



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

VIROLA SEBIFERA

SUMMARY REPORT

1. *Virola sebifera* L, synonym *Myristica sebifera*, belongs to the family of *Myristicaceae* and is a tall tree with trunk and branches covered by a thick brown reticular bark, growing in tropical regions of Middle and South America predominantly in the Amazon basin. The homeopathic mother tincture is prepared according to the German Homeopathic Pharmacopoeia (HAB, method 5a) by ethanolic extraction of the fresh red juice obtained by incising the bark of *Virola sebifera* L. In veterinary homeopathy a dilution of 1:100 is used for treatment of food producing animals. The degree of extractability of the individual bark exudate constituents by homeopathic manufacturing procedures is not known. The use of the preparation follows the principles of homeopathic therapy where animal are diagnosed on basis of the individual pattern of clinical signs. The recommended maximum parenteral dose is 10 ml for large animals (assuming a body weight of 500 kg). Corresponding doses for oral treatment with (e.g. tablets, globules) are reported to contain lower amounts of plant extract than the injectable form. Dosing may be repeated but a fixed dosage schedule is not common in homeopathy.

In human homeopathic medicine preparations of *Virola sebifera* in dilutions of 1:10 and higher are used. The exudate of *Virola* species is used by Native Americans to prepare snuff.

2. Constituents of the bark of *Virola* species are indole alkaloids derived from the amino acid tryptophan and its decarboxylation product tryptamine: the main alkaloid has been identified as N,N-dimethyltryptamine. Other alkaloids are dimethyltryptamine-N-oxid, 5-hydroxy-N,N-dimethyltryptamine (bufotenine), 5-methoxy-N,N-dimethyltryptamine, N-methyl-N-acetyltryptamine, N-methyl-N-formyltryptamine, N-monomethyltryptamine and 2-methyl-1,2,3,4-tetrahydro- β -carboline. Additional constituents are leucanthocyanes, tannic acids and carbohydrates. Available quantitative information relates mainly to the dried bark or snuff preparations thereof. The tryptamine content was found to vary considerably among different preparations. Contents of 65 to 250 mg alkaloids of the tryptamine type (mainly N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine) in 100 g bark have been reported (0.065 to 0.25 %). In snuff prepared from *Virola* bark and/or bark exudate a content of tryptamines of 11% has been reported (8% thereof was N,N-dimethyltryptamine).
3. Pharmacological activity of *Virola sebifera* constituents can mainly be attributed to the tryptamine-like alkaloids. Derivatives of tryptamine are among the most widely distributed alkaloids in plants and animals, and have been detected as endogenous metabolites in mammals including humans. Tryptamine derivatives can have a physiological function as neurotransmitters of the central nervous system and intracellular mediators (e.g. 5-hydroxytryptamine). The major tryptamines detected in *Virola* species, the dimethylated N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine, possess psychoactive potency and can produce central nervous system effects in humans similar to those of lysergic acid diethylamide. These effects include behavioural changes, hyperreflexia, hallucinations tachycardia, tachypnea and mydriasis. These substances act as antagonists on some types of serotonin receptors in the brain. N,N-dimethyltryptamine and also 5-methoxy-N,N-dimethyltryptamine or 5-hydroxy-N,N-dimethyltryptamine at very small amounts occur as endogenous products of tryptophan metabolism as demonstrated in animals and humans. In humans the amount of endogenously formed N,N-dimethyltryptamine excreted in 24-hour urine was up to 3 μ g.

4. The major tryptamine alkaloid of *Virola sebifera* bark, N,N-dimethyltryptamine, has been demonstrated to have only very low oral systemic bioavailability in humans. This is most probably due to first pass desamination/degradation by visceral monoamine oxidases and mixed functional oxidases. An oral intake of more than 1000 mg was reported to show no activity while parenteral administration of 1 mg/kg bw (approximately 70 mg per person) was found to induce psychotropic effects. The derivative 5-methoxy-N,N-dimethyltryptamine was also reported to be virtually inactive via oral route. There are reports, which indicate that N,N-dimethyltryptamine and other tryptamine derivatives may be partly bioavailable in cases of inhibition of monoamine oxidases by β -carbolines, which are present in the plant extracts and reversibly inhibit this enzyme. However, β -carbolines have been reported to occur in *Virola* species only in trace amounts not reaching physiological significance.

Data for rats show that following intraperitoneal administration of 10 mg/kg bw N,N-dimethyltryptamine and 5-hydroxy-N,N-dimethyltryptamine maximum tissue concentrations were achieved within 10 minutes in brain, liver, kidney and blood. Elimination was found to be complete within a period of 30 to 70 minutes. In humans, less than 0.2% of an administered dose of N,N-dimethyltryptamine is recovered unmetabolised in urine. Metabolism includes oxidative desamination, demethylation and N-oxidation. N-oxides have been identified as major metabolites. A rapid clearance of the characteristic metabolites has been reported.

5. Data on acute toxicity of *Virola sebifera* and constituents thereof were not provided.
6. Specific data on repeated dose toxicity and reproductive effects of *Virola sebifera* and constituents thereof were not available. Long term use of *Virola* snuff may lead to degenerative changes of nasal mucous membrane. Based on the scientific literature there is no indication for reproductive toxicity of *Virola* preparation or major constituents.
7. Specific data on genotoxic and carcinogenic properties of *Virola sebifera* or its constituents were not available. There were however no indications for genotoxic properties of the class of tryptamine derived constituents.
8. The juice/gum or dried powder obtained from the bark of *Virola sebifera* is traditionally used as hallucinogenic snuff or smoking drug by the Native Americans in South America. The nasal dose of snuff was reported as 3 to 6 g. The drug *Virola sebifera* in a dilution of 1:10 is used orally and parenterally in human homeopathy. The recommended parenteral doses of 1 to 2 ml correspond to 100 to 200 mg of the original bark juice. Adverse effects and contraindications are not known.
9. The available information did not allow to establish a complete pharmacological and toxicological profile including NOELs and an ADI for *Virola sebifera* extracts and its constituents. When assessing consumer safety one may consider the following: If one assumes as a worst case that i) the content of tryptamine derived alkaloids in the bark juice is arbitrarily high with 30%, ii) a maximum parenteral dose of 10 ml (assuming a body weight of 500 kg) is used for large animals, and iii) no metabolism and excretion occurs in the target animal, a 1:100 diluted preparation could lead to a maximum residue of 30 μ g in a standard edible meat portion which is considered comparatively low. A similar calculation can be done for milk. Assuming a very high proportion of 2% of the dose excreted into milk, residues would amount to 30 μ g/l (based on a milk production of 20 l/day by a 500 kg cow).

Having further in mind that the oral bioavailability of the tryptamine derived alkaloids of concern is very poor due to extensive first-pass metabolism and the two characteristic tryptamine derivatives of *Virola* species have been found as endogenous metabolites in mammals and humans, a recommendation for *Virola sebifera* extract 1:100 into Annex II seems justified.

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:

- *Virola sebifera* is used as a diluted extract not exceeding one part per hundred,
- the metabolism and elimination of *Virola sebifera* constituents of possible concern like the tryptophan derived alkaloids can be considered as rapid,
- the oral bioavailability of these constituents of possible concern is considered very poor,
- constituents of possible concern, at trace amounts, have been found as endogenous metabolites of tryptophan in animals and humans,
- *Virola sebifera* in a dilution of 1:100 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 *Virola sebifera* at concentrations not exceeding one part per hundred 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>Virola sebifera</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