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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

APOCYNUM CANNABINUM

SUMMARY REPORT

1. *Apocynum cannabinum L.*, synonym Canadian hemp or Hemp dogbane, is a plant species of the family *Apocynaceae*. The mother tincture of *Apocynum cannabinum* is prepared according to the German Homeopathic Pharmacopoeia (HAB, method 3a) by ethanolic extraction of the fresh underground parts of the plant, mainly the roots. In veterinary homeopathy a 1:100 dilution of the mother tincture is used for oral treatment and a 1:1000 dilution for oral and parenteral treatment of food producing animals. The use of the preparations follows the principles of homeopathic therapy where animal are diagnosed on basis of the individual pattern of clinical signs. The usual maximum dose for oral administration to large animals ranges from 10 to 20 drops, 1 to 3 times per day, the parenteral dose for large animals is up to 10 ml. Dosing may be repeated but a fixed dosage schedule is not common in homeopathy.

   In human homeopathy, *Apocynum cannabinum* may be used orally (dilutions of 1:100 or higher) or parenterally. Dilutions of less than 1:10 000 are not authorised for parenteral use in humans. The drug derived from dried roots is also used in traditional human phytotherapy for treatment of cardiovascular disorders and as diuretic. A usual daily oral dose is for instance 0.3 to 0.6 ml of a 1:10 tincture (corresponding to about 30 to 60 mg dry root matter, approximately 60 to 240 µg of total cardenolides).

2. Constituents of *Apocynum cannabinum* are the pharmacologically active cardenolides (cardiac glycosides). A total cardenolide content of 0.29% was determined in the fresh roots (water content 59%). So far, 17 cardenolides have been identified derived from 5 aglycones: strophanthidin, cannogenin, cannogenol, (20 R,S)-18,20-epoxy-strophanthidin and (20 S)-18,20-epoxycannogenin. The cardenolides (0.2 to 0.4% in the dry matter of the root) are reported to consist mainly of cymarin (synonym: k-strophanthin-α,), apocannoside and cynocannoside. Further cardenolides are k-strophanthin-ß, helveticoside and apobioside. Other constituents are apocynin, tannins, resin, fatty oil and starch.

3. The principle pharmacodynamic activity of *Apocynum cannabinum* constituents is associated with the cardenolides exerting their action mainly by inhibition of the membranous adenosine triphosphatase (of cardiomuscular tissue. Additionally, it may be noted that apocynin appears to be a selective inhibitor of NADPH oxidase preventing the production of reactive oxygen.

4. Specific pharmacokinetic data for extracts of *Apocynum cannabinum* were not provided. Generally, the degree of gastrointestinal absorption of cardiac glycosides is largely determined by the polarity of the individual glycosides. Some *Apocynum* cardenolides are closely related to the more polar strophanthin and absorption of cardenolides of the strophanthin type were reported to be below 10%. On the other hand, enteral absorption of the more hydrophobic cymarin in humans was reported to amount up to 47%. The terminal elimination half-life for cymarin was 3.4 hours in rabbits and 13 hours in humans following intravenous dosing. In humans, around 50% of injected cymarin was eliminated in urine, mainly in form of conjugated metabolites. Data on absorption and excretion of other cardenolide types in *Apocynum* were not available.

7 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

The general metabolism of cardenolides can be characterised by hydrolytic cleavage of sugar moieties and hydroxylation, hydrogenation and conjugation of the steroid aglycone. As with absorption, excretion routes of cardenolides are largely dependent on their hydrophilicity. Hydrophilic species are excreted predominantly via urine.

5. Limited data on acute parenteral toxicity were available for cymarin, the main cardiac glycoside, and apocannoside. The LD_{50} values following intravenous administration in cats were 0.095 mg/kg bw for cymarin and 0.160 mg/kg bw for apocannoside. The intravenous LD_{50} for cymarin in mice was 7 mg/kg bw. Data on acute oral toxicity of the cardenolides of *Apocynum cannabinum* were lacking.

6. Information on repeated dose toxicity was not available.

7. No studies on reproductive effects including teratogenicity of *Apocynum cannabinum* or its constituents have been performed. So far, substances of the class of cardiac glycosides have not been associated with reproductive toxicity or teratogenic effects.

8. Studies on genotoxic or mutagenic activities of *Apocynum cannabinum* were not available. There is, however, no published evidence of genotoxic or mutagenic properties of *Apocynum* cardenolides or other known cardenolides, nor do these substances appear to possess chemical structures alerting for genotoxicity. Concerning apocynin no genotoxic activities have been found in the *Salmonella*-microsomal assay (tester strains: TA 97, TA 98, TA 100, TA 102) and in the sister chromatid exchange assay (SCE-Test) performed with human peripheral lymphocytes.

9. No studies on carcinogenic properties were provided.

10. No specific studies on immunotoxicity were provided.

11. The main symptoms of acute toxicity in humans were reported to be disorders of the gastrointestinal tract with vomitus and diarrhoea. A dose of 10 to 30 drops, 3 times per day of a fluid extract of *Apocynum cannabinum* may cause the described symptoms of intoxication.

12. It was not possible from available information to establish a complete pharmacological and toxicological profile including NOELs and an ADI for *Apocynum cannabinum* extracts and its preparations. Considerations regarding consumer safety may be based on the following worst case assumptions: i) The content of total cardenolides in fresh roots used as starting material for the homeopathic product was measured with about 0.3%. Not knowing the actual range of biological variability, one may assume that in an extreme case the root cardenolide content of a plant may be 5-fold higher than the measured one (i.e. 1.5%). Dilutions of 1:100 of root constituents would in this case contain about 150 µg/ml of total cardenolides. ii) Using oral administration at the maximum dose of 60 drops (approx. 1.5 ml) to large animals (500 kg bw), the dose of total cardenolides can be calculated with 225 µg/animal. iii) Assuming complete oral bioavailability and no metabolism/excretion, a standard edible portion of meat would contain about 0.2 µg of total cardenolides. In a similar calculation for milk, assuming a very high proportion of 2% of the dose excreted into milk, the residues would amount to 0.2 µg/l (based on a milk production of 20 l/day by a 500 kg cow).

    Considering these low amounts of calculated worst case residues of less than 1 µg and having also in mind that the actual rates of oral absorption/bioavailability of the cardenolides of concern are low to moderate, inclusion of the 1:100 dilution of *Apocynum cannabinum* for oral use was considered justified.

    For the parenteral use of *Apocynum cannabinum* a more conservative approach was considered: For this route of administration recommended doses are several fold higher than those used orally and the systemic bioavailability of the cardenolide fraction of concern must be considered as being complete leading to considerably higher amounts of residues. Additionally, injection sites may contain amounts of cardenolides, which are approaching doses of pharmacological significance. Owing to these considerations, an Annex II recommendation for parenteral uses at a concentration 1:1000 could not be made. This is also consistent with the use in human homeopathy where injectable forms of *Apocynum cannabinum* should only be used in dilutions of 1:10 000 and higher.

Conclusions and recommendations

Having considered that:

- *Apocynum cannabinum* is used as a diluted extract not exceeding one part per hundred for oral administration only,
- the absorption from the gastro-intestinal tract of *Apocynum cannabinum* glycosides is considered limited,
- *Apocynum cannabinum* 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,
- estimated residues after parenteral use of a dilution of *Apocynum cannabinum* not exceeding one part per thousand do not allow a recommendation of this use in food producing animals;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for the oral use of homeopathic preparations of *Apocynum cannabinum* at concentrations not exceeding one part per hundred 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
Apocynum cannabinum	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 hundred only. For oral use only.