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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

HYPERICUM PERFORATUM
(use in veterinary homeopathy)

SUMMARY REPORT

1. *Hypericum perforatum* (synonym: St. John's wort) is a plant of the family *Hypericaceae.* The homeopathic mother tincture is prepared by ethanolic extraction of the fresh flowering aerial parts of *Hypericum perforatum* according to homeopathic pharmacopoeias.

   Hyperici oleum, the oily extract of the flowers, contains as characteristic pharmacologically and toxicologically relevant components naphtodianthrones mainly hypericin and pseudohypericin; further flavonoids (e.g. quercetin, kaempferol and biapigenin, total 2.5 to 4%), tetrahydroxyxanthon (1.28 mg/100 g) and volatile oils (0.3%; main components of the volatile oils are: aliphatic hydrocarbons, including, among others, 2-methyloctane, undecane, furthermore dodecanol, the prenylated phloroglucine derivative hyperforin (approximately 2%) and mono- and sesquiterpenes, including, among others, α-pinene, caryophyllene, additionally also 2-methyl-3-buten-2-ol. The aerial parts of the plant, *Hyperici herba*, used for homeopathic preparations contain a similar spectrum of constituents. The content of naphtodianthrones as hypericin and pseudohypericin in the herbal parts (approximately 0.15%) is reported to be lower than in the flowers (approximately 0.4%), the content of flavonoids and of xanthones as tetrahydroxyxanthon appears to be roughly similar and the amount of essential oils (up to 1%) and the phloroglucine derivative hyperforin (2 to 4%) appears to be somewhat higher. Additionally, the aerial parts contain procyanidins and tannins.

   Hyperici oleum, the oily extract of the flowers of *Hypericum perforatum*, has previously been assessed by the Committee for Veterinary Medicinal Products (CVMP) in respect to its use in veterinary phytotherapy and is included in Annex II of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Animal species	Other provisions
Hyperici oleum	All food producing species	For topical use only

2. This application relates to the homeopathic mother tincture of *Hypericum perforatum* and dilutions thereof, which are intended for use in all food-producing animals. The use follows the principles of homeopathic therapy where animals are diagnosed on basis of the individual pattern of clinical signs. The recommended maximum parenteral dose for large animals is 10 ml/animal. Treatment may be repeated but a fixed dose schedule is not common in homeopathy.

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Hypericum perforatum is also used in human homeopathy in dilutions beginning with the mother tincture. *Hyperici oleum* is used in human phytotherapy for oral treatment of dyspepsia, and topically for the treatment of open wounds and blunt injuries, myalgia and first-degree bums. *Hyperici herba* or its hydro-ethanolic preparations are used internally for treatment of psycho-vegetative disturbances, depressive moods, anxiety and/or nervous unrest. The average daily dose for oral use is 2 to 4 g of the crude drug (*Hypericum perforatum*) or 0.2 to 1.0 mg of total hypericin in other forms of drug application. For infusions 2 teaspoons of crude drug in 150 ml boiling water steeped for 10 minutes are recommended. For depressive moods an intake of *Hyperici herba* or its hydro-ethanolic preparations over a duration of 4 to 6 weeks is recommended.

3. *Hyperici oleum* is also used as a flavouring agent in food. It was listed by the Council of Europe as a natural source of food-flavouring, which may be added to foodstuffs, provided that the hypericin concentration in the finished product does not exceed 0.1 mg/kg (with the exception of lozenges, which may contain a concentration of 1 mg/kg, and alcoholic beverages, which may contain a concentration of 2 mg/kg).

4. No data on the pharmacokinetics of *Hypericum perforatum* was provided. Limited summary information was available on the pharmacokinetics of hypericin and pseudohypericin in mice and humans. After oral administration of ^{14}C-labelled hypericin and pseudohypericin to mice, these substances are absorbed to 80% and 60%, respectively. In humans after oral administration of hydromethanolic extracts of *Hypericum perforatum*, containing 0.1% total hypericin (300 to 1800 mg per person) a plasma half-life of approximately 6 hours was observed for hypericin. After administration of an extract containing 0.3% total hypericin the plasma half-life was approximately 25 hours for hypericin and 16 to 36 hours for pseudohypericin.

5. No data on acute toxicity, repeated dose toxicity, reproductive toxicity and teratogenicity for *Hypericum perforatum* were provided.

6. Mutagenicity tests have been reported for *Hyperici oleum* in two test systems (*Salmonella typhimurium* strain TA 98 with metabolic activation, and induction of DNA repair in primary rat liver cells). *Hyperici oleum* was found to be mutagenic in the *Salmonella typhimurium* test. Hydro-ethanolic extracts of *Hypericum perforatum* were tested in vitro in the Ames test, the HPRT-test, the unscheduled DNA synthesis test and the cell transformation test using Syrian hamster embryo cells. *In vivo* tests included the mouse spot test, the chromosome aberration test in the bone marrow of Chinese hamsters and the micronucleus test in the bone marrow of mice. The extracts contained 0.2 to 0.3% of total hypericin and usually less than 0.1% of quercetin. The majority of these tests did not indicate genotoxic effects of this *Hypericum perforatum* extract; the only positive findings were observed in the Ames test. Positive findings in mutagenicity tests were also observed in tests with the crude drug and are found to be related to the quercetin content of the drug.

7. No carcinogenicity data for *Hypericum perforatum* were provided.

8. Hypericin as well as pseudohypericin are photosensitising agents and exposure can cause allergic skin reactions following exposure to UV light.

   Photosensibilisation due to the intake of fresh or dried *Hyperici herba* via the feed has been reported for animals on pasture (sheep, calves, cattle, horse) following intake of large quantities of the drug (3 g/kg bw or more). In humans no cases of photosensibilisation have been reported at the normal oral therapeutic dose equivalent to 1 mg hypericin per day. Intravenous administration of 35 times the highest oral dose of total hypericin did cause phototoxicity. From studies in animals it can be estimated that approximately 30 times the oral therapeutic dose of total hypericin would be necessary to elicit the first phototoxic symptoms in humans.

9. The use of *Hypericum perforatum* in veterinary homeopathy was further considered in a preliminary risk evaluation procedure by the Committee for Veterinary Medicinal Products, considering all defended old substances used in veterinary homeopathy in concentrations greater than 1:10 000. Further information made available and extensive search of published literature did not provide any further evidence for pharmacological or toxicological properties of *Hypericum perforatum* alerting to specific health risks, which may result from residues in food producing animals following the intended uses. It was concluded, that *Hypericum perforatum* in all concentrations including the mother tincture can be considered as not giving rise to any specific consumer health concerns.

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:

- *Hyperici oleum* has already been included in Annex II Council of Regulation (EEC) No 2377/90 for topical use,
- *Hypericum perforatum* is a normal component of the feed of food producing animals,
- photosensitisation has only been reported in animals after ingestion of the hypericin containing drug in large quantities,
- quercetin, which was mutagenic in a few tests, is a natural componenet of the human diet and the normal daily intake in the human diet exceeds the maximum possible intake resulting from treatment of food-producing animals,
- *Hypericum perforatum* is used only in a small number of individual animals for non-regular treatments,
- animals are unlikely to be sent for slaughter during or immediately after treatment,
- any residues of *Hypericum perforatum* constituents in treated animals following the intended uses are considered to be well below the limits of hypericin (0.1 to 2 mg/kg) established by the Council of Europe for use of plant extracts as a flavouring agent in human food and beverages, a restriction as concerns the route of administration was not deemed necessary;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for *Hypericum perforatum* and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Animal species	Other provisions
Hypericum perforatum	All food producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only