening of the cycle, thereafter longer irregular cycles, increase in early follicular FSH; often low progesterone levels in second half. Contraception needs and climacteric complaints. Empty nest situation; midlife crisis. (Kenemans P, 2003)

As shown above, the first symptoms of menopausal complaints start in the fertile period of women. Therefore, contraception is absolutely needed and pregnancy should be excluded before starting with Cimicifuga treatment because of the furthermore possible hormonal properties of this drug. Though perimenopausal women have unsteady hormone levels which can lead to divergent results in efficacy, a reduction on the hot flushes for assessment would reflect the therapeutic effects more powerful.

Ad c.) All investigations until now showed incoherent results due to the extended variety of diagnostically used instruments. The attempt was to cover almost all symptoms that appear in the menopause. As mentioned above, for assessing hormone replacement therapies, only the hot flushes and secondarily the sweating and sleep disturbances are evaluated. This procedure would support

claimed indications (hot flushes, sweating and sleep disturbances/disorders) for Cimicifuga preparations.

As there is no good quality controlled clinical study which covers all relevant symptoms of the validated total scales to substantiate efficacy, it is necessary to proceed in a case-by-case assessment, to prove efficacy , "Guideline on the assessment of clinical safety and efficacy in the preparation of community herbal monographs for well-established and of community herbal monographs / entries to the community list for traditional herbal medicinal products / substances / preparations (EMEA/HMPC/104613/2005)" – see Chapter "Elements of the clinical documentation supporting a monograph.")

Out of the 27 studies 23 were selected as supportive for the indication proposed. (11, 12 were excluded due to very poor available data, because not performed by physicians or medical staff (25) or because of other study goals (27)).

In these 23 investigations most of the menopausal symptoms were shown to be influenced more or less positively by treatment with Cimicifuga preparations. As no high level study has demonstrated significant results for the used scores in total or especially for "hot flushes", the positive results of all studies were subsumed covering the indication "minor symptoms of menopausal complaints".

As there are no alternative therapeutic options, especially in perimenopausale women, in women with breastcancer or other tumours, the long standing use of these herbal medicinal products and the suggested extremely high sales numbers in the Community and worldwide are accepted as indicators for efficacy in the framework of a well-established use.

The duration of treatment in the studies was from 6 weeks (25), 8 weeks (4, 23), 6 months (8, 10, 16,17, 26) up to 12 months (19, 20, 24); all others were 12 weeks.

Four of the studies were non-interventional studies, 8 of them were open, uncontrolled and 2 of them were open and randomized, 7 of them were double-blind and randomized.

There is sufficient evidence by clinical trials to use specified herbal preparations of Cimicifuga racemosa for the treatment of minor menopausal symptoms. (Indication: Herbal medicinal product for the relief of minor neurovegetative menopausal complaints (such as hot flushes and sweating)).

Patients with breast cancer should be excluded from treatment with Cimicifuga preparations.

II.3.3 Clinical Safety/Pharmacovigilance

II.3.3.1 Patient exposure

II.3.3.2 Adverse events

Liver toxicity has been associated with the use of Cimicifuga containing products.

Allergic reactions of skin (urticaria, itching of the skin, exanthema), facial oedema,

peripheral oedema and gastrointestinal symptoms (i.e. dyspeptic disorders, diarrhoea) have been reported. The frequency is not known.

The report of the HMPC of 8 May 2007, the assessment of case reports connected to herbal medical products containing Cimicifuga root reported about cases with liver damages, even noticed as undesirable effects or cases from literature. There are 44 partially poor documented cases, for 4 of them there is a coherence between liver damage and intake of Cimicifuga, in 2 cases the coherence is probable, the patients developed an autoimmune-hepatitis. Until now, there is no known dose dependence. A correlation to a pathophysiological mechanism is not known. Meanwhile 15 further cases have been reported; nearly all are poorly documented and are not assessable.

There are two literature reports of as yet unknown adverse events.

Muscle damage induced by black cohosh, Minciullo et al, 2006, in Phytomedicine 13 (2006) 115-118:

This is a case report about a 54-year old woman with a severe asthenia. Some days after the appearance of symptoms, the patient underwent, under medical counselling, blood laboratory exams, showing: CPK 237, 230 U/l (normal 24-170 U/L), LDH 504, 548 (normal 230-460 U/l9, total cholesterol 277, 282 mg/ml (normal 120-250), all samples were repeated after 9 days. Other parameters such as blood cell count, AST, ALT GGT, kidney and thyroid functionally indexes were in normal range. The same laboratory exams including muscle enzymes, effectuated by the patient three month before, had shown no alteration. The patient referred to take Remifemin® for ameliorating menopause vasomotor symptoms, each tablet contains 20 mg of dried rhizome and root extract. The patient had taken 1 tablet twice a day for 1 year and then discontinued the therapy, she restarted the same therapy 2 months later. Asthenia appeared 2 months later the re-assumption of Remifemin®. Patient did not change life, no sports and no other drugs. The author hypothesised a causative role for Cimicifuga in this case.

Cutaneous Pseudolymphoma induced by Cimicifuga racemosa, S. Meyer et al, 2007, in Dermatology 2007; 214: 94-96:

There is a report about a 56-year –old female patient who presented with asymptomatic, localized erythematous plaques on arms and legs. Histologically, the diagnosis of pseudolymphoma was confirmed. Because of menopausal complaints, the patient has taken Remifemin®, for 1 year. Six months after initial administration first skin lesions appeared. Withdrawal of Remifemin® resulted in regression and complete remission of the lesions within 12 weeks. This is the first report of a pseudolymphoma. However allergic skin reactions have been reported.

The problems linked to the quality of reports on hepatotoxicity have been considered in evaluation and discussion of all data available. The proposals concerning re-assessment of hepatotoxicity recently published by Teschke et al. cannot be accepted. (Causality assessment in hepatotoxicity by drugs and dietary supplements. Rolf Teschke, Alexander Schwarzenboeck & Karl-Heinz Hennermann, British Journal of Clinical Pharmacology (BJCP) / 66:6 / 758 – 766. Suspected hepatotoxicity by Cimicifuga racemosa rhizoma (black cohosh, root): Critical analysis and structured causality assessment, R. Teschke, A. Schwarzenboeck, Phytomedicine 16 (2009) 72-84; Black cohosh hepatotoxicity: quantitative causality evaluation in nine suspected cases, R. Teschke, R. Bahre, J. Fuchs, A. Wolff, Menopause, Vol. 16, No. 5, 2009 (Ahead of print)) The changes in Teschke's Assessment Score compared with the established RUCAM Score (see below) are not validated. It is an artificial selection of criteria (post-test) which cannot be covered by the recently used pharmacovigilance information system. To commemorate the history and rationale for choice of the Rucam-score in the assessments of hepatotoxicity of Cimicifuga racemosa, the following text might be helpful, which was published in EMEA/HMPC/269258/2006, Rev. 1.

RUCAM Score (Roussel UCLAF causality assessment method)

At the request of CIOMS, international meetings were organised by Roussel UCLAF. Eight international experts formed a group dealing with hepatotoxicity: Benhamou JP, Danan G (France), Bircher J (Germany), Maddrey WC, Zimmermann HJ (USA), Neuberger J (UK), Orlandi F (Italy) and Tygstrup N (Denmark). In 1993, the international group of experts published the so-called RUCAM Score to evaluate cases of hepatotoxicity (Danan et al 1993). The score was validated and the results published (Benichou et al. 1993).

Conclusion:

The procedures, recommended by Teschke et al. for assessment of hepatotoxicity, are not practicable. The data, which would be needed for assessment (especially post-test data), are not available and therefore nearly all cases would be "not assessable" due to insufficient reports.

II.3.3.3 Serious adverse events and deaths

There was one death according to hepatic failure and consecutive liver transplantation. The causal relationship to Cimicifuga seems to be plausible. It is important to add, that interaction of concomitant Fluoxetine, paracetamol and propoxyphene, together with alcohol-abuse may have contributed to the hepatic failure.

II.3.3.4 Laboratory findings

If examined, there were no significant changes in laboratory values. Patients suffering from hepatic disorders showed an increase in liver enzymes.

Spangler et al 2007, A study to examine the laboratory parameters in 45-55 years old, peri- or postmenopausal women experiencing vasomotor symptoms. 351 women participated in a 3-months, double blind trial randomized to Cimicifuga alone (160 mg daily), a .multibotanical with Cimicifuga 200 mg daily and 9 other ingredients, a. multibotanical plus dietary soy counselling, a. conjugated equine oestrogen 0.625 mg daily, with or without medroxyprogesteron acetate 2.5 mg daily, and at least placebo. Baseline and month 3 total cholesterol, high density lipoprotein (HDL) cholesterol, low density (LDL) cholesterol, triglyceride, insulin, glucose and fibrinogen serum concentrations were measured in 310 women. There were no statistically significant differences in the adjusted mean change from baseline to 3 month between the herbal groups and placebo in total cholesterol, high density lipoprotein (HDL) cholesterol, low density (LDL) cholesterol, triglyceride, insulin, glucose. Adjusted fibrinogen levels appear to increase in the multibotanical treatment group in comparison with the other herbal groups and placebo. Liver enzymes not have been examined.

II.3.3.5 Safety in special populations and situations

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

No data available on children, due to the indication menopausal symptoms children are excluded and studies are not necessary. In very few and less well-documented studies the examined women had an age up to 70 years, no conspicuous findings in elderly were seen in this studies. No special studies for elderly have been conducted.

II.3.5.5.2 Drug interactions

Pharmacokinetic studies in healthy volunteers showed no clinical relevant influence in safety of Cimicifuga. Cimicifuga weakly inhibited CYP 2D6. Clinically relevant interactions with drugs metabolised by the CYP P450 enzymes were not found (Bill J. Gurley et al. American society for clinical pharmacology and therapeutics 2005).

Cimicifuga is not a potent modulator of P-gp activity in vivo and therefore does not pose a significant interaction risk with digoxin (Bill J. Gurley et al. Department of pharmaceutical science 2005).

Cimicifuga appears to have no clinically relevant effect on the CYP3A activity in vivo. Whether the effect is a function of dose, solubility, bioavailability or a combination of factors remains to be seen (Gurley et al. 2006).

Patel et al. (2007) reports about a possible increase in liver enzymes secondary to Atorvastatin and Cimicifuga administration. A 53 years old woman with a history of atypical chest pain, familial history of coronary artery disease and menopause discontinued oral HRT, started Cimicifuga. The patient also took atorvastatin, aspirin, glucosamin/chondroitin and topical vaginal estradiol. Routine laboratory results revealed an acute elevation of liver enzymes. After discontinuing Cimicifuga her liver enzymes decreased within 1 month. The use of Cimicifuga concomitantly with atorvastatin may potentially lead to a drug-herb interaction resulting in an elevation of liver enzymes and should be observed closely. Particular attention should be given to the potential CYP3A4 drug interactions.

Use in pregnancy and lactation

There is a lack of basic knowledge on use of Cimicifuga racemosa in pregnancy and lactation. In Germany for the well-established (strong scientific evidence B1) indication menopausal symptoms, this patient-group is excluded.

A search in 7 databases (AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database and Natural standard) about using Cimicifuga racemosa in pregnancy and lactation led to an abstract by Dugoua, J-J et al. : Safety and Efficacy of Black Cohosh (Cimicifuga racemosa) during Pregnancy and Lactation. This article was published in Can J Clin Pharmacol Vol 13 (3) Fall 2006: e257-e261; November 3, 2006. It is shown that Cimicifuga racemosa in the United States is used by 45% of midwifes to induce labour. Cimicifuga in the United States is part of a combination (in addition Mitchella ripens, Rubus idaeus, Caulophyllum thalictroides and Chamaelirium luteum) of herbal medicines that have been traditionally used in the third trimester to prepare women for delivery. A low-level (4) incidence of harm, i.e. indirect evidence based on scientific theory or expert opinion, shows the following concerns to the use of Cimicifuga during pregnancy: labour inducing effects, hormonal effects, emmenagogue properties and anovulatory effects. During lactation there is a low level evidence. Cimicifuga should be used with caution as in vitro evidence suggests hormonal properties. It is unclear whether Cimicifuga has an oestrogenic or anti-oestrogenic effect or no effect on the oestrogenic receptor.

II.3.3.5.4 Overdose

As reported in Hager in not specified dose vertigo, nausea, headache, stiffness and tremor of limbs could occur. In lower dose, even not specified gastrointestinal discomfort occurs. (Hagers Enzyklopädie, Springer Medizin Verlag Heidelberg, 6. Auflage 2007: 644-661)

II.3.3.5.5 Drug abuse

No data available

II.3.3.5.6 Withdrawal and rebound

No data available

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

No data available

II.3.3.6 Overall conclusions on clinical safety

The data from clinical trials with defined herbal preparations from Cimicifuga are demonstrating a reasonable safety. Except the possibility of hepatotoxic reactions, which has to be taken into consideration during treatment there are no major safety concerns. Patients with a history of liver disorder or liver diseases should take Cimicifuga preparations with caution. For patients who are or have been treated because of a tumour disease the use of Cimicifuga preparations is not recommended.

II.4 OVERALL CONCLUSIONS

Cimicifuga racemosa is a well known herb which has been used worldwide for decades in many herbal medicinal products, as for example since 1940 in Germany. To date in Germany 20 preparations for more than 10 years, 4 preparations for more than 30 years are in use. It is known, that huge amounts of daily dosages of Cimicifuga racemosa preparations are sold worldwide since years. Cimicifuga racemosa is positively described in a Monograph of the German Commission E (BAnz Nr. 43) published 2 March 1989 and in ESCOP Monographs, second edition 2003. Furthermore, the scientific interest in the use of the substance reflects the importance of Cimicifuga preparations for treatment of menopausal complaints. In summary, in more than 5000 patients included in more than 20 clinical trials an improvement of minor menopausal symptoms could be demonstrated. Also numerous preclinical studies have been performed which cover aspects for safety and efficacy. Comparing the huge amount of worldwide sold daily dosages of Cimicifuga racemosa preparations with the small number of reported adverse events, the use of Cimicifuga racemosa appears to be safe under appropriate labelling. Hormone replacement therapy is no therapeutic alternative and is obsolete in pre- and perimenopausal women. Its use is strictly limited to postmenopausal women (Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women; EMEA/CHMP/021/97 Rev. 1). All these Arguments indicate the benefit of Cimicifuga racemosa in the use for relief of minor menopausal symptoms.

On the other hand, the potential risks of preparations containing Cimicifuga racemosa can be minimised sufficiently by adequate labelling under “contraindications” and “special warnings and precautions for use”. Except for the published cases concerning effects of Cimicifuga racemosa on the hepatic function and increased laboratory values of liver function tests, there are only few reports on serious adverse events or side effects of the drug. The risks of hepatotoxicity are covered by the following wording under “special warnings and precautions for use”:

“Patients with a history of liver disorder should take Cimicifuga preparations with caution, see under undesirable effects.

Patients should stop taking Cimicifuga preparations and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (tiredness, loss of appetite, yellowing of skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine)."

This also reflects the contents of the German graduated plan regarding Cimicifuga racemosa which came into effect in June 2009.

There are two literature reports of before unknown adverse events; these are regarded as signals, the causal connection to the intake of Cimicifuga preparations was assessed as probably related. ("Muscle damage induced by black cohosh", Minciullo et al., 2006 in Phytomedicine 13 (2006) 115-118 and "Cutaneous Pseudolymphoma induced by Cimicifuga racemosa", S. Meyer et al., 2007 in Dermatology 2007; 214: 94-96.)

As there is an ongoing discussion on the mode of action of preparations containing Cimicifuga racemosa, a hormonal or hormone-like activity of any kind cannot be excluded at this stage. For safety reasons it seems appropriate to use Cimicifuga racemosa under supervision of medical staff and not as self-medication. Also, the recently discussed probability of an increased risk of metastasis under Cimicifuga racemosa treatment supports the need for information of patients through concrete labelling of the risks and through appropriate advice by involved health care professionals.

Under consideration of all these arguments, a "Well-Established-Medicinal-Use" indication for the treatment of minor menopausal symptoms with Cimicifuga racemosa seems appropriate. The benefit / risk assessment has to be judged positive regarding the benefit.

There is a formal tradition for a product which is traditionally used for treatment of rheumatism in the UK. Data on tradition in the treatment of rheumatism and also data on usage of other than the specified extracts in the treatment of menopausal symptoms are limited. The possibility of a hormone-like action on oestrogenic receptors, the risks related to hepatotoxicity and possible promotion of metastases in tumour bearing individuals are indicators that Cimicifuga preparations are not suitable for a registration as tradition herbal medicinal product.

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPHS ON *CIMICIFUGA RACEMOSA* (L.) NUTT., RHIZOMA[6,7]

III.2 LITERATURE REFERENCES

[6] According to the 'Procedure for the preparation of Community monographs for traditional herbal medicinal products' (EMEA/HMPC/182320/2005 Rev.2)

[7] According to the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMEA/HMPC/182352/2005 Rev.2)