



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

HIPPOCASTANI SEMEN

SUMMARY REPORT

1. *Hippocastani semen* are the seeds originating from the tree *Aesculus hippocastanum*.

The constituents of the seeds are a mixture of triterpene saponins (aescine), tannins, phospholipids, sugars (saccharose, glucose, mannose), starch, flavonoids, vegetable oil, purine derivatives (adenine, adenosine, guanine, uric acid) and enzymes (laccase, esculinase, amylase). The saponins are the main pharmacologically active constituents. The content in fresh seeds is 7 to 15%. The flavonoids are also considered as pharmacologically active.

In veterinary medicine *Hippocastani semen* is used in a product containing 8 active ingredients including 1.2% of a tincture prepared from 183 g of the crude drug (with hull) and 1 litre of diluted ethanol (corresponding to 0.22% of *Hippocastani semen* in the final product). The product is used topically as a skin antiseptic to support the healing of wounds in cattle, horses, pigs, goats, sheep, rabbits and poultry. The daily dose is estimated to be 0.44 g of the product, corresponding to 5.28 mg of the tincture, corresponding to 0.001 g of the crude drug. The content of aescin in the tincture is 1 to 2%. The daily dose corresponds to a maximal dose of 0.1 mg of aescin.

Other veterinary uses reported in the literature include the oral use of decorticated seeds to treat emphysema in horses at doses of 100 to 300 g. Ethanol extracts are used to treat phlebitis in horses (dose: 50 to 150 mg dry extract).

Ethanol extracts of decorticated seeds (containing up to 70% aescin) are used in human medicine against haemorrhoids, varices and phlebitis. They are also used against varicocele and dysmenorrhoea of circulatory origin. The daily oral dose corresponds to 0.01 to 0.03 g decorticated seed. Much higher doses are used for treatment of severe cases of haemorrhoids.

The seeds are used as winter-feed for deer in some Member States.

2. Extracts of *Hippocastani semen* have a venotonic effect, diminish cutaneous capillary hyperpermeability induced by phlogistic or irritating agents, and display anti-oedematous and anti-inflammatory properties. A hypocholesterolic effect is also reported.

Aescin is active against oedema and inflammation and diminishes the fragility of capillaries. Immunologically induced polyarthritis of rats is not influenced by aescin. Topically it causes necrosis. It is irritating to the gastrointestinal tract and is toxic on intravenous injection due to haemolysis. Isolated saponins from the aescin fraction have ethanol-absorption-inhibitory effect and hypoglycaemic activity. Cytotoxic activity in the 9-KB (human nasopharyngeal carcinoma) cell culture assay are reported for hippoaesculin and barringtonenol-C21-angelate.

3. No information was provided on pharmacokinetics of *Hippocastani semen* or its constituents.
4. Oral LD₅₀ values are reported for extracts of seeds (solvent and the weight relation crude drug/extract not given) in the following animal species: Guinea pig: 1120 mg/kg bw, mouse: 990 mg/kg bw, rat: 2150 mg/kg bw and rabbit: 1530 mg/kg bw.

In an American report on human exposures during 1993 to 1994 to 8 species of *Aesculus* comprising 571 cases, gastrointestinal symptoms were reported for 5% of the cases. Drowsiness was reported in one case. In a Swiss study over 29 years only 3 cases of allergy were reported, two of which involved anaphylactic shock.

The following LD₅₀ values are given for the mixture of triterpene saponins (aescin): mouse: 164 mg/kg bw (oral), 4.8 mg/kg bw (intravenous), 6.7 mg/kg bw (intraperitoneal), 38.5 mg/kg bw (subcutaneous); rat: 862 mg/kg bw (oral), 2.8 mg/kg bw (intravenous), 10.1 mg/kg bw (intraperitoneal), 150 mg/kg bw (subcutaneous). Another report states that the lethal intravenous dose in mice and dogs is in the range 2 to 4 mg/kg bw, while in Guinea pigs 7.5 mg/kg bw will kill 40% of the animals.

No side effects were reported from clinical testing of extracts containing 70% aescin in doses of 100 mg. In another report it is mentioned that single therapeutic doses of aescin ranging from 5 to 60 mg have no side effects in man. Man seems to be less susceptible to aescin poisoning than animals.

The seeds are eaten without adverse effects by sheep, goats and cows. In chicken intake of the seeds causes inflammation of the gastrointestinal tract, a condition which is also seen in the dog following subcutaneous injection of the sap.

5. No information was provided on repeated dose toxicity, reproductive toxicity or on teratogenicity.
6. No information was provided on mutagenicity or carcinogenicity.

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:

- *Hippocastani semen* is part of the animal feed in some Member States,
- *Hippocastani semen* is of low acute oral toxicity,
- *Hippocastani semen* is used only topically 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 *Hippocastani semen* 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>Hippocastani semen</i>	All food producing species	For topical use only