



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

HYPERICI OLEUM

SUMMARY REPORT

1. *Hyperici oleum* is the oily extract of the flower of *Hypericum perforatum* (St. John's wort). The pharmacologically and toxicologically relevant components are: hypericin, pseudohypericin, flavonoids (quercetin, kämpferol and biapigenin), tetrahydroxyxanthon and volatile oil (0.3%; main components of the volatile oil are: aliphatic hydrocarbons, including, among others, 2-methyloctane, undecane, furthermore dodecanol, the prenylated phloroglucine derivative hyperforin and mono- and sesquiterpenes: including, among others, α -pinene, caryophyllene, additionally also 2-methyl-3-buten-2-ol).
2. *Hyperici oleum* is contained in two veterinary medicinal products for topical use in combination with 6 and 5 other active ingredients, respectively.

The first product one is an ointment for disinfection of the udder. *Hyperici oleum* constitutes 10% of the product. The second preparation is an ointment for treatment of wounds, eczema, dermatosis, inflammation and otitis externa and contains *Hyperici oleum* at a concentration of 6.25%. Target species are cattle, horses, goats, sheep and pigs, and all food producing animals, respectively. The ointment is applied twice per day, and treatment can be repeated over several days, when appropriate.

Hyperici oleum is used in human medicine orally for treatment of dyspepsia and topically for the treatment of open wounds and blunt injuries, myalgia and first-degree burns. *Hyperici herba* or its hydroethanolic preparations are used internally for treatment of psychovegetative 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 hydroethanolic preparations over a duration of 4 to 6 weeks is recommended.

Hyperici oleum is also used as a flavouring agent in food. It is 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 with a concentration of 1 mg/kg and alcoholic beverages with a concentration of 2 mg/kg).

3. Oily *hypericum* preparations demonstrate an anti-inflammatory action due to their high flavonoid content.
4. No data on the pharmacokinetics of *Hyperici oleum* were provided.

Limited summary information was available on the pharmacokinetics of hypericin and pseudohypericin in mice and humans. After oral administration of C^{14} -labelled hypericin and pseudohypericin to mice, these substances are absorbed to 80% and 60%, respectively. The main radioactivity was found in the blood.

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 *Hyperici oleum* were provided.
6. In the summary information available mutagenicity tests have been reported for *Hyperici oleum* in two test systems (mutagenesis in *Salmonella typhimurium* strain TA 98, metabolic activation with S9 mix, and induction of DNA repair in primary rat liver cells). *Hyperici oleum* was mutagenic in *Salmonella typhimurium* TA 98.

Summary information was also available on the genotoxicity of hydroethanolic extracts of *Hypericum perforatum*. The extract was tested *in vitro* in the Ames test, the HRGPT-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 *Hyperici oleum* were provided.

Summary information was available on a 2-year carcinogenicity study with quercetin in rats. An increase in the rate of tubular cell adenomas was reported for male rats of the highest dose group only. The result has been interpreted in the scientific literature as irrelevant to humans.

Anticarcinogenic activity of quercetin in rats has also been reported.

In-vitro cytotoxicity against human colon carcinoma cells (CO 115) has been described for hyperforin-related constituents, isolated from *H. calycenum* and *H. revolutum*.

8. Hypericin as well as pseudohypericin are photosensitising agents and consumption can cause allergic skin reactions following exposure to UV light. The intensity of the reaction is related to the type of skin.

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 (starting at 3 g per kg body weight). 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 flavonoid quercetin, the constituent of *Hypericum oleum* related to the observed mutagenic effects in individual test systems, is contained in many fruits and vegetables. Its genotoxic potential has been studied intensively, mainly leading to negative results in the *in vivo* studies. The reported borderline tumourigenicity of quercetin in rats stands in opposition to reports on anticarcinogenic effects of the substance, also observed in rats.

The daily dietary intake of quercetin from fruits and vegetables is estimated to be at least 25 mg per person, while the quercetin-intake from human therapeutic doses of *Hypericum* preparations is estimated to amount to approximately 1 mg per person. An estimate of the therapeutic daily doses of *Hyperici oleum* topically applied in veterinary medicine corresponds to approximately 0.5 mg quercetin per animal per day.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances in Annex II of Council Regulation (EEC) No. 2377/90 and in particular that:

- *Hyperici oleum* is contained in *Hypericum perforatum*, which is a normal component of the feed of food producing animals,
- photosensitisation has only been reported in animals after having eaten the hypericin containing drug in high quantities; similarly high hypericin concentration are not expected in tissues from food producing animals after topical treatment with *Hyperici oleum* containing products,
- quercetin, which was mutagenic in a few tests, is a natural component 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,
- *Hyperici oleum* is used only in a small number of animals for infrequent and non-regular treatments;
- animals are unlikely to be sent for slaughter immediately after treatment;

the Committee concludes that there is no need to establish an MRL for *Hyperici oleum* 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>Hyperici oleum</i>	All food producing species	For topical use only