



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ADONIS VERNALIS

SUMMARY REPORT

1. *Adonis vernalis* L., synonym Pheasant's eye, is a plant species of the family *Ranunculaceae*. The mother tincture of *Adonis vernalis* is prepared by ethanolic extraction of the aerial parts of the fresh, flowering plant according to the German Homeopathic Pharmacopoeia (HAB) or by using the total plant according to the Homeopathic Pharmacopoeias of France and the USA. The dilution 1:100 is containing a maximum of 1% of the original plant material. The degree of extractability of the plant 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. A usual dose for a parenteral administration is in the range from 5 ml for pig, sheep and goat to 10 ml for horse and cattle once daily. Dosing may be repeated but a fixed dosage schedule is not common in homeopathy. It was not indicated if the substance is used orally.

In human phytotherapy *Adonis vernalis* preparations are used against cardiac dysfunction mostly in combination with other active principles of plant origin. Standardised adonis drug powder contains about 0.25% cardiac glycosides (i.e. 250 mg/100 g) and is adjusted to a pharmacological activity equivalent to 0.2% cymarín. The oral intake of a median daily dose of 0.6 g drug powder corresponds to 1.5 mg cardenolides, the maximum single dose of 1 g contains 2.5 mg cardenolides and the maximum daily dose of 3 g up to 7.5 mg.

2. Constituents of *Adonis vernalis* of possible relevance for consumer safety are the pharmacologically active cardenolides (cardiac glycosides): The total cardenolide content of the overground parts of the plant is reported to be 0.2 to 1.0% in the dry matter while the cardenolide content in the roots appears to be below 0.2% or even nil. About 30 cardenolides derived from 5 genins have been identified. The main glycosides of the total cardenolides are adonitoxin (15 to 20%) being an isomeric form of convallatoxin, cymarín (synonym: k-strophanthin- α ; 5 to 6%), k-strophanthin- β (15 to 18%) and k-strophanthoside (synonym k-strophanthin- γ ; 5 to 8%). Further constituents in the dried herbs and flowers of *Adonis vernalis* are flavone-C-glykosyles (about 1%).
3. The principle pharmacodynamic activity of *Adonis vernalis* 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 adonis glycosides are reported to have predominantly strophanthin-like effects.

4. Specific pharmacokinetic data for herbal or total plant extracts of *Adonis vernalis* were not provided. Generally, the degree of gastro-intestinal absorption of cardiac glycosides is largely determined by the polarity of the individual glycosides. The main adonis 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 cymar in humans was reported with up to 47%. The 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 dependant on their hydrophilicity. Adonis glycosides being mostly polar are reported to be excreted predominantly in urine.
5. Limited data on acute toxicity were available for cymar and adonitoxin. The following LD₅₀ values have been reported for the cat: cymar 0.095 mg/kg bw intravenously, adonitoxin 0.191 mg/kg bw intravenously. Data on acute oral toxicity of the cardenolides or single constituents of *Adonis vernalis* were lacking. Taking into account the chemical relationship to strophanthin the following information on g-strophanthin (ouabain) might be valuable: LD₅₀ (cat): 0.15 mg/kg bw intravenously; LD₅₀ (rat): 14 mg/kg bw intravenously. Lethal doses of g-strophanthin for humans were indicated with approximately 1 mg intravenously or about 75 mg orally.
6. Information on repeated dose toxicity was not available.
7. No studies on reproductive effects including teratogenicity of *Adonis vernalis* 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 *Adonis vernalis* or its constituents were not available. There is, however, no published evidence of genotoxic or mutagenic properties of adonis cardenolides or other known cardenolides 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 intoxications, have been observed following overdosage of *Adonis vernalis* preparations during therapy. The main symptoms of oral overdoses were associated with disorders of the gastrointestinal tract like nausea, vomiting, stomach trouble and diarrhoea. 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 *Adonis vernalis* extracts and its preparations.
13. Consumer safety considerations for *Adonis vernalis* may be based on a sequence of worst-case assumptions:
 - in the absence of data for extraction yields, it is assumed that all plant constituents are completely soluble in the mother tincture. The 1:100 dilution would then contain a maximum of 10 mg/ml (1%) of plant material,
 - a maximum of 100 µg/ml of total cardenolides is expected in homeopathic preparations of *Adonis vernalis* 1:100 derived from plant material with the highest cardiac glycosides contents reported in published literature (1%),
 - using intravenous administration, the total bioavailable cardenolide content in a maximum dose can be calculated between 1 to 0.5 mg of cardiac glycosides for large (500 kg bw) and smaller animals (150 kg bw), respectively,

- assuming no metabolism and excretion, a standard edible portion for meat would in this hypothetical worst-case contain less than 2 µg of cardenolides (1.25 to 1.7 µg),
- using a similar calculation assuming a very high proportion of 2% of the dose excreted in milk, residues would amount to approximately 1 µg/l milk (20 l/day/500 kg cow).

Having also in mind the only low to moderate rate of gastro-intestinal absorption of *Adonis vernalis* cardenolides, these calculated worst-case amounts can be considered being by orders of magnitude below levels of pharmacological cardenolide effects or toxicological significance.

Conclusions and recommendation

Having considered:

- *Adonis vernalis* is used as a diluted extract not exceeding one part per hundred prepared according to homeopathic pharmacopoeias,
- the absorption from the gastro-intestinal tract of adonis cardenolides is considered low,
- *Adonis vernalis* 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 the homeopathic preparation *Adonis vernalis* 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
<i>Adonis vernalis</i>	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.