EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

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

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HMPC decision on review of monograph *Cimicifuga racemosa* (L.) Nutt., rhizoma adopted on 27 March 2018	31 January 2024
Call for scientific data (start and end date)	From 15 February 2024 to 15 May 2024
Discussion in Committee on Herbal Medicinal Products (HMPC)	January 2025 March 2025 May 2025 November 2025
Adoption by HMPC	19 November 2025

Review of new data

Periodic review (from 2018 to 2024)

Sources checked for new information:

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

- ☒ Scientific/Medical/Toxicological databases
  EBSCOhost database was searched on 11.12.2024; period covered: January 2018 – December 2024. Filters used were cimicifugae rhizoma, meonopausal complaints, and clinical trial/toxicology.
- ☒ Pharmacovigilance databases
  - ☒ data from EudraVigilance
  - ☐ from other sources (e.g. data from VigiBase, national databases)
- ☐ Other

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Regulatory practice

☒ Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10 years of WEU on the market)

☒ New market overview (including pharmacovigilance actions taken in member states)

☒ PSUSA: Due to the possible risk of hepatotoxicity, *Cimicifuga racemosa* (L.) Nutt., rhizoma was put on the EURD list and a PSUSA-procedure has been finalised during the review period (PSUSA/00000755/202301).

☒ Feedback from experiences with the monograph during MRP/DCP procedures

☒ Ph. Eur. monograph 2069: no changes

☐ Other

Consistency (e.g. scientific decisions taken by HMPC)

☒ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☐ Other

Availability of new information that could trigger a revision of the monograph

Scientific data	Yes	No
New non-clinical safety data that could trigger a revision of the monograph	☒	☐
New clinical safety data that could trigger a revision of the monograph	☐	☒
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation that could trigger a revision of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☒	☐
Other scientific data that could trigger a revision of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒
New recommendations from a finalised PSUSA	☐	☒
Feedback from experiences with the monograph during MRP/DCP procedures that could trigger a revision of the monograph	☐	☒
New/Updated Ph. Eur. monograph that could trigger a revision of the monograph	☐	☒
Other regulatory practices that could trigger a revision of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions that could trigger a revision of the monograph	☐	☒

Relevant inconsistencies with other monographs within the therapeutic area that could trigger a revision of the monograph	☐	☒
Other relevant inconsistencies that could trigger a revision of the monograph	☐	☒

Summary of new references

During the review, 153 new references not yet available during the previous assessment were identified. Out of these new references, four of them were considered to be relevant for the EU herbal monograph and one reference could trigger the revision of the monograph.

Sixty-nine references were provided by Interested Parties during the Call for data.

Assessment of new data

New scientific data that could trigger a revision of the monograph

- **Clinical studies**

Several clinical studies and a meta-analysis have been published during the review period:
The aim of the monocentric retrospective cohort study by Friederichsen *et al*. (2019) was to compare the influence of *Cimicifuga racemosa* extract (CR dry extract Ze 450, DER 4.5-8.5:1, extraction solvent: ethanol 60%) and menopausal hormone therapy (MHT) on metabolic parameters and body weight in symptomatic menopausal women. Included in the final analysis were 174 women treated with either MHT (n=142) or CR (n=25 with a daily single dose of 13.0 mg, n=7 with a daily single dose of 6.5 mg CR dry extract) and having at least one follow-up consultation. Metabolic serum parameters [lipids, glucose, insulin, and HOMA-IR (short for Homeostasis Assessment Model to assess Insulin Resistance)], body weight, and menopausal symptoms [Menopause Rating Scale (MRS)-II] were the main outcome measures. Statistical analysis was done by uni- and multi variable linear mixed-effects regression models assuming a linear effect of time. There was no difference between the groups regarding baseline characteristics (age, BMI, serum metabolic parameters, hormones, and blood pressure) and total MRS-II score, while reproductive stage differed significantly with more postmenopausal women treated with CR (83%) than MHT (55%) (p=0.038). Median follow-up time was 12 months. The study results showed no evidence for a within-group change in body weight, carbohydrate metabolism (glucose, insulin, and HOMA-IR), and serum lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides), neither in women treated with CR nor with MHT. For MHT, a significant improvement was found over time of the MRS-II total score (− 0.99 [95% CI − 1.42, − 0.55] per year; p < 0.0001), the MRS-II vegetative subscore (− 0.24 [95% CI − 0.45, − 0.03] per year; p = 0.023), the MRS-II psychological subscore (− 0.48 [95% CI − 0.71, − 0.25]; p < 0.0001), and the MRS-II urogenital subscore (− 0.28 [95% CI − 0.45, − 0.11]; p = 0.001). Treatment with CR significantly improved the MRS-II vegetative subscore (− 0.81 [95% CI − 1.57, − 0.04]; p = 0.039) and the urogenital subscore (− 0.64 [95% CI − 1.26, − 0.01]; p = 0.045). The MRS-II total score had the same trend (− 1.43 [95% CI − 3.16, 0.30]; p = 0.11). The authors concluded that both MHT and CR improved menopausal symptoms. Body weight and serum metabolic parameters did not change in MHT- or CR-treated women.

Assessor's comment
The extract used is included in the EU herbal monograph as herbal preparation b). While the one posology (6.5 mg daily) is according to the monograph, the other CR dry extract group received a much higher (double) daily dose. As the study was retrospective and observational, the results have to be interpreted accordingly. Sample size per group (MHT: n=142, CR: n=32) was small. No reason is given for the dosage in the CR group. Thus, a revision of the EU herbal monograph is not triggered

by the study results.

In 2021, the effectiveness of an isopropanolic extract of CR (iCR dry extract, DER 6-11:1, extraction solvent: propan 2-ol 40% (V/V), 2 x 2.5 mg per tablet, equivalent to 40 mg herbal substance per day) on reducing menopausal symptoms was investigated (Guida *et al*., 2021). A single-centre observational prospective case-control study was performed to assess the improvement of menopausal symptoms in menopausal women undergoing iCR administration (cases) or no treatment (controls). Menopausal symptoms were assessed through a modified Menopause Rating Scale (mMRS) questionnaire at T0 (baseline), T1 (1-month follow-up), and T2 (3-month follow-up). Univariate comparisons between cases and controls were performed by using the unpaired t-test for two-tailed p-value with $\alpha = 0.05$ significance level. A total of 163 women (83 cases and 80 controls) were enrolled in the study. The difference in menopausal symptoms between cases and controls from T0 to T2, and from T0 to T1, was found significant for all analyses. In particular, the difference in all menopausal symptoms was 20.56 ± 0.90 points (95% confidence interval [CI]: 18.77, 22.33, $p < 0.001$) from T0 to T2, and 10.69 ± 0.6 (95% CI: 9.49, 11.88, $p < 0.001$) from T0 to T1. The authors concluded that iCR may be effective in reducing menopausal symptoms, both after 1 month and after 3 months of treatment. The improvement was higher in vasomotor symptoms, sleep problems, and irritability.

Assessor's comment
The extract and posology used are described in the EU herbal monograph as herbal preparation c). A randomized placebo-controlled study would be necessary to prove efficacy. Due to the observational design of the study, the results are of limited value and can only be considered as supportive. The study does not trigger a revision of the EU herbal monograph.

There was one clinical study in breast cancer patients (Wang *et al*., 2019). Aim of the prospective randomised study was to investigate efficacy and safety of CR on menopausal symptoms induced by LHRH-a (luteinizing hormone releasing hormone analogue) in breast cancer. Patients planning for LHRH-a treatment were randomly divided into 2 groups: the control group which was being treated with the standard treatment of LHRH-a and the other group which was being treated with an isopropanolic extract of Cimicifuga racemosa (iCR dry extract, DER 6-11:1, propan 2-ol 40% (V/V), 2 x 2.5 mg per tablet, equivalent to 40 mg herbal substance per day) combined with LHRH-a. Main endpoint was the Kupperman menopause index (KMI). Hormone levels in peripheral blood and gynaecological complications were also evaluated. Eighty-five patients (42 in iCR group and 43 in control group) were enrolled. At the 4th, 8th and 12th week after using LHRH-a, the KMI scores were all significantly lower in the iCR group than in control group ($P<0.01$), while the hormone levels, including estradiol (E2), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were similar in the two groups. A statistically significant higher incidence however, of cervical cysts in the treated group could be seen. The cause and relevance of this finding is unclear. Overall, Wang *et al*. (2019) concluded that the short-term use of CR extract was safe in breast cancer patients, whereas further research is needed to confirm whether long-term use of CR is safe.

Assessor's comment
Since CR is used as add-on to LHRH-a, and due to limited group size and limited number of outcome parameters investigated in this study, no firm conclusions on the safe use in breast cancer patients can be drawn. The study does not question the previous assessment by HMPC (see chapter 4.4 of the monograph: Patients who have been treated or who are undergoing treatment of breast cancer or other hormone dependent tumours should not use CR preparations without medical advice) and does

not trigger a revision of the EU herbal monograph.

- **Meta-analysis**

Castelo-Branco *et al*. (2021) published a review and meta-analysis on the use of the isopropanolic extract of CR (iCR) for menopausal symptoms. The authors searched for clinical studies with iCR extract (irrespective of design) and meta-analyses thereof, published from 1997 to January 2020, as a basis for their review. The 35 clinical studies identified were all published in the period 1987-2015, except for a study by Wang *et al*. (2019). The one meta-analysis identified was published in 2011 (Naser *et al*., 2011). The authors included all placebo controlled randomized clinical trials (RCTs) examining efficacy for neurovegetative and psychological climacteric symptoms in their meta-analysis (irrespective of publication date). In total, six RCTs published in the period 1987-2015 were included in their meta-analysis (e.g. Stoll, 1987; Osmers *et al*., 2005; Li *et al*., 2011). One of these RCTs included breast cancer patients (Jacobsen *et al*., 2001) while another one examined the efficacy of the fixed combination of iCR plus Hypericum perforatum (Uebelhack *et al*., 2006).

Assessor's comment
Since the meta-analysis by Castelo-Branco et al. contains no new studies from the review period – except the study by Wang et al. (2019) that is summarised above – it does not provide any new information and does not trigger a revision of the EU herbal monograph.

- **Non-clinical studies**

Two 2-year carcinogenicity studies in rats and mice, administering black cohosh root extract (BCE) (a 50% aqueous ethanolic extract standardized to 7.8% (w/w) total triterpene glycosides) via gavage, were conducted by the National Toxicology Program of the United States (NTP, 2023). To emulate a potential human exposure scenario in which a woman might use black cohosh throughout pregnancy and lactation, perinatal exposure was included for the rat study.
Time-mated female rats Hsd:Sprague Dawley SD were administered 0, 75, 250, or 750 mg/kg bw/day BCE by gavage starting on gestation day 6 and continuing through lactation. After weaning, female offspring were administered the same doses as their respective dam for 2 years; male offspring were not administered BCE but were maintained for the remainder of the study. Female B6C3F1/N mice, approximately 5–6 weeks of age, were administered 0, 30, 100, 300, or 1,000 mg/kg bw/day BCE for 2 years. Interim evaluations of micronucleated peripheral blood erythrocytes, haematology, and bone marrow cytology in these mice were conducted at 3 and 12 months to evaluate the persistence of haematological effects observed in previous studies of BCE.
Under the conditions of these 2-year gavage studies, there was equivocal evidence of carcinogenic activity of BCE in female rats based on marginal increases in the incidence of uterine squamous cell papillomas. There was no evidence of carcinogenic activity of perinatal BCE exposure in male rats at maternal doses of 75, 250, or 750 mg/kg/day.
There was no evidence of carcinogenic activity of BCE in female mice at doses of 30, 100, 300, or 1,000 mg/kg/day.
Dose-related nonneoplastic lesions were observed in the uterus and ovary in rats and in the liver and thyroid gland in female mice. A significant decrease in litter size was observed in rats.
Interim haematological evaluations and micronucleus assays in female mice showed disruption of normal erythropoiesis and increased frequency of micronucleated erythrocytes at 3 months; at 12 months, the same effects were observed with similar severity and frequency.

Assessor's comment
The extract used is not described in detail. It is unclear to what extent the extract used in the NTP is comparable to the extracts covered by the monograph (e.g. DER, extraction solvent, pharmaceutical

grade). The marginal increase in the incidence of rare uterine squamous cell papillomas in the female rat group was considered to be equivocal evidence of carcinogenicity in female rats by NTP. A dose-response relationship could not be established. No such effects were seen in mice. The human relevance is unknown.
The nonneoplastic lesions were seen in rats starting from the lowest dosage group which equals (taking into account allometric factors) a human dose of 12 mg/kg bw/day. The posology of the monograph equals approx. 0.13 mg/kg bw/day for a 50 kg human adult. Taking into account this very high dosage together with the uncertainty regarding the preparation and the relevance of the results, an inclusion in chapter 5.3 of the monograph is not necessary but could be discussed for the next revision.
The study results do not trigger a revision of the EU herbal monograph.

New regulatory practice that could trigger a revision of the monograph

- **Market overview**

A new indication and posology for an herbal preparation included in the EU herbal monograph were reported by member state AT:

Active substance	**Indication**	**Pharmaceutical form, Strength (where relevant), Posology, Duration of use**	**Regulatory status (date, Member State)**
Dry extract; DER 4.5-8.5:1, extraction solvent: ethanol 60% (V/V)	For the relief of moderate to severe menopausal complaints such as hot flushes and profuse sweating	Tablet: each tablet contains 13 mg of dry extract Posology: 1 tablet daily Duration of use: as a minimum duration of use 6 weeks are recommended. The product should not be taken for more than 6 months without medical advice.	AT, WEU, 01/2024

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

Products no longer on the market, containing the following herbal preparations:

1. Liquid extract, DER 1:20-25, extraction solvent: ethanol 40% (m/m); AT, authorized in 1973, withdrawn in 2019

2. Tincture, DER 1:10, extraction solvent: ethanol 69.7% (V/V), DE, authorized in 1993, withdrawn in 2017

3. Dry extract, DER 4–9:1, extraction solvent: ethanol 58% (V/V), DE, authorized in 1998, withdrawn in 2018

4. Dry extract, DER 4.1-6.5:1, extraction solvent: ethanol 60% (V/V), DE, authorized in 1999, withdrawn in 2018

Assessor's comment
The herbal preparation of the medicinal product reported by AT which has been authorised in 01/2024 is included in the EU herbal monograph as herbal preparation b). Posology and indication however deviate from the monograph (see chapter 4.1 and chapter 4.2 of the monograph: 6.5 mg once daily for the relief of menopausal complaints such as hot flushes and profuse sweating). The decision on posology and indication in this national procedure was mainly based on data already discussed in the HMPC assessment (Schellenberg et al., 2012; Drewe et al., 2013), but also other aspects including data not available for HMPC were considered. According to the HMPC assessment, the results of published clinical studies indicated a possible dose dependency of the effect especially in patients with severe symptoms. However, HMPC concluded that patient numbers were rather small, and a confirmation for other extracts was missing. Therefore, a revision of the EU herbal monograph is not triggered by the products on the market.

- **PSUSA**

Due to the possible risk of hepatotoxicity, *Cimicifuga racemosa* (L.) Nutt., rhizoma was put on the EURD list and a PSUSA-procedure has been finalised during the review period (PSUSA/00000755/202301). Based on the review of data on safety and efficacy by the Lead Member State and taking into account any comments provided by the PRAC, the PRAC considers that the risk-benefit balance of medicinal products containing the active substance *Cimicifuga racemosa* (L.) nutt., rhizoma, remains unchanged and therefore recommends the maintenance of the marketing authorisations. Hepatotoxicity should further be closely monitored. The current 5-year frequency for the submission of PSURs should remain unchanged.

Assessor's comment
The risk of hepatotoxicity is already addressed in the monograph and no changes of the EU herbal monograph result from the PSUSA-procedure.

Inconsistency that could trigger a revision of the monograph

Not applicable.

Other issues that could trigger a revision of the monograph

Not applicable.

New information not considered to trigger a revision at present but that could be relevant for the next review

Not applicable.

References

Castelo-Branco C, Gambacciani M, Cano A, Minkin MJ, Rachoń D, Ruan X *et al*. Review & meta-analysis: Isopropanolic black cohosh extract iCR for menopausal symptoms—An update on the evidence. *Climacteric* 2021, 24: 109–119

Drewe J, Zimmermann C, Zahner C. The effect of a Cimicifuga racemosa extracts Ze 450 in the treatment of climacteric complaints - an observational study. *Phytomed* 2013, 20(8-9):659-666

Friederichsen L, Nebel S, Zahner C, Bütikofer L, Stute P. Effect of Cimicifuga racemosa on metaBOLIC parameters in women with menopausal symptoms: A retrospective observational study (CIMBOLIC). *Arch Gynecol Obstet* 2019, 301: 517–523

Guida M, Raffone A, Travaglino A, Neola D, Reppuccia S, Borgo M *et al*. Cimicifuga racemosa

isopropanolic extract for menopausal symptoms: an observational prospective case-control study. *Gynecol Endocrinol* 2021, 37(12):1132-1137

NTP. Technical Report on the Toxicology and Carcinogenesis Studies of Black Cohosh Root Extract (CASRN 84776-26-1) Administered by Gavage to Sprague Dawley (Hsd: Sprague Dawley SD) Rats and Female B6C3F1/N Mice: Technical Report 603. Research Triangle Park (NC): National Toxicology Program, 2023

Schellenberg R, Saller R, Hess L, Melzer J, Zimmermann C, Drewe J *et al*. Dose-dependent effects of the Cimicifuga racemosa extract Ze 450 in the treatment of climacteric complaints: a randomized, placebo-controlled study. *Evid Based Complement Alternat Med* 2012, 2012:260301

Wang C, Huang Q, Liang CL, Zhang YW, Deng DH, Yu Y *et al*. Effect of Cimicifuga racemosa on menopausal syndrome caused by LHRH-a in breast cancer. *J Ethnopharmacol* 2019, 238:111840

Rapporteur's proposal on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☐ Revision likely to have an impact on the corresponding list entry (if applicable)

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

HMPC decision on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph