



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 November 2010
EMA/HMPC/3968/2008
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Cimicifuga racemosa* (L.) Nutt., rhizoma

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Cimicifuga racemosa</i> (L.) Nutt., rhizoma (black cohosh)
Herbal preparation(s)	a) Dry extract (DER 5-10:1), extraction solvent ethanol 58% (V/V) b) Dry extract (DER 4.5-8.5:1), extraction solvent ethanol 60% (V/V) c) Dry extract (DER 6-11:1), extraction solvent propan-2-ol 40% (V/V)
Pharmaceutical forms	Herbal preparation in solid dosage forms for oral use.
Rapporteur	Dr Werner Knöss



Table of contents

Table of contents	2
1. Introduction	3
1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof .	3
1.2. Information about products on the market in the Member States	4
2. Historical data on medicinal use	5
2.1. Information on period of medicinal use in the Community	5
2.2. Information on traditional/current indications and specified substances/preparations ...	5
2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications.....	12
3. Non-Clinical Data	13
3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof	13
3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof	15
3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof	15
3.4. Overall conclusions on non-clinical data	16
4. Clinical Data	17
4.1. Clinical Pharmacology	17
4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents	17
4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents	19
4.2. Clinical Efficacy	19
4.2.1. Dose response studies.....	19
4.2.2. Clinical studies (case studies and clinical trials).....	19
4.2.3. Clinical studies in special populations (e.g. elderly and children).....	30
4.3. Overall conclusions on clinical pharmacology and efficacy	30
5. Clinical Safety/Pharmacovigilance	33
5.1. Overview of toxicological/safety data from clinical trials in humans.....	33
5.2. Patient exposure	33
5.3. Adverse events and serious adverse events and deaths	33
5.4. Laboratory findings	34
5.5. Safety in special populations and situations	35
5.6. Overall conclusions on clinical safety	36
6. Overall conclusions	38
Annex	39

1. Introduction

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

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 the literature on the potential oestrogenic activity of some medicinal plants. One of these plants is *Cimicifuga racemosa*. Concepts have been suggested describing the effects as phytoestrogens 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. Besides, women with menopausal complaints, especially women undergoing breast cancer therapy are looking for alternatives to HRT, which is contraindicated in these patients. 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 glycosides; amongst them actein, cimifugosid and cimircemosids. 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. Amounts up to 3.5 µg/g dry weight have been isolated from rhizomes by means of methanolic extraction. 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 small amounts.

Common names in Germany are: *Cimicifuga*-Wurzelstock, Frauenwurz, Nordamerikanische Schlangenzwurz, Wanzenkrautwurz. In English the plant is known as black cohosh; other common names are: black snakeroot, blackroot, rattleroot.

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

- Herbal substance(s)

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

- Herbal preparation(s)
 - a) Dry extract from *Cimicifugae rhizoma* (DER 5-10:1); ethanol 58% (V/V)
 - b) Dry extract from *Cimicifugae rhizoma* (DER 4.5-8.5:1); ethanol 60% (V/V)
 - c) Dry extract from *Cimicifugae rhizoma* (DER 6-11:1); propan-2-ol 40% (V/V)

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Combinations with *Hypericum* can be found on the market¹.

This monograph refers exclusively to *Cimicifuga racemosa*.

1.2. Information about products on the market in the Member States

Regulatory status overview

Member State	Regulatory Status				Comments (not mandatory field)
Austria	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	6 authorised mp
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Bulgaria	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	5 authorised mp
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Czech Republic	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	2 authorised mp
Denmark	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	2 authorised mp
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Finland	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	1 authorised mp
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Germany	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	37 authorised mp
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Hungary	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	6 authorised mp
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	none
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	none
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	none
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Lithuania	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	1 authorised mp
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Medicinal product
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	none
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response
Spain	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No response

¹ Assessment according to the 'Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations' (EMA/HMPC/166326/2005)

Member State	Regulatory Status				Comments (not mandatory field)
Sweden	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	1 registered tmp
United Kingdom	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	1 registered tmp

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'

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

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Cimicifuga has been used in North American indigenous medicine for hundreds of years, in the treatment of different conditions, such 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 1830, in the US pharmacopoeia under the name "black snakeroot".

In Germany *Cimicifuga* has been used since 1940 as a natural agent for treating premenstrual, dysmenorrhoeal and menopausal neurovegetative symptoms. Nowadays only menopausal neurovegetative symptoms (such as hot flushes and profuse sweating) are accepted as indications. The dried rhizome of the plants is used according to the Monograph of the Commission E (Bundesanzeiger Nr. 43, published 2 March 1989, revised 14 December 1994) 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 marketing authorisations since 1999.

Extracts that are listed in the USP 32, NF 27 Volume 1 (The United States Pharmacopeia; The National Formulary, Official from May 1; 2009. Dietary Supplements: Black Cohosh pp 986-990) were not taken into account. The USP is not relevant for the preparation of the Community herbal monograph on *Cimicifugae racemosae radix*. There are no herbal medicinal products marketed in the European Union with the specification of the USP. Studies on efficacy and safety have not been performed with these preparations.

A "new extract ... produced by a special technique which prevents losses of compounds by the transfer from the plant into the extract" (ZE 450) was also not taken into account. This extract is not marketed as a medicinal product in the European Union. Therefore, the studies published by Brattström (2005) and Schmidt et al. (2005) were excluded from the assessment.

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

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

1. Austria: Well-established use

- a) Drops containing liquid extract, 58% (m/m) ethanol, DER 1:5, 20 g root per 100 g preparation, (since 1973), 3 times 30 drops corresponding to 0.9 g root, later 3 times 20 drops.

Tablets containing dry extract, 26.64 mg per tablet, corresponding to 150 mg root, (since 1995), initially 3 times 2 tablets corresponding to 0.9 g root, later 4 tablets daily.
- b) Tablets containing dry extract, 50% (m/m) ethanol, DER 7-12:1, 1.66-2.86 mg extract per tablet corresponding to approximately 43 mg root, (since 2001), 1 tablet daily.
- c) Film coated tablets containing dry extract, 58% (V/V) ethanol, DER 7-12:1, 1.66-2.86 mg extract per tablet corresponding to approximately 21.5 mg root per tablet, (since 2002), 2 times 1 tablet corresponding to 43 mg root.
- d) Tablets containing 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 to 20 mg root, (since 1999), 2 times 1 tablet corresponding to 40 mg root.
- e) Tablets containing dry extract, 50% (m/m) ethanol, DER 7-12:1, 4.5 mg extract per tablet corresponding to approximately 43 mg root per tablet, (since 2000), 1 tablet daily corresponding to 43 mg root.

Indications:

Product a, b) Dysfunctions of sex hormone balance, particularly in the pre- and post-menopausal climacterium.

Product c, e, f) Perimenopausal complaints, PMS (premenstrual syndrome).

Product d) Neurovegetative and psychic climacteric disorders.

Risks: None reported.

2. Bulgaria: Well-established use

- a) Oral drops 50 ml, 100 ml, 150 ml, Extractum, cimicifugae racemosae fluidum (1:5), 60% ethanol (V/V), 12 mg extract is equal to 2.4 mg of the herbal substance, (31 October 2001), 2 times 20 drops daily.
- b) Tablets x60, x100, x200, Extractum, cimicifugae racemosae siccum, 40% Isopropanol, 0.018-0.026 mg extract is equal to 20 mg of the herbal substance, (31 October 2001), 2 times 1 tablet daily.
- c) Oral drops 50 ml, 100 ml, Extractum, cimicifugae racemosae fluidum (1:10), 20 g/100 ml, 69.7% ethanol (V/V), (07 August 2002), 30-40 drops daily.
- d) Capsules x50, x100, Extractum, cimicifugae racemosae siccum (4:1), 5 mg/capsule, (07 August 2002), 2 times 1 capsule daily.
- e) Film-coated tablets x60, x90, Extractum, cimicifugae racemosae siccum (5-10:1), 2.8 mg in a tablet, 58% ethanol (V/V), (26 May 2005), 2 times 1 film tablet daily.

Indications for all products:

Premenstrual syndrome, menopause associated with nervous disorders, painful menstruation.

3. **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 capsules after meal.
- c) Dry extract (other data not available), tablet, 1 tablet (53.34 mg of extract) daily after meal during a month.

Indications:

Product a) PMS (pre-menstrual-syndrome) and menopause difficulties relief; support at menstrual disorder.

Product b) Menopause difficulties removal.

Product c) Menopause difficulties relief.

Risks:

Product a) Contraindicated in pregnancy and lactation.

Product b) Not mentioned.

Product 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).

4. **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/tablet, (since 1999), 1 tablet per day (after 6 months of use a gynaecologist should be contacted).
- b) *Cimicifuga* dry extract (7-12:1), extracted with ethanol 58% (V/V), 1.66-2.86 mg/tablet (corresponding to 20 mg of herbal substance), 1 tablet two times daily.

Indications:

Product a) Mild pre- and post-menopausal neurovegetative symptoms such as nervousity, mood swings, irritability, profuse sweating, hot flushes and sleep disorders.

Product b) Mild to moderate pre- and post-menopausal neurovegetative symptoms such as nervousity, mood swings, irritability, profuse sweating, hot flushes, sleep disorders and concentration disorders.

Risks:

Product a) Contraindications: known hypersensitivity to active substance, tumours of breast or uterus (even if suspected), pregnancy and lactation, risk of hepatotoxicity (see EMA public statement).

Product 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 a gynaecologist should be contacted. Risk of hepatotoxicity (see EMA public statement).

5. **Denmark: Well-established use**

- a) Tablets containing 0.018-0.026 ml extract of black cohosh (*Cimicifuga racemosa*) rhizoma, corresponding to 20 mg rhizome. Extraction solvent: isopropanol 40% (V/V), (09 March 1999),

1 tablet 2 times daily. Should not be used continuously for more than 6 months without medical advice.

- b) Tablets containing extract of black cohosh (*Cimicifuga racemosa*) rhizoma, corresponding to 20 mg rhizome. Extraction solvent: ethanol 58% (V/V), (25 August 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 have been reported, as well as few reports of postmenopausal bleedings. Special warnings: Not to be used by women who have 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 have been reported.

Further information on existing standard marketing authorisations, combination products etc.:

Cimicifuga is not permitted as a food supplement in Denmark.

6. Finland: Well-established use

- a) *Cimicifugae racemosae* rhizoma extractum siccum (1:1) 20 mg, (25 October 2000), 1 tablet 2 times daily.

Indication:

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

Risks:

Contraindicated: hormone dependent breast cancer (past or known), hepatic insufficiency, hypersensitivity to active ingredients or excipients. Not recommended if liver values have been/are abnormal.

Adverse effects:

Vaginal bleeding, breast tension, liver injury.

7. Germany: Well-established use

- a) 20 preparations (No. 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 (No. 3, 35) containing liquid extract (1:1), extraction solvent: ethanol 60% (V/V); tincture (No. 4) (1:10), extraction solvent: ethanol 69.7% (V/V); dry extract (No. 5, 33) (7-12:1), extraction solvent: ethanol 50% (m/m); dry extract (No. 7) (4-9:1), extraction solvent: ethanol 58% (V/V); 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); dry extract (No.21, 31) (4.1-6.5:1), extraction solvent: ethanol 60% (V/V); tincture (No. 26) (1:5), extraction solvent: ethanol 50% (V/V); dry extract (No. 29) special extract BNO 1055 (5-10:1), extraction solvent: ethanol 58% (V/V); tincture (No. 36) (1:5), extraction solvent: ethanol 40% (V/V); dry extract (No. 37) (6.6-8.7:1), extraction solvent: 60% (V/V).

10 preparations since 1998 (No. 1, 7, 9, 10, 13, 18, 22, 26, 28, 34); 12 preparations since 1997 (No. 2, 5, 6, 8, 11, 12, 14, 23, 24, 25, 27, 30); one (No. 3) since 2001; one (No. 4) since 1993; 3 (No. 15, 16, 17) since 2006; 4 (No. 19, 29, 36, 37) at least since 1976; 2 (No. 20, 33) since 2004; one (No. 21) since 1999; one (No. 31) since 1996; one (No. 32) since 2000; one (No. 35) since 1995.

- b) Pharmaceutical forms: capsules, hard; film-coated tablets; tablets; oral liquids, coated tablets.
- c) Posology: 1 times 1 containing 6.5 mg dry extract (No. 1, 2, 6, 8, 9, 18, 22, 23, 24, 25, 27, 28, 30, 32, 34); 1 times 1 ml containing 40 mg liquid extract (=25-30 drops) (No. 3); 2 times 30-40 drops, 1 g (=1 ml) = 33 drops, 100 g (=100 ml) contain 20 g tincture (No. 4); 1 times 1 containing 4.5 mg dry extract (No. 5, 33); 1 times 1 containing 6 mg dry extract; (No. 7); 2 times 1 containing 2.5 mg dry extract (No. 15, 16, 17, 19); daily 25 ml (1 times 15 ml + 1 times 10 ml), 100 ml (=104.4 g) liquid contain 658 mg tincture (No. 20); 1 times 1 containing 7 mg dry extract (No. 21); 2 times 30 drops (2 times 0.9 ml, corresponding to 206.4 mg tincture per day), 100 g liquid contain 12 g tincture (No. 26); 2 times 1 containing 2.8 mg dry extract (No. 29); 1 times 1 containing 8 mg dry extract (No. 31); 1 times 20 drops, 100 ml liquid containing 4.5 g liquid extract (No. 35); 2 times 10 drops, 100 ml liquid containing 19.8 ml tincture (No. 36); 2 times 1 containing 2.675 mg dry extract (No. 37).

Indications:

No. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 20, 21, 22, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37:

For improvement of psychological and neurovegetative complaints due to the menopause.

No. 15, 16, 19: For improvement of psychological and neurovegetative complaints due to the menopause such as hot flushes, sweating, sleep disorders, nervousness and depressive mood.

No. 23: For symptomatic treatment of psychological and neurovegetative complaints, due to the menopause.

Risks:

Since 9 June 2009 a graduated plan is effective in Germany concerning the risks of hepatotoxicity and the consumption of *Cimicifuga* containing medicinal products.

8. Hungary: Well-established use

- a) Tablets (original or mixed), *Cimicifugae rhizoma* liquid extract (0.78-1.14:1) 0.018-0.026 ml/tablet, extraction solvent: 40% isopropanol (V/V) (corresponding to 20 mg herbal substance), (28 February 2000), 1 tablet twice daily (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) Film-coated tablets (original or mixed application), *Cimicifuga rhizoma* dry extract (7-12:1), 1.66-2.86 mg/film-coated tablet, extraction solvent: ethanol 58% (V/V), (26 April 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) Tablets, *Cimicifuga racemosa* rhizoma dry extract (4-9:1) 4.5 mg/tablet, ethanol 50% (w/w), (20 April 2004). The daily dosage 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) Mono hard capsules, *Cimicifuga racemosa* rootstock dry extract, native (6.6-8.7:1), extraction solvent: ethanol 60% (V/V), 2.675 mg/caps.; (16 October 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) Film-coated tablets, dry extract of *Cimicifuga rhizoma*, (4.5-8.5:1), 6.5 mg/ tablet, extraction solvent: ethanol 60% (V/V), (1 October 2001/1 June 2007). Unless otherwise prescribed, 1 film-coated tablet daily. Tablet should be taken with enough liquid, preferable at the same time (in the morning or in the evening).
- f) Capsules, *Cimicifugae rhizoma extractum siccum* (4.5-8.5:1), 6.5 mg/capsule, extraction solvent: ethanol 60% (V/V), (29 April 2004). Take one capsule daily. Capsules should be taken at the same time of the day (in the morning or in the evening). The duration of treatment is generally 6 months, but the application of capsule is not recommended for more than 3 months without medical advice.

Indications:

Product a, c, e) Relief of menopausal (climacteric) neurovegetative complaints such as hot flushes, profuse sweating, sleeping problems, nervousness and depressive mood.

Product b) Relief of menopausal (climacteric) neurovegetative complaints.

Product d) For improvement of psychical and neurovegetative disorders caused by the menopause.

Product f) Symptomatic treatment of menopausal (climacteric) complaints.

Risks:

Product 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 rhizoma*. 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.

Product b) In very rare cases gastrointestinal disorders (dyspepsia, diarrhoea), allergic skin reaction (urticaria, pruritus, rash), facial oedema, peripheral oedema and weight increase may occur. 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.

Product c) Occasional gastrointestinal disturbances. In the case of feeling tension or swelling in the breasts a doctor should be consulted. 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.

Product d) Rarely (less than 1 of 1000, but more than 1 of 10000 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.

Product e) Rarely gastro-intestinal complaints can occur and an increase in weight is also possible. 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.

Product f) Rarely gastro-intestinal complaints can occur and an increase in weight is also possible.

9. **Iceland:** No marketing authorisation and not on the market.

10. **Ireland:** No authorised products on the Irish market containing *Cimicifuga racemosa*.

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

12. **Lithuania: Well-established use**

Extractum siccum (4:1), ethanolum, (9 November 2000). Oral + 5 mg 2 times daily.

Indications:

Climacteric complaints; premenstrual disorders; dysmenorrhoea disorders.

Risks: Not mentioned.

13. **Norway:**

Cimicifuga racemosa L. (NUTT.) is classified as medicinal product.

Not on the market.

14. **Portugal:** No marketing authorisation and not on the market.

15. **Sweden: Traditional Use**

Rhizoma, 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.

16. United Kingdom: Traditional use

Liquid extract of black cohosh 5 ml contain 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 daily. Not for children.

Indications:

An 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.

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

Daily dose:

Extracts corresponding to 40 mg of the herbal substance. This dosage is in line with the German Commission E Monograph on *Cimicifugae racemosae rhizoma* (02 March 1989; revised 14 December 1994). A benefit of a higher dose treatment could not be shown.

Evidence regarding the duration of use:

Cimicifuga should not be taken for more than 6 months without medical advice.

In 7 clinical trials (Lehmann-Willenbrock, Lindén Hirschberg, Liske, Munoz, Pethö, Raus, Reed) 758 patients were treated for 6 or more months with *Cimicifuga racemosa* preparations. In addition, non-interventional studies with a total of 3 074 patients (Briese, Fischer) support the duration of use for 6 months. Therefore, 3 832 patients could be taken into account in the safety assessment. Bearing in mind possible risks as regards a duration exceeding 6 months, a 6 months' treatment constitutes a scientifically justified compromise.

Three studies had to be excluded due to deficient quality of data and/or unspecified extracts (Georgiev & Iordanova, Mielnik and Oktem).

- Briese 2007 [n=3027, iCR] non-interventional study, 6 months
- Fischer 2006 (= Bartsch, Fischer, Stammwitz) [n=47, iCR + tamoxifen] non-interventional study, 6 months
- Georgiev and Iordanova 1997 [n=50, unspecified extract], 6 months, to be excluded
- Lehmann-Willenbrock and Riedel 1988 [n=13, iCR], 6 months
- Lindén Hirschberg 2007 (= von Schoultz, = Lindén Hirschberg 2005) [n=74, iCR], 6 months
- Liske 2002 [n=116, iCR], 6 months
- Mielnik 1997 [n=34, unspecified extract], 6 months, to be excluded
- Munoz 2003 [n=90, dried ethanolic (58% V/V) extract CR BNO 1055], 12 months
- Öktem 2007 [n=60, unspecified extract], to be excluded
- Pethö 1987 [n=50, iCR], 6 months
- Raus 2006 [n=335; dried ethanolic (58% V/V) extract CR BNO 1055], 12 months

- Reed 2008 (=Newton: Halt study) [n=80; black cohosh (160 mg/d 2.5% triterpene glycosides, 70% ethanol extract)], 12 months

There are no safety data available allowing a recommendation for an additional treatment with *Cimicifuga* after interruption of an initial *Cimicifuga* treatment of 6 months.

To estimate the frequency of adverse events, the "Rule of Three" is commonly used (Hanley, Lippman-Hand 1983). To be 95% confident that an interval estimate of the long-run risk is correct, the "Rule of Three" which states that if none of n patients shows the event about which we are concerned, we can be 95% confident that the chance of this event is at most three in n (i. e. 3/n).

In this context this leads to: $3/3 \cdot 832 = 0.00078$, which is 7.8 patients of 10 000 (rare: ($\geq 1/10\ 000$ to $\leq 1/1.000$)). In consequence in these study populations uncommon ($\geq 1/1\ 000$ to $\leq 1/100$) adverse events can be excluded in case of 3 832 study participants.

As long as any hormonal effects of *Cimicifuga* preparations cannot be excluded and furthermore liver toxicity remains possible, the duration of use must be restricted. In the context of data from long-term studies and the huge amounts of daily doses sold worldwide, a limitation to 6 months for the use of *Cimicifuga* preparations is appropriate and scientifically justified.

3. Non-Clinical Data

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

Around 1980, the first investigations were performed in order to examine the binding to oestrogen receptors and the influence on breast cancer cells and endometrium.

***In vitro* tests**

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

No proliferative virility was observed with the breast cancer cell line MDA-MB 435 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). No information on extracts is available.

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

Different ethanolic extracts [no more information] in very low concentrations caused a significant increase in cell number of oestrogen dependent MCF-7-Cells (Löhning 1999). Dixon-Shanies and Shaikh (1999) showed that a 0.1% ethanolic extract of *Cimicifuga* had significant growth inhibitory effects on serum stimulated T-47D cells.

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. (2001) observed oestrogen-like proliferation at low *Cimicifuga* concentrations but antioestrogen-like inhibition at high concentrations in human breast cancer MCF cells (CR extract; active ingredient, 2.5%; Pure world Botanicals Ltd., Bedminster, NJ, USA).

Amato et al. (2002) 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 [no more information].

Cimigenol and 39 related compounds (isolated from *C. japonica*, "commercially available *Cimicifuga* plants" and *Cimicifuga simplex*) 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 was 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) extract containing 2 mg triterpene glycol deoxyactein and 1 mg isoflavenoids as formononetin (Rockwell et al. 2005).

The interpretation of the results must rely on a thorough understanding of the 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 hormones FSH, prolactin and LH did not change after a 14 day treatment in ovariectomised rats with a 50% ethanolic *Cimicifuga* extract. After a three day treatment LH and prolactin levels were significantly reduced; after a one day treatment prolactin levels were increased (Jarry & Harnischfeger 1985).

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

Ovariectomized DA/Han rats were treated with an isopropanolic *Cimicifuga* extract alone or in combination with the anti-estrogen fulvestrant in comparison to estradiol and controls. Uterine and vena cava gene expression were investigated. *Cimicifuga* extracts had no uterotrophic effects and does not seem to act as an estrogen agonist, but possibly as a weak antioestrogen (Kretschmar et al. 2005).

Ovariectomized (ovx) rats were treated with an ethanolic *Cimicifuga* extract (BNO 1055) = 33 mg per day for 3 months; 3 parallel groups were treated with 0.325-0.35 mg E₂ or 12.5 mg soy extract containing 0.6 mg genistein and 1.3 mg daidzein or placebo. The study was performed to demonstrate the pharmacology of the *Cimicifuga* extract on bones, fat and uterus of the treated rats. Conclusion: The extract BNO 1055 exerted estrogenic effects in the bone (particularly in osteoblasts) and in fat tissue, but not in the uterus of ovx rats. The extract appears to contain rat organ-specific selective estrogen receptor modulators (SERMs). If these findings can be confirmed in human, it may be an alternative to HRT (Seidlová-Wuttke et al. 2003).

An *in vivo* investigation of a clinically tested isopropanolic extract showed that treatment with *Cimicifuga* extract did not stimulate cancer 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 ovariectomised, allowed to recover, and 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 were administered. The animals were sacrificed 6 weeks later and tumours (number and 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 cancer growth. The hormone levels, organ weights and endometrial proliferation were unaffected (Freudenstein et al. 2002).

A study with MMTV-neu transgenic mice was performed in order 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* (isopropanolic extract) was provided via diet in order 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 modify women's risk of developing breast cancer either beneficially or adversely. In contrast to its lack of effect on primary mammary tumour development, *Cimicifuga* negatively influenced the 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 in order to examine the 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 metastases were analysed. *Cimicifuga* did not promote further growth or metastatic potential of the primary tumour. Pulmonary metastases were frequently found in all groups (Nißlein and Freudenstein 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-fluorouracil; the ethylacetate fraction enhanced doxorubicin (Einbond et al. 2006, 2007).

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

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

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

Acute toxicity

There are no studies on acute toxicity.

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 body weight (equals to 250, 1 800 and 5 000 mg granulate/kg body weight). 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 values returned to normal after 8 weeks of recovery. The NOEL was therefore defined with 21.06 mg/kg body weight (Korn 1991; Freudenstein 1997).

Genotoxicity

The mutagenicity of the isopropanolic extract was studied in an Ames test. The test was conducted with the *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538. The highest concentration was 1 000 µg per 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 et al. 1998; Dixon-Shanies et al. 1999; Freudenstein et al. 1999, 2002; Liu et al. 2001; Amato et al. 2002; Rockwell et al. 2005; Einer-Jensen et al. 1996; Nißlein and Freudenstein 2004; Einbond et al. 2006). In a study with MMTV-neu transgenic mice *Cimicifuga* accelerated the 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 at or above 75 µg/ml and mitochondrial beta-oxidation was impaired at concentrations at or above 10 µg/ml. The mitochondrial membrane potential was decreased at concentrations at or above 100 µg/ml and the oxidative phosphorylation was impaired at concentrations at or above 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.

3.4. Overall conclusions on non-clinical data

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 hormone dependent or oestrogen dependent tumours like breast or endometrial cancer.

Pharmacokinetic

No specific information available.

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 body weight for the isopropanolic extract could be found (human equivalent dose of 3.23 mg/kg body weight). The daily dosage of the isopropanolic extract is about 0.08 mg/kg body weight (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 to the extract preparation. Because of this fact and the lack of 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 body weight. This can be calculated to a human equivalent dosage of ~0.1 mg/kg body weight. The therapeutic dose in humans is ~0.08 mg/kg body weight. In all clinical studies and in the preclinical study with the isopropanolic extract microvesicular steatosis was not detected in humans, even when 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 the sole evidence basis for eventually 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.

4. Clinical Data

4.1. Clinical Pharmacology

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

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 summarises the existing knowledge concluding that the mode of action of *Cimicifuga* still remains unknown (Piersen 2003). This also reflects the inconsistent results of numerous preclinical and clinical investigations. An overview article about *Cimicifuga* (Walji et al. 2007) reported 5 clinical studies with patients with breast cancer and treatment with *Cimicifuga* (in the order of quality, highest to lowest):

1. Jacobson et al. (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 of other menopausal symptoms except sweating was observed.
2. Pockaj et al. (2006): A randomized, crossover, double-blinded, with two 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* (twice daily), which is supposed to be similar to Remifemin, standardised to 1 mg triterpene glycosides twice per day or placebo. No significant difference for hot flushes or quality of life, no adverse event. This trial failed to provide any evidence that black cohosh reduces hot flushes more than the placebo. No data on safety aspects were published.
3. Munoz & Pluchino (2003): 136 young (35-52 years) premenopausal breast cancer survivors were involved (usual care group [tamoxifen]: n=46, intervention group [tamoxifen + CR BNO 1055]: [n=90]) 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® [=CR BNO 1055]) corresponding to 20 mg of herbal substance 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.
4. Pockaj et al. (2004): A pilot study open-label, non-randomized, non-blinded, 23 patients (21 evaluable), 13 of them had a history of breast cancer, 4 week treatment with standardized extract of *Cimicifuga* 20 mg (Remifemin®) twice daily. Results: Significant reduction of hot flushes, one report of joint pain. Lack of placebo group, small sample size, short treatment period; there is no safety data available.
5. Rebbeck et al. (2007): A retrospective case-control study; in 949 cases of women with breast cancer and 1524 controls without breast cancer, interviews were performed about use of any hormone-related supplements, including *Cimicifuga*. The exact number of patients using Remifemin and/or black cohosh is not listed. The reported use of *Cimicifuga* (brand names, specific compounds, time of treatment and dosage are unknown) was found to have a significant protective effect for breast cancer (as cited in the preface of this publication). Additional confirmatory studies are required to determine whether black cohosh can be used to prevent breast cancer. There is only poor information concerning the use of *Cimicifuga* alone or in combination with tamoxifen in the patient group. Consequently, the authors conclude: "Substantial additional research must be

undertaken before it can be established that black cohosh, or some compound found in black cohosh, is a breast cancer chemopreventive agent. Furthermore, women may wish to seek guidance from their physician before using these compounds, and the data presented here do not suggest that the use of black cohosh is an appropriate substitute for standard hormone replacement therapy”.

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

Cimicifuga weakly inhibits 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 does 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 & Derkits (2007) reported a possible increase in liver enzymes secondary to combined atorvastatin and *Cimicifuga* administration. A 53 years old woman with a history for atypical chest pain, family history of coronary artery disease and menopause discontinued oral HRT and started *Cimicifuga*. The patient also took atorvastatin, aspirin, glucosamine/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.

4.2. Clinical Efficacy

4.2.1. 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 herbal substance).

One study has been performed comparing a daily dosage of 39 mg *Cimicifuga* (40% isopropanol) with 127.3 mg per day (Liske et al. 2002). The duration of this study 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. (2002), 40% isopropanolic extract, 39 mg versus 127.3 mg per day, showed the same effects in both treatment groups: the 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. (2006) study the results of the high dose group (*Cimicifuga* standardised to 27-deoxyactin, 160 mg daily) are 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 higher dose treatment.

As in both studies no benefit of higher dose treatment could be demonstrated, the results support the recommended daily dose of 40 mg herbal substance.

4.2.2. 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 et al. 1953)

The Kupperman Index (KMI) has also been used for the characterisation and quantification of menopausal symptoms. A quantitative assessment of symptoms is achieved by a grading according to their severity:

- 3 = severe
- 2 = moderate
- 1 = mild
- 0 = not present

Useful categories for describing clinical relevance of the index are (Schneider et al. 2000b):

No symptoms	0
Minor symptoms:	1-14
Mild symptoms:	15-19
Moderate symptoms:	20-34
Severe symptoms:	>=35

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. 2003, International versions of the menopause rating scale (MRS). The Menopause Rating Scale (MRS I) comprises 10 items with symptom intensities ranging from 0.0 (no symptoms) to 1.0 (very severe symptoms).

The individual degree of severity of an item is defined as follows (Schneider et al. 2000a):

Mild:	0.1-0.3
Moderate:	0.4-0.5
Severe:	0.6-0.7
Very severe:	0.8-1.0

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; an imbalance might trigger hot flushes (Boekhout et al. 2006). In addition, excitability, irritability and sleep disturbances are reported. These complaints were preferably treated with oestrogens or combinations of oestrogen with progestogen in the past, but extracts of *Cimicifuga racemosa* are used for this indication, too, especially after the results of the publication of the "Million Women Study" on HRT and associated risks (Beral 2003).

At present, the use of HRT is limited due to existing risks (Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women; [Doc. Ref. EMEA/CHMP/021/97 Rev. 1]). Perimenopausal women are out of the scope of HRT and therefore in search of therapeutic alternatives like many other patients who prefer herbal medicines.

The term "climacteric (menopausal) 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).

Due to lack of guidelines concerning herbal medicinal products for diagnosis and treatment of menopausal complaints it is appropriate to use the guideline for Hormone Replacement Therapy (EMEA/CHMP/021/97, Rev. 1) and other diagnostic instruments, derived from other established therapies.

For planning and conduction of adequate studies, the study population has to be predefined precisely. Only comparable complaints in comparable groups of patients can provide acceptable results concerning efficacy, safety and tolerability. Therefore, the target groups should be investigated separately, for example pre- and perimenopausal women on the one hand and postmenopausal women on the other hand. Additionally, breast cancer patients with and without other therapies except surgery should be included in the considerations about the conduct of studies. Different results are to be expected for the subgroups.

As the HRT deviates in target groups and indications from *Cimicifuga* preparation therapies, basic parameters have to be predefined for the use of herbal medicinal products in order to achieve reliable results; i.e. character, severity, duration and improvement of complaints have to be measured and compared from baseline over treatment up to follow up. Although the Kupperman scale, the different MRS scales and the guideline for Hormone Replacement Therapy (EMEA/CHMP/021/97, Rev. 1) are validated instruments, they were not developed for herbal medicinal products.

The large variety of different study protocols, inclusion and exclusion criteria, interpretation of results and conclusions thereof shows the need for validated and commonly used instruments.

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. Partly results were not shown in the publications, the sample

sizes were too small or the Kupperman Index and the Menopause Rating Scale were not validated for the study population (Asians). Therefore, the trials could not be accepted in their entirety.

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

(1) Wuttke et al. (2003, 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 (17β -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. The duration of the 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 substance) in comparison to a standard hormone replacement therapy and placebo, improve menopausal complaints and have positive oestrogenic effects in the vagina and on bone metabolism, without showing uterotrophic activity. Medication used: Klimadynon® 58% ethanol tablets, equivalent to 40 mg herbal substance 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 these 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 into account 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 herbal substance, 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 by 37% in the black cohosh group and by 30% in the placebo group. The Kupperman index decreased by 26% in the black cohosh and by 17% in the placebo group. Data for the claimed significant improvement of MRS-score (decrease of score values

by 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 perimenopausal patients (n=28 verum, 15 placebo) the active preparation showed superiority with a trend to significance (p=0.052).

The study demonstrates the predominance of *Cimicifuga* over placebo with nearly significance regarding patients with moderate menopausal symptoms, as laid down in the Kupperman Index.

(3) Osmer et al. (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 times 1 tablet) equivalent to 40 mg herbal substance per day. The efficacy was measured as the decrease in MRS score after treatment compared to baseline. The total score of the MRS improved by 0.03-0.05 Menopause rating scale units (p=0.01). However, the data are not shown in the publication. Three subscores (hot flushes, atrophy and psyche) improved, while 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 authors report superiority of *Cimicifuga* compared to placebo. However, 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 times 40 drops, lack of placebo group, no validated scales. Descriptive improvement of symptoms (%) was shown in detail. Neurovegetative complaints such as hot flushes: 86.6%, sweating: 88.8%, headache: 81.9%, dizziness 86.6%, palpitations: 90.4%, tinnitus: 92.9%. Emotional complaints such as nervousness: 85.6%, sleep-disorders: 76.8%, depressive disorders: 82.5%.

(5) Daiber (1983): An open, uncontrolled study, n=36, 45-62 years old, 3 months 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 times 40 drops; lack of placebo group.

(6) Vorberg (1984): An open, uncontrolled study, 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 times 40 drops; lack of placebo group.

(7) Warnecke (1985): An open, controlled, randomized study, n=60 (20/20/20 treated with Remifemin® 60% ethanol 2 times 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 times 2 tablets; lack of placebo group.

(9) Stoll (1987): A double-blind, randomized, placebo and reference controlled study, n=80 (30/30/20) treated with Remifemin® (40% isopropanolic extract) 2 times 2 tablets, conjugated oestrogen or placebo, 46-58 years old, 3 months, 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 study, n=60 hysterectomized women. 4 treatment groups: Remifemin® (40% isopropanolic extract) 2 times 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 and Iordanova (1997): An open uncontrolled study, 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 study, 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. Very poor data available.

(13) Nesselhut and 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 on 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 herbal substance per day, which is approximately the threefold recommended daily dose; lack of placebo group.

(14) Liske et al. (2002): A double-blind, randomized, GCP-conform study, n=152 (76/76 Remifemin® (40% isopropanolic extract) tablets, equivalent to 39 mg herbal substance per day or 127.3 mg herbal substance 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 such 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, $n = 6141$, 3 027 treated with Remifemin® (40% isopropanolic extract) 2 tablets, equivalent to 40 mg herbal substance per day ($n = 2 798$ received tablets, $n = 229$ received medication as solution) and 3114 patients treated with Remifemin® plus (contains 3.75 mg iCR extract and 70 mg of an ethanolic extract from 245 to 350 mg St. John's wort (*Hypericum perforatum*), age on average 52 years, 6 months duration, after 3 months an interim 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. These 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 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 times 1 tablets, equivalent to 40 mg herbal substance 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) were observed. There is only limited information. Due to the design one could not follow the conclusion of the study. Lack of placebo group, small sample size.

(18) Bai (2005): A double-blind, parallel-controlled study, efficacy and tolerability of 40% isopropanol 2 times 1 tablet, 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. The Kupperman Index and the MRS are not validated for Asian women.

(19) Newton et al. (2006): A one year lasting randomized, double-blind, placebo controlled trial with 351 women aged 45 to 55 years 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 and 12 months or for the average over all the follow-up time points. The author gives independently from these 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 substance, 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. Three 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, two-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-25 deoxyactein) *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* triterpenes 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) Jacobson et al. (2001): A double-blind, randomised, placebo controlled study in 85 patients with breast cancer, 59 under additional tamoxifen therapy, age 50-60 years, 8 weeks treatment, no significant decrease in hot flushes, but in sweating; compared to placebo, no significant change in LH and FSH level, significantly 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 herbal substance daily.

(24) Munoz and Pluchino (2003): An open controlled, randomised study, n=136 (90 CR + tamoxifen / 46 tamoxifen only) premenopausal breast cancer patients with primary therapy, aged 35-52 years, 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 herbal substance per day, tamoxifen 20 mg daily.

(25) Look and 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 herbal substance per day, venlafaxine 24 mg daily; 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 and Fischer et al. (2006): Non-interventional study, 50 patients with breast cancer and menopausal symptoms under the therapy of tamoxifen, six months, Remifemin® (40% isopropanolic extract) 2 tablets per day, equivalent to 40 mg herbal substance, 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. (2005): A pharmaco-epidemiological cohort study in patients with breast cancer, including hormone-receptor-positive tumours; 18.861 patients with breast cancer were examined, 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 by the authors in this abstract. The result remains unproven and has to be verified.

This pharmacoepidemiologic observational retrospective cohort study was later published by Henneicke-von Zepelin et al. (2007). Objective: "To investigate the influence of an isopropanolic *Cimicifuga racemosa* extract (iCR) on recurrence-free survival after breast cancer, including estrogen-dependent tumours." In conclusion, the authors summarized that an increase in the risk of breast cancer recurrence for women having had iCR treatment, compared to women not treated with iCR is unlikely. "Our study provides some evidence that the isopropanolic black cohosh extract (iCR) does not increase the risk of breast cancer recurrence, even among patients with estrogen-dependent tumours".

(28) Obi et al. (2009) (Marie study): Title: "The Use of Herbal Preparations to Alleviate Climacteric Disorders and Risk of Postmenopausal Breast Cancer in a German Case-Control Study". Herbal preparations (HEP) investigated in this study: Remifemin®, Remifemin® plus, other *Cimicifuga*, St. John's wort, Phytoestrogens (soy isoflavones and red clover), *Vitex agnus castus*, other specified HEP (including *Pulsatilla* and *Rheum rhaponticum*), unknown HEP.

A German case-control study including 10 121 postmenopausal women (3 464 cases, 6 657 controls). 409 patients (controls) [n=320 Remifemin or Remifemin plus; n=89 other *Cimicifuga*] treated with *Cimicifuga* or *Cimicifuga* plus St. John's Wort, 146 invasive breast cancer cases [112 + 34] under the same medication.

Confusing study design with many confounders. Author's conclusion: "In summary, we conclude that in postmenopausal women HEP use may exert a protective effect on risk for invasive breast cancer, irrespective of histologic type and receptor status. The specific ingredients responsible for this potential benefit need to be further elucidated".

The author's hypothesis still has to be verified and cannot be accepted to support the claimed protective effects of HEP (herbal preparations) against breast cancer in postmenopausal women particularly with regard to *Cimicifuga* preparations.

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

- Moyad (2002) reported about the study by Jacobson (2001); he found that more studies relating to safety and mechanism of action are necessary.
- Chlebowski (2003) reported about the study by Jacobson (2001).
- Simpson (2004) reported about the study by Jacobson (2001) and the study by Morris et al. (2001).
- Hickey (2005) reported about the study by Jacobson (2001), and the study by Munoz & Pluchino (2003); she found that there are no convincing data to show a benefit greater than placebo.

- Carpenter (2005) reported about the study by Jacobson (2001); he found that *Cimicifuga* has been shown to act as a mixed competitive ligand and partial agonist of the 5-HT-7 receptor.
- Boekhout (2006) reported about the study by Jacobson (2001), the study by 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 about the study by Jacobson (2001), the study by Osmer (2005) and the study by 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 about the study by Jacobson (2001) and the study by 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 available. One of them showed no statistical 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

Greene Climacteric Scale

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 (Rand-36 QoL)

Cervantes QoL (intended to be used in Spanish women aged between 45 and 64 years) (Palacios et al. 2004).

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

No data are available for use 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.

4.3. Overall conclusions on clinical pharmacology and efficacy

Pharmacodynamics

To date the most widely accepted explanation for climacteric or menopausal complaints is still 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 regard, results of clinical studies were inconsistent as shown in section 4.1.1. 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 a so-called selective estrogen-receptor-modulator (SERM). There are no randomised, controlled trials assessing the efficacy of *Cimicifuga* as a treatment for breast cancer.

Efficacy of *Cimicifuga* preparations was demonstrated in two studies (Munoz et al. 2003; Pockaj et al. 2004) in patients with breast cancer as regards the relief of hot flushes or sweating.

The available data show inconclusive results for the efficacy of *Cimicifuga* preparations in women with breast cancer under additional treatment with tamoxifen (see section 4.1.1).

The safety of *Cimicifuga* alone or in combination with tamoxifen could not be demonstrated for patients with breast cancer. The small number of patients and the short term duration of the studies are not sufficient to prove safety and efficacy of *Cimicifuga* preparations in patients with breast cancer. Due to the lack of data the use of *Cimicifuga* preparations or combined therapy with tamoxifen for patients with a history of or treated breast cancer or hormone dependent tumours is not recommended and should be avoided. Effects on other oestrogen-sensitive tissues have been investigated in clinical trials to prove efficacy and safety; these are assessed under 4.2.2.

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

Pharmacokinetics

There is only poor information on the 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.

Efficacy

A total of about 22 clinical trials (1-10, 13-15, 17-20, 22, 23-26, numeration as cited above under point 4.2), including studies in women with breast cancer, with approximately 2 200 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 menopausal complaints (such as hot flushes and profuse sweating)". Additionally a non-interventional study (16) and a pharmacoepidemiological study

(27) have to be taken into account with n=3 027 respectively n=1 102 patients. On the whole more than 6 300 patients were treated with *Cimicifuga* preparations in clinical studies.

In accordance with Article 10a of Directive 2001/83/EC, only studies were considered, which demonstrated that the active substance of the medicinal products fulfil the criteria of a well-established medicinal use.

Studies in patients with hormone-dependent breast cancer are assessed separately. Results for efficacy of *Cimicifuga* preparations in women with breast cancer and menopausal complaints with or without tamoxifen treatment are conflicting. As to date women with breast cancer or other hormone dependent tumours are excluded from the use of *Cimicifuga* containing preparations, the results claimed for efficacy are not relevant. For safety assessment, the number of included patients is too small to yield sufficient results.

The large variety of different study protocols, inclusion and exclusion criteria, interpretation of results and conclusions thereof shows the need for validated and commonly used instruments for further clinical studies and assessments of efficacy. None 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. 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 (EMA/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 the primary efficacy endpoint.

Ad b) The only group of women with menopausal complaints that is precisely defined 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.

For herbal medicinal products perimenopausal women represent the preferred target group for the 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 the second half of the cycle; contraception needs and climacteric complaints; i.e. empty nest situation; midlife crisis (Kenemans 2003).

As shown above, the first symptoms of menopausal complaints start still during the fertile period of women. Therefore, contraception is absolutely needed and pregnancy should be excluded before starting with *Cimicifuga* treatment because of the possible hormonal properties of this herbal substance. 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 in a more powerful way.

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 controlled clinical study of good quality 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 in accordance with the "Guideline on the assessment of clinical safety and efficacy in the preparation of community herbal monographs for well-established use and of community herbal monographs / entries to the community list for traditional herbal medicinal products / substances / preparations (EMA/HMPC/104613/2005)" (Chapter "Elements of the clinical documentation supporting a monograph").

Out of the 27 studies, 23 were taken into account supporting the indication proposed. Two studies (Georgiev & Iordanova 1997 and by Mielnik 1997) were excluded due to very poor data available, one study because it was not performed by physicians or medical staff (Look et al. 2001), and one study because of other study goals (Becher et al. 2005).

In these 23 investigations most of the menopausal symptoms were influenced more or less positively by the treatment with *Cimicifuga* preparations. As no study of high quality has demonstrated significant results for the used scores in total or in particular for "hot flushes", the positive results of all studies were taken into account and summarised in the indication "Herbal medicinal product for the relief of menopausal complaints (such as hot flushes and profuse sweating)".

As there are no alternative therapeutic options, especially for perimenopausal women, for women with breast cancer or other hormone dependent tumours, the long standing use of these herbal medicinal products and the high sales numbers in the Community and worldwide are accepted as indicators for efficacy in the framework of a well-established use. Nevertheless, *Cimicifuga* preparations should not be used by women with a history of breast cancer or other hormone depending tumours for safety reasons.

The duration of treatment in the studies varied from:

6-8 weeks

(Stolze (1982) [n=629]; Jacobson et al. (2001) [n=85]; Look et al. (2001) [n=21]),

3 months

(Wuttke et al. (2003, 2006) [n=62, n=20 on *Cimicifuga*]; Frei-Kleiner et al. (2005) [n=122, n=83 on *Cimicifuga*]; Osmers (2005) [n=304, n=153 on *Cimicifuga*]; Daiber (1983); Vorberg (1984); Warnecke (1985); Stoll (1987); Nesselhut and Liske (1999); Liske et al. (2000); Nappi et al. (2005); Bai (2005); Ruhlen et al. (2007),

6 months:

(Pethö (1987) [n=50]; Lehmann-Willenbrock (1988) [n=60]; Briese et al. (2007) [n=6141, n=3027 on *Cimicifuga*]; von Schoultz et al. (2005) (Lindén Hirschberg) [n=74]; Bartsch and Fischer et al. (2006) n=50],

up to 12 months

Newton et al. (2006) [n=351, n=80 on *Cimicifuga*]; Raus et al. (2006) [n=375].

There is sufficient evidence from clinical trials to use specified herbal preparations of *Cimicifuga racemosa* for the treatment of menopausal symptoms with the indication: Herbal medicinal product for the relief of menopausal complaints (such as hot flushes and profuse sweating).

Patients with breast cancer and hormone dependent tumours should be excluded from treatment with *Cimicifuga* preparations for safety reasons.

5. Clinical Safety/Pharmacovigilance

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

See sections 4.2 and 4.3 and 5.6.

5.2. Patient exposure

Overall, more than 6 300 patients were treated with *Cimicifuga* preparations in clinical studies. See also sections 2.3, 4.2 and 4.3 and 5.6.

5.3. Adverse events and serious adverse events and deaths

Adverse events

Liver toxicity has been associated with the use of *Cimicifuga* containing products. The frequency is not known.

The HMPC document EMEA/HMPC/269258/2006 Rev. 1 dated 8 May 2007 on the assessment of case reports linked to herbal medical products containing *Cimicifuga* root reported cases with liver damages, either reported as undesirable effects or taken from the literature. Out of 44 partially poorly documented cases, four show coherence between liver damage and intake of *Cimicifuga*, wherof in two cases the coherence is probable and the patients developed an autoimmune hepatitis. Until now, there is no known dose dependence. A correlation to a pathophysiological mechanism is not known. Fifteen further cases have been reported; nearly all are poorly documented and are not assessable. Meanwhile, four new cases of liver injury have been reported; two spontaneous reports in the German pharmacovigilance database in 2010 and two more cases from the literature (Guzman et al. 2009). Three of these cases were assessed as "probable" using the RUCAM Score; one was "unrelated" due to insufficient data. To date, there are five cases assessed as "probable".

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.

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

Muscle damage induced by black cohosh, Minciullo et al. (2006):

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/l, 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 the normal range. The same laboratory exams including muscle enzymes, performed three months before, had shown no alteration. The patient reported to take a *Cimicifuga* product for ameliorating menopause vasomotor symptoms; each tablet contains 20 mg of dried rhizome and root extract. The patient had taken 1 tablet twice daily for 1 year and then discontinued the therapy. She restarted the same therapy 2 months later. Asthenia appeared 2 months after the restart of the medication. The patient did not change life, did not exercise and did not take other drugs. The author hypothesised a causative role for *Cimicifuga*.

Cutaneous Pseudolymphoma induced by *Cimicifuga racemosa*, Meyer et al. (2007):

There is a report about a 56 year-old female patient with asymptomatic, localized erythematous plaques on arms and legs. Histologically, the diagnosis of pseudolymphoma was confirmed. Because of menopausal complaints, the patient has taken a product containing *Cimicifuga*, for 1 year. Six months after initial administration, first skin lesions appeared. Withdrawal of the product 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 the evaluation and discussion of all available data. The proposals concerning re-assessment of hepatotoxicity recently published by Teschke et al. (2008, 2009) cannot be accepted.

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 & Benichou 1993). The score was validated and the results published (Benichou et al. 1993).

Conclusion

Due to limited data, patients have to be carefully observed for signs of liver toxicity. Therefore, patients are advised to pay particular attention to symptoms of a possible liver injury (such as tiredness, loss of appetite, yellowing of skin and eyes or severe upper stomach pain with nausea and vomiting, or dark urine). To date, based on available preclinical or clinical data, liver toxicity of *Cimicifuga* preparations cannot be excluded. Therefore, case reports have to be assessed thoroughly using the RUCAM Score which can be considered to be the most practicable one for spontaneous adverse event report systems.

The procedures, recommended by Teschke et al. (2008, 2009) in several publications for the assessment concerning 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.

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.

5.4. 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) performed 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 finally 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 months 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 have not been examined.

5.5. Safety in special populations and situations

Intrinsic (including elderly and children) / extrinsic factors

There are no data available for use of *Cimicifuga* in children. Due to the indication (menopausal complaints), children are excluded from use, 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 these studies. No special studies for elderly have been conducted.

Drug interactions

Pharmacokinetic studies in healthy volunteers showed no clinically relevant influence in the safety of *Cimicifuga*. *Cimicifuga* weakly inhibited CYP 2D6. Clinically relevant interactions with drugs metabolised by the CYP P450 enzymes were not found (Gurley et al. 2005).

Cimicifuga is not a potent modulator of P-gp activity *in vivo* and therefore does not pose a significant interaction risk with digoxin (Gurley et al. 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 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, glucosamine/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. Taking into account the indication "menopausal symptoms" the use in pregnancy and lactation 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 published by Dugoua et al. (2006). It is shown that *Cimicifuga racemosa* in the United States is used by 45% of midwives 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, emenagogue properties and anovulatory effects. During lactation there is low level evidence. *Cimicifuga* should be used with caution as *in vitro* evidence suggests hormonal properties. It is still unclear whether *Cimicifuga* has an oestrogenic or anti-oestrogenic effect or no effect on the oestrogenic receptor.

Overdose

As reported in HAGER (2007), in unspecified doses vertigo, nausea, headache, stiffness and tremor of limbs could occur. In lower doses, not further specified, gastrointestinal discomfort may occur.

Drug abuse

No data available.

Withdrawal and rebound

No data available.

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

No data available.

5.6. Overall conclusions on clinical safety

The data from clinical trials with defined herbal preparations from *Cimicifuga* demonstrate a reasonable safety. Except for 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. Liver toxicity (including hepatitis, jaundice, disturbances in the liver function tests) is associated with the use of *Cimicifuga* containing products. 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).

For patients who have been treated or are undergoing treatment of breast cancer or other hormone dependent tumours, the use of *Cimicifuga* preparations is not recommended.

Patients from clinical studies:

Overall, more than 6 300 patients were treated with *Cimicifuga* preparations in clinical studies.

Patients in long term studies:

About 3 832 patients were treated with *Cimicifuga* preparations in 7 clinical trials and 2 observational studies between six and twelve months. See section 2.3 "Evidence regarding the duration of use".

Patients with a history of breast cancer (n=378):

- Up to 3 months:

Jacobson et al. (2001): n=85 (59 on tamoxifen plus CR), isopropanolic extract (40% (V/V)) Remifemin[®], 40 mg per day, 2 months treatment.

Look (2001), n=21, undefined extract, 40 mg per day, 2 months treatment.

Pockaj (2006): n=132, 2 times 20 mg daily (20 mg *Cimicifuga racemosa* and rhizoma extract standardized to contain 1 mg of triterpene glycosides as calculated by 27-deoxyacetin mixed in

dicalcium phosphate, whey, microcrystalline cellulose, stearic acid, peppermint flavor, silica and magnesium stearate), 40 mg per day, 1 month.

- Up to 12 months:

Munoz and Pluchino (2003): n=90 (under CR and tamoxifen treatment), Klimadynon[®] ethanolic (58% (V/V)) extract CR BNO 1055 of CR, 40 mg daily, 12 months.

Bartsch and Fischer et al. (2006): n=50, isopropanolic extract (40% (V/V)) Remifemin[®], 40 mg per day, 6 months treatment.

- Unknown duration:

Becher et al. (2007): n=1102, Remifemin[®] or Remifemin[®] plus, dosage and duration unknown (to be excluded from calculation).

Obi (2009) (MARIE study): n=455, Remifemin[®] (40% isopropanolic extract), 40 mg per day or under treatment with Remifemin[®] plus contains 3.75 mg iCR extract and 70 mg of an ethanolic extract from 245 to 350 mg St. John's wort (*Hypericum perforatum*) or other *Cimicifuga* preparations; treatment duration unknown (to be excluded from calculation).

- Patients in higher dose studies:

Liske et al. (2000): n=62 on 127.3 mg iCR (Remifemin[®]) per day for 6 months.

Neßelhut and Liske (1999): n=28, iCR (Remifemin[®]) 136 mg per day for 3 months.

Newton (also Reed) (2006): n=80 on black cohosh, 160 mg per day for 12 months.

Neither hepatotoxic reactions nor tumours or metastases of breast cancer or other hormone dependent tumours have been observed under the treatment with *Cimicifuga* preparations within the study populations of six and more months of treatment. Using the "Rule of Three" (see above) this leads to 3/3 832 which is 7.8 patients out of 10000 (rare: $\geq 1/10\ 000$ to $\leq 1/1000$). As a consequence, in these study populations uncommon ($\geq 1/1000$ to $\leq 1/100$) adverse events can be excluded in case of 3 832 study participants. For all 6300 treated patients this is 4.8 patients out of 10000 (rare: $\geq 1/10000$ to $\leq 1/1000$); in these study populations uncommon ($\geq 1/1000$ to $\leq 1/100$) adverse events can be excluded in case of 6300 study participants.

The following wording for the monograph safety relevant sections is proposed:

- 4.2: Posology and method of administration: "If the symptoms persist during the use of the medicinal product, a doctor or a pharmacist should be consulted. *Cimicifuga* should not be taken for more than 6 months without medical advice".

- 4.4: Special warnings and precautions for use: "Patients with a history of liver disorder should take *Cimicifuga* preparations with caution (see section 4.8 '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)", "Patients who have been treated or who are undergoing treatment for breast cancer or other hormone-dependent tumours should not use *Cimicifuga* preparations without medical advice (see section 5.3. 'Preclinical safety data').

- 4.6: Pregnancy and lactation: "Women of childbearing potential should consider using effective contraception during treatment".

- 4.8: Undesirable effects: "If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted".

In view of the study results and the appropriate wording given in the SmPC as outlined above, the use of *Cimicifuga* containing medicinal products can be considered to be safe. However, without further

preclinical and/or clinical studies hepatotoxicity and hormonal activity of *Cimicifuga* preparations cannot be completely excluded.

6. 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, 20 preparations have been in use for more than 10 years and 4 preparations have been in use for more than 30 years in Germany. It is common knowledge that an extremely high number of daily dosages of *Cimicifuga racemosa* preparations have been sold worldwide over the years. *Cimicifuga racemosa* is positively described in a Monograph of the German Commission E (BAnz. Nr. 43) published 2 March 1989, revised 14 December 1994 (not published) 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 6300 patients included in more than 24 clinical trials a relief of menopausal complaints (such as hot flushes and profuse sweating) could be demonstrated. Also numerous preclinical studies have been performed that cover aspects of safety and efficacy. Comparing the high number of daily dosages of *Cimicifuga racemosa* preparations sold worldwide with the small number of reported adverse events, the use of *Cimicifuga racemosa* can be considered to be safe under appropriate labelling. HRT is not therapeutic alternative and is obsolete in pre- and perimenopausal women as well as in patients with breast cancer. 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* used for the relief of menopausal complaints (such as hot flushes and profuse sweating).

On the other hand, the potential risks of preparations containing *Cimicifuga racemosa* can be minimised sufficiently by adequate labelling under "duration of use", "contraindications", "special warnings and precautions for use", "pregnancy and lactation" and "undesirable effects". 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 a few reports on serious adverse events or side effects of the herbal substance. The risks of hepatotoxicity are covered by the following wording under 4.4 "special warnings and precautions for use":

"Patients with a history of liver disorder should take *Cimicifuga* preparations with caution (see section 4.8 '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 content of the German graduated plan regarding pharmacovigilance measures for *Cimicifuga racemosa*, which came into effect in June 2009.

There are two literature reports of previously unknown adverse events; these are regarded as signals, the causal connection to the intake of *Cimicifuga* preparations was assessed as 'probably related' (Minciullo et al. 2006; Meyer et al. 2007).

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 specific labelling of the risks and through appropriate advice by involved health care professionals.

Taking due account of all these arguments, a “Well-Established-Medicinal-Use” indication for the relief of menopausal complaints (such as hot flushes and profuse sweating) with *Cimicifuga racemosa* is appropriate. The benefit/risk assessment comes to a favourable conclusion. In many cases there are no therapeutic alternatives and most of the affected patients are looking for safe and effective treatment options. However, no advice can be given to women under treatment with tamoxifen or similar medicinal products with respect to a parallel treatment with *Cimicifuga* preparations. There is no data available giving sufficient evidence of the safety of such co-medication.

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 studies published by Brattström (2005) and Schmidt (2005) with extract ZE 450 were not taken into account. There is no evidence that this extract is or has been used as a medicinal product in a Member State of the European Union.

The possibility of a hormone-like action on oestrogen 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 a traditional herbal medicinal product.

Annex

List of references