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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CENTELLAE ASIATICAE EXTRACTUM

SUMMARY REPORT

1. *Centella asiatica* is a small perennial herbaceous plant, belonging to the *Umbelliferae* family. Both the leaves and the entire plant can be used therapeutically. The commercial veterinary formulation contains madecassic acid (1.2 mg/ml) and asiaticoside (0.5 to 0.7 mg/ml). The ratio of madecassic acid to asiaticoside varies between 1.5 and 2.3 to 1, depending on the source of the plant used to manufacture the final commercial formulation. In literature it is reported that leaves of *Centella asiatica* contains quercetin-3-glycoside and kämpferol-3-glycoside, these may be removed during the extraction process. Extract of *Centella asiatica* is used in veterinary medicine for its wound healing properties and is applied locally to wounds of the skin or mucous membranes. *Centella asiatica* is indicated for cattle, horses, goats, sheep, pigs, rabbits and poultry. It is applied topically on a daily basis for a maximum of up to 2 months.

   The major clinical indications for the use of *Centella asiatica* in human include the treatment of wounds, venous insufficiency of the limbs, certain mycobacterial infections and cellulitis. The product is normally used orally or topically in man. Dosage levels used orally in man are reported to be between 330 to 680 mg of the herb up to 3 times per day.

2. The active ingredients of *Centella asiatica* are claimed to possess wound healing properties. Madecassic acid, asiaticoside and asiatic acid (a metabolite *in vivo* of asiaticoside) act on fibroblast cells and equilibrate collagen fibre synthesis, whenever it is modified. The overall effect contributes to the restoration of elastic connective tissue, a reduction in fibrosis and a shortening in the time necessary for wound healing. Most such effects of *Centella asiatica* on collagen synthesis have been demonstrated on human fibroblasts. *In vitro*, the addition of *Centella asiatica* to culture medium results in an increase in collagen synthesis, which is proportional to the administered dose. This effect, however, does not appear to be related to cell proliferation. Studies on human fibroblasts have shown that the addition of 0.25 µg/ml of *Centella asiatica* extract had no effect on cell division, total protein synthesis or proteoglycan synthesis; it did nonetheless, result in a significant increase in collagen and fibronectin synthesis.

   Reference is made to the antiseptic properties of *Centella asiatica*. Asiaticoside has been reported in the scientific literature to show some efficacy against *Mycobacterium tuberculosis*, *Bacillus leprae* and *Entamoeba histolytica.*

3. No information is available on the pharmacokinetics of *Centella asiatica* extract in the indicated species. Studies were conducted in rats to evaluate the percutaneous absorption of the active ingredients extracted from the parent plant, *Centella asiatica*. Tritiated molecules were administered with a gauze patch. Madecassic acid crosses the skin rapidly but only to a limited extent. The plasma concentration did not exceed 0.02 to 0.05% of the initial applied concentration. Samples of skin at the application site contained only 0.4% of the administered dose at the 1 hour time point and only 0.06% of the administered dose at the 24 hour time point. In the underlying abdominal muscles only 0.09% of the administered dose was found after 1 hour, with the corresponding figure at the 24 hour time point being 0.04% (dosage levels not reported). The results for asiatic acid were similar to those of madecassic acid. In man, the active ingredients of *Centella asiatica* extract are reported to be excreted

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primarily in the faeces over a 24 to 76 hour period, with a smaller percentage being eliminated *via* the kidneys (dosage levels not reported).

4. In mice, a dose of 1 g/kg bw of an extract of *Centella asiatica* (in 50% ethanol) did not lead to any toxic effects (literature reference, no raw data are available). No mortalities were recorded. Reports in the medical literature indicate that the active ingredients of *Centella asiatica* are known to be cytotoxic. High concentrations of asiaticoside applied dermally did not give rise to any signs of systemic toxicity, but did lead to hyperkeratinization of the skin at the application site (species not specified).

5. No repeated dose toxicity data were included.

6. No tolerance data in target species were included. However, no such data was considered necessary.

7. No information was available on reproductive toxicity nor teratogenicity. *In vitro* fertility studies reported in the literature indicated a detrimental effect of asiaticoside on human and rat sperm. A crude extract of *Centella asiatica* has been reported to significantly reduce the fertility of female mice when administered orally (dosage levels not reported). Teratogenicity studies in the rabbit for a *Centella asiatica* extract containing the three active ingredients concerned have reported negative findings (dosage levels not reported).

8. No information was provided on mutagenicity. In a lifetime study performed in mice, malignant skin tumours (type of tumours not specified) were recorded in animals receiving a daily topical application of a 0.1% commercial formulation. No internal tumours were recorded in this study (no raw data were provided). There is no clear information whether the veterinary formulation with *Centella asiatica* contains quercetin-3-glycoside and kämpferol-3-glycoside. Quercitin and kämpferol, the hydrolysis products of the respective glycosides, are both known to be carcinogenic to laboratory animals. In literature reference was made to a 2-year carcinogenicity study with quercetin in rats. An increase in the rate of tubular cell adenomas was reported for male rats of the highest dose group only. The result has been interpreted in the scientific literature as irrelevant to humans. Anticarcinogenic activity of quercetin in rats has also been reported in the literature.

9. No studies on the potential immunotoxicity of *Centella asiatica* are available. Reports exist in the medical literature of human patients suffering contact allergic dermatitis with the use of *Centella asiatica*.

10. No information is included dealing with the microbiological properties of residues of *Centella asiatica*.

11. *Centella asiatica* has been widely used in man for several decades. Reports exist in the medical literature relating to the development of allergic contact dermatitis in human patients receiving this treatment. Asiaticoside increased the mean concentrations of blood glucose, cholesterol and total protein, whilst decreasing the urea and serum acid phosphatase levels in a study involving 43 adult humans. A recent pharmacokinetic study in healthy human volunteers investigated the effects of single or repeated administrations of *Centella asiatica*. 30 or 60 mg was administered orally to humans on a single occasion or once daily for 7 consecutive days. The assay method was only able to investigate levels of asiatic acid. The elimination half-life was 2 to 3 hours irrespective of the dose used. The t_{max} occurred in approximately 4.2 hours irrespective of the dose used. The peak plasma concentration, area under curve (0 to 24 hours) and the plasma half life were significantly increased following repeated administration of *Centella asiatica*. These increases may in part be explained by the fact that asiaticoside is metabolised *in vivo* to asiatic acid.

12. No further information was presented with regard to pharmacokinetics in target species or residue depletion data from such species. In view of the minimal dermal absorption demonstrated in the rat pharmacokinetic studies residues in edible tissues arising from the use of *Centellae asiaticae extractum* in veterinary medicinal products were considered unlikely to be of concern to the consumer. No further data on residue depletion was considered necessary.

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:

- the intended use of the product is by the topical route only,
- extract of *Centella asiatica* is used infrequently on an individual animal basis,
- minimal dermal absorption was demonstrated in rat pharmacokinetic studies,
- treated animals are unlikely to be sent for slaughter either during or immediately after treatment;

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

Pharmacologically active substance(s)	Target species	Other provisions
Centellae asiaticae extractum	All food producing species	For topical use only