EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 November 2010
EMA/HMPC/439318/2010
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Community herbal monograph on *Cimicifuga racemosa* (L.) Nutt., rhizoma (EMA/HMPC/600717/2007)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Cimicifuga racemosa* (L.) Nutt., rhizoma as released for public consultation on 15 September until 15 February 2010.

	Organisations and/or individuals
1	AESGP (Association of the European Self-Medication Industry)
2	Naturex S/A
3	ESCOP (European Scientific Cooperative on Phytotherapy)
4	GA - Gesellschaft für Arzneipflanzen- und Naturstoff-Forschung e.V. (Society for Medicinal Plant and Natural Product Research)
5	Kooperation Phytopharmaka
6	Professor Dr. Rolf Teschke

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Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	**Comment and Rationale**	**Outcome**
AESGP	AESGP welcomes the preparation of the above-mentioned Community herbal monograph which may facilitate mutual recognition in Europe by providing harmonised assessment criteria for herbal medicinal products. We also welcome the publication of the draft assessment report in parallel to the draft monograph because it provides useful background information on the preparation of the HMPC draft. We thank for the opportunity to provide our input, which you will find as follows:	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
2 Well-established use, Part (ii) Herbal preparations	Naturex SA	**Comments:** The ratio proposed for: "Dry extract from Cimicifugae rhizoma (4.5-8.5:1) ethanol 60% V/V" is too limiting and does not take into account the efficiency of the extraction process and number of extractions **Proposed change (if any):** "Dry extract from Cimicifugae rhizoma (5-8:1) ethanol 75% V/V" We note that the only approved monograph for Black Cohosh is USP32 NF27 (which is also the most reliable one). We present as Annex 1 to this response a comparison of HPLC profiles an extract prepared with an extraction solvent of 75% ethanol achieving a 5-8:1 yield compared to an extract	Not endorsed: The extract (5-8:1) ethanol 75% V/V is not covered by the studies that support the well-established use of *Cimicifuga racemosa* preparations. The cited USP is not relevant for the preparation of the Community Herbal Monograph on C*imicifugae racemosae* radix. USP 32, NF 27 Volume 1, The United States Pharmacopeia; The National Formulary, Official from

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		prepared with 60% ethanol and a 4.5-8.5:1 yield using the US Pharmacopoeia methodology. It can be clearly seen that the HPLC "fingerprints" overlay nearly exactly and that no new substances have been introduced as a result of the slight change in the ethanol ratio. It can clearly be seen that the identity and purity of the extract remains true to the original USP monographs and the currently proposed Community Herbal Monograph.	May 1, 2009; Dietary Supplements: Black Cohosh pp 986 – 990.
4.1 Therapeutic indications	AESGP	In this section, the following wording is proposed by the HMPC: "*Herbal medicinal product for the relief of minor neurovegetative menopausal complaints (such as hot flushes and sweating)".* We do not agree with this wording and propose the following modifications: 1. **Deletion of the word "minor"** 2. **Inclusion of "sleeping disorders" as a further example of neurovegetative complaints** 3. **Inclusion of "psychic" menopausal complaints**	1. endorsed "deletion of minor" 2. Not endorsed by majority decision of HMPC on 25.11.2010. After discussion it was agreed to keep 'hot flushes' and 'sweating' as symptoms in the wording of the indication. Other symptoms are not backed by clinical data. 3. Not endorsed by majority decision of HMPC on 25.11.2010. After discussion it was agreed to keep 'hot flushes' and 'sweating' as symptoms in the wording of

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		JUSTIFICATIONS 1. **Deletion of the word "minor"** **Intensity of climacteric complaints investigated in clinical studies:** "Minor" complaints have never been investigated in clinical studies with *Cimicifuga racemosa* (CR), apparent in inclusion criteria and basic values (see table 1). 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 The *Kupperman Index (KMI)* has also been used for the characterisation and quantification of menopausal symptoms. A quantitative assessment of symptoms is achieved by grading in severity: severe = 3, moderate = 2, mild = 1, not present = 0.	the indication. Other symptoms are not backed by clinical data. The wording of the indication should express the efficacy of the herbal medicinal product as shown by the results of clinical studies. While bearing in mind the quality of these studies, the results of the investigations should lead to an acceptable wording. The wording "neurovegetative" should be deleted in view of Art. 63(2) of Directive2001/83/EC according to which "The package leaflet must be written and designed to be clear and understandable, enabling the users to act appropriately, when necessary with the help of health professionals. The package leaflet must be clearly legible in the official language or languages of the Member State in which the medicinal product is placed on the market". The not defined term "neurovegetative" should be avoided in the monograph. 1. The word "minor" in this context is not correct. It should be deleted, as "minor symptoms" are defined as shown in the comments (1-14 points according to Schneider et al. (2000)). 2. "Not endorsed by majority decision of HMPC on 25.11.2010. After discussion it was agreed to keep 'hot flushes' and 'sweating' as symptoms in the wording of the indication. Other symptoms are not backed by clinical data. 3. Not endorsed by majority decision of HMPC on

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<tr><td></td><td></td><td>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

Table 1. Intensity of symptoms in clinical studies with Cimicifuga racemosa
<table><tr><th>Reference</th><th>INCLUSION CRITERIA</th><th>Mean basic values (CR group)</th></tr></table>
Double-blind, randomised, placebo-controlled studies
<table><tr><td>Osmers et al. 2005</td><td>MRS ≥ 0.4 (moderate) in at least 3 items</td><td>MRS: 0.35 ± 0.12</td></tr><tr><td>Stoll 1987</td><td>menopausal complaints</td><td>KMI: 33</td></tr><tr><td>Frei-Kleiner et</td><td>climacteric complaints</td><td>KMI: 19 (ITT population); KMI : 27 (subgroup)</td></tr></table></td><td>Indication wording:
Endorsed wording by majority decision of HMPC on 25.11.2010:
“Herbal medicinal product for the relief of menopausal complaints such as hot flushes and profuse sweating”.

The examples of improved symptoms under treatment were shown in different studies, mostly in subscores or secondary target parameters.
By the above chosen wording the expression “neurovegetative” can be avoided.

The wording “psychic” seems inappropriate in this context. The term “changes in mood” covers the symptoms of the subscore psyche.

“Changes in mood” was not endorsed by majority decision of HMPC on 25.11.2010. After discussion it was agreed to keep ‘hot flushes’ and ‘sweating’ as symptoms in the wording of the indication. Other symptoms are not backed by clinical data.</td></tr>
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al. 2005		
Wuttke et al. 2003, 2006	MRS ≥ 0.3 in at least 3 items	MRS: basic data not shown; decrease of total score by –1.8 points

Double-blind, randomised, placebo-controlled studies

Osmers et al. 2005	MRS ≥ 0.4 (moderate) in at least 3 items	MRS: 0.35 ± 0.12
Stoll 1987	menopausal complaints	KMI: 33
Frei-Kleiner et al. 2005	climacteric complaints	KMI: 19 (ITT population); KMI : 27 (subgroup)
Wuttke et al. 2003, 2006	MRS ≥ 0.3 in at least 3 items	MRS: basic data not shown; decrease of total score by –1.8 points

Double-blind, randomised, reference-controlled studies

Bai et al. 2007	KMI ≥ 15	KMI: 24.7 ± 6.1
Oktem et al. 2007	climacteric complaints	modified KMI: 25.1 ± 6.7
Liske et al. 2002	KMI ≥ 20	KMI: 31

Open-label, controlled studies

Lehmann-Willenbroc	climacteric complaints	modified KMI: 48.73 ± 8.72

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k, Riedel 1988		
Warnecke 1985	climacteric complaints	modified KMI: severe symptoms
Briese et al. 2007	climacteric complaints	MRS: 0.30 ± 0.17; 0.36 ± 0.17

Non-controlled studies with Cimicifuga racemosa

Schmidt et al. 2005	climacteric complaints	VAS (Visual Analogue Scale): moderate (upper limit)
Vermes et al. 2005	KMI ≥20	KMI: 28
Pethö 1987	climacteric complaints	KMI: 17.6 ± 5.3
Vorberg 1984	climacteric complaints	KMI: moderate (approx. 27)
Daiber 1983	climacteric complaints	KMI: 19
Ruhlen et al. 2007	climacteric complaints	KMI: 24.6 ± 1.4
Raus et al. 2006	climacteric complaints	MRS II: 13.92 ± 7.45 (total score classes, acc. to Heinemann et al. 2004: No/little 0-4; mild 5-8; moderate 9-15; severe 16+)

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		Efficacy of *Cimicifuga racemosa* in patients with at least moderate complaints: The HMPC draft assessment report (page 22/36 II.3.2.2 Clinical studies) comes to the conclusion that: *"Clinical studies indicated an efficacy of Cimicifuga extracts in patients with menopausal symptoms though none of them completely showed a significant improvement of the total Kupperman Score or the total Menopause Rating Scale Score"*. In fact, *Cimicifuga racemosa* preparations were clearly superior to placebo in reducing the pre-defined primary efficacy parameters MRS-I/ KMI mean score change from baseline in 3 placebo-controlled studies (Osmers et al. 2005, Stoll 1987, Brattström 2005). In the study by Osmers et al. (2005) the effect size was 0.03 to 0.05 Menopause Rating Scale units, which is similar to HT study results (0.036 units; Wuttke et al. 2003). Frei-Kleiner et al. (2005) found a significant superiority of CR over placebo in the subgroup of women with at least moderate symptoms (KMI >= 20). A decrease of 47% and 21% was observed in the CR and placebo groups for the KMI or by 48% and 14% concerning the Menopause Rating Scale, respectively. In the study of Wuttke et al. (2003) the analysis of the total MRS score items marginally failed statistical significance, but it was shown that CR was as effective as conjugated estrogens in reducing climacteric complaints, when compared with the placebo group. Three reference-controlled studies (table 1) used total scores:	These details have already been discussed in MLWP. There are no new details that demonstrate a significant improvement of the total Kupperman Score or the total Menopause Rating Scale Score. In the Osmers study the changes of the pre-defined primary efficacy parameters of MRS-I are not listed. The results for the claimed improvement ("In the study by Osmers et al. (2005) the effect size was 0.03 to 0.05 Menopause Rating Scale units") are not shown. Stoll (1987): Only 26 patients under *Cimicifuga* treatment. After 12 weeks of treatment the Kupperman Index improved to values <15 (p=0,001). With only 26 patients in this study the efficacy cannot be established. Bai et al. (2007): Kupperman Index and Menopause

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		KMI showed a significant non-inferiority of CR to tibolone suggesting that both approaches are equally effective (Bai et al. 2007). Versus fluoxetine, the KMI decreased significantly in the CR group, compared to the fluoxetine group (Oktem et al. 2007). In another double-blind, randomised and controlled clinical trial with two different dosages of CR extract the mean KMI was significantly reduced in both treatment groups (Liske et al. 2002). Concerning the qualitative and quantitative amelioration of climacteric symptoms, the results of open trials and observational studies confirm the effects known from controlled clinical trials. Total scores (KMI, MRS II), vasomotor and psychic symptoms were significantly reduced. In most of the studies, the results were again demonstrated by means of Kupperman-Index, after descriptive analyses of pre- vs. post-treatment values. Some studies assessed the intensity of complaints, e.g. hot flushes and sweating (Schmidt et al. 2005; Stolze 1982; Raus et al. 2006; Georgiev, Iordanova 1997), or psychic symptoms (Julia Molla et al. 2009; Schmidt et al. 2005; Vorberg, 1984; Stolze 1982; Georgiev, Iordanova 1997). Julia Molla et al. (2009) used a quality of life scale and observed a significant improvement in postmenopausal women with Cimicifuga extract.	Rating Scale are not fully validated for Asian women (see: Heinemann (2004)). Oktem et al. (2007): Study was not accepted due to insufficient quality. The Liske (2002) study was conducted without a placebo group. 123 subjects completed the 12-week study, 116 subjects were evaluated after 24 weeks. Per protocol the treatment groups of 39 mg/day and 127.3 mg per day comprised 61 respectively 62 subjects. This study supports the well established use of *Cimicifuga* preparations in the above mentioned indication but it should be taken into account that the results might also be observed under placebo-treatment. Brattström (2005) respectively Schmidt et al. (2005): Brattström (2005) shows study-results of an unspecified extract (ZE-450). ["Dose dependent superiority of a new developed *Cimicifuga*-extract ZE-450." Translation by the assessor: "The results of clinical studies on the efficacy of *Cimicifuga* extracts vary. This is probably due to the difference in composition of the extracts used. Therefore, the efficacy of the new extract ZE 450 has been investigated in a clinical study. This extract is produced by a special technique which prevents losses of compounds by the transfer from the plant into the

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			extract."] The comparability of the two isopropanolic extracts used in the studies is not shown (no details about quality of ZE 450 are known). Furthermore, it is unknown whether the ZE 450 extract is marketed in the European Union for at least 10 years and in which countries.
		Studies in patients with hormone-dependant breast cancer have to be assessed separately: in these cases tamoxifen is the first-line therapy. The most frequent adverse reaction to tamoxifen is severe vasomotor episodes. Therefore most of the studies with breast cancer survivors restrain to the frequency and intensity of hot flushes. Indeed, the evidence for CR's ability to relieve hot flushes associated with menopause in women with breast cancer remains inconclusive. All in all, in patients diagnosed with breast cancer the response rates seem to be lower than in otherwise healthy women with climacteric complaints. In a prospective cohort study, 8% of the patients reported breast cancer in the anamnesis (Briese et al. 2007). A subgroup analysis was conducted in the group of patients under current therapy with tamoxifen (n=286). These patients had higher baseline values than the overall population, especially vasomotor and psychic symptoms were more severe. Women under tamoxifen also benefited from the cimicifuga-based therapy, but the baseline-adjusted overall MRS score decreased less than in the overall population (−0.09 MRS-units and −0.15 MRS-units at Months 3 and 6 in contrast to −0.11 and −0.16 MRS-units). <u>Instruments used for measurement of treatment benefits:</u>	Endorsed: Studies in patients with hormone-dependent breast cancer have to be assessed separately. The corresponding chapter in the BRIESE (2002) study: "As anti-estrogen therapy might induce menopause-like symptoms, such therapy was one of the pre-defined confounders in the test model. A subgroup analysis was conducted in this group of patients (n=286). These patients also benefited from the *Cimicifuga*-based therapies, but the baseline-adjusted overall MRS score decreased less than in the overall population (−0.09 MRS-units and −0.15 MRS-units at Months 3 and 6 in contrast to −0.11 and −0.16 MRS-units)". 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. 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

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			patients with breast cancer.
		Most of the clinical studies with CR used the Menopause Rating Scale (MRS) or the Kupperman Index (KMI) as target criterion. This is criticised in the HMPC draft assessment report on *Cimicifuga racemosa*, because the severity of climacteric symptoms as indicated in the KMI or in the MRS is divergent to the assessment in the *Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women* (EMEA/CHMP, 2005).	
		It does not seem appropriate to adopt the guideline for hormonal replacement therapy on clinical studies with herbal medicinal products like Cimicifuga.	Due to lack of "special" guidelines concerning herbal medicinal products for diagnosis and treatment of menopausal complaints it is appropriate to use the guideline for Hormone Replacement Therapy (EMA/CHMP/021/97, Rev. 1).
		According to this guideline, *"Hormone Replacement Therapy (HRT) in postmenopausal women is generally defined as treatment with oestrogen or a combination of oestrogen plus progestogen."* HRT is indicated for "oestrogen deficiency symptoms in postmenopausal women" and assessed as effective in women with severe symptoms. The population of perimenopausal women is out of the scope of this guideline. In view of the risk profile of HRT, the minimum effective dose for the shortest duration should be used.	Endorsed. Endorsed. Menopausal complaints are the targets to be treated with *Cimicifuga racemosa* preparations. Perimenopausal and postmenopausal women are using *Cimicifuga* preparations.
		In contrast, Cimicifuga preparations are generally used for the relief of menopausal complaints. Perimenopausal women and	Due to the possibility of risks of the treatment, it should be well considered whether "mild menopausal

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		women with mild or moderate complaints are not excluded from CR treatment. The risk profile of CR is not comparable with HRT. Many patients are treated with CR - independently of the severity of their symptoms - because they refuse HRT or have contraindications. According to the "HRT guideline", the most important oestrogen deficiency symptoms are vasomotor symptoms (hot flushes). So, the proposed primary endpoint for efficacy trials with HRT is the frequency of moderate to severe hot flushes • 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. With regard to symptomatic indications of natural products in the treatment of menopausal symptoms, the "frequency of moderate to severe hot flushes" is no adequate instrument for the assessment of the efficacy in clinical trials. Additionally, a 3-point scale is no appropriate measure for clinical studies. MRS or KMI are more suitable, because they allow an overall evaluation of the degree of severity of the somatic and psychic or neurovegetative findings by way of indices, total scores or subscores. The MRS scale was developed (a) to assess symptoms of aging/menopause (independently from those that are disease-related) or HRQoL between groups of women under different conditions, (b) to evaluate the severity of symptoms over time, and (c) to measure changes pre- and post hormone	complaints" need any treatment. 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 and postmenopausal women on the other hand. Additionally breast cancer patients with and without additional therapies except surgery should be included in the considerations about study conducts. Different results are to be expected for the subgroups. As the HRT (hormone replacement therapy) deviates from target groups and indications from *Cimicifuga* preparation therapies, basic parameters have to be predefined for the herbal medicinal products. By this, reliable results can be achieved. I.e. character, severity, duration and improvement of complaints have to be measured and compared from baseline over treatment up to follow up. Neither the Kupperman scale nor the different MRS scales were developed for herbal medicinal products. Both are validated instruments like the guideline for Hormone Replacement Therapy (EMA/CHMP/021/97, Rev. 1).

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		replacement therapy. The reliability (internal consistency and test-retest stability) of the MRS was found to be good across countries. Regarding validity, it was shown that the internal structure of the MRS across countries is sufficiently similar to conclude that the scale really measures the same phenomenon. The comparison with the Kupperman Menopause Index showed sufficiently good correlations of the total score, which is compatible with the notion of a good criterion-oriented validity. The MRS scale is able to detect a marked improvement of the HRQoL in response to hormone therapy. Therefore the MRS was recommended as standardised/validated "objective" scale for use in clinical studies (Heinemann et al. 2004). In conclusion, the therapeutic efficacy of CR was clearly demonstrated in women with moderate climacteric symptoms. Consequently, the word "minor" should be deleted. 2. **Inclusion of "sleeping disorders" as a further example of neurovegetative complaints** Hot flushes, sweating and sleeping disorders are interindependent neurovegetative symptoms. Together with cardiac symptoms they characterise the subscore <u>hot flushes</u> of the Menopause Rating Scale (MRS I). As shown by a post-marketing surveillance study with more than 10,000 women,	The large variation of different study protocols, inclusion- and exclusion criteria, interpretation of results and conclusions thereof shows the need of validated and commonly used instruments. Partially endorsed: According to Heinemann et al. (2004) the MRS and the use of 3 subscales (Psychological subscale, Somatic subscale and Urogenital subscale) can be accepted as validated except for the Asian and South American population. "Sleep disorders" not endorsed by majority decision of HMPC on 25.11.2010. After discussion it was agreed to keep 'hot flushes' and 'sweating' as symptoms in the wording of the indication. Other symptoms are not backed by clinical data.

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		sleeping disorders are the second most frequent climacteric symptom (Schneider et al. 2000a). At least, the European *Guideline on the readability of the labelling and package leaflet of medicinal products for human use* (12 January 2009) demands a clear and understandable wording of the package leaflet. *"Medical terms should be translated into language which patients can understand".* There is no lay term for "neurovegetative menopausal complaints", therefore it should be exemplified. This can simply be done by specifying the most common neurovegetative symptoms in brackets: hot flushes, sweating and sleeping disorders. Therefore, sleeping disorders should be mentioned as a further example for neurovegetative menopausal complaints, additionally to hot flushes and sweating. 3. **Inclusion of "psychic" menopausal complaints** <u>Importance of psychic symptoms in the context of menopausal complaints:</u> The menopausal syndrome presents a polysymptomatic clinical picture. Besides vasomotor symptoms such as hot flushes, night sweating and sleeping disorders, menopausal women complain about psychic problems primarily such as depressive mood and emotional dysbalance. Psychic symptoms can be a relevant and typical feature of symptomatic menopausal women, without criteria of apparent depressive episodes or conditions.	Not endorsed by majority decision of HMPC on 25.11.2010. After discussion it was agreed to keep 'hot flushes' and 'sweating'as symptoms in the wording of the indication. Other symptoms are not backed by clinical data.

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		Psychic complaints - beside neurovegetative complaints - are the most frequent symptoms of the menopausal syndrome. Taking into account the various stages of menopause, the following frequencies are obtained (Lauritzen 1987): **Table 2**. Frequencies of menopausal symptoms regarding the stage of menopause (Lauritzen 1987) Recent investigations showed associations between the	

Symptoms	**Premenopause [%]**	**Menopause [%]**	**Postmenopause**	
			1 - 3 Years [%]	**> 3 Years [%]**
Hot flushes	36	69	74	42
Sweating	28	58	67	31
Dizziness	**14**	**33**	**41**	**25**
Circulatory disorders	8	20	28	11
Depressive mood	**25**	**72**	**76**	**58**
Nervousness	**67**	**51**	**48**	**22**
Irritability	**65**	**49**	**46**	**17**
Feelings of tension	**44**	**40**	**33**	**25**
Headaches	41	31	24	19
Insomnia	53	56	63	41
Anxiety	**33**	**44**	**26**	**12**

predominating symptoms hot flushes/sweating, depressive moods and insomnia: frequency of moderate/severe hot flushes is independently associated in a graded manner with severity of insomnia symptoms (Ensrud et al. 2009) and depressive symptoms amplify the menopausal experience or alternatively, severe vasomotor symptoms induce or worsen depressive moods (Cohen et al. 2006; Reed et al. 2009; Freeman et al. 2009).

Nevertheless, psychic symptoms are an independent factor in special rating scales for the menopausal syndrome. In the standardised *Menopause Rating Scale (MRS)* "PSYCHE" is one of four important dimensions, which have been characterised as subscores by cluster and factor analysis. It comprises the items (4) depressive mood; (5) nervousness, nervous irritability; (6) generally impaired performance and memory.

Table 3. Menopause Rating Scale I (Schneider et al. 2000a)

Item	Symptom group	Climacteric symptoms
1	hot flushes, sweating	sensation of rising heat, outbreaks of sweating (frequency / intensity per 24 hours)
2	cardiac complaints	palpitations, racing heartbeat, irregular beats, tightness in chest
3	sleep disorders	difficulty in falling asleep, difficulty in remaining asleep through the night, waking too early

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4	depressive mood	despondency, sadness, tearfulness, lack of drive, mood fluctuations
5	nervousness, nervous irritability	nervousness, inner tension, aggressivity
6	impaired performance / memory	susceptibility to physical and mental exhaustion, poor concentration, forgetfulness
7	disorders of sexuality	reduced libido, sexual activity and satisfaction
8	urinary complaints	symptoms during urination, frequent need to pass urine, accidental incontinence
9	vaginal dryness	feeling of dryness of the vagina, symptoms during sexual intercourse
10	joint and muscle symptoms	pain predominantly affecting the finger joints, rheumatic symptoms, itching

The *Kupperman Menopause Index (KMI)* assigns significance to the typical menopausal complaints by way of a multiplication constant. The psychic symptoms of KMI are (weighting factor in brackets):

- nervousness/irritability (2),
- depressive moods (1),
- inability to concentrate (1).

<u>Efficacy of *Cimicifuga racemosa* on psychic menopausal symptoms:</u>

Clinical investigations performed with Cimicifuga extracts show

that they have a beneficial effect on psychic symptoms. Menopausal psychic complaints were evaluated by means of standardised and validated scientific scales for the detection of therapeutic efficacy. Beside the rating scales and Quality of Life-scales, special psychometric scales or symptom scores were used:

- Hamilton Anxiety scale (HAMA)
- Self-assessment Depression Scale (SDS)
- Beck's depression scale
- Profile Of Mood States (POMS)
- MRS subscore PSYCHE

Table 4. Clinical studies with CR investigating psychic symptoms

Reference	**Study type**	**N** (CR/Ref.)	**Psychometric Scale/ psychic parameter**
Osmers et al. 2005	Double-blind, placebo-controlled	304 (153/151)	Menopause Rating Scale (MRS), subscore PSYCHE
Stoll 1987	Double-blind, placebo- and reference (HT) controlled	80 (30/30/20)	HAMA
Oktem et al. 2007	Reference controlled (fluoxetine)	120 (60/60)	Beck's depression scale, RAND-36 (Quality of life)

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		Liske et al. 2002	Reference controlled (dose-finding)	149 (74/75)	SDS	
		Warnecke 1985	Reference controlled (Conjugated estrogens, Diazepam)	60 (20/20/20)	Modified Kupperman Index; SDS (Self-evaluation Depression Scale); HAMA (Hamilton Anxiety Scale)	
		Briese et al. 2007	Reference controlled (CR extract + Hypericum perforatum)	6,141 (3,027/3,114)	MRS-subscore "PSYCHE"	
		Julia Molla et al. 2009	Non controlled	122	Cervantes HR-QoL scale (Quality of Life)	
		Vorberg 1984	Non controlled	50	POMS scale (Profile Of Mood States)	
		Stolze 1982	Non controlled	629	psychic symptoms	
		Georgiev, Iordanova 1997	Non controlled	50	HAMA	
		Fischer 2006	Non controlled	47	MRS-subscore "PSYCHE"	

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		Psychic symptoms were mostly used as secondary endpoints in double-blind, placebo- or reference-controlled clinical trials. Nappi et al. (2005) showed that both CR and low-dose TTSE2 significantly reduced psychic symptoms, without any significant difference between the two treatments. An effect was evident for both anxiety and depression which were significantly reduced following 3 months of both CR and low-dose TTSE2. In the study by Stoll (1987), the *Cimicifuga racemosa* preparation significantly and time-dependently improved psychological complaints, measured by means of Hamilton Anxiety scale, compared with placebo. Osmers et al. (2005) found statistically relevant treatment differences in the MRS-factor "PSYCHE" in a placebo-controlled clinical trial. In some other studies (Oktem et al. 2007, Juliá Mollá et al. 2009) Cimicifuga treated patients have shown an improved quality of life. In contrast, a subgroup analysis of 1,511 women of the WHI trial showed no clinically meaningful effect of estrogen plus progestin on health-related quality of life (Hays et al. 2003). Compared to fluoxetine, Cimicifuga extract was less successful in reducing symptoms of Beck's depression scale than the SSRI, but no significant differences between groups were observed in health-related quality of life, measured with the RAND-36 Questionnaire, which improved in all parameters, except pain (Oktem et al. 2007).	The Oktem (2007) study could not be accepted due to design, conduct and reporting (see assessment report). Oktem (2007): Remixin (No details on DER or extraction solvent): following text from manufacturer's homepage (Turkish wording): Her tablet içinde 40 mg Black Cohosh Extract (standardize edilmiş *Cimicifuga racemosa* Rhizoma ekstresi) bulunur ve patentli standardize içeriği ile dünyadaki tek Black Cohosh tabletidir. (Her 40 mg aktif madde içinde %2.5 Triterpen Glikozid olarak 1mg 26-deoksiaktein). Mollá (2009), an observational study of 150 patients. 3 months, 40 mg CR per day, final analysis: n=122, postmenopausal, healthy, mild to severe hot flushes; Cervantes QoL (31 items) psychical domain with 9

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			items. Data supporting the total score and/or subscore validation are not cited in the publication. Palacios et al.: Med Clin (Barc). 2004 Feb 21;122(6):205-11. Health-related quality of life in the Spanish women through and beyond menopause. Development and validation of the Cervantes Scale: "The Cervantes Scale is included in the new generation of instruments of health-related quality of life specific for the menopause and is intended to be used in Spanish women aged between 45 and 64 years"; i.e. not validated for other populations.
		Some non-controlled studies assessed the intensity of psychic symptoms (Julia Molla et al. 2009; Schmidt et al. 2005; Vorberg 1984; Stolze 1982; Georgiev, Iordanova 1997). Julia Molla et al. (2009) used a quality of life scale and observed a significant improvement in postmenopausal women with Cimicifuga extract. The analysis of single symptoms (e. g. nervousness, depressive moods), the mood profile (POMS), the Hamilton Anxiety scale (HAMA), and the "psychic" domain in the Cervantes QoL scale, respectively, confirmed a very good therapeutic efficacy of Cimicifuga products in the psychological field (Nappi et al.	Georgiev, Iordanova (1997): no information about the extracts, bad quality of reporting. Schmidt (2005): Cimifemin (Zeller) no sufficient data on the extract.

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		2005; Stolze 1982; Vorberg 1984; Georgiev, Iordanova 1997; Julia Molla et al. 2009). Cimicifuga alleviated the psychic symptoms of the Menopause Rating Scale, including item 6 "generally impaired performance and memory" (Briese et al. 2007). In contrast, no positive effect on cognitive functions could be found in postmenopausal women treated with HT (Kurt et al. 2006). Consequently, psychic complaints should be mentioned in the indication of the monograph, because – beside neurovegetative complaints – they are the most frequent symptoms of the menopausal syndrome and clinical studies confirm a good therapeutic efficacy of Cimicifuga products on psychic symptoms.	"Psychic complaints" not endorsed by majority decision of HMPC on 25.11.2010. After discussion it was agreed to keep 'hot flushes' and 'sweating' as symptoms in the wording of the indication. Other symptoms are not backed by clinical data.
4.1. Therapeutic indication	ESCOP	Well-established use We propose modification of the text to read: Herbal medicinal product for the relief of climacteric symptoms such as hot flushes, profuse sweating, sleep disorders and nervous irritability. This is in line with the indication in the 2003 ESCOP monograph (and a revised version due in 2010) and based on published clinical studies.	Not endorsed. (see 4.1: AESGP): Not endorsed by majority decision of HMPC on 25.11.2010. Endorsed wording by majority decision of HMPC on 25.11.2010: "Herbal medicinal product for the relief of menopausal complaints such as hot flushes and profuse sweating".
4.1. Therapeutic Indication	GA	For Well-established use minor neurovegetative menopausal complaints (such as hot flushes and sweating) are specified.	Not endorsed. (see 4.1: AESGP): Not endorsed by majority decision of HMPC on

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		Proposed is the following wording: *Herbal medicinal product for the relief of neurovegetative and psychic menopausal complaints (such as hot flushes, sweating, sleeping disorders and depressive mood).* Reason: For persons concerned symptoms as hot flushes or sweating are no minor but serious complaints which together with other symptoms greatly reduce their quality of life. In clinical studies all menopausal complaints have been investigated and evaluated, not only hot flushes and sweating. This includes various neurovegetative as well as psychic complaints, of which hot flushes, sweating, sleeping disorders and depressive mood are just the most important ones. Others e.g. are heart discomfort, irratibility and anxiety, physical and mental exhaustion and sexual problems.	25.11.2010. Endorsed wording by majority decision of HMPC on 25.11.2010: "Herbal medicinal product for the relief of menopausal complaints such as hot flushes and profuse sweating".
4.2 Posology and method of administration	AESGP	**<u>Posology</u>** We propose the following wording: *"Extracts corresponding to 40-140 mg of the drug; other corresponding preparations."* <u>Reasons:</u> • "Corresponding to" seems a better expression than "equivalent". This is in line with the monograph published by ESCOP (2003). • Furthermore, in most of the clinical studies the daily dosage was established at 40 mg drug. Newton et al. (2006) used an experimental preparation with 160 mg per day and Brattström (2005) tested the ethanolic preparation	Endorsed: "corresponding to". Not endorsed: 140 mg. The safety data from high-dose studies are limited. Undesirable effects, hepatotoxicity and hormone-like mode of action might be dose-dependent. So the dose extension to 140 mg of the drug is not endorsed, as any benefits of higher dose treatments could not be shown in clinical studies. Newton (2006): black cohosh (*Actaea racemosa* or *Cimicifuga racemosa*, 160 mg daily; 2.5% triterpene

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		ZE450 with 40 and 111 mg herbal drug, respectively. In another double-blind, randomised, controlled clinical trial (conform to GCP) two different dosages of *Cimicifuga racemosa* extract (40 and 127 mg of drug/day) were used for the treatment of menopausal patients (n = 149) over a treatment period of 6 months (Liske et al. 2002). The mean Kupperman Menopausal Index was significantly reduced in both treatment groups without significant group differences, and after a further period of 3 months (extension study; n = 116). In a smaller study Neßelhut and Liske (1999) evaluated the influence of 136 mg drug/day on estrogen-sensitive target organs and hormone values. • Importantly, no differences related to safety and tolerability have been observed in all these clinical studies where higher doses where tested.	glycosides; 70% ethanol extract), no more information available, no safety data available. Brattström (2005): ZE 450, special extract, the comparability with the Schaper and Brümmer extract is not demonstrated. Neßelhut & Liske (1999): small sample size (n=28), neither data on liver function nor data on breast tissues are available.
4.2 Posology and method of administration	AESGP	**Duration of use** Instead of the second sentence, we propose the following wording: *"Cimicifuga should not be taken for more than 12 months without medical advice".* Reasons: • A treatment longer than 3 months is justified on the basis of clinical safety data up to 12 months (Raus et al. 2006; Reed et al. 2008). Furthermore, this statement is also in agreement with the ESCOP monograph which states "No restriction". • In general, patients were treated with CR in the context of clinical studies for periods of 3, 6 and 12 months. Efficacy	Cimicifuga should not be taken for more than 6 months without medical advice. Raus (2006): 12 months treatment can support a 6 months limitation. (n=400); Extract: CR BNO 1055. Reed (2008): 12 months treatment; 160 mg daily; 2.5% triterpene glycosides; 70% ethanol extract; n=80, no safety data on liver function available. (=Newton (2006)). Oktem (2007): 6 months treatment, n=40, extract not specified. Mielnik (1997): 6 months treatment, n=34, only few data available, no data on extract available, to be

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		studies with a 6-month treatment were: Oktem (2007), Mielnik (1997), Georgiev and Iordanova (1997) as well as Pethö (1987). In a prospective, observational study patients were treated for 6 and 12 months (Briese et al. 2007). Fischer (2006) as well as Muñoz and Pluchino (2003) treated breast cancer patients over a period of 6 and 12 months, respectively.	excluded. Georgiev & Iordanova (1997): to be excluded due to quality of data. Pethö (1987): 6 months treatment, n=50, 80 mg daily (?); isopropanolic extract. Munoz (2003): n=90, 12 months treatment, no safety data available. Extract: CR BNO 1055. 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 3,074 patients from non-interventional studies (Briese, Fischer) support the duration of use for 6 months. Therefore 3 832 patients are to be selected for safety concerns and to support duration of treatment for 6 months.
		• Based on the current clinical data, there are no safety reasons to restrict the duration of the treatment. A preventive gynaecological check-up in otherwise healthy women is indicated once a year. In case of unclear vaginal bleeding or other unclear symptoms patients are in any case advised to see their doctor.	3 studies had to be excluded due to deficient quality of data and/or unspecified extracts (Georgiev & Iordanova, Mielnik, and Oktem). 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.
		• Clinical studies with treatment durations of 6 and 12 months did not reveal safety concerns. Therefore, it is recommended that Cimicifuga preparations should be taken	Not endorsed: 12 months due to safety considerations.

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		not longer than 12 months without medical advice.	
4.2. Posology and method of administration	GA	Duration of use A duration of use of not more than 3 months without medical advice is declared. Proposed is the following wording: *Cimicifuga should not be taken for more than 6 months without medical advice. After 6 months of use medical consultation is thought to support further use. In case of any complaints potentially caused by Cimicifuga preparations medical consultation should be sought.* Reason: Cimicifuga extract may produce clear improvement in menopausal symptoms only after four to eight weeks of treatment. Then a 3 months treatment seems to be too short for a definite judgement of the Cimicifuga therapy. Also patients whose menopausal complaints recur after a successful Cimicifuga treatment some weeks or months later would like to repeat taking Cimicifuga. Existing clinical studies show no severe safety problems within time periods of up to 12 months. Moreover a yearly medical check-up is recommended to all menopausal women independent of taking Cimicifuga preparations or not.	Not endorsed: Symptoms (complaints) caused by *Cimicifuga* cannot be diagnosed by patients. Preferred wording: see above. Cimicifuga should not be taken for more than 6 months without medical advice. 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. Of course patients would like to repeat treatment of their complaints after positive experience but no advice can be given to patients or their doctors due to lack of data. About 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 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.

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			To estimate the frequency of adverse events, the "Rule of Three" ["Interpreting Zero Numerators": "If nothing goes wrong, is everything all right"] is commonly used (s Hanley, Lippman-Hand, Jama, April 1 1983; 249(13)). 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: 3/3 832 = 0.00078, which is 7.8 patients of 10,000 (rare: (≥1/10,000 to ≤1/1,000)). In consequence in these study populations uncommon (≥1/1,000 to ≤1/100) adverse events can be excluded in case of 3,832 study participants.
4.4 Special warnings and precautions for use	AESGP	In this section, the following wording is proposed by the HMPC in the 4th paragraph: *"Cimicifuga preparations should not be used together with oestrogens unless advised by a doctor".* We suggest deleting this sentence. According to recent data, an oestrogenic effect of Cimicifuga preparations can be excluded (see below). Furthermore, we do not agree with the following warning in the last paragraph: *"Patients who have been treated or who are undergoing treatment for breast cancer or any other tumour disease should not use Cimicifuga preparations".*	Not endorsed: Oestrogenic effects of *Cimicifuga* preparations appear to be unlikely but cannot be completely excluded.

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		We propose the following modification: *"Patients who have been treated or who are undergoing treatment for breast cancer should not use Cimicifuga preparations <u>without medical advice.</u>"* <u>Reasons:</u> 1. Cimicifuga does not exert estrogenic effects on estrogen-sensitive tissues such as breast and endometrium. 2. Studies evidence an adequate safety regarding the use of Cimicifuga rootstock in patients with an anamnesis of cancer. 3. Clinical studies with Cimicifuga found no higher or even a reduced risk of tumour development and tumour recurrence / metastazation. <u>Justifications</u> 1. **Cimicifuga does not exert estrogenic effects on estrogen-sensitive tissues such as breast and endometrium.** Both hormone therapy (HT) and *Cimicifuga racemosa* (CR) are used for relief of menopausal symptoms. So it has long been presumed that the mode of CR action involves hormonal signalling through the estrogen receptor (ER). Consequently concerns were raised about the potential impact of the botanical in patients with breast and other hormone-dependent	Endorsed wording after extended MLWP discussion: "Patients who have been treated or who are undergoing treatment for breast cancer or other hormone-dependent tumours should not use Cimicifuga preparations <u>without medical advice</u>. Please see section 5.3 Preclinical safety data". Results of preclinical studies (n=50) support safety concerning estrogen-sensitive tissues. Clinical studies found no higher and even a reduced risk of tumour development and tumour recurrence / metastatic spread was postulated but in conclusion the authors only remarked that "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". Endorsed.

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		cancers. The assumption of an estrogenic effect of Cimicifuga was also based on some older experimental and clinical studies. An LH-suppression was found without influence on prolactin and FSH (Jarry and Harnischfeger 1985; Jarry et al. 1985). This effect was attributed to the presence of the phytoestrogen formononetin, an adulterant of CR extracts, which however was in later studies shown to be not present in CR containing herbal medicinal products (Kennelly et al. 2002; Avula et al. 2009). In the meantime, studies have demonstrated that Cimicifuga is, in fact, not estrogenic (Betz et al. 2009). This is clearly proven by the state-of-the-art of scientific findings based on the results of more than 20 *in vitro* and *in vivo* experimental studies (**See appendix 1**: Table 1: Relevant preclinical studies with Cimicifuga racemosa regarding "Breast and other tumours"). • Experimental investigations concordantly prove that Cimicifuga has no influence on estrogen receptors, particularly not on the alpha-receptors existing in breast and uterus and thus relevant for this issue (Liu, Burdette, Xu et al. 2001; Amato et al. 2002; Pockaj et al. 2004). • *In vivo* studies primarily focus on the question of estrogenic effects on typical target organs (uterus, vaginal epithelium, endometrium); neither in these investigations could any estrogenic effects be detected (Einer-Jensen et al. 1996; Amato et al., 2002; Davis et al. 2008; Kretzschmar et al. 2005; Bolle et al. 2007; Alves et al 2008). • Influences on hormone levels (LH, FSH, Prolactin)	

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		(Freudenstein et al. 2002) and β-estradiol and progesterone, respectively, were not found (Davis et al. 2008). Instead, in an *in vitro* investigation an inhibition of the local estrogen production in human breast tissue was proven (Stute et al. 2007). Nine clinical studies have verified the absence of a systemic estrogenic effect in patients treated with CR. Particularly, in estrogen-sensitive organs such as breast and endometrium no proliferation (no estrogen-agonistic) activity was demonstrated (see table 1). • No changes were observed in mean values of systemic estrogen-related hormones such as LH, FSH, prolactin, estradiol or SHBG after 3 to 12 months of CR treatment (Reed et al. 2008; Ruhlen et al. 2007; Nappi et al. 2005; Liske et al. 2002; Nesselhut and Liske 1999). • CR therapy for 6 and 12 months did not increase mammographic breast density in postmenopausal women (Lindén-Hirschberg et al. 2007; Raus et al. 2006). For the purpose of the study Lindén-Hirschberg mammograms were performed before and after treatment, fine needle bioptates were obtained and ultrasonic examinations of the endometrial mucosa were carried out. The bioptic material was investigated for cellular markers (Ki-67) that indicate a cell proliferation. After 6 months of CR therapy, no single case of mammographic increase in breast tissue density was identified. A hormonal stimulation of breast tissue by Cimicifuga therapy was neither supported by means of quantification of Ki-67 positive cells. Ultrasonic	Safety data endorsed. Lindén-Hirschberg et al. (2007) and Raus et al. (2006): CR therapy for 6 and 12 months did not increase mammographic breast density in postmenopausal women.

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		measurements in regard to endometrial thickness did not suggest any indications as to estrogenic uterotrophic effects. These data are of safety-relevant significance, since under classic hormone therapy in parallel studies with identical design and comparable sample sizes, an increase in breast tissue density was mammographically proven for every second woman (Lundström et al. 2002; Conner 2004). • No significant changes of breast-specific (nipple aspirate fluid [NAF]-cytology, NAF pS2) estrogenic markers were observed after CR therapy for 3 months in postmenopausal women (Ruhlen et al. 2007). • No changes on the endometrium thickness were observed during the course of a 3 to 12-month CR treatment in 7 clinical studies (Reed et al. 2008; Lindén-Hirschberg et al. 2007; Bai et al. 2007; Raus et al. 2006; Nappi et al. 2005; Nesselhut and Liske 1999; Georgiev and Iordanova 1997). **Table 1.** Clinical studies investigating an estrogen-like effect of *Cimicifuga racemosa* in estrogen-sensitive tissues **Reference** / **Medication; treatment duration** / **Patients; safety parameter** / **Safety results on estrogen-sensitive tissues**	Safety data endorsed: Ruhlen et al. (2007) (N=61). Safety data endorsed: except Georgiev and Iodanova (1997); their data are not shown.

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		Raus et al. 2006	CR: n=400; 1year	n=138 mammograms evaluated according to Wolfe and BI-RADS; endometrium thickness; n=335 patients with evaluable endometrial biopsy	No increase in breast density by mammography, with the exception of one woman who had an abnormal mammogram already at study start (no relationship with the study medication). No influence on endometrium after 1 year of treatment	
		Lindén-Hirschberg et al. 2007	CR: n=74; 6 months	mammograms and fine needle bioptates in postmenopausal women	No increase in mammographic breast density and breast cell proliferation; no change in endometrium thickness	
		Ruhlen et al. 2007	CR: n=61; 3 months, followed by 3 months washout	estrogenic markers (serum, nipple aspirate fluid) in postmenopausal women	No significant changes of circulating (serum levels of E2, LH, FSH, pS2) and breast-specific (nipple aspirate	

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					fluid [NAF]-cytology, NAF pS2) estrogenic markers	
			Reed et al. 2008	CR: n=80; other botanicals, HT, placebo; 1year	endometrium, E2, LH, FSH, SHBG in 351 symptomatic women	No effects on endometrium, gynaecological hormones after 1 year of treatment with CR
			Bai et al. 2007	CR: n=122, Tibolone: n=122; 3 months	Endometrium thickness in symptomatic women	No effects of CR on endometrium in postmenopausal women, slight increase in perimenopausal patients. Tibolone increased endometrium thickness in both subgroups
			Nappi et al. 2005	CR: n=60, low dose $TTSE_2$: n=60; 3 months	E2, LH, FSH, prolactin, endometrium thickness in postmenopausal women	No effects on endometrium or gynaecological hormones
			Liske et al. 2002	CR : n=150 6 months	E2, LH, FSH, prolactin, SHBG	No effects on gynaecological hormones
			Georgiev	CR: n=50	Endometrium	No effects on

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, Iordanova 1997	6 months	thickness in postmenopausal women	endometrium
Neßelhut, Liske 1999	CR: n=28 3 months	Endometrium thickness, E2, LH, FSH, prolactin	No effects on endometrium or gynaecological hormones

Data from clinical studies are in agreement with findings obtained from experimental studies. No estrogen-like action of CR, especially on critical estrogen-sensitive organs, e.g. breast tissue and endometrium, was detected.
Due to the fact that an estrogen-like risk in patients with estrogen-dependent tumours is not to be expected the proposed labelling "patients who are undergoing treatment for breast cancer should not use Cimicifuga preparations without medical advice" is sufficient.

2. **Studies evidence an adequate safety regarding the use of Cimicifuga rootstock in patients with an anamnesis of cancer.**

***In vitro* investigations in different cell lines**

Extracts of CR were *in vitro* applied in different mammary carcinoma cell lines using different investigation methods. (**see appendix 1**: Table: Relevant preclinical studies with Cimicifuga racemosa regarding "Breast and other tumours").

<u>MCF-7-cells (ER+; HER2 – or HER2 low):</u>

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		With this human estrogen-sensitive breast cancer cell line 22 recent investigations were performed showing the safety of CR. • In 7 investigations no proliferation of breast cancer cells (Zava et al. 1998; Amato et al. 2002; Zierau et al. 2002; Bodinet and Freudenstein 2004; Stromeier et al. 2005; Nuntanakorn et al. 2006; Omer-Adam et al. 2008), and • in 12 other studies even a growth inhibition was found (Nesselhut et al. 2001, EP 0847755; Bodinet and Freudenstein 2002; Einbond et al. 2004; Hostanska et al. 2004a; Hostanska et al. 2004b; Garita-Hernandez 2006; Al-Akoum et al. 2007; Gaube et al. 2007; Rice et al. 2007; Einbond et al. 2008a; Einbond et al. 2008b; Einbond et al. 2008, USP 7407675). All recent investigations prove that MCF-7 cells do not proliferate under Cimicifuga or their growth is even inhibited. In older studies using the MTT-assay a proliferative increase was described (Kruse et al. 1999; Löhning 1999; Liu, Yu, Huo et al. 2001). However, the results were later disproved by the same group (Stromeier et al. 2003). Sensitivity and specificity of the MTT-assay are influenced by different factors, e.g. colorants, cell volume (Wang et al. 2006), serum concentrations, medium (Talorete et al. 2006) and also by interactions with the tested substances. Brugisser et al. (2002) could show false positive test results for herbal extracts and single substances, respectively. Already in cell-free system a direct reductive potential was observed for extracts of *Cimicifuga racemosa*, as well as for phytoestrogens and for antioxidants. Shoemaker et al. (2004)	

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		were able to assign this effect to certain organic compounds. Peng et al. (2005) showed that for flavonoids the results of the MTT-assay had been adulterated already in cell-free system. Kok et al. (2007), too, stated false results in MTT and similar test systems for flavonoids (MTT), enodin (MTT), iron II-sulphate (MTS). For ursolic acid, a triterpene with cytostatic and cytotoxic activity, differences between MTT-test (MCF-7 cells) and direct cell counting were detected. Moreover, the mechanism of action of the test substance seems to be of importance for these incorrect findings in MTT-assay (Es-Saady et al. 1996). Meanwhile, the test systems have been modified as necessary adaptation to the substances to be tested. So the results of the publication by Liu, Yu, Huo et al. (2001) have to be critically analysed, too. MDA-MB 453 (human breast cancer, not estrogen-sensitive (ER-), overexpressing HER2). • 5 investigations resulted in a growth inhibition (Einbond et al. 2004; Einbond et al. 2006; Einbond et al. 2008a; Einbond et al. 2008b; Einbond et al. 2008, USP 740767548), • in 2 studies a reduced expression of cell cycle genes and an increased expression of genes causing the programmed cell death, was detected (Einbond et al. 2007a; Einbond et al. 2007b). In none of the 7 investigations a proliferation of breast cancer cells was found. MDA-MB 231 (ER-receptor negative breast cancer cell line) • This human cell line was tested in 5 experimental investigations, resulting in an inhibition (Hostanska et al.	

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		2004a; Al-Akoum et al. 2007; Rice et al. 2007; Einbond et al. 2008, USP 740767548) or • a reduced invasiveness of breast cancer cells (Hostanska et al. 2007). <u>Other breast cancer cells (ER+, PR+; ER-, PR-):</u> Also for breast cancer cell lines expressing the progesterone receptor, thus being hormone-sensitive, too, such as the cell line T-47-D (ER+, PR+), no proliferation promoting effects were detected (Zava et al. 1998; Morris et al. 2003) and even a growth inhibition was recorded, respectively (Dixon-Shanies and Shaikh 1999; Garita-Hernandez 2006). A study with the cell line MDA-468 (ER-/PR-) showed no influence of Cimicifuga on the cell growth (Zava et al. 1998). The same applies to the neither hormone-sensitive breast cancer cells HCC-1937 (Morris et al. 2003) and to the breast cancer cell line EMT-6 (Rockwell et al. 2005). <u>Other relevant tumour cell lines:</u> No effects of Cimicifuga on the cell growth was found in the Ishikawa cell system (estrogen-receptor positive endometrial adenocarcinoma cell line) (Liu, Burdette, Xu et al. 2001; Lupu et al. 2003). In other models with hormone-dependent tumour cells such as e.g. prostate carcinoma an inhibition of cell growth was recorded (Jarry et al. 2005; Hostanska et al. 2005; Jarry et al. 2007). *Cimicifuga racemosa* has hence been tested in comprehensive *in vitro* experiments with different cancer cell lines. Furthermore, these investigations reflect the possible constellations regarding breast cancer in women. Whether	

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		estrogen-receptor positive or negative, progesterone-receptor positive or negative, whether with or without overexpression of the epidermal growth factor HER2, growth-promoting effects have never been detected in Cimicifuga-treated cells. Overall, in none of the test systems currently considered as relevant any proliferative or tumour-promoting characteristics could be detected. Interactions with tumour-influencing substances: • *Cimicifuga racemosa* increased the effects of the antiestrogen tamoxifen (Nesselhut et al. 2001, EP 0847755; Al-Akoum et al. 2007; Einbond et al. 2008, USP 7407675). • Synergistic effects with various chemotherapeutics (Einbond et al. 2006, Einbond et al. 2008) were shown, among others with the monoclonal antibody herceptin (Einbond et al. 2008, USP 7407675). • The proliferation of EMT6 mouse breast cancer cells was not altered by 3 different preparations of Cimicifuga, nor was the response of the EMT6 cells to radiation or cisplatin; however, Cimicifuga did increase the toxicity of adriamycin and docetaxel (Taxotere) toward those cancer cells (Rockwell et al. 2005). ***In vivo* studies on the growth of hormone-dependent and other tumours** **See appendix 1**: Table 1: Relevant preclinical studies with *Cimicifuga racemosa* regarding "Breast and other tumours": DMBA-tumour model (rat): • CR-extract did not show any tumour-promoting effects	

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		(Nißlein and Freudenstein, 2003a). • Growth, number and malignancy of breast tumours were reduced (not significantly) under the influence of CR-extract compared to controls, whereas under the influence of estrogen (mestranol) an increase in growth was recorded (Freudenstein et al. 2002). • In the same model an inhibition of the tumour growth as well as a significantly extended lifetime of the animals treated with CR in contrast to controls was shown (Nißlein and Freudenstein 2002). <u>Transgenic mouse model</u> (MMTV-neu; synonym: erb-B2 or HER2): • No differences were found with respect to the incidence of breast cancer between CR-extract and the placebo group, neither an increased expression of the epidermal growth factor HER2 (Davis et al. 2008). <u>Other relevant tumours</u> (endometrial carcinomas of the rat): • No increased tumour incidence and no accelerated tumour growth under CR-extract was observed; rather a decreased pathogenicity of the tumours. The metastazation rate remained uninfluenced (Nißlein and Freudenstein 2003b; Nißlein and Freudenstein, 2004). <u>Interactions with tumour-influencing substances:</u> • In the DMBA rat model no impairment of tumour-inhibiting effects of an aromatase inhibitor by CR (Nißlein and Freudenstein 2007), or • even increased effects of the antiestrogen tamoxifen could be shown (Nißlein and Freudenstein, 2003a). Thus, in none of the *in vivo* studies stimulating the effects of	

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		Cimicifuga on the development and growth of hormone-dependent and other tumours was proven. Quite to the contrary, several times an inhibition of the tumour development was despite found. **Preclinical studies on the development of metastases** As demonstrated in this comment, several authors clearly show that Cimicifuga does not exert tumourigenic or proliferative effects on breast cancer (primary tumours). In the transgenic mouse model used by Davis et al. (2008) the CR treated animals showed also, anyhow, no increased mortality in comparison to the control. However, an increased incidence of lung metastases with c-erbB2 expressing breast tumours was observed under CR-extract. These results seem to be the main reason for the warning extended for all tumours in the HMPC draft monograph. For various reasons, however, the results of this mouse model are not relevant to humans, thus the results of this preclinical studies do not justify the proposed warning of the HMPC including "all tumours". Two expert reports by Professor Berger (German Cancer Research Center; Heidelberg, Germany **see appendix 3**) and Professor Vollmer (Technical University, Dresden; Germany **see appendix 4**) recently discussed in detail the methods and results of this paper. The main concerns are the following: • *Artificial mouse model (MMTV-neu/ c-erbB2) with viral promoter* This mouse model generates without further external	The frequency of metastases was cited from the original publication (Nißlein & Freudenstein 2004); to be completed as follows: Group / Lung metastases / Abdominal metastases Control: 3 / 6 / 0 / 6 Tamoxifen: 4 / 5 / 2 / 5 iCR: 2 / 6 / 0 / 6 Tamoxifen + iCR: 1 / 6 / 0 / 6

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		influences spontaneously and with fast progress mammacarcinomas including development of lung metastases, thus reflecting in no way the situation in case of human breast cancer. In addition, overexpression of the ErbB2 protein in humans is mainly subject to an amplification of the gene, while in the transgenic mouse model mutations of the ErbB2 gene in the tumours are detectable. Furthermore, the activity of the viral promoter is increased. This experimental mouse model is – if at all – only for 20 – 30 % of human mammacarcinomas – i.e. the HER2-overexpressing breast tumours – a typical example. • *Development of lung metastases* Yet before primary tumours occur the mentioned procedures result in a very early dissemination of tumour cells into the lung. This is also a specific characteristic of the used model and not known for humans. In the transgenic mouse line MMTV-neu (c-erbB2) the development of metastases is, moreover, to a far extent limited to the lung. Thus, the natural wide range of possible metastases in all kinds of organs, as it is observed in breast cancer patients, is not at all reflected. • *Lifelong therapy* A patient will take Cimicifuga-containing products in case of climacteric complaints or if she is already in a postmenopausal phase. Thus, the intake is limited to a certain period in the second half of life. In this model, however, started treating the MMTV-neu mice already after	

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		2 months and maintained this for the whole life period. This can be put on a level with a nearly lifelong exposition in humans. Consequently, this model does not reflect the situation in humans, since the duration of use in humans is without medical advice limited to several months. • The authors choose an early treatment start because tumour development of the MMTV-neu model begins comparatively early. This early onset of tumorigenesis can be observed for humans predominantly in case of hereditary types of mammacarcinomas. These hereditary tumours are, however, on the other hand not relevant for mammacarcinomas of menopausal women. Moreover, a comparable drug exposition to pre-existing disseminated tumour cells is largely excluded for humans, since cancer is a typical age-related disease. • *High dosage* The dosage is clearly higher than the human dosage (up to approx. 18-fold). Together with the nearly lifelong duration of use in the experiment an exposition results that is not at all comparable to practical use of Cimicifuga-containing medicinal products. • *Estrogen-independency of tumour development* It was clearly stated that tumorigenesis of the breast in the MMTV-neu model is characteristically estrogen-independent. Consequently, an inference on estrogen-dependent breast cancer in humans is not possible.	

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		This limited relevance to the clinical situation of mammacarcinoma patients, by the way, was also discussed at the NIH-workshop ("Workshop on the Safety of Black Cohosh in Clinical Studies", Bethesda, Maryland) already in 2004. Further publications are worth mentioning, that do not suggest any increased metastasis risk under Cimicifuga treatment. Except one study (Nißlein and Freudenstein 2004) these data have not been addressed in the draft assessment report: • Investigations in cell culture proved an inhibition of the invasiveness of the highly invasive estrogen-independently growing MDA-MB231 mammacarcinoma cell line after treatment with Cimicifuga extract. This shows that the extract can inhibit at least the first step of metastastic progressive effects (Hostanska et al. 2007). • In a further *in vitro* investigation regarding colony formation of estrogen-receptor positive breast cancer cells which indicates a possible progress of early breast cancer stages into a more aggressive stage, no increased metastasizing activity was found under Cimicifuga (Lupu et al. 2003). • In an *in vivo* model of spontaneous hormonal carcinogenesis of the endometrium of DA/Han rats neither effects of Cimicifuga on the degree of metastazation of endometrial carcinoma cells were detectable nor did the gene expression analysis in the tumour tissue show conspicuous changes in the level of genes principally relevant for metastazation. The authors found no difference	

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		in metastases incidence between the two groups, making an increased malignancy via induction of metastatic growth rather improbable (Nißlein and Freudenstein 2003b). • Cimicifuga extract did not show any influence on the metastazation of inoculated RUCA-I endometrial carcinoma cells of the rat. In this model a treatment with Cimicifuga resulted neither in an increased tumour growth of endometrial adenocarcinoma cells at the ectopic site, nor in an increased degree of metastazation with regard to the development of lung metastases (Nißlein and Freudenstein 2004). In contrary to the draft assessment report (II.2.1.1, *in vivo* tests stating that "Pulmonary metastases were frequently found in all groups") the Cimicifuga treated group showed fewer pulmonary metastases than the untreated controls. Even though Davis et al. (2008) raises questions regarding the safety of Cimicifuga, the relevance of the data generated with this transgenic mouse model should not be overestimated. The warning in the HMPC draft monograph addresses all tumours, independently from estrogen-sensitivty and malignancy. This is not justified by the results of Davis et al. (2008). No increased invasiveness or metastatic activity was found under Cimicifuga treatment in other investigations. All in all, the current scientific data do not support the warning in the HMPC draft monograph. No evidence of increased risk was seen in patients with hormone-dependent tumours like breast and endometrium cancer. 3. **Clinical studies with Cimicifuga found no higher or**	

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		even a reduced risk of tumour development and tumour recurrence / metastazation. **Tumour development** Within the MARIE (Mammary carcinoma Risk factor Investigation) study, funded by the German Cancer Aid (Deutsche Krebshilfe e.V.) Obi et al. 2009 investigated in a recent German case-control study the associations between use of herbal preparations like CR and incident breast cancer. 10,121 postmenopausal women (3,464 cases, 6,657 controls) were investigated. The use of herbal preparations was associated with ~ 26% risk reduction for breast cancer (OR 0.74). The most frequently used CR product (Remifemin®) in this study was found to exert even a protective effect on risk for breast cancer: the authors found a risk reduction of about 20 %. In case of a longer duration of herbal preparations use an increasing risk reduction (4 % per year of use) was found. The results were not modified by healthy lifestyle (physical activity and diet), or by histologic type and receptor status (ER, PR, HER2 neu) of the tumour. This study is comparable to the investigation conducted on a US population (Rebbeck et al. 2007). Both studies demonstrated that the consumption of herbal preparations in menopausal women is associated with a reduced risk of breast	German case-control study in 10,121 postmenopausal women (3,464 cases; 6,657 controls). 409 patients (controls) treated with *Cimicifuga* or *Cimicifuga* plus St. John's Wort, 146 invasive cases under same medication. Author's hypothesis still has to be verified. 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. Author's hypothesis still has to be verified and cannot be accepted to support the claimed protective effects of HEP against breast cancer in postmenopausal women particularly with regard to Cimicifuga preparations. Consequently the authors (Rebbeck et al.) 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

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		cancer. Patients with breast cancer in the anamnesis were investigated in 9 clinical studies (Jacobson et al. 2001; Morris 2003; Munoz and Pluchino 2003; Pockaj et al. 2004; Pockaj et al. 2006; Fischer 2006; Raus 2006; Henneicke-von Zepelin et al. 2007; Rebbeck et al. 2007), in 6 studies thereof a part of the patients (such with estrogen-dependently growing tumours) simultaneously received an antiestrogenic therapy with tamoxifen. The duration of use of Cimicifuga was between 2 months and one year. None of the investigations did result in safety concerns, especially regarding a promotion of existing tumours (**see appendix 2**: Table: Relevant clinical studies with Cimicifuga racemosa regarding "Breast and other tumours"). In a critical assessment of clinical and preclinical studies of Cimicifuga racemosa and cancer (breast and prostate) (Walji et al. (2007) it is stated that there are no indication of estrogenic activity of *Cimicifuga racemosa* on breast tissue ("… potentially protective against breast cancer through an opposed inhibition of tumour cell growth"). The authors conclude that the use of *Cimicifuga racemosa* appears safe in breast cancer patients. In another review, Borrelli and Ernst (2008) conclude that "there seems to be little reason for excluding patients with estrogen-responsive tumours from using *Cimicifuga racemosa*".	chemopreventive agent. Results of the case-control studies remain unconfirmed.

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		Tumour recurrence and metastazation The population of this comparative database-based cohort study (Henneicke-von Zepelin et al. 2007) with a moved-back baseline consisted of breast cancer patients in the anamnesis (including estrogen-dependent tumours) who had been treated between 1992 and 2003 in medical offices connected to the IMS 'Disease Analyzer' - mediplus® - database. The target criterion was the tumour-free survival time after the breast cancer diagnosis. 18,861 breast cancer patients were included in the analysis. Of these, 1,102 patients were assigned to the CR (Remifemin®/Remifemin® plus) group and 17,759 to the control group. • The frequency of recurrences in case of using Cimicifuga-extract products was 10.3 % (n=113) compared to 17.7 % (n=3,261) in the control group. Overall and in all age classes, the direct group comparison rather showed lower rates of recurrences in CR-treated patients than in the control group. **Table 2**: Recurrence rates in age groups	

Altersgruppe	REMIFEMIN-Gruppe			KONTROLL-Gruppe			GESAMT		
	GESAMT	REZIDIV	REZIDIV %	GESAMT	REZIDIV	REZIDIV %	GESAMT	REZIDIV	REZIDIV %
<=40	60	7	11,67%	1.122	280	24,96%	1.182	287	24,28%
41-45	120	12	10,00%	1.052	251	23,86%	1.172	263	22,44%
46-50	184	24	13,04%	1.507	303	20,11%	1.691	327	19,34%
51-55	245	24	9,80%	1.901	366	19,25%	2.146	390	18,17%
56-60	216	29	13,43%	2.414	438	18,14%	2.630	467	17,76%
61-65	142	8	5,63%	2.576	405	15,72%	2.718	413	15,19%
66-70	77	6	7,79%	2.280	341	14,96%	2.357	347	14,72%
71-75	40	2	5,00%	1.962	341	17,38%	2.002	343	17,13%
>75	18	1	5,56%	2.945	423	14,36%	2.963	424	14,31%
SUMME	1.102	113	10,25%	17.759	3.148	17,73%	18.861	3.261	17,29%

• 2 years after initial diagnosis, 86% of all patients in the control group were recurrence-free, while this same proportion in the CR group was not reached until the 6.5-

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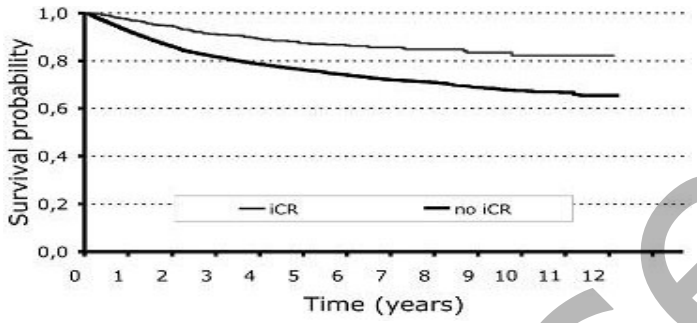
		year mark. This difference remained, even when the analysis was stratified by age group (Figure 1).  **Figure1**. Recurrence-free survival in years, stratified by use of Cimicifuga (Remifemin®) This database analysis provides a substantial contribution to the issue of drug safety of Cimicifuga extract products in mammacarcinoma patients (including estrogen-dependent tumours): • for the first time the frequency of recurrences and the time until recurrences occurred were ascertained in a large number of patients compared to a control group not treated with Cimicifuga extract. • the sample size of this study is higher than in known epidemiological studies regarding frequency of relapses under hormone therapy (HABITS-study, Stockholm-study, Köninger et al. 2008). • It provides greatly important evidence as to the safety, since it reflects the "situation on the market".	

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This study was recently re-evaluated (IMS 2009 **see appendix 5**). The type of recurrence was classified by means of ICD-10-codes (e.g. C77.0: secondary lymph nodes metastasis) or corresponding free text remarks. This re-evaluation resulted into the following main findings:

- All types of recurrences, including lung metastases, occurred less frequently in mammacarcinoma patients treated with CR than in the control group (Table 3):

Table 3. Type of recurrence (% of patients)

ICD-10 text	**Remifemin®/ Remifemin® plus**	**Control group**
Mamma	5.4 %	6.0 %
Neoformation without specifying site	2.6 %	7.1 %
Secondary malignant neoformation of the liver	0.8 %	1.2 %
Secondary malignant neoformation bone/bone marrow	0.6 %	1.6 %
Secondary malignant neoformation of the lung	**0.4 %**	**0.6 %**
Remaining neoformations	0.4 %	1.1 %

- Within an observation period of more than 4 years an increased rate of lung metastases for breast cancer patients treated over a long-term period with Cimicifuga-containing medicinal products was not proven.

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		Comparison with studies regarding hormone therapy (HT) The validity of the data from the pharmacoepidemiological cohort study with Remifemin® in mammacarcinoma patients as well as from the re-evaluation regarding frequency of recurrences and metastases will become apparent if the results of this study are related to comparable approaches of hormone therapy. Two randomised studies performed in Scandinavia (HABITS-study and Stockholm-study) investigated whether a two-year hormone therapy is safe enough to treat climacteric complaints in women with a history of breast cancer. While the HABITS-study (Köninger et al. 2008) showed an increase in the relative recurrence risk under HT (2.4; 95 % KI: 1.3 – 4.2), the recurrence risk in the Stockholm study was not increased (0.82; 95 % KI: 0.35 – 1.9). In contrast, a relative recurrence risk of 0.83 (95 % KI: 0.69 – 0.99) was calculated for CR (Henneicke-von Zepelin et al. 2007). Whereas the rate of distant metastases was comparable in both control groups (3.6 % and 3.4%), it was 4.5 % in the HT-group (HABITS-study) and in the CR (Remifemin®/ Remifemin® plus) occurred in only 1.8 % of the cases. These comparative data support the informative value of the pharmacoepidemiological cohort study with CR in mammacarcinoma patients including the re-evaluation. In case of comparable observation periods the recurrence risk during treatment with Cimicifuga-containing medicinal products is lower than under HT. The rate of distant metastases (including lung metastases) is even clearly lower (1.8 %) under	

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		Cimicifuga than in the control groups of both the hitherto largest randomised HT studies regarding recurrence risk for breast cancer patients (3.2 %). Thus, recent results in humans disprove the data obtained in an experimental mouse model. All in all, the current scientific data do not support the warning in the HMPC draft monograph. **Conclusions** *Cimicifuga racemosa* neither influences hormone levels nor stimulates estrogen-sensitive tissues like breast and endometrium. No such evidence could be provided from large-scale preclinical and clinical studies. No relevant interaction was found in patients with estrogen-dependent tumours treated with tamoxifen or raloxifene. No evidence was found that Cimicifuga stimulates the tumour growth or the development of recurrences. In contrast, many *in vitro*, *in vivo* and clinical studies with CR even showed a reduced risk of tumour development, tumour recurrence and metastazation. Contradictory results have only been obtained in a model with breast tumours of transgenic mice. For purpose of this paper, the mention *"to use CR with caution in patients with pre-existing breast cancer"* may be stated at the most, although clinical data and worldwide experience suggest a lack of risk. Extrapolation to other tumours is not justified and not substantiated. In summary the suggested warning in the HMPC draft is not	

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		justified. We propose deleting "any other tumour disease" but patients who have been treated or who are undergoing treatment for breast cancer should not use Cimicifuga preparations without medical consultation.	
4.4. Special warnings and precautions for use	GA	The following sentence should be deleted: Cimicifuga preparations should not be used together with oestrogens unless advised by a doctor. Reason: According to recent publications Cimicifuga preparations exhibit no estrogenic effects and therefore can't intensify the action of estrogen supplementation. The following sentence should be completed: Patients who have been treated or who are undergoing treatment for breast cancer or any other tumour disease should not use Cimicifuga preparations *without medical advice.* Reason: According to recent publications Cimicifuga preparations exhibit no estrogenic effect in estrogen sensitive breast cancer or endometrium. In contrast, Cimicifuga even seems to reduce proliferation and to induce apoptosis of cancer cells. Safety of Cimicifuga was shown to be sufficiently good for all women.	Not endorsed. There are no data on co-medication of *Cimicifuga* preparations and oestrogens. Due to safety considerations and lack of indication for both treatments in combination, *Cimicifuga* preparations and oestrogens should not be used together. Partially endorsed. 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. Please see section 5.3. Preclinical safety data.
4.4. Special warnings and precautions for use	ESCOP	Well-established use We recommend replacement of the last paragraph Patients who have been treated or who are undergoing	Not endorsed. Recently proposed wording: Patients who have been treated or who are undergoing

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		treatment for breast cancer or any other tumour disease should not use Cimicifuga preparations. by: The use of black cohosh in patients with pre-existing breast cancer should be approached with caution. The evidence from *in vitro* [1-25] and *in vivo* [26-29] pharmacological studies suggests that black cohosh extracts do not influence the latency or development of breast cancer, and may have inhibitory effects [1-4,10-23]; however, contradictory results have been obtained in isolated *in vitro* experiments [30]. Clinical experience suggests a lack of risk [31-33].	treatment for breast cancer or other hormone-dependent tumours should not use *Cimicifuga* preparations without medical advice. Please see section 5.3. Preclinical safety data. Not endorsed. But the following wording will be cited under 5.3: "Evidence from *in vitro* and *in vivo* pharmacological studies suggests that *Cimicifuga* extracts do not influence the latency or development of breast cancer. However, contradictory results have been obtained in other *in vitro* experiments".
4.4. Special warnings and precautions for use AR II.3.3.6	GA	Caution for liver disorders as written seems to be sufficient. Data also indicate that medical supervision seems to be sufficient in case of tumour diseases. Therefore the last 2 sentences of this paragraph should be: *Patients with a history of liver disorder or liver diseases should take Cimicifuga preparations with caution. For patients who are or have been treated because of a tumour disease the use of Cimicifuga preparations should be under medical supervision.*	Not endorsed. Wording concerning liver disorders is derived from the German graduated plan on *Cimicifuga racemosa*. The English wording (German pharmacovigilance section): "Liver toxicity has been associated with the use of black cohosh containing products".
4.6 Pregnancy and lactation	AESGP	We suggest deleting the sentence *"Women of childbearing potential should consider using effective contraception during treatment"*. Reasons: • The use of contraception during treatment with CR seems logic since CR does not prevent from becoming pregnant. Therefore, it is not necessary to make a special mention.	Not endorsed. This wording results from the discussions in the MLWP.

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		• In addition, CR products are not expected to be used by climacteric women who desire to have children since the probability to become pregnant during climacterium is very low. • The use of CR products during pregnancy and lactation is not recommended. Dugoua et al. (2006) suggested that CR should be used "with caution" during pregnancy. Preclinical safety studies did not reveal any risks of CR extracts. No genotoxic or mutagenic activities of CR are known. For this reason, and based on recent data, there is no suspicion of direct teratogenic effects of Cimicifuga.	Women in the perimenopause are in the transition period. They are of childbearing potential. As in traditional use *Cimicifuga* preparations are used as abortifacient herbs and by midwifes to "ripen the cervix" for birth, any pregnancy under treatment has to be avoided (Dugoua 2006).
4.7 Effects on ability to drive and use machines	AESGP	The HMPC text reads: *"No studies on the effects on ability to drive and use machines have been performed"*. We suggest adding. *"An influence is not to be expected".* <u>Reasons:</u> From our point of view, such an addition is useful for explanation. This is justified because there are no hints that Cimicifuga might have any influence on the ability to drive or use machines.	Not endorsed. The wording is derived from actual wording in the template for a community herbal monograph, section 4.7 (EMEA/HMPC/107436/05 Rev. 4).
4.7. Effects on ability to drive and use machines	GA	The following sentence should be completed: *Although no specific* studies on the effects on the ability to drive and use machines have been performed, *according to existing data on adverse effects an influence is unlikely.*	Not endorsed. The wording is derived from actual wording in the template for a community herbal monograph, section 4.7 (EMEA/HMPC/107436/05 Rev. 4).

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4.8 Undesirable effects	AESGP	In this section, the following wording is proposed by the HMPC regarding liver toxicity: 1. *"Liver toxicity (including hepatitis, jaundice, disturbances in the liver function tests) is associated with the use of Cimicifuga containing products. ….* 2. *The frequency of undesirable effects is not known".* We do not agree with this HMPC proposal: 1. **"Causal" association** 2. **Frequency statement** <u>Justifications</u> 1. **"Causal" association** According to the recently revised *Guideline on Summary of Product Characteristics (SmPC)*[1]: *"The section undesirable effects should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, <u>after thorough assessment</u>, a causal relationship between the medicinal product and the adverse event is at least <u>a reasonable</u> possibility, …".* Such a "thorough assessment" seems to be extremely	This wording results from discussions in the MLWP and is derived from the German graduated plan on *Cimicifuga* containing products. The English wording (German pharmacovigilance section): "Liver toxicity has been associated with the use of black cohosh containing products".

1 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/smpc_guideline_rev2.pdf

2 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/smpc_guideline_rev2.pdf

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		important, especially in case of liver toxicity under Cimicifuga, since, as scientific justification for including a side effect about hepatotoxicity into the monograph, the HMPC refers to EMEA's assessments of case reports connected to herbal medicinal products containing Cimicifuga root from 8 May 2007. These assess the causal relationship on the basis of all worldwide reported 44 cases in 2 cases as "possible" and in 2 further cases as "probable". Based on the validated causality algorithm according to "CIOMS" exactly these 4 questionable cases have recently been reanalysed by Teschke et al. [1]. In none of these cases a causal relationship between Cimicifuga and the liver damage could be detected. According to the authors' assessment, one of the cases is probably due to an autoimmune hepatitis and two others are rather due to a herpes infection with subsequent liver damage. Finally the authors draw the conclusion: "*Using a thorough causality assessment in the form of a diagnostic algorithm we have shown that there is no evidence for a causal relationship between treatment by black cohosh and the observed liver disease in the 4 patients".* Thus, according to the authors' opinion and based on a current scientific investigation the causality is in none of the 44 "EMEA-cases" "possible" or even "probable". It is however surprising that the HMPC does not accept this re-assessment. It should be noted, that the use of the CIOMS scale has been criticised by Mahady et al. [2] referring to the report by Rochon et al. [3]. Furthermore, for causality assessment, the HMPC employed the CIOMS scale and Teschke	The new developed "post-Test" (Teschke et al. 2008 and 2009) is not validated. Data which are needed for such an assessment almost never are available in the pharmacovigilance system.

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		et al. its updated form. This updated scale has also frequently been used in the assessment of hepatotoxicity by drugs and dietary supplements [4]. Thus, we do not see any validation problems.	
		On the occasion of an NIH-workshop about black cohosh in Gaithersburg (USA) on June 28, 2007 which was attended by experts of numerous authorities (FDA, TGA, MHRA, BfArM, Health Canada, MPA, NIH, WHO) the experts arrived at a similar conclusion [5]. In summary, it was stated that *"Overall, 18 were considered sufficiently documented; of these, only 3 were considered to represent a possible relationship between black cohosh and liver damage, and 2 more were judged to have a probable relationship. Because the documentation in the latter 5 cases was not complete, a hepatologist carried out a more thorough qualitative/quantitative causality assessment of these files. No relationship between black cohosh and hepatotoxicity could be found in 4 of the 5 cases, and the remaining case was judged as unlikely to be due to black cohosh. The Federal Institute for Drugs and Medical Devices in Germany has examined, in detail, these same 44 case reports, plus 2 additional literature reports, and reached the same conclusions. In one of the ''probable causality'' cases, a very high dose of black cohosh was used, more than 10-fold the usually recommended dose. It is also notable that this case seems to have been inaccurately reported."*	Origin and quality of data in any kind of re-assessment have to be observed very critically concerning verification and validity. Due to available data from spontaneous reporting systems for adverse events, the CIOMS/RUCAM Score remains the preferred instrument for causality assessment. The Federal Institute for Drugs and Medical Devices in Germany has examined four new cases of liver injury from the German database recorded in 2010. Two were spontaneous reports of German cases and two were reports from literature. To date, the latter cases appear to be published for the first time.
		Since the EMEA-report (2007) further cases of liver damage under Cimicifuga have individually been reported, especially from the literature. In agreement with the HMPC nearly all are	All four cases were assessed with the established RUCAM score. Case 1 (DE-BFARM-10036475) was assessed RUCAM 6

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		poorly documented and are not assessable. By means of the causality algorithm according to "CIOMS" only in one of 9 suspicious cases the causal relationship has been assessed as "possible" [6]. On closer examination even this as "possible" assessed case has to be regarded as controversial, since according to the authors other reasons than Cimicifuga have to be considered as cause for the liver damage. The causality in the other 8 cases was assessed as "unlikely" (n=4) or "unclassifiable" (n=4). Like in their first analysis the authors now conclude that *"In summary, review of these cases alleged to show Black cohosh-related hepatotoxicity illustrates the lack of substantive evidence supporting this association"*. The authors add: *"The present study shows little, if any, hepatotoxic risks by the use of Black cohosh in the analyzed cases".* In a further recently published review article, the latest findings on this subject have been presented [7]. On the one hand, failures, shortcomings and challenges of the hitherto existing case evaluations by other experts are discussed in detail in this article. For example, problems regarding the documentation of the cases, identification of the Cimicifuga-products as well as shortcomings in ad-hoc evaluation of the causality are mentioned. Thus, problems that are of great importance especially when adverse events in connection with herbal products are evaluated. On the other hand, various other causes of liver damage are mentioned that have not been considered in the other assessments or not with due diligence. In total, data of more than 69 cases are discussed, and 11 cases thereof are described and analysed in detail.	which indicates "probable" causality (Liver values increased). Case 2 (DE-BFARM-100422305) was assessed RUCAM 7 which indicates "probable" causality (Drug induced hepatitis after treatment with Cimicifuga). Case 3 (US-BFARM-10023612) = (Guzman case 1) is the first of the two reported literature cases: "Liver Injury with Features Mimicking Autoimmune Hepatitis following the Use of Black Cohosh" Guzman G, Kallwitz ER, Wojewoda C, Chennuri R, Berkes J, Layden TJ, Cotler SJ Hindawi Publishing Corporation Case Reports in Medicine Volume 2009, Article ID 918156, 8 pages doi:10.1155/2009/918156 Guzman Case 1: this case (42 years old women) was assessed RUCAM 6 which indicates "probable" causality. Guzman Case 2: this case (53 years old women) was assessed as unrelated due to insufficient documentation.

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		The authors report, that in general, the cases were poorly documented and found confounding variables like: failure to identify the BC product; use of herbal mixtures with multiple ingredients in addition to BC; co-medication with synthetic drugs and dietary supplements including herbal ones; missing temporal association between BC use and development of liver disease; not specified modalities of BC treatment; failure of dechallenge after BC discontinuation; pre-existing liver diseases; insufficiently excluded other liver diseases; presence of alternative liver diseases. In summary the authors conclude: *"The analysis of 69 cases shows little, if any, supportive evidence for a significant hepatotoxic risk of black cohosh".* According to these latest comprehensive analyses the causal relationship for liver damage reportedly caused by Cimicifuga turns out to be completely different and represents an essentially lower risk than supposed by the HMPC in the year 2007. In addition to the postulated hepatotoxicity risk in human, the HMPC monograph considers a study showing microvesicular steatosis which was found in rats treated with > 500 **µg/kg** body weight Cimicifuga extract. (Lüde et al 2007). It should however, be noted, that the cited abstract of this study is confusing. The histological finding of steatosis was observed by a dose of > 500 **mg/kg.** This can be calculated to a human equivalent dosage of ~ **100 mg/kg** b.w. In contrast, the therapeutic dose in humans is ~ 0.08 mg/kg. Additionally, in all clinical studies and in the preclinical study with the isopropanolic extract microvesicular steatosis was not detected in humans, even taking the same	

SPECIFIC COMMENTS ON TEXT			
		amount. In agreement with authors this toxicity (steatosis) is not clinically relevant. Therefore, in our opinion, it is not necessary to consider this study of Lüde et al. 2007 in the monograph. Strictly speaking, it should be taken into account on this basis whether an appropriate information in the section "special warnings and precautions for use" of the monograph would already be sufficient and whether an indication under "Undesirable effects" would be dispensable. Nevertheless, we further agree to list the alleged hepatotoxicity caused by Cimicifuga as adverse event also in the section "Undesirable effects". The matter in this connection is not whether hepatotoxicity as such is listed under the section "Undesirable effects" or not. This had already been implemented by individual companies prior to the HMPC-assessment. Rather, the issue here is an adequate and balanced presentation of the pretended risk under consideration of all currently available scientific evidence. 2. **Frequency statement** The HMPC does not approve the inclusion of information on the frequency of a side effect. Presumably, this is based on past requirement by the *Guideline on Summary of Product Characteristics (SmPC)*, stating that *"The frequencies based on reporting rates from a spontaneous reporting system should not be used for choosing a frequency category <u>in any situation</u>."*	The proposed wording in the draft monograph reflects the discussion in the MLWP on the scientific data regarding the risk and benefit of the use of Cimicifuga preparations. The recently added three new cases of hepatotoxic reactions (see above) confirm the appropriateness of the wording under "special warnings and precautions for use" and under "undesirable effects". According to the template for Community Herbal Monographs (EMEA/HMPC/107436/2005 Rev. 4) from 16 July 2009 and due to available data the wording "The frequency of undesirable effects is not known" is appropriate. Calculation of adverse events for example needs: - number of treated patients

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		This quotation has recently been revised and specified more precisely in respect to content in the recently published version 2 of the SPC Guideline dated September 2009[2]. It is now for example acceptable that *"In case of an unexpected adverse reaction detected from spontaneous reporting, each adequately designed study where this adverse reaction could have been detected should be reviewed to choose a frequency category".* As great emphasis is placed on this subject – how to state the frequency of Undesirable effects in the Product Information – a new chapter titled "Further guidance on the estimation of frequency of adverse reactions" has been included. It is of special importance that a frequency statement exclusively based on spontaneous reports may definitely be listed, and this particularly in the case if – as for Cimicifuga – corresponding side effects did not occur in these studies despite thorough clinical investigation (more than 15 clinical studies). *"The estimation of frequency of an adverse reaction depends on the data source (i.e. clinical trial, post authorization safety study, or spontaneous reporting) the quality of data collection and causality evaluation." … "Frequencies of cited adverse reactions should be stated as accurately as possible"…"The table should be introduced by a short paragraph stating the source and the extent of the safety database (e.g. from …spontaneous reporting)."* Independently from a causality assessment of the single hitherto known cases (see under point 1), and given the	- studies of comparable quality - comparable safety data (liver function tests etc.) These data needed for calculation are not completely available.

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		widespread use of Cimicifuga-containing preparations/products all over the world, the frequency statement "very rare" may be used. The SPC Guideline, however, recommends, for calculating frequency rates of side effects from spontaneous reports, to relate these to the number of patients of all performed clinical studies in which these side effects could theoretically have occurred. In agreement with the evaluation by the EMEA, more than 15 clinical studies with several thousand patients have been performed in which no indications as to liver damages were shown. The latest results were recently presented on the occasion of the ACOG congress confirming these findings on the basis of a placebo-controlled double-blind study [8]. Two further recent studies showed no indications suggestive of liver damage even after a 12-month treatment duration [9, 10]. The participants of the NIH workshop [5], too, confirmed that in clinical studies no liver damage under Cimicifuga was reported. *"It is noteworthy that all the reported clinical trials and other human studies of black cohosh involved a total of more than 3,000 subjects; of these, about 1,200 were given black cohosh, but only about one-third of those were monitored directly for liver function. Nonetheless, there was not a single report of serious liver problems in any of these trials. There were 2 cases of mildly elevated liver enzymes, but these were judged as clinically insignificant by the investigators".* If the recommendation of the SPC Guideline for calculating frequency rates was fully implemented for Cimicifuga, this	[8] Liske E. Placebo-controlled Trial Shows No Effects of an Isopropanolic Black Cohosh Extract on Liver Function Belal Naser, MD Schaper & Bruemmer GmbH & Co. KG, Salzgitter. Data not shown in detail [8].

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		would at most result in the frequency statement "rare", which would, however, rather correspond to "very rare" in the market presence and OTC-use of Cimicifuga in Europe. As already mentioned above, the particularities of phytopharmaceuticals and their well-established use status should be considered for the application of this SPC Guideline too. Not every recommendation/requirement of a guideline applies to this class of medicines. It is generally accepted that for phytopharmaceuticals of well-established use normally fewer clinical studies and mainly studies with low case numbers have been performed than for conventional chemically defined medicinal products. Moreover, reference to the sum of all clinical studies performed with a certain medicinal product is much more complex than for e.g. chemically defined generics due to different extract qualities/dosages. Furthermore, is has to be considered that in contrast to the widespread use of Cimicifuga with the status "medicinal product" in numerous countries within and outside the EU (e.g. The Netherlands, Belgium, Romania, Portugal, USA, Canada, Australia, Israel) it is marketed as food supplement and not as medicinal product. While thus clinical studies for these products are normally not performed in these countries, spontaneous reports and case reports regarding Cimicifuga-containing food supplements are fully incorporated into the safety consideration of Cimicifuga-containing medicinal products. Many of the liver-relevant side effects (especially the two "EMEA-cases" that were assessed as "probable" by the HMPC) were observed in connection with the use of food supplements and not of	

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		medicinal products. This could be due to the difference in quality requirements. **Conclusion** Referring to the current assessments of suspicious cases of liver side effects as well as to the findings of more than 15 clinical studies with Cimicifuga-containing medicinal products from which no indications suggestive to liver damages resulted, we do not agree with the drafted text by the HMPC. We therefore, propose to change the wording of the section 4.8 "Undesirable effects" regarding liver toxicity and consider the following formulation as appropriate: "Liver toxicity (including hepatitis, jaundice, disturbances in the liver function tests) has been reported in very rare cases with the use of Cimicifuga containing products. In more than 15 clinical studies with Cimicifuga-containing medicinal products no liver injury has been observed to date."	Not endorsed: "Very rare" is not accepted (see above). The proposed wording: "In more than 15 clinical studies with *Cimicifuga*-containing medicinal products no liver injury has been observed to date" is misleading as it does not reflect the existing spontaneous reports.
4.8. Undesirable effects	ESCOP	Well-established use In view of the numerous reports linking Cimicifuga with liver toxicity caution is obviously necessary, as expressed in section 4.4. of the draft monograph. However, from assessments and re-assessments by various authors and organizations, none of the available case reports can be considered to provide evidence of probable or certain causality [34-38]. No adverse effects on the liver were evident in a follow-up study of 107 patients treated for more than 12 months with a	Reports on dose dependency of hepatotoxic reactions caused by *Cimicifuga* preparations are conflicting.

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		high daily dose of a Cimicifuga extract, corresponding to 500-1000 mg of herbal substance; the authors concluded that Cimicifuga should not be considered to be a potentially hepatotoxic substance [39]. We therefore recommend modification of the first paragraph, to read: Liver toxicity (including hepatitis, jaundice and disturbances in liver function parameters) has been associated with the use of Cimicifuga-containing products, but a causal relationship has not been substantiated.	[39] No exact details on the extract given. Not endorsed: there are new case-reports on hepatotoxic reactions (see above).
4.8. Undesirable effects	Kooperation Phytopharmaka	<u>Hepatoxicity</u> We propose to change the following wording regarding the in vitro and in vivo findings of Lüde et al (2007). "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" in "The authors conclude, that the ethanolic Cimicifuga extract is associated with hepatic mitochondrial toxicity both in vivo in rats and in vitro using hepatoma cell cultures and isolated rat liver mitochondria. This toxicity is not clinically relevant (toxic concentrations can most probably not be reached in humans	

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		treated with the recommended doses). If there is a relation to the rare hepatotoxic findings in men is questionable." <u>Reasons:</u> • The sentence "These findings might be compatible with an idiosyncratic hepatotoxicity as observed in patients treated with Cimicifuga extracts" shoud be omitted, as it assumes that these in vitro findings might give hints on human idiosyncratic reactions. This deduction is highly speculative as it supposes that the same metabolism of the same Cimicifuga constituents takes place in rat (hepatoma) cells, in rats and in patients. But results with rat hepatoma cells even cannot be reliably transferred to those with rat hepatocytes as there is a considerable difference in their receptor and enzymatic settings. Thus the meaning of these in vitro findings is doubtul. The finding that higher concentrations of a preparations are cytotoxic to liver cells and a dose related hepatotoxicity is seen in high extract dosages in rats in no way proves hepatotoxicity in men. • The definition of Goodman and Gilman´s "The pharmacological basis of therapeutics" (11th ed 2006, McGraw-Hill Companies Inc.) for idiosyncratic reactions is: Idiosyncrasy is an abnormal reactivity to a chemical that is peculiar to a given individual.....We now know that certain idiosyncratic reactions can result from genetic polymorphisms that cause individual differences in drug pharmacokinetics;... the polymorphisms also can be due to pharmacodynamic factors such as drug-receptor interactions."	

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		As the pharmacokinetics of Cimicifuga constituents are not studied, with the exception of the paper of Johnson et al. (Chem Res Toxicol 10, 838-846, 2003), who did not find toxic metabolites in the urine of volunteers after ingestion of Cimicifuga, it is impossible to determine whether indeed aberrant pharmacokinetics of Cimicifuga constituents, i.e. endogenous impairment of an detoxification step, is responsible for hepatotoxicity in some patients. Other mechanisms may be responsible for the rare hepatotoxicity in man.	
4.8. Undesirable effects	GA	The following sentence should be completed: *Very rare and questionable isolated cases of* liver toxicity (including hepatitis, jaundice, disturbances in the liver function tests) *are reported for* the use of Cimicifuga containing products. If any symptoms of liver toxicity occur take medical advice. Reason: Causality for liver toxicity of Cimicifuga preparations in our opinion is extremely low according to clinical studies as well as postmarketing surveillance. Reported cases of liver toxicity were investigated in detail e.g. by Teschke et al. (3 papers) or Thomsen (references read but unfortunately not included) but also by other authors (e.g. Mahady et al. 2008). The information to take medicinal advice in cases of symptoms of liver toxicity is adequate.	Not endorsed. See comments above.
4.8. Undesirable effects AR II.3.3.2	GA	Concerning liver toxicity there is little, if any, convincing evidence for a significant hepatotoxic risk of preparations with Cimicifuga extracts.	Not endorsed.
4.8.	Rolf Teschke	**Comments:** At present, the section concerning hepatotoxicity	Not endorsed.

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Undesirable effects AR II.3.3.2 Adverse events, page 32, last paragraph (which starts with "The problems..")		is not acceptable. Revisions as outlined below are urgently required. **Proposed change (if any):** Line 3: "cannot be accepted" should be replaced by "are at variance to this assessment report" Line 5: Please replace "/ 66: 6 /" by "66 (2008)" Line 9: Please replace "(Ahead of print)" by "956 - 965; Suspected black cohosh hepatotoxicity - Challenges and pitfalls of causality assessments, R. Teschke, R. Bahre, A. Genthner, J. Fuchs, W. Schmidt-Taenzer, A. Wolff, Maturitas 63 (2009) 302-314" Line 9, starting with "The changes in" down to the last word on line 14 ("Rev. 1.") should be replaced by " In the latter reports the authors claim that there is little if any supportive evidence for a significant hepatotoxic risk of black cohosh, using the main-test as the updated scale of CIOMS (Council for International Organizations of Medical Sciences). When the original CIOMS scale was used in addition to the main-test, identical results regarding causality grades were obtained (Black cohosh and suspected hepatotoxicity - inconsistencies, confounding variables, and prospective use of a diagnostic causality algorithm. A critical review, R. Teschke Menopause 17 (2010) No. 2, in press; DOI: 10.1097/gme.0b013e3181c5159c). The thorough assessment of cases with primarily assumed hepatotoxicity by black cohosh revealed various confounding variables: failure to identify the black cohosh product; use of herbal mixtures with multiple ingredients in addition to black cohosh; co-medication with synthetic drugs and dietary supplements including herbal ones;	See comments above. Citations will be updated in the assessment report.66:6 is correct; line 9: 956-965. Not endorsed.

SPECIFIC COMMENTS ON TEXT			
		missing temporal association between black cohosh use and development of liver disease; not specified modalities of black cohosh treatment; failure of de-challenge after black cohosh discontinuation; pre-existing liver diseases; insufficiently excluded other liver diseases; presence of alternative liver diseases.	
4.8. Undesirable effects AR II.3.3.2 Adverse events, Page 33	Rolf Teschke	Line 1: This sentence is unnecessary and should be deleted. Lines 8-11: The complete section of "Conclusions" should be deleted.	Not endorsed.
5.1. Pharmacodynamic properties	AESGP	1. We do not agree with the first sentence *"Neither the mode of action, nor the constituents relevant for the improvement of minor symptoms of menopausal complaints are known."* We propose to replace it as follows: *"Neither the exact mode of action, nor the relevant therapeutic active constituents responsible for the clinical efficacy are known.* *Triterpenoid glycosides and phenolic compounds are known to be major components and active constituents of Cimicifuga rhizome".* 2. Furthermore, we suggest to replace the second statement *"Clinical pharmacological studies indicate that especially the vasomotor symptoms of menopausal complaints such as hot flushes and sweating can improve under treatment with medicinal products from Cimicifuga racemosa root."* by the following text:	Not endorsed, but the term "minor" will be deleted. Updated wording: "Neither the mode of action nor the constituents relevant for the improvement of menopausal complaints are known". Partially endorsed. Updated wording: "Clinical pharmacological studies indicate that menopausal complaints such as hot flushes and profuse sweating can improve under treatment with medicinal

SPECIFIC COMMENTS ON TEXT			
		"Clinical pharmacological studies indicate that especially the psychic and neurovegetative menopausal complaints (such as hot flushes, sweating and sleeping disorders) can improve under treatment with medicinal products from Cimicifuga racemosa root." Reasons: • It is not possible to attribute all of the therapeutic effects of CR extracts that have been demonstrated by clinical studies, to either a single constituent or a group of compounds, in a reproducible and reliable way. Triterpene glycosides (TTG) are considered to be the main and characteristic constituents of black cohosh rhizome, mainly the xylosides actein and cimicifugoside. The second main component class are cinnamic acid esters, phenolic compounds which include caffeic acid, isoferulic acid, piscidic acid, fukiic acid, fukinolic acid and the cimicifugic acids A, B, F, and E. • Experimental data support the beneficial effects of CR on vasomotor and psychic symptoms such as hot flushes, impaired sleep and emotional disturbances (Löhning 1998; Löhning 1999a,b; Borrelli et al. 2003; Burdette et al. 2003; Jarry et al. 2003; Winterhoff et al. 2003; Woo et al. 2004; Nisslein et al. 2006; Rhyu et al. 2006; Powell et al. 2008). • The mechanism of action by which CR reduces neurovegetative climacteric complaints is as multifaceted as complex, since it acts by combining different pathways. This assumption is explicable as the CR extract may contain several active principles. • The mode of action is not completely understood, but two	products from *Cimicifuga racemosa* root". This wording is in line with the proposed indication.

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		mechanisms seem to be essential: CR extracts have been characterised as selective estrogen receptor modulators (SERM) and they have been shown to bind to serotonergic, dopaminergic and μ-opioid receptors. Thus, pharmacodynamic effects implicated in the known mechanisms of action do not support the drafted wording by the HMPC.	
5.1. Pharmaco-dynamic properties	GA	The following sentence should be completed / modified: Neither the *exact* mode of action, nor *all of* the constituents relevant for the improvement of ~~*minor*~~ symptoms of menopausal complaints are known. *Triterpenoid glycosides (mainly actein and cimicifugoside) and phenolic compounds (various phenolcarbonic acids and phenylpropanoids) are known to be specific and active components of Cimicifuga preparations.* Reason: Not only minor symptoms of menopausal complaints, but important symptoms are improved by Cimicifuga preparations. The exact mode of action is not known, but publications show that especially the fraction of triterpenoid glycosides and phenolic compounds are significantly involved in the mode of action. As characteristic for HMPs there seems to be a multi component / multi target mode of action of Cimicifuga preparations. The following sentence should be completed: Clinical pharmacological studies indicate that *the neurovegetative and psychic symptoms* of menopausal	Not endorsed: See above. Updated wording: "Neither the mode of action nor the constituents relevant for the improvement of menopausal complaints are known". Partially endorsed. Not endorsed by majority decision of HMPC on 25.11.2010.

SPECIFIC COMMENTS ON TEXT			
		complaints such as hot flushes, sweating, *sleeping disorders and depressive mood* can improve under treatment with medicinal products from Cimicifuga racemosa root. Reason: see 4.1	Endorsed wording by majority decision of HMPC on 25.11.2010. "Herbal medicinal product for the relief of menopausal complaints such as hot flushes and profuse sweating".
5.1. Pharmaco-dynamic properties AR II.3.1.1.2 Second paragraph	GA	There is no binding of compounds in Cimicifuga extracts to extrogen receptors. The definition of Cimicifuga as selective estrogen receptor modulator (SERM) to our opinion must be seen critically.	As the mode of action of CR remains unknown and the data on hormonal or hormone-like activity are inconclusive, binding of *Cimicifuga* compounds to estrogen receptors cannot be excluded.
5.3. Preclinical safety data	AESGP	1. We suggest the following addition to the first paragraph: "In a six-month study in rats the no-observed-effect-level (NOEL) for the isopropanolic extract was defined with 21.06 mg native extract/kg bodyweight, *which corresponds to nearly the 200-fold human dose."* Reasons: This addition is useful to demonstrate the relation to the therapeutic dose in humans. 2. The next paragraph of the HMPC draft relates to the publication of Davis (2008): *"In Cimicifuga-treated, tumour-bearing, female transgenic mice, the percentage of mice with detectable lung tumours at necropsy was increased compared to those on the control diet. However, in the same experimental model, no increase in primary breast tumour was seen."*	Not endorsed. The amount of native extract is not given in the monograph.

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		We suggest some addition to this paragraph, resulting in the following wording: *"In clinical studies no effect on endometrial thickness or hormonal parameters (LH, FSH, oestradiol and prolactin) was seen.* *Further, in all preclinical studies Cimicifuga did not increase or stimulate mammary tumour growth in vitro and in vivo. Also in Cimicifuga-treated, tumour-bearing, female transgenic mice no increase in primary breast tumour was seen. However, in the same experimental model, the percentage of mice with detectable lung tumours at necropsy was increased compared to those on the control diet.* *In humans no increased risk of tumour recurrence was seen in a database-supported cohort study on 18,861 breast cancer patients, 1,102 of which took Cimicifuga."* <u>Reasons:</u> • The lack of effect of CR on estrogen-dependent tissues like breast and endometrium as well as on hormonal parameters should be described, because this information is important for the treating physician. • The results of Davis et al. (2008) should be described completely. • The results of the experimental model of Davis (2008) are not fully transferable to humans. Two recent expert statements by Professor Berger (DKFZ; ***see appendix 3 in attachment II***) and Professor Vollmer (TU Dresden; ***see appendix 4 in attachment II***) deal in detail with the methods and results of Davis et al.	Not endorsed.

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		• Therefore, the results of this mouse model should be seen in light of other results of *in vitro*, *in vivo* and studies in cancer patients, because safety evaluation should be well-balanced.	
		Please see our comments under Section 4.4 Special warnings and precautions for use	
		3. The following paragraph should be deleted: "In an *in vivo* study in rats microvesicular steatosis was found in animals treated with > 0.5 mg ethanolic extract/kg bodyweight". Reasons: • According to the chapters "results" and "discussion" and in contrast to the "abstract" of the relevant publication (Lüde et al. 2007), microvesicular steatosis in rats was found in animals with 1,000 mg ethanolic extract/kg b.w. (i.e > 300 mg / kg b.w.) and not in rats with > 0.5 mg extract / kg b.w. • Because these data are inconsistent and the appearance of microvesicular steatosis in rats under such enormous dosage is not surprising the sentence should be deleted. • It is not justified to focus "the safety" on results from a single preclinical study; all preclinical data should be considered in the safety evaluation.	Endorsed.
		Please see our comments under Section 4.8 Undesirable effects	

SPECIFIC COMMENTS ON TEXT			
		4. The last sentence in this section states that there are no conclusive studies on genotoxicity, carcinogenicity and reproductive toxicity. We however would like to provide additional information on a study with the dry extract from Cimicifugae rhizoma (4.5-8.5:1) ethanol 60% V/V on genotoxicity which so far was not available for the HMPC (Assessment Report; p 18/36): For the ethanolic extract an AMES-Test was performed which fulfils the requirements of the current guidelines (5 test strains of Salmonella typhimurium in the presence and absence of a metabolizing system, highest concentration of native extract 5,000 µg/plate). The results indicate that the ethanolic extract was not mutagenic under the experimental conditions (Final test report is enclosed). Additionally no evidence for mutagenic effects has been shown with the isopropanolic extract (Assessment Report p. 16/36). Even though the AMES test used does not fulfil current standards it can be concluded from both studies that there is no evidence of mutagenic activity for both extracts. The last sentence in section 5.3. may be replaced by the following wording: *"Genotoxicity studies (AMES tests) did not show mutagenic effects. There are no conclusive studies on carcinogenicity and reproductive toxicity."*	Partially endorsed. The Guideline-conform AMES test was provided for the ethanolic extract (4.5-8.5:1, ethanol 60% (V/V)). For concentrations higher than 1000 µg/plate precipitations were observed. Therefore these concentrations can not be assessed. Therefore it should be stated: "A genotoxicity study (AMES-test) of the ethanolic extract (4.5-8.5:1, ethanol 60% (V/V)) was performed until a concentration of 1 mg/plate. The test does not fulfil the recent criteria of such a testing and therefore the relevance of these results for safety assessment is doubtful".
5.3. Preclinical safety data	GA	Put together into 1 paragraph the following 2 sentences: *In Cimicifuga-treated, tumour-bearing, female transgenic mice, no increase in primary breast tumour was seen. However, in the same experimental model the percentage of mice with*	Endorsed.

SPECIFIC COMMENTS ON TEXT			
		detectable lung tumours at necropsy was increased compared to those on the control diet. Reason: These two conclusions from the publication of Davis et al. 2008 belong together. The important result of no induction of primary breast cancer should be mentioned first. Add the following paragraph: *Neither in preclinical nor in clinical studies Cimicifuga extracts exhibited estrogen effects concerning proliferation of estrogen-dependent tissues, uterotrophic activity and induction or proliferation of breast cancer.* Reason: Preclinical safety data should not concentrate on harmful effects only but also should mention data demonstrating safety of application. The following sentence should be omitted or at least completed: In an *in vivo* study in rats microvesicular steatosis was found in animals treated with > 0.5 mg ethanolic extract/kg bodyweight. *In an in vivo study in rats microvesicular steatosis was found in animals treated with the very high dose of 1000 mg ethanolic extract/kg bodyweight.* Reason: According to the paper of Lüde et al. (2007) only rats treated with the extremely high dose of an ethanolic (60 %) extract of 1000 mg/kg body weight developed microvesicular steatosis of	The following text which was similarly proposed by ESCOP under 4.4 should be added here under "Preclinical safety data": "Evidence from *in-vitro* and *in-vivo* pharmacological studies suggests that Cimicifuga extracts do not influence the latency or development of breast cancer. However, contradictory results have been obtained in other in-vitro experiments".

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		the hepatocytes which may reflect mitochondrial damage and association with cytotoxicity. It remains very doubtful whether these results are of importance for a regular application in Cimicifuga therapy.	
5.3. Preclinical safety data AR II.2.1.1 In vitro tests	GA	Indeed Jarry et al. (1985, a+b) 25 years ago proposed binding of compounds of Cicmicifuga extracts to oestrogen receptors, but rat pituitary glands have not been used for testing binding to estrogen receptors. Therefore delete "*and rats-pituitary glands*" In all subsequent papers, however, it could be shown that fractions or compounds of Cimicifuga extracts do not bind neither to estrogen receptor alpha nor to estrogen receptor beta, do not interact with estrogen regulated genes and never show uterotrophic activity and thus do not induce proliferation of any uterine cell type or of estrogen sensitive mamma carcinoma cells. *This should be mentioned.* The cited thesis of Löhning et al. (1999) is the only one showing proliferation of MCF-7-cells. Other publications in contrast show inhibition of growth of MCF-7-cells. Some other missing papers which should be cited and considered are: *Einbond LS, Shimizu M, Xiao D, Nuntanakorn P, Lim JT, Suzui M, Seter C, Perei T, Kennelly EJ, Kroneneberg F, Weinstein IB. Growth inhibitory activity of extracts and purified components of black cohosh on human breast cancer cells. Breast Cancer Res Treat 2004, 83(3): 221-31*	Not endorsed. See Jarry et al. 1985. "…Rezeptorpräparation aus Rattenhypophysen…" Planta Medica 1985: 2. In vitro-Bindung zur endokrinen Wirksamkeit von Inhaltsstoffen an Östrogenrezeptoren: Ergebnisse.

SPECIFIC COMMENTS ON TEXT			
		A triterpene glycoside fraction and some specific triterpeneglycosides inhibited growth of MCF-7 human breast cancer cells and induced cell cycle arrest at G1 phase. *Einbond LS, Wen-Cai Y, He K, Wu HA, Cruz E, Roller M, Kronenberg F. Growth inhibitory activity of extracts and compounds from cimicifuga species on human breast cancer cells. Phytomedicine 2008, 15(6-7):504-11* Triterpene glycosides from Cimicifuga extracts induced stress response and apoptosis in human breast cancer cell line MDA-MB-453 characterised by overexpression of ER(-) Her2. *Bodinet C, Freudenstein J. Influence of Cimicifuga racemosa on the proliferation of Estrogen-receptor positive human breast cancer cells. Breast Cancer Res Treat 2002, 76(1):1-10, 2002.* In the estrogen-dependent human breast adenocarcinoma cell line MCF-7 a Cimicifuga extract inhibited cell proliferation under estrogen-deprived conditions as well as after estrogen induction. The proliferation-inhibiting effect of tamoxifen was enhanced by the Cimicifuga extract. The study of Rockwell et al. (Breast Cancer Res Treat 90(3):233-9, 2005) with the mouse mamma carcinoma cell line (EMT6) is said to be "not useful to give valid information" but from our point of view demonstrates inhibition of growth of mammary tumour cells by Cimicifuga extracts. Data concerning investigations on binding to recombinant estrogen receptors and cytosol preparations from human endometrium should be presented. They are described in:	

SPECIFIC COMMENTS ON TEXT			
		Jarry H, Metten M, Spengler B, Christoffel V, Wuttke W. In vitro effects of the Cimicifuga racemosa extract BNO 1055. Maturitas 2003; 44(Suppl 1): 31-38 The Cimicifuga extract contains compounds which displace estrogen from a yet unknown estrogen-binding site in the endometrium. No such displacement is seen at estrogen receptor alpha or beta. The Cimicifuga extract also contains compounds with dopaminergic activity.	
5.3. Preclinical safety data AR II.2.1.1 In vivo tests	GA	Some further important papers are missing (partially read but not included) and should be added : *Kretzschmar G, Nisslein T, Zierau O, Vollmer G. No estrogen-like effects of an isopropanolic extract of Rhizoma Cimicifugae racemosae on uterus and vena cava of rats after 17 day treatment. Journal of steroid biochemistry & molecular biology 2005, 97: 271-277* Ovariectomized DA/Han rats were treated with a 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 do not act as an estrogen agonist, but rather as a weak antiestrogen. *Seidlová-Wuttke D, Jarry H, Becker T, Christoffel V, Wuttke W. Pharmacology of Cimicifuga racemosa extract BNO 1055 in rats: bone, fat and uterus. Maturitas 2003, 44(Suppl 1): 39-50* The Cimicifuga extract BNO 1055 exerts no estrogenic effects in the uterus of ovariectomized rats. Neither uterus weight is enhanced nor gene expression of E2-regulated genes is stimulated. In contrast, bone mineral density, serum	Included in AR with original citation of the wording of the authors. No changes in the conclusions in the AR. Included in AR. No changes in the conclusions in the AR.

SPECIFIC COMMENTS ON TEXT			
		osteocalcin levels and paratibial fat depots are reduced demonstrating osteoprotective effects by Cimicifuga extracts.	
AR II.4 Overall Conclusions	GA	The possibility of a hormone-like action on oestrogenic receptors, the risks related to hepatoxicity and possible promotion of metastase in tumour bearing individuals are indicators that Cimicifuga preparations are not suitable for a registration as tradition herbal medicinal product. To our opinion newer existing data show that there is no interaction with estrogen receptors alpha or beta, that there is no uterotrophic activity or promotion of breast cancer, that there is only little evidence for a hepatotoxic risk, and that especially for treatment of menopausal complaints of women with or after treatment of breast cancer there is no better or safer alternative provided medical subervision is performed.	Not endorsed.

List of literature references mentioned under:

4.1 Therapeutic indications

Bai W, Henneicke-von Zepelin HH, Wang S, Zheng S, Liu J, Zhang Z, Geng L, et al. Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. Maturitas 2007;58(1):31-41.

Brattström A. Dosisabhängige Überlegenheit eines neu entwickelten *Cimicifuga* Extraktes (Ze 450). Eine doppelblinde, randomisierte und Plazebo kontrollierte klinische Studie bei menopausalen Beschwerden [Abstract]. [Dose-dependent superiority of a newly developed *Cimicifuga* extract (Ze 450). A double-blind, randomised and placebo-controlled clinical study in case of menopausal complaints (abstract)]. Congress book Phytopharmaka Phytotherapie 2005:S6.

Briese V, Stammwitz U, Friede M, Henneicke-von Zepelin HH. Black cohosh with or without St. John's wort for symptom-specific climacteric treatment-results of a large-scale, controlled, observational study. Maturitas. 2007;57(4):405-14.

Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for New Onset of Depression During the Menopausal Transition. Arch Gen Psych. 2006;63:385-90.

Daiber W. Klimakterische Beschwerden: ohne Hormone zum Erfolg ! [Climacteric complaints: successful without hormones !] Ärzt Praxis 1983; 35(65):1946-7.

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

Ensrud KE, Stone KL, Blackwell TL, Sawaya GF, Tagliaferri M, Diem SJ, Grady D. Frequency and severity of hot flashes and sleep disturbance in postmenopausal women with hot flashes. Menopause 2009;16(2):286-92

Fischer J. *Cimicifuga racemosa* Extrakt (Remifemin®) bei Mamma-Ca-Patientinnen mit klimakterischen Beschwerden unter hormontherapeutischer Behandlung mit Tamoxifen - eine Anwendungsbeobachtung. [*Cimicifuga racemosa* extract (Remifemin®) in mammacarcinoma patients with climacteric complaints under hormone-therapeutic treatment with tamoxifen – a drug-monitoring study.] Dissertation, Albert-Ludwigs-University Freiburg, Germany 2006.

Freeman EW, Sammel MD, Lin H. Temporal associations of hot flashes and depression in the transition to menopause. Menopause 2009;16(4):728-34

Frei-Kleiner S, Schaffner W, Rahlfs VW, Bodmer C, Birkhäuser M. *Cimicifuga racemosa* dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. Maturitas 2005;51:397-404.

Georgiev DB, Iordanova E. Phytoestrogens - the alternative approach. Maturitas 1997;27(Suppl 1):213 (Abstract P309).

Hays J, Ockene JK, Brunner RL, Kotchen JM, Manson JE, Patterson RE, et al. Effects of Estrogen plus Progestin on Health-Related Quality of Life. New Engl J Med 2003; 348 (19): 1839-54.

Heinemann L, DoMinh T, Strelow F, Gerbsch S, Schnitker J, Schneider H. The Menopause Rating Scale (MRS) as outcome measure for hormone treatment? A validation study. Health and Quality of Life Outcomes 2004; 2:67-73.

Juliá-Mollá MD, García-Sánchez Y, Sarri AR, Pérez-lópez FR. Cimicifuga racemosa treatment and health related quality of life in post-menopausal Spanish women.Gynecol Endocrinol. 2009; 25(1):21-6.

Kurt M, Bekci B, Karakas S. Hormone replacement therapy and cognitive function in postmenopausal women. Maturitas 2006;53:39-48.

Lauritzen C, editor. Gynäkologische Endokrinologie. (Gynecological endocrinology]. 2nd edition; München, Wien, Baltimore: Urban und Schwarzenberg; 1987 p. 223-4.

Lehmann-Willenbrock E, Riedel H-H. Klinische und endokrinologische Untersuchungen zur Therapie ovarieller Ausfallserscheinungen nach Hysterektomie unter Belassung der Adnexe. [Clinical and endocrinologic examinations concerning therapy of climacteric symptoms following hysterectomy with remaining ovaries]. Zentralbl Gynakol 1988;110:611-8.

Liske E, Hänggi W, Henneicke von Zepelin HH, Boblitz N, Wüstenberg P, Rahlfs VW. Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosae rhizoma): a 6 month clinical study demonstrates no systemic estrogenic effect. J Womens Health Gend Based Med 2002;11(2):163-74.

Nappi RE, Malavasi B, Brundu B, Facchinetti F. Efficacy of Cimicifuga racemosa on climacteric complaints: A randomized study versus low-dose transdermal estradiol. Gynecol Endocrinol 2005;20(1):30-5.

Oktem M, Eroglu D, Karahan HB, Taskintuna N, Kuscu E, Zeyneloglu HB. Black cohosh and fluoxetine in the treatment of postmenopausal symptoms: A prospective, randomized trial. Adv Ther 2007;24:448-61.

Osmers R, Friede M, Liske E, Schnitker J, Freudenstein J, Henneicke-von Zepelin H-H. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. Obstet Gynecol 2005;105:1074-83.

Pethö A. Klimakterische Beschwerden. Umstellung einer Hormonbehandlung auf ein pflanzliches Gynäkologikum möglich? [Menopausal complaints - change-over of a hormone treatment to a herbal gynecological remedy practicable?]. Ärzt. Praxis 1987;39(47):1551-3.

Raus K, Brucker C, Gorkow C, Wuttke W. First-time proof of endometrial safety of the special black cohosh extract (*Actaea* or *Cimicifuga racemosa* extract) CR BNO 1055. Menopause 2006;13(4):678-91.

Reed SD, Ludman EJ, Newton KM, Grothaus LC, LaCroix AZ, et al. Depressive symptoms and menopausal burden in the midlife. Maturitas 2009;62:306-10

Ruhlen RL, Haubner J, Tracy JK, Weizhu Z, Ehya H, Laberson WR et al. Black cohosh does not exert an estrogenic effect on the breast. Nutrition and Cancer 2007;59(2):1-9.

Schmidt M, Polasek W, Käufeler R. Efficacy and safety of black cohosh (*Cimicifuga racemosa*, Cimifemin®) in menopause discomfort: Surveillance study in practical terms. J Menopause 2005;12(1):27-32.

Schneider HPG, Rosemeier HP, Schnitker J, Gerbsch S, Turck R. Application and factor analysis of the menopause rating scale (MRS) in a post-marketing surveillance study of Climen®. Maturitas 2000 a;37:113-24.

Schneider HPG, Heinemann AJ, Rosemeier HP, Potthoff P, Behre HM. The Menopause Rating Scale (MRS) in comparison with Kupperman index and quality-of-life scale SF-36. Climacteric 2000 b;3:50-58.

Stoll W. Phytotherapeutikum beeinflusst atrophisches Vaginalepithel: Doppelblindversuch Cimicifuga vs. Oestrogenpräparat. [Phytpharmacon influences atrophic vaginal epithelium:Double blind study – Cimicifuga vs. estrogenic substances]. Therapeutikon 1987;1:23-31.

Stolze H. Der andere Weg, klimakterische Beschwerden zu behandeln. [An alternative to treat menopausal complaints]. Gyne 1982;3(l):14-6.

Vermes G, Bánhidy F, Acs N. The effects of remifemin on subjective symptoms of menopause. Adv Ther. 2005;22(2):148-54.

Vorberg G. Therapie klimakterischer Beschwerden: Erfolgreiche hormonfreie Therapie mit Remifemin®. [Treatment of menopausal complaints. Successful hormone-free therapy with Remifemin®.] Z Allgemeinmed 1984;60(13):626-9.

Warnecke G. Beeinflussung klimakterischer Beschwerden durch ein Phytotherapeutikum. [Influencing menopausal symptoms with a phytotherapeutic agent]. Med Welt 1985;36:871-4.

Wuttke W, Seidlová-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. Maturitas. 2003 14;44 Suppl 1:S67-77.

Wuttke W, Gorkow C, Seidlová-Wuttke D. Effects of black cohosh (*Cimicifuga racemosa*) on bone turnover, vaginal mucosa, and various blood parameters in postmenopausal women: a double-blind, placebo-controlled, and conjugated estrogens-controlled study. Menopause 2006;13(2):185-96.

4.4 Special warnings and precautions for use

Al-Akoum M, Dodin S, Akoum A. Synergistic cytotoxic effects of tamoxifen and black cohosh on MCF-7 and MDA-MB-231 human breast cancer cells: an in vitro study. Can J Physiol Pharmacol 2007;85(11):1153-9.

Alves DL, Lima SM, da Silva CR, Galvão MA, Shanaider A, de Almeida Prado RA, Aoki T. Effects of Trifolium pratense and Cimicifuga racemosa on the endometrium of wistar rats. Maturitas. 2008 Dec 20;61(4):364-70.

Amato P, Christophe S, Mellon PL. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms Menopause 2002;9(2):145-50.

Avula B, Wang YH, Smillie TJ, Khan IA. Quantitative determination of triterpenoids and formononetin in rhizomes of black cohosh (Actaea racemosa) and dietary supplements by using UPLC-UV/ELS detection and identification by UPLC-MS. Planta Med. 2009;75:381-6.

Bai W, Henneicke-von Zepelin HH, Wang S, Zheng S, Liu J, Zhang Z, Geng L, et al.. Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. Maturitas 2007;58(1):31-41.

Berger MR. Gutachten zum Tiermodell der FVB/N Maus mit dem Transgen MMTV-neu und Hypothese zum Pathomechanismus der erhöhten Inzidenz von Lungenmetastasen bei diesem Modell nach Applikation von Cimicifuga racemosa. Deutsches Krebsforschungszentrum, AG Toxikologie und Chemotherapie, Heidelberg, 23.03.2009

Betz JM, Anderson L, Avigan MI, Barnes J, Farnsworth NR, Gerdén B, Henderson L, et al.. Black Cohosh – Considerations of Safety and Benefit. Nutrition Today, 2009;44(4):155-62

Bodinet C, Freudenstein J. Influence of Cimicifuga racemosa on the proliferation of estrogen receptor positive human breast cancer cells. Breast Cancer Research and Treatment 2002;76:1-10.

Bodinet C, Freudenstein J. Influence of marketed herbal menopause preparations on MCF-7 cell proliferation Menopause 2004;11:281-9.

Bolle P, Mastrangelo S, Perrone F, Evandri MG. Estrogen-like effect of a Cimicifuga racemosa extract sub-fraction as assessed by in vivo, ex vivo and in vitro assays. J of Steroid Biochem & Molec Biol. 2007;107:262-9.

Borrelli F, Ernst E. Black cohosh /Cimicifuga racemoasa): a systematic review of adverse events. American Journal of Obstetrics and Gynecology 2008; 199: 455-466

Brugisser R, von Daeniken K, Jundt G, Schaffner W, Tullberg-Reinert H. Interference of plant extracts, phytoestrogens and antioxidants with the MTT tetrazolium assay. Planta med 2002; 68 (5):445-8.

Conner P. Hormone Therapy and the Breast – aspects on proliferation, apoptosis and mammographic density. Department of Woman and Child Health, Division of Obstetrics and Gynecology, Karolinska Institute, Stockholm, Sweden, 2004 (ISBN 991-7349-918-8).

Davis VL, Jayo MJ, Ho A, Kotlarczyk MP, Hardy ML, Foster WG, Hughes CL. Black cohosh increases metastatic mammary cancer in transgenic mice expressing c-erbB2. Cancer Res. 2008;68(20):8377-83.

Dixon-Shanies D, Shaik N. Growth inhibition of human breast cancer cells by herbs and phytoestrogens. Oncology Reports 1999;6:1383-7.

Einbond LS, Shimizu M, Xiao D, Nuntanakorn P, Lim JTE, Suzui M et al.Growth inhibitory activity of extracts and purified components of Black Cohosh on human breast cancer cells. Breast Cancer Research and Treatment 2004;83:221-31.

Einbond LS, Shimizu M, Nuntanakorn P, Seter C, Cheng R, Jiang B et al. Actein and a fraction of black cohosh potentiate antiproliferative effects of chemotherapy agents on human breast cancer cells. Planta Med 2006;72(13):1200-6.

Einbond LS, Su T, Wu HA, Friedman R, Wang X, Jiang B, Hagan T, Kennelly EJ, Kronenberg F, Weinstein B. Gene expression analysis of the mechanisms whereby black cohosh inhibits human breast cancer cell growth. Anticancer Research 2007a;27:697-712.

Einbond LS, Su T, Wu H-a, Friedman R, Wang X, Ramirez A, Kronenberg F, Weinstein IB. The growth inhibitory effect of actein on human breast cancer cells is associated with activation of stress response pathways. Int J Cancer 2007b; 121:2073-83.

Einbond LS, Weinstein IB. Anti-neoplastic compositions comprising extracts of black cohosh. United States Patent 7407675, 2008.

Einbond LS, Wen-Cai Y, He K, Wu HA, Cruz E, Roller M, Kronenberg F. Growth inhibitory activity of extracts and compounds from Cimicifuga species on human breast cancer cells. Phytomedicine 2008a;15(6-7):504-11.

Einbond LS, Shimizu M, Ma H, Wu HA, Goldsberry S, Sicular S, Panjikaran M, Genovese G, Cruz E. Actein inhibits the Na+-K+-ATPase and enhances the growth inhibitory effect of digitoxin on human breast cancer cells. Biochem Biophys Res Commun 2008b;375(4):608-13.

Einer-Jensen N, Zhao J, Andersen KP, Kristoffersen K. Cimicifuga and Melbrosia lack oestrogenic effects in mice and rats. Maturitas1996;25:149-53.

Es-Saady D, Simon A, Jayat-Vignoles C, Chulia AJ, Delage C. MCF-7 cell cycle arrested at G1 through ursolic acid, and increased reduction of tetrazolium salts. Anticancer Res. 1996 Jan-Feb; 16 (1): 481 – 486.

Fischer J. *Cimicifuga racemosa* Extrakt (Remifemin®) bei Mamma-Ca-Patientinnen mit klimakterischen Beschwerden unter hormontherapeutischer Behandlung mit Tamoxifen - eine Anwendungsbeobachtung. [*Cimicifuga racemosa* extract (Remifemin®) in mammacarcinoma patients with climacteric complaints under hormone-therapeutic treatment with tamoxifen – a drug-monitoring study.] Dissertation [Thesis], Albert-Ludwigs-University Freiburg, Germany 2006.

Flesch-Janys D, Slanger T, Mutschelknauss E, Kropp S, Obi N, Vettorazi E, Braendle W, et al.. Risk of different histological types of postmenopausal breast cancer by type and regimen of menopausal hormone therapy. Int. J. Cancer 2008;123:933-42.

Freudenstein J, Dasenbrock C, Nißlein T. Lack of promotion of estrogen-dependent mammary gland tumors in vivo by an isopropanolic Cimicifuga racemosa extract. Cancer Res 2002;62:3448-52.

Garita-Hernandez M, Calzado MA, Caballero FJ, Macho A, Munoz E, Meier B et al.. The growth inhibitory activity of the Cimicifuga racemosa extract Ze 450 is mediated through estrogen and progesterone receptors-independent pathways. Planta Med 2006;72:317-23.

Gaube F, Wolfl S, Pusch L, Kroll TC, Hamburger M. Gene expression profiling reveals effects of Cimicifuga racemosa (L.) NUTT. (black cohosh) on the estrogen receptor positive human breast cancer cell line MCF-7. BMC Pharmacol 2007;7:11.

Georgiev DB, Iordanova E. Phytoestrogens - the alternative approach. Maturitas 1997; 27 (Suppl 1):213 (Abstract P309).

Henneicke-von Zepelin H-H, Becher H, Schröder-Bernhardi D, Stammwitz U. Isopropanolic black cohosh extract and recurrence-free survival after breast cancer. Intern. Journal of Clinical Pharmac. and Therap. 2007;45(3):143-54.

Hostanska K, Nißlein T, Freudenstein J, Reichling J, Saller R. Evaluation of cell death caused by triterpene glycosides and phenolic substances from Cimicifuga racemosa extract in human MCF-7 breast cancer cells Biol Pharm Bull 2004a; 27:1970-75.

Hostanska K, Nißlein T, Freudenstein J, Reichling J, Saller R. *Cimicifuga* racemosa extract inhibits proliferation of estrogen receptor-positive and negative human breast carcinoma cell lines by induction of apoptosis. Breast Cancer Res Treat 2004b;84:151-60.

Hostanska K, Nißlein T, Freudenstein J, Reichling J, Saller R. Apoptosis of human prostate androgen-dependent and -independent carcinoma cells induced by an isopropanolic extract of black cohosh involves degradation of cytokeratin (CK) 18. Anticancer Res 2005; 25: 139-48.

Hostanska K, Nißlein T, Freudenstein J, Reichling J, Saller R. Inhibitory effect of an isopropanolic extract of black cohosh on the invasiveness of MDA-MB 231 human breast cancer cells. In vivo 2007;21:349-56.

IMS. Nachauswertung zur Remifemin®-Studie (2004) "Studiencode: SB-FEM1400". [Post-evaluation of the Remifemin®-study (2004) "study code: SB-FEM1400".] IMS Disease Analyzer, February 5, 2009.

Jacobsen JS, Troxel AB, Evans J, Klaus L, Vahdat L, Kinne D, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 2001;19(10):2739-45.

Jarry H, Thelen P, Christoffel V, Spengler, B, Wuttke, W. Cimicifuga racemosa extract BNO 1055 inhibits proliferation of the human prostate cancer cell line LNCaP. Phytomedicine 2005;12:178-82.

Jarry H, Stromeier S, Wuttke W, Nahrstedt A. Petasiphenone, a phenol isolated from Cimicifuga racemosa, in vitro inhibits proliferation of the human prostate cancer cell line LNCaP. Planta Med 2007;73:184-87.

Kennelly EJ, Baggett S, Nuntankorn P, Osokski AL, Mori SA, Duke J et al. Kronenberg F. Analysis of thirteen populations of Black Cohosh for formononetin. Phytomedicine 2002;9(5):461-67.

Köninger A, Kümmel S, Kimmig R. Besonderes Dilemma der Brustkrebspatientinnen. MMW-Fortschr. Med. 2008, (150 Jg.) Nr. 43: 32 – 34.

Kok SH, Gambari R, Chui CH, Lau FY, Cheng GY, Lai PB, Lam WS, Chan AS, Cheng CH, Teo IT, Yu MW, Tang JC, Cheung F, Wong RS. Paradoxical proliferative protential of iron (II) sulphate on cancer cells after the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. Int J Mol Med 2007 Jun; 19 (6): 971 – 975.

Kretzschmar G, Nißlein T, Zierau O, Vollmer G. No estrogen-like effects of an isopropanolic extract of Rhizoma Cimicifugae racemosae on uterus and vena cava of rats after 17 day treatment. J Steroid Biochem Mol Biol 2005;97;271-277.

Kruse SO, Löhning A, Pauli GF, Winterhoff H, Nahrstedt A. Fukiic and piscidic acid esters from the rhizome of *Cimicifuga racemosa* and the in vitro estrogenic activity of fukinolic acid. Planta Med 1999;65:763-4.

Lindén-Hirschberg A, Edlund M, Svane G, Azavedo E, Skoog L, von Schoultz B. An isopropanolic extract of black cohosh does not increase mammographic breast density or breast cell proliferation in postmenopausal women. Menopause 2007;14(1):89-96.

Liske E, Hänggi W, Henneicke von Zepelin HH, Boblitz N, Wüstenberg P, Rahlfs VW. Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosae rhizoma): a 6 month clinical study demonstrates no systemic estrogenic effect. J Womens Health Gend Based Med 2002;11(2):163-74.

Liu ZP, Yu B, Huo JS, Lu CQ, Chen JS. Estrogenic effects of Cimicifuga racemosa (Black Cohosh) in mice and on estrogen receptors in MCF-7 cells. J Med Food 2001;4(3):171-178.

Liu J, Burdette JE, Xu H, Gu C, van Breemen RB, Bhat K, Booth N, et al. Evaluation of Estrogenic Activity of Plant Extracts for the Potential Treatment of Menopausal Symptoms. J Agric. Food Chem. 2001;49:2472-79.

Löhning AM. Beitrag zur pharmakologischen Charakterisierung von Zubereitungen aus Cimicifuga racemosa Nutt., Ranunculaceae, NSD Thesis, Westfälische Wilhelms-Universität Münster 1999

Lundström E, Christow A, Kersemaekers W, Svane G, Azavedo E, Söderqvist G, Mol-Arts M, Barkfeldt J, von Schoultz B. Effects of tibolone and continuous combined hormone replacement therapy on mammographic breast density. Am J Obstet Gynecol 2002 Apr;186 (4):717 – 722.

Lupu R, Mehmi I, Atlas E, Tsai MS, Pisha E, Oketch-Rabah, HA et al. Black Cohosh, a menopausal remedy, does not have estrogenic activity and does not promote breast cancer cell growth. International Journal of Oncology 2003;23(5):1407-12.

Morris K, Look RM, Hudson V, Toth-Fejel S, Pommier R et al. The efficacy and safety of black cohosh for managing menopausal symptoms in breast cancer survivors. Breast Cancer Res. and Treatm. 2003;82, Suppl.1:S159.

Munoz G, Pluchino S. *Cimicifuga racemosa* for the treatment of hot flushes in women surviving breast cancer. Maturitas 2003;44(Suppl 1):59-65.

Nappi RE, Malavasi B, Brundu B, Facchinetti F. Efficacy of Cimicifuga racemosa on climacteric complaints: A randomized study versus low-dose transdermal estradiol. Gynecol Endocrinol 2005;20(1):30-5.

Nesselhut T, Liske E. Pharmacological measures in postmenopausal women with an isopropanolic aqueous extract of Cimicifugae racemosae rhizoma. Menopause 1999;6(4):331.

Nesselhut T, Bodinet C, Schneider P. Verwendung eines Extraktes aus Cimicifuga racemosa. European Patent No. 0847755, 2001.

Nißlein T, Freudenstein J. Prepubertal treatment with Black Cohosh attenuates pathogenicity in the DMBA rat model of mammary carcinoma. Climacteric 2002;5(Suppl.1):139-40.

Nißlein T, Freudenstein J. Synergistic effects of Black Cohosh and Tamoxifen in an animal model of mammary carcinoma. Maturitas 2003a;44(Suppl.2):128.

Nißlein T, Freudenstein J. Long-term treatment of uterine carcinoma prone Dar Agouti rats with a standardized isopropanolic extract of Cimicifuga racemosa. Book of Abstracts, 51st Annual Congress of the Society of Plant Research, Kiel, Germany, 2003b:208.

Nißlein T, Freudenstein J. Concomitant administration of an isopropanolic extract of black cohosh and tamoxifen in the in vivo tumor model of implanted RUCA-I rat endometrial adenocarcinoma cells. Toxicology Letters 2004;150: 271-275

Nißlein T, Freudenstein J. Coadministration of the aromatase inhibitor formestane and an isopropanolic extract of black cohosh in a rat model of chemically induced mammary carcinoma. Planta Med 2007;73:318-22.

Nuntanakorn P, Jiang B, Einbond LS, Yang H, Kronenberg F, Weinstein B, Kennelly EJ. Polyphenolic Constituents of Actaea racemosa. J Nat Prod 2006;69:314-8.

Obi N, Chang-Claude J, Berger J, Braendle W, Slanger T, Schmidt M, Steindorf K, et al. The Use of Herbal Preparations to Alleviate Climacteric Disorders and Risk of Postmenopausal Breast Cancer in a German Case-Control Study Cancer Epidemiol Biomarkers Prev 2009;18(8):2207-13.

Omer-Adam MA, Zieg H, Volk RB, Bodinet C, Liske E. Quantification of characteristic marker substances in various Cimicifuga racemosa products and evaluation of their effects on MCF-7 cell proliferation. Planta Med 2008;74:1105.

Peng L, Wang B, Ren P. Reduction of MTT by flavonoids in the absence of cells. Colloids Surf B Biointerfaces 2005 Oct 10; 45 (2): 108 – 111.

Pockaj BA, Loprinzi CL, Sloan JA, Novotny PJ, Barton DL, Hagenmaier A. et al. Pilot evaluation of black cohosh for the treatment of hot flashes in women. Cancer Investigation 2004;22(4):515-21.

Pockaj BA, Gallagher JG, Loprinzi CL, Stella PJ, Barton DL, Sloan JA et al. Phase II double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG trial N01CC. J Clin Oncol 2006;24:2836-41.

Raus K, Brucker C, Gorkow C, Wuttke W. First-time proof of endometrial safety of the special black cohosh extract (*Actaea* or *Cimicifuga racemosa* extract) CR BNO 1055. Menopause 2006;13(4):678-91.

Rebbeck TR, Troxel AB, Norman S, Bunin GR, DeMichele A, Baumgarten M, et al. A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. Int J Cancer 2007;120:1523-8.

Reed SD, Newton KM, LaCroix AZ, Grothaus LC, Grieco VS, Ehrlich K. Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (HALT) Study. Menopause 2008;15(1):51-8.

Rice S, Amon A, Whitehead SA. Ethanolic extracts of black cohosh (Actaea racemosa) inhibit growth and oestradiol synthesis from oestrone sulphate in breast cancer cells. Maturitas. 2007 Apr 20;56(4):359-67.

Rockwell S, Liu Y, Higgins SA. Alteration of the effects of cancer therapy agents on breast cancer cells by the herbal medicine Black Cohosh. Breast Cancer Res Treat. 2005;90: 233-39.

Ruhlen RL, Haubner J, Tracy JK, Weizhu Z, Ehya H, Laberson WR et al. Black cohosh does not exert an estrogenic effect on the breast. Nutrition and Cancer 2007;59(2):1-9.

Shoemaker M, Cohen I, Campbell M. Reduction of MTT by aqueous herbal extracts in the absence of cells. J Ethnopharmacol 2004 Aug; 93 (2 – 3): 381 – 384.

Stromeier S, Teigeler T, Nahrstedt A. Effects on proliferation of MCF-7-cells of phenolic compounds from the rhizomes of Cimicifuga racemosa (L.) Nutt. Pharmacology/Abstracts of posters, 51th Annual Congress of the Society for Medicinal Plant Research, Kiel (Germany), August 31st – September 4th 2003: 202.

Stromeier S, Petereit F, Nahrstedt A. Phenolic esters from the rhizomes of *Cimicifuga racemosa* do not cause proliferation effects in MCF-7 cells. Planta Med 2005;71(6):495-500.

Stute P, Nißlein T, Götte M, Kamischke A, Kiesel L, Klockenbusch W. Effects of black cohosh on estrogen biosynthesis in normal breast tissue in vitro. Maturitas. 2007; 57:382-91.

Talorete TP, Bouaziz M, Sayadi S, Isoda H. Influence of medium type and serum on MTT reduction by flavonoids in the absence of cells. Cytotechnology 2006 Nov; 52 (3): 189 – 198. Epub 2007 Feb 24.

Vollmer G. Stimulieren Extrakte aus Cimicifuga racemosa das Wachstum von Brustdrüsentumoren – kritische Evaluierung von Befunden aus präklinisch experimentellen Modellen, einschließlich des transgenen c-erbB2 Mausmodell. Institut für Zoologie, TU Dresden, 27.03.2009.

Walji R, Boon H, Guns E, Oneschuk D, Younus J. Black cohosh (Cimicifuga racemosa [L.] Nutt.): safety and efficacy for cancer patients. Support Care Cancer 2007;15(8):913-21.

Wang X, Ge J, Wang K, Qian J, Zou Y. Evaluation of MTT assay for measurement of emodin-induced cytotoxicity. Assay Drug Dev Technol. 2006 Apr; 4 (2): 203 – 207

Workshop on the Safety of Black Cohosh in Clinical Studies. Workshop Sponsors: National Center for Complementary and Alternative Medicine NIH Office of Dietary Supplements. National Institutes of Health, Bethesda, Maryland, November 22, 2004.

Zava DT, Dollbaum CM, Bien M. Estrogen and progestin bioactivity of foods, herbs, and spices. Proc Soc Exp Biol Med 1998;217:369-78.

Zierau O, Bodinet C, Kolba S, Wulf M, Vollmer G. Antiestrogenic activities of Cimicifuga racemosa extracts. J Steroid Biochem Mol Biol 2002;80:125-30.

4.8 Undesirable effects

[1] Teschke et al. Suspected hepatotoxicity by Cimicifugae racemosae rhizoma (black cohosh, root): Critical analysis and structured causality assessment. *Phytomedicine 16 (2009):72-84*

[2] Mahady G, Low Dog T, Sarma DN, Giancaspro G. Suspected black cohosh

104 hepatotoxiciy-causality assessment versus safety signal, quality versus quantity. *Maturitas. 2009 Oct 20;64(2):139-40; author reply 141-2. Epub 2009 Sep 24*

[3] Rochon J, Protiva P, Seeff LB, et al. Reliability of the Roussel Uclaf causality assessment method for assessing causality in drug-induced liver injury. *Hepatology 2008;48:1175–83.*

[4] Teschke R. Hepatotoxicity by drugs and dietary supplements: safety perspectives on clinical and regulatory issues. *Ann Hepatol. 2009 Jul-Sep;8(3):184-95.* *http://www.ncbi.nlm.nih.gov/pubmed/19841496?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=3.*

[5] Betz et al Black Cohosh: Considerations of Safety and Benefit. Nutrition Today (Vol. 44, Number 4, July/August 2009; 155 - 162).

[6] Teschke et al. Black cohosh hepatotoxicity : quantitative causality evaluation in nine suspected cases. *Menopause Vol 16, No 5 (2009), [Epub ahead of print].*

[7] Teschke R, Bahre R, Genthner A, Fuchs J, Schmidt-Taenzer W, Wolff A Suspected black cohosh hepatotoxicity-Challenges and pitfalls of causality assessment. *Maturitas. 2009 Aug, 20; 63 (4): 302-14*

[8] Naser, B and Liske, E. Placebo-controlled Trial Shows No Effects of an Isopropanolic Black Cohosh Extract on Liver Function. The American College of Obstetricians and Gynecologists. *http://www.acog.org/acm/pdf/postersMon.pdf.*

[9] Nasr A, Nafeh H. Influence of black cohosh (Cimicifuga racemosa) use by postmenopausal women on total hepatic perfusion and liver functions. *Fertil Steril. 2009 Nov;92(5):1780-2. Epub 2009 Jun 21*

[10] Geller SE, Shulman LP, van Breemen RB, et al. Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. *Menopause. 2009 Nov-Dec;16(6):1156-66*

Remainder sections

Berger MR. Gutachten zum Tiermodell der FVB/N Maus mit dem Transgen MMTV-neu und Hypothese zum Pathomechanismus der erhöhten Inzidenz von Lungenmetastasen bei diesem Modell nach Applikation von Cimicifuga racemosa. [Expert Report on the animal model of FVB/N mice with the transgene MMTV-neu and hypothesis regarding the pathomechanism of the increased incidence of lung metastases in this model after application of Cimicifuga racemosa.] German Centre of Cancer Research, Study Group Toxicology and Chemotherapy, Heidelberg, 23.03.2009

Brattström A. Dosisabhängige Überlegenheit eines neu entwickelten *Cimicifuga* Extraktes (Ze 450). Eine doppelblinde, randomisierte und Plazebo kontrollierte klinische Studie bei menopausalen Beschwerden [Abstract].[Dose-dependent superiority of a newly developed *Cimicifuga* extract (Ze 450). A double-blind, randomised and placebo-controlled clinical study in case of menopausal complaints (abstract)]. Congress book Phytopharmaka Phytotherapie 2005:S6.

Fischer J. *Cimicifuga racemosa* Extrakt (Remifemin®) bei Mamma-Ca-Patientinnen mit klimakterischen Beschwerden unter hormontherapeutischer Behandlung mit Tamoxifen - eine

Anwendungsbeobachtung. [*Cimicifuga racemosa* extract (Remifemin®) in mammacarcinoma patients with climacteric complaints under hormone-therapeutic treatment with tamoxifen – a drug-monitoring study.] Dissertation, Albert-Ludwigs-University Freiburg, Germany 2006.

IMS. Nachauswertung zur Remifemin®-Studie (2004) "Studiencode: SB-FEM1400". [Post-evaluation of the Remifemin®-study (2004) "study code: SB-FEM1400".] IMS Disease Analyzer, February 5, 2009

Jarry H, Metten M, Spengler B, Christoffel V, Wuttke W. In vitro effects of the Cimicifuga racemosa extract BNO 1055. Maturitas 2003;44(Suppl 1):S31-S38.

Liske E, Hänggi W, Henneicke von Zepelin HH, Boblitz N, Wüstenberg P, Rahlfs VW. Physiological investigation of a unique extract of black cohosh (Cimicifugae racemo-sae rhizoma): a 6 month clinical study demonstrates no systemic estrogenic effect. J Womens Health Gend Based Med 2002;11(2):163-74.

Löhning A, Verspohl EJ, Winterhoff H. Pharmacological studies on the central activity of Cimicifuga racemosa in mice. Abstract. Presented at the 46th Annual Congress of the Society for Medicinal Plant Research, August 31th - September 4th, Vienna, Austria 1998; Abstract J 10

Löhning A, Diel P, Verspohl EJ, Winterhoff H. In vitro studies on the estrogenic and dopaminergic activity of Cimicifuga racemosa. Poster presentation, 40th Deuschen Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie, 09-11 March 1999a, Mainz.

Löhning A, Verspohl EJ, Winterhoff H. Pharmacological studies on the dopaminergic activity of Cimicifuga racemosa. Poster presentation, 23. Int. LOF Symposium "PhytoOestrogens", Gent, January 1999b.

Nisslein T, Koetter U, Freudenstein J. In vitro binding of an isopropanolic extract of black cohosh to selected central nervous receptors. Maturitas 2006;54S; S65

Powell SL, Gödecke T, Nikolic D, Chen SN, Ahn S, Dietz B, Farnsworth NR, van Bremen RB, Lankin DC, Pauli GF, Bolton JL. In vitro serotoninergic activity of black cohosh and identification of N-methylserotonin as a potential active constituent. J Agric Food Chem 2008; 56: 11718-26

Reed SD, Newton KM, LaCroix AZ, Grothaus LC, Grieco VS, Ehrlich K. Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (HALT) Study. Menopause 2008;15(1):51-8.

Vollmer G. Stimulieren Extrakte aus Cimicifuga racemosa das Wachstum von Brustdrüsentumoren – kritische Evaluierung von Befunden aus präklinisch experimentellen Modellen, einschließlich des transgenen c-erbB2 Mausmodell. [Do extracts of Cimicifuga racemosa stimulate the growth of mammary gland tumors - critical evaluation of findings from preclinical experimental models, including the transgenic c-erbB2 mouse model.] Institute for Zoology, Technical University of Dresden, 27.03.2009

Woo KC, Park YS, Jun DJ, Lim JO, Baek WY, Suh BS Kim KT. Phytoestrogen cimicifugoside-mediated inhibition of catecholamine secretion by blocking nicotinic acetylcholine receptor in bovine adrenal chromaffin cells. Journal of Pharmacology and Experimental Therapeutics 2004;309:641-9

Mutagenicity study of Cimicifugawurzelstock-TE SteiCim 73 (100% native) in the Salmonella typhimurium/mammalian microsome reverse mutation assay (Ames-Test). Project No. AM02102N. Freiburger Labor für Mutagenitätsprüfung der King & Harnasch GmbH. Kirchzarten 2002.

References (ESCOP)

1. Bodinet C and Freudenstein J. Influence of *Cimicifuga racemosa* on the proliferation of estrogen receptor-positive human breast cancer cells. Breast Cancer Res Treat 2002;76:1-10.
2. Zierau O, Bodinet C, Kolba S, Wulf M, Vollmer G. Antiestrogenic activities of *Cimicifuga racemosa* extracts. J Steroid Biochem Mol Biol 2002;80:125-30.
3. Dixon-Shanies D, Shaikh N. Growth inhibition of human breast cancer cells by herbs and phytoestrogens. Oncology Reports 1999;6:1383-7.
4. Neßelhut T, Schellhase C, Dietrich R, Kuhn W. Untersuchungen zur proliferativen Potenz von Phytopharmaka mit östrogenähnlicher Wirkung bei Mammakarzinomzellen. Arch Gynecol Obstet 1993;254:817-8.
5. Amato P, Christophe S, Mellon PL. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. Menopause 2002;9:145-50.
6. Zava DT, Dollbaum CM, Blen M. Estrogen and progestin bioactivity of foods, herbs and spices. Proc Soc Exp Biol Med 1998;217:369-78.
7. Liu J, Burdette JE, Xu H, Gu C, van Breemen RB, Bhat KPL et al. Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms. J Agric Food Chem 2001;49:2472-9.
8. Pockaj BA, Loprinzi CL, Sloan JA, Novotny PJ, Barton DL, Hagenmaier A et al. Pilot evaluation of black cohosh for the treatment of hot flashes in women. Cancer Invest 2004;22:515-21.
9. Stromeier S, Petereit F, Nahrstedt A. Phenolic esters from the rhizomes of *Cimicifuga racemosa* do not cause proliferation effects in MCF-7 cells. Planta Med 2005;71:495-500.
10. Bodinet C, Freudenstein J. Influence of marketed herbal menopause preparations on MCF-7 cell proliferation. Menopause 2004;11:281-9.
11. Einbond LS, Shimizu M, Xiao D, Nuntanakorn P, Lim JTE, Suzui M et al. Growth inhibitory activity of extracts and purified components of black cohosh on human breast cancer cells. Breast Cancer Res Treat 2004;83:221-31.
12. Einbond LS, Shimizu M, Nuntanakorn P, Seter C, Chen R, Jiang B et al. Actein and a fraction of black cohosh potentiate antiproliferative effects of chemotherapy agents on human breast cancer cells. Planta Med 2006;72:1200-6.
13. Einbond LS, Su T, Wu H-A, Friedman R, Wang X, Jiang B et al. Gene expression analysis of the mechanisms whereby black cohosh inhibits human breast cancer cell growth. Anticancer Res 2007a;27:697-712.
14. Einbond LS, Su T, Wu H-A, Friedman R, Wang X, Ramirez A et al. The growth inhibitory effect of actein on human breast cancer cells is associated with activation of stress response pathways. Int J Cancer 2007b;121:2073-83.
15. Einbond LS, Wen-Cai Y, He K, Wu HA, Cruz E, Roller M, Kronenberg F. Growth inhibitory activity of extracts and compounds from *Cimicifuga* species on human breast cancer cells. Phytomedicine 2008;15:504-11.
16. Garita-Hernandez M, Calzado MA, Caballero FJ, Macho A, Muñoz E, Meier B et al. The growth inhibitory activity of the *Cimicifuga racemosa* extract Ze 450 is mediated through estrogen and progesterone receptors-independent pathways. Planta Med 2006;72:317-23.

17. Al-Akoum M, Dodin S, Akoum A. Synergistic cytotoxic effects of tamoxifen and black cohosh on MCF-7 and MDA-MB-231 human breast cancer cells: an in vitro study. Can J Physiol Pharmacol 2007;85:1153-9.

18. Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R. *Cimicifuga racemosa* extract inhibits proliferation of estrogen receptor-positive and negative human breast carcinoma cell lines by induction of apoptosis. Breast Cancer Res Treat 2004a;84:151-60.

19. Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R. Evaluation of cell death caused by triterpene glycosides and phenolic substances from *Cimicifuga racemosa* extract in human MCF-7 breast cancer cells. Biol Pharm Bull 2004b;27:1970-5.

20. Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R. Inhibitory effect of an isopropanolic extract of black cohosh on the invasiveness of MDA-MB 231 human breast cancer cells. In Vivo 2007;21:349-55.

21. Rice S, Amon A, Whitehead SA. Ethanolic extracts of black cohosh (*Actaea racemosa*) inhibit growth and oestradiol synthesis from oestrone sulphate in breast cancer cells. Maturitas 2007;56:359-67.

22. Stute P, Nisslein T, Götte M, Kamischke A, Kiesel L, Klockenbusch W. Effects of black cohosh on estrogen biosynthesis in normal breast tissue *in vitro*. Maturitas 2007;57:382-91.

23. Gaube F, Wolfl S, Pusch L, Kroll TC, Hamburger M. Gene expression profiling reveals effects of *Cimicifuga racemosa* (L.) Nutt. (black cohosh) on the estrogen receptor positive human breast cancer cell line MCF-7. BMC Pharmacol 2007;7:11 (19 pages). Open access at: www.biomedcentral.com/1471-2210/7/11.

24. Rockwell S, Liu Y, Higgins SA. Alteration of the effects of cancer therapy agents on breast cancer cells by the herbal medicine black cohosh. Breast Cancer Res Treat 2005;90:233-9.

25. Lupu R, Mehmi I, Atlas E, Tsai M-S, Pisha E, Oketch-Rabah HA et al. Black cohosh, a menopausal remedy, does not have estrogenic activity and does not promote breast cancer cell growth. Int J Oncol 2003;23:1407-12.

26. Freudenstein J, Dasenbrock C, Nißlein T. Lack of promotion of estrogen-dependent mammary gland tumors *in vivo* by an isopropanolic *Cimicifuga racemosa* extract. Cancer Res 2002;62:3448-52.

27. Davis VL, Jayo MJ, Ho A, Kotlarczyk MP, Hardy ML, Foster WG, Hughes CL. Black cohosh increases metastatic mammary cancer in transgenic mice expressing c-*erb*B2. Cancer Res 2008;68:8377-83.

28. Nisslein T, Freudenstein J. Synergistic effects of black cohosh and tamoxifen in an animal model of mammary carcinoma. In: Abstracts of 6th European Congress on Menopause, 24-28 May 2003. Maturitas 2003a;44(Suppl 2):S128 (Abstract P01.07).

29. Seidlová-Wuttke D, Wuttke W. Effects of various phytoestrogens and of *Cimicifuga racemosa* (CR) in the mammary gland of ovariectomized (ovx) rats. Z Phytotherapie 2008;29(Suppl 1):S16.

30. Liu ZP, Yu B, Huo JS, Lu CQ, Chen JS. Estrogenic effects of *Cimicifuga racemosa* (black cohosh) in mice and on estrogen receptors in MCF-7 cells. J Med Food 2001;4:171-8.

31. Wuttke W, Jarry H, Becker T, Schultens A, Christoffel V, Gorkow C, Seidlová-Wuttke D. Phytoestrogens: endocrine disrupters or replacement for hormone replacement therapy? Maturitas 2003;44(Suppl 1):S9-S20.

32. Low Dog T, Powell KL, Weisman SM. Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief. Menopause 2003;10:299-313.

33. Borrelli F, Ernst E. Black cohosh (*Cimicifuga racemosa*): a systematic review of adverse events. Am J Obstet Gynecol 2008;199:455-66.

34. Teschke R, Schwarzenboeck A. Suspected hepatotoxicity by Cimicifugae racemosae rhizoma (black cohosh, root): Critical analysis and structured causality assessment. Phytomedicine 2009;16:72-84.

35. Teschke R, Bahre R, Fuchs J, Wolff A. Black cohosh hepatotoxicity: quantitative causality evaluation in nine suspected cases. Menopause 2009;16:956-65.

36. Teschke R, Bahre R, Genthner A, Fuchs J, Schmidt-Taenzer W, Wolff A. Suspected black cohosh hepatotoxicity - Challenges and pitfalls of causality assessment. Maturitas 2009;63:302-14.
with comment:
Mahady G, Low Dog T, Sarma DN, Giancaspro GI. Suspected black cohosh hepatotoxicity - Causality assessment versus safety signal. *ibid.* 2009;64:139-40.
and authors' reply:
Teschke R, Bahre R, Genthner A, Fuchs J, Schmidt-Taenzer W, Wolff A. Suspected black cohosh hepatotoxicity - Causality assessment versus safety signal. Quality versus quantity. *ibid.* 2009;64: 141-2.

37. Mahady GB, Low Dog T, Barrett ML, Chavez ML, Gardiner P, Ko R et al. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. Menopause 2008;15:628-38.

38. Hudson T. Women's health update: Black cohosh - concerns and controversies. Altern Complement Ther 2007;13:102-6.

39. Firenzuoli F, Gori L, Roberti di Sarsina P. Black cohosh hepatic safety: follow-up of 107 patients consuming a special *Cimicifuga racemosa* rhizome herbal extract and review of literature. eCAM Advance Access published online February 20, 2008. eCAM 2008:1-7, doi:10.1093/ecam/nen009