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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

HARUNGA MADAGASCARIENSIS

SUMMARY REPORT

1. *Harunga madagascariensis L.*, Dragon's blood tree, is a plant of the family *Hypericaceae* (*Glusiaceae, Guttiferae*) The homeopathic mother tincture is prepared according to the German Homeopathic Pharmacopoeia (HAB , method 4a) by ethanolic extraction of a mixture of dried leaves (1 part) and dried bark (2 parts) of the branches of the tree Harunga madagascariensis. In veterinary homeopathy a dilution of 1:1000 of the mother tincture, which theoretically contains 0.1% of original plant material, is used for treatment of food producing animals. The actual content of plant constituents soluble in the mother tincture and its subsequent dilutions is not known. The preparation is intended for oral or parenteral use in all food-producing species. 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 is 10 ml for large animals. Corresponding doses in form of tablets, globules or drops are containing lower amounts of Harunga madagascariensis than the injectable form. Dosing may be repeated but a fixed dosage schedule is not common in homeopathy.

   Harunga madagascariensis is also used in human homeopathic medicine including the mother tincture and in phytotherapy (*extraxtum folii et corticis*). In phytotherapy dry extracts of dried leaves and bark (one plus two parts) standardised to a content of 0.1% chrysophanic acid derivatives are used for treatment of digestive disorders and exocrine pancreatic insufficiency. The daily oral dose is 7.5 to 15 mg of an aqueous-ethanolic dry extract, which corresponds to 25 to 50 mg of the original dried plant material.

2. *Harunga madagascariensis* leaves and barks are characterised by a great variety of constituents: In the leaves these include anthranoids (e.g. madagascarin, hypericin, pseudohypericin), polyphenolic compounds (quercitrin, hyperoside, quercetin-3-arabinoside, quercetin-3-xyloside, astilbin, epicatechin, procyanidin B_2) and essential oils (0.4%, e.g. mainly a-pinen, up to 40 monoterpenes, sesquiterpenes and anthranoids). Predominant bark constituents are polyphenolic compounds (e.g. epicatechin, procyanidin B_2, B_6, B_7, catechin derivatives), anthranoids (harunganin, euxanthone, haronginanthrone, madagascinanthrone, madagascin, physcion, chrysophanol), triterpenes (e.g. friedelin, betulinic acid). The essential bark oil contains more than 60 components with a-pinene, ß-farnesene and γ-terpineol being typical compounds.

3. Extracts of *Harunga madagascariensis* (*folii et corticis*) have been reported to stimulate excretory pancreas function and gastric juice secretion and to excert choleretic and cholecystokinetic effects in humans. Oral administration of an ethanolic leaf extract to rats (70 mg/kg bw) was found to significantly lower carbon tetrachloride induced serum concentrations of aspartate aminotransferase and alanine aminotransferase and to reduce pentobarbital-induced sleeping time in carbon tetrachloride intoxicated rats. An antihepatotoxic activity was postulated. The aqueous methanolic extract of the stem bark showed anti-inflammatory and analgesic activities like increase of heat reaction time of mice, inhibition of carrageenan-induced rat paw and oedema and reduction of prostaglandin synthetase activity *in vitro*. Experimental details for pharmacological experiments were not available.

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4. Specific information on the pharmacokinetics and metabolism of *Harunga madagascariensis* extracts or constituents thereof was not provided.

5. Data on acute toxicity of *Harunga madagascariensis* extracts were limited. The intraperitoneal LD_{50} of an ethanolic leaf extract of *Harunga madagascariensis* was reported as 200 mg/kg bw in mice and of an ethanolic extract of stem bark as 500 mg/kg bw in rats.

6. Studies on repeated dose toxicity have been reported for mice given *Harunga madagascariensis* dry extracts (*folii et corticis*) in the feed at doses of 3%, 5% and 20% over 6 and 45 days and 9 month. Short and medium term effects at all dose levels were enhanced metabolic activity in liver, pancreas, duodenal epithelium and kidneys as measured by an increase of nucleic acid and protein content or enzyme activity. Possibly due to adaptive processes, these effects were not observed after long-term feeding. In male rats *Harunga madagascariensis* dry extracts (*folii et corticis*) given at doses of 0.3% and 0.5% in feed over 6 and 30 days led to a several fold increase in gastric, pancreatic and intestinal juice and bile production. Digestive enzyme amounts were increased. As with mice, these effects were not observed after long-term feeding (270 days). Experimental details for the repeated dose studies were not available.

7. Studies on developmental effects including teratogenicity were not available. Abortifacient effects have been reported for the aqueous root extract of *Harunga madagascariensis* in rats.

8. Specific data on mutagenicity effects of *Harunga madagascariensis* extracts were not provided. In published literature *Harunga madagascariensis* has not been associated with genotoxic effects so far. Extracts of *Hypericum*, a related plant species of the *Hypericaceae* family, have been reported to be mutagenic in a *Salmonella*-microsomal assay using strains TA98 and TA100 of *Salmonella typhimurium*, but genotoxic activity was not observed in different *in vivo* and *in vitro* test systems with mammalian cells (e.g. gene mutation at the HPRT locus, induction of unscheduled DNA synthesis, embryo cell transformation test, fur spot test of the mouse, Chinese hamster bone marrow chromosome aberration test).

9. Studies on carcinogenic effects of *Harunga madagascariensis* were not available.

10. Ethanolic leaf extracts of *Harunga madagascariensis* were found to possess antimicrobial (e.g. against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella B, D, and Shigella dysentericae*) and antifungal activity (e.g. *Aspergillus flavus* and *Candida albicans)*. Experimental details including MIC values were not available. Leaf and bark extracts were also reported to possess antimalarial activity.

11. Due to the presence of hypericin and pseudohypericin in the leaves (0.03 to 005%), *Harunga madagascariensis* extracts could possess photosensitising activity. Specific data or reports were not available. A warning of possible phototoxicity was however included in the leaflet for human phytotherapeutic uses.

12. In traditional African medicine *Harunga madagascariensis* leaves and bark are used orally, e.g. in form of teas, and/or dermally (bath treatment, washings) for treatment of a variety of diseases including gastrointestinal disorders, jaundice, haemorrhoids, tapeworms, malaria, dermatitis, leprosy. Reports on doses used, efficacy of treatment and adverse reactions were not available.

13. It was not possible from the available information to establish a complete pharmacological and toxicological or microbiological profile including NOELs and an ADI for *Harunga madagascariensis* extracts or its constituents. Consumer safety considerations may be based on worst-case assumptions: i) in the absence of precise data, it is assumed that the plant starting material contains an arbitrarily high proportion of 30% of constituents of possible concern and further, that all these constituents are completely soluble upon homeopathic manufacturing procedures. Preparations of *Harunga madagascariensis* of a dilution of 1:1000 then contain a maximum of 0.3 mg dry leaf and bark constituents per ml, ii) using intravenous administration, the maximum bioavailable dose corresponds to 3 mg for a large animal (6 µg/kg bw at an assumed body weight of 500 kg), iii) assuming no metabolism and excretion, this amount could lead to a maximum of 3 µg of total residues in a standard edible meat portion, iv) in a similar calculation for milk assuming a very high proportion of 2% of the dose excreted into milk, residues would amount to 3 µg/l (based on a milk producion of 20 l/day by 500 kg cow). As these calculated worst situation concentrations can be considered negligible compared to levels of possible pharmacological or toxicological activity, no appreciable risk could be identified from veterinary homeopathic use of for *Harunga madagascariensis.*

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:

- *Harunga madagascariensis* is used as a highly diluted leaf and bark extract not exceeding one part per thousand, prepared according to homeopathic pharmacopoeias,
- *Harunga madagascariensis* is used in a small number of individual animals for 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 homeopathic preparations of *Harunga madagascariensis* at concentrations not exceeding one part per thousand 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
Harunga madagascariensis	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 thousand in the product only.