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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CONVALLARIA MAJALIS

SUMMARY REPORT

1. ***Convallaria majalis L.*, synonym Lily of the valley, is a plant species of the family *Liliaceae*. The mother tincture of *Convallaria majalis* is prepared by ethanolic extraction of the aerial parts of the fresh, flowering plant according to the German Homeopathic Pharmacopoeia (HAB). The dilution 1:1000 is containing a maximum of 0.1% of the original plant material. The degree of extractability of the constituents by homeopathic manufacturing procedures is not known. The use follows the principles of homeopathic therapy where animals are diagnosed on basis of the individual pattern of clinical signs. Usual doses for a single administration are in the range from 1 ml (about 5 kg bw) to 10 ml (about 400 kg bw) for parenteral use depending on the size of the animal. Corresponding doses for oral treatment with tablets or globuli are reported to contain lower amounts of convallaria constituents than the injectable form. Dosing may be repeated but a fixed dosage schedule is not common in homeopathy. In human phytotherapy *Convallaria majalis* preparations are used against cardiac dysfunction. Standardized convallaria drug powder contains 0.2 to 0.3% cardiac glycosides and is adjusted to a pharmacological activity equivalent to 0.2% convallatoxin. The oral intake of a median daily dose of 0.6 g of prepared drug powder corresponds to 1.2 to 1.8 mg cardiac glycosides. The recommended daily oral dose for a mono-preparation containing the natural cardenolide fraction of convallaria corresponds to a total glycoside content of 3.6 to 7.2 mg.**

2. **Constituents of *Convallaria majalis* of possible relevance for consumer safety are cardenolides (cardiac glycosides): The total cardenolide content in the dried drug is reported to be 0.1 to 0.5%. About 40 cardenolides deriving from 9 genins have been identified. The main glycosides of the total cardenolides are convallatoxin (4 to 40%), convalloside (4 to 24%), convallatoxol (10 to 20%), desglucocheirotoxin (3 to 15%) and lokundjoside (1 to 25%). Further constituents in the dried herbs and flowers of *Convallaria majalis* are flavonoids (0.93 to 1.16%), chelidonic acid (1.63%), choline (0.405%) and azetidine-2-carbonic acid. Steroid saponins predominate in rhizomes and roots.**

3. **The principle pharmacodynamic activity of *Convallaria majalis* constituents is associated with the cardenolides exerting their action mainly by inhibition of the membranous Na,K-adenosine triphosphatase (ATPase) of cardiomuscular tissue. The main convallaria glycosides are reported to have predominantly strophanthin-like effects.**

Public7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8447
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

4. **Pharmacokinetic information on the dried herb or complex herb extract of *Convallaria majalis* was not provided. The available information on pharmacokinetics relates to the most prominent cardenolide of the drug, the convallatoxin. Following oral intake absorption of convallatoxin in humans has been reported to be very low with only 10% of the dose. Tissue distribution as observed in guinea pigs at 6 hours after intraperitoneal administration (about 40 µg/kg) showed highest concentrations in kidney (7.4 µg/kg), muscle (6.6 µg/kg) and liver (4.4 µg/kg). The metabolism of cardenolides can generally be characterised by hydrolytic cleavage of sugar moieties and hydorxylation, hydrogenation and conjugation of the steroid aglycone. Data on elimination half-lives are limited. Convallaria glycosides are reported to be excreted predominantly in urine but also in faeces with the total dose in humans being excreted within 2 days.**

5. **Data on acute toxicity were available for the cardenolides convallatoxin and convallatoxol. The following LD_{50} values were: cat: convallatoxol 0.14 mg/kg bw intraperitoneally, (convallatoxin is reported to be of lower toxicity, but no value given); guinea pig: convallatoxol 0.2 mg/kg bw intraperitoneally, convallatoxin 0.3 mg/kg bw intraperitoneally; mouse: convallatoxol 30 mg/kg bw intraperitoneally; rat: convallatoxol 56 mg/kg bw intraperitoneally (in mouse and rat convallatoxin is reported to be more toxic than convallatoxol). Following intravenous administration to guinea pigs the lethal dose of the glycoside complex (0.189 mg/kg bw) was lower than that of convallatoxin alone (0.309 mg/kg bw) indicating a higher toxicity of the glycoside complex in this animal species. Data on acute oral toxicity were lacking.**

6. **Information on repeated dose toxicity was not available.**

7. **No studies on reproductive effects including teratogenicity of *Convallaria majalis* or its constituents have been performed. So far substances of the class of cardenolides have not been associated with reproductive toxicity or teratogenic effects.**

8. **Studies on genotoxic or mutagenic activities of *Convallaria majalis* or its constituents were not available. There is, however, no published evidence of genotoxic or mutagenic properties of convallaria cardenolides or other known cardinolides nor do these substances appear to possess chemical structures alerting for genotoxicity.**

9. **No studies on carcinogenic properties were provided.**

10. **No specific studies on immunotoxicity were provided.**

11. **In humans the predominant clinical signs of intoxication are assumed to be similar to those of digitalis overdose. Main symptoms may be arrhythmia and disorders of the gastrointestinal tract (e.g. nausea, vomiting, diarrhoea) and central nervous system (e.g. headache, somnolence, visual disturbances). As a general rule in human therapy it is said that toxic effects of cardiac glycosides occur in a dosage range exceeding the therapeutic dose by the factor 1.5 to 3.**

12. **It was not possible from available information to establish a complete pharmacological and toxicological profile including NOELs and ADI for convallaria extracts and its preparations.**

13. **Consumer safety considerations may be based on a combination of worst-case assumption:**

    - **in the absence of data, it is assumed that raw plant material is completely soluble upon ethanolic extraction. Preparations of *Convallaria majalis* 1:1000derived from plants with the highest total cardiac glycosides concentrations reported in literature (0.5%) are then containing a maximum of 5 µg/ml of cardenolides (1 mg plant material/ml),**
    - **using intravenous administration, the total bioavailable cardenolide contents in one dose can be calculated between 50 µg to 5 µg of cardiac glycosides for large (10 ml/500 kg) and small animals (1 ml/5 kg), respectively,**

- **assuming no metabolism and excretion, a standard edible portion for meat would contain far less than 1 µg of total cardenolides (0.05 to 0.5 µg),**
- **in a similar calculation for milk assuming a very high proportion of 2% of the dose excreted, the milk residues would amount to approximately 0.05 µg/l (20 l/day/500 kg cow).**

As these concentrations can be considered as being well below any level of pharmacological cardenolide action or toxicological significance and having in mind the low rate of gastrointestinal absorption no appreciable consumer risk could be identified and the following conclusions are recommended.

Conclusions and recommendation

Having considered:

- ***Convallaria majalis* is used as a diluted extract not exceeding one part per thousand prepared according to homeopathic pharmacopoeias,**
- **the absorption from the gastro-intestinal tract of convallaria constituents of concern is poor,**
- ***Convallaria majalis* is used in a small number of individual animals for non-regular treatments in accordance with the principles of homeopathic therapy,**
- **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 *Convallaria majalis* 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
Convallaria majalis	All food producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per thousand only