The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CIMICIFUGAE RACEMOSAE RHIZOMA

SUMMARY REPORT

1. *Cimicifugae racemosae rhizoma* is the dried rhizome and roots of *Cimicifuga racemosa*.

   Cimicifugae racemosae rhizoma contains the following constituents: Resins, 15 to 20%, known as cimi(ci)fugin, macrotin or resina cimicifugae; triterpene glycosides, one of which is actein with acetylacteol as aglycone and xylose in the sugar part and the other is cimigoside (= cimifugoside) with cimigenol as aglycone. Also 27-desoxyacetylacteol and other aglycones have been isolated as well as the alkaloids cytisine *N*-methylcytisine, tannins, acetic acid, butyric acid, formic acid, isoferulic acid, fatty acids, salicylic acid, phytosterols, volatile oil and an unidentified resinous mixture called acteina. The triterpene glycosides, cytisine, N-methylcytisine, isoferulic acid and salicylic acid can be regarded as pharmacologically active. No information on the quantitative content of these substances is provided.

   Cimicifugae racemosae rhizoma is contained in a concentration of 1% (w/w) as one of 14 active ingredients in powder for oral administration to cows, horses, sheep and goats used for the induction of heat and rut. The doses are 50 g twice a day on two consecutive days for cattle and horses, and 10 to 20 g twice a day on 3 to 4 consecutive days for sheep, goats and pigs.

   Cimicifugae racemosae rhizoma is also used in human medicine. Clinical studies have indicated efficacy of extracts of *Cimicifugae racemosae rhizoma* on neurovegetative and psychic problems associated with the menopause and early post-menopause as an alternative to hormone therapy. Other indications are muscular rheumatism, rheumatoid arthritis, tinnitus. The crude drug is also stated to possess antiinflammatory, antitussive, sedative and emmenagogue properties. It has also been used for intercostal myalgia, sciatica, whooping cough, chorea and uterine colic. The dosage corresponds to 40 mg up to 6 g/day of the crude drug. Single doses are 40 mg up to 2 g. The daily dose of 40 mg can be taken for up to 6 months.

2. Acteina, a chemically not characterised substance from the resin, has hypotensive activity in unanaesthetised rabbits as well as in anaesthetised cats. The effective dose is 1 mg/kg bw and maximum hypotension was attained with 10 mg/kg bw, route of administration was not stated. This activity is of no importance in humans.

   A methanolic rhizome extract reduced the serum concentration of luteinising hormone in the ovariectomised rat and showed binding affinity to oestrogen receptors in the isolated rat uterus. The activity *in vivo* was significantly reduced following hydrolysis of glycosides present in the extract. Subsequent *in vitro*-studies resulted in isolation of three compounds with endocrine activity, which exhibited competitive oestrogen receptor activity but did not cause reduction in serum concentrations of luteinising hormone.

   Triterpene compounds have been shown to possess hypocholesterolaemic activity *in vivo* and to inhibit phytohaemagglutinin-induced proliferative response *in vitro*. Triterpene glycosides such as cimicifugoside are assumed to have an effect on the hypothalamus-pituitary system, leading to secondary effects on the reproductive and central/peripheral nervous systems.

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In ovariectomized rats, the chloroform extractable part of a methanolic extract significantly reduced the serum level of luteinizing hormone after 3 days of treatment with daily doses of 47 mg of the fraction/rat. Further fractionation yielded four fractions. One fraction inhibited luteinizing hormone secretion but did not bind to estrogen receptors. Two fractions were active in both tests and the fourth fraction showed strong binding to estrogen receptors and inhibited secretion of luteinizing hormone in acute experiments but not upon chronic treatment.

A 50% aqueous ethanol extract of *Cimicifugae racemosae rhizoma* was found to have no oestrogenic effect in ovariectomized rats in contrast to previous findings.

3. No information on pharmacokinetics was provided.

4. The minimal lethal dose for a 50% aqueous ethanol extract in mice is greater than 500 mg/kg bw (intraperitoneal administration). Orally in rats the minimal lethal dose is greater than 1000 mg/kg bw. The corresponding figure, intravenously to rabbits, is greater than 70 mg/kg bw.

5. Applied for more than 30 days the minimal lethal dose was greater than 10 mg/kg bw/day (intraperitoneally, mice) and greater than 6 mg/kg bw/day (orally, rabbits), respectively.

6. It was reported without any supporting information that in a six months GLP compliant study "the no effect level" of an orally administered 50% aqueous ethanolic extract was found to be 1.8 g/kg bw for mice, rats and rabbits. A six month oral toxicity study in female Wistar rats followed by an 8 week recovery period indicated no toxic potential of the isopropanolic extract even at a very high dose (up to 5000 mg of *Cimicifuga* granulate/kg bw. The content of extract in the "granulate" is not given). No anomalies were noted in clinical, chemical, histopathologic, or macroscopic organ findings compared with the simultaneously treated control group (amount of inactive additives corresponded to the highest dose).

7. No information on reproductive toxicity or on teratogenicity was provided.

8. The ethanolic extract of *Cimicifugae racemosae rhizoma* has no mutagenic effect in the *Salmonella*-microsomal assay.

9. No information on carcinogenicity studies was provided.

10. It was reported but without supporting data that large doses of *Cimicifugae racemosae rhizoma* can cause strong headache, stiff joints and strong priapism. Gastroentritis, dyspnoe and delirium are also reported but no doses are given. Also reported (without doses) are: nausea, vomiting, dizziness, visual and nervous disturbances, together with reduced pulse rate and increased perspiration. *Cimicifugae racemosae rhizoma* is contraindicated in pregnancy. Overdose were reported in old publications to cause premature birth. These findings were not substantiated and should be considered in the context of the conflicting results on oestrogenic effects in ovariectomised rats.

    Cimicifugin can cause erythema and formation of blisters in the skin (dose not reported).

    Treatment of menopausal women for 8 weeks with daily doses of 8 mg (equal to 0.13 mg/kg bw at an assumed body weight of 60 kg) of an aqueous ethanolic extract (corresponding to 40 mg crude drug) of *Cimicifugae racemosae rhizoma*, resulted in a significant reduction *versus* placebo in serum luteinizing hormone levels, whereas the follicle-stimulating hormone levels were not affected.

    Treatment of hysterectomized women with at least one functional ovary with daily doses of 8 mg of an extract of *Cimicifugae racemosae rhizoma* (approximately equal to 0.13 mg/kg bw, assuming a body weight of 60 kg) did not cause a change of the luteinizing hormone and follicle-stimulating hormone levels in the blood.

    Several papers describe clinical experiences with a preparation of *Cimicifugae racemosae rhizoma* with daily oral doses of 8 mg, corresponding to 40 mg of the rhizome. No adverse effects were reported.

Treatment of menopausal women for 8 weeks with daily doses of 8 mg (equal to 0.13 mg/kg bw at an assumed bodyweight of 60 kg) of an aqueous ethanolic extract (corresponding to 40 mg crude drug) of *Cimicifugae racemosae rhizoma*, resulted in a significant reduction versus placebo in serum luteinizing hormone levels, whereas the follicle-stimulating hormone levels were not affected.

11. No information on residue studies was provided but a worst case calculation can be made based on a cow weighing 500 kg of which 250 kg are edible tissues. The daily dose of the product is 100 g corresponding to 1 g crude drug. This would result in 4 mg crude drug/kg edible tissue thus corresponding to 2 mg considering the arbitrary daily intake of 500 g edible tissue. For a cow producing 20 l milk per day 1 g of crude drug corresponds to 50 mg/l and thus 75 mg in the arbitrary daily intake of 1.5 l of milk.

    According to the worst case calculation the theoretical maximum residues in meat is considerable lower than the doses used in human therapy. This is, however, not the case for residues in milk and it is therefore recommended that *Cimicifugae racemosae rhizoma* should not be use in lactating animals.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for Veterinary Medicinal Products for the inclusion of substances in Annex II of Council Regulation (EEC) No. 2377/90 and in particular that:

- *Cimicifugae racemosae rhizoma* is of low acute and sub-chronic oral toxicity,
- *Cimicifugae racemosae rhizoma* is used only in a small number of individual animals, for infrequent or non-regular treatments,
- the animals are unlikely to be sent for slaughter during or immediately after treatment;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for *Cimicifugae racemosae rhizoma* and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Cimicifugae racemosae rhizoma	All food producing species	Not for use in animals from which milk is produced for human consumption