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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

GINKGO BILOBA

SUMMARY REPORT

1. *Ginkgo biloba* L. (synonyms *Pterophyllus salisburiensis, Salisburia macrophylla*, maiden hair tree) is a tree of the family *Ginkgoaceae* widely distributed in Eastern Asia (China, Japan, Korea) but nowadays also cultivated in Europe and North America. The homeopathic mother tincture is prepared by ethanolic extraction of the fresh leaves of *Ginkgo biloba* according to homeopathic pharmacopoeias.

   Characteristic compounds of *Ginkgo biloba* leaves are the ginkgolides - diterpene lactones (0.23%). Further constituents are 0.5 to 1.8% flavonol glycosides, 0.06 to 0.2% flavonol acetyl glycosides, 0.4 to 1.9% biflavonoids, 0.04% tannins such as catechin, 8 to 12% procyanidins, and 0.2% sesquiterpens. Additionally bilobalide (0.4%), a sesquiterpene alcohol, 2-hexenal (the main volatile component), steroids, polyphenols, simple organic acids, long-chain benzoic acid derivatives (ginkgolic acids), phenols, lower aliphatic acids, carbohydrates, cyclitols, the nitrogen containing 6-hydroxykynurenic acid, ß-lectine and carotenoids have been identified as constituents. The amount of ginkgolic acids in various batches of the homeopathic mother tincture ranges from 600 mg/kg to 1500 mg/kg. The homeopathic preparation of mother tincture does not include a step to reduce the content of ginkgolic acids.

2. In veterinary homeopathy the homeopathic mother tincture of *Ginkgo biloba* and dilutions thereof 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.

   Ginkgo biloba is also used in human homeopathy. For use in human phytotherapy, the drug is prepared by a special acetone-water extraction of the dried leaves of *Ginkgo biloba*, where the major part of alkylphenols is discarded, leaving an extract with a content of ginkgolic acids of less than 5 mg/kg. The therapeutically recommended oral dose of this specific drug preparation is 120 mg to 240 mg daily, e.g. for treatment of cerebral circulation disorders. This corresponds to a maximum dose of ginkgolic acids of 600 to 1200 ng/person.

3. LD_{50}-values for the acetone-water ginkgo extract used in human phytotherapy were reported. In mice 7.7 g/kg bw after oral and 1.1 g/kg bw after intraperitoneal administration, and in rats as 2.1 g/kg bw after intraperitoneal and 1.1 g/kg bw after intravenous administration were determined.

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4. The pharmacological and toxicological activity of *Ginkgo biloba* has been extensively described for the acetone-water ginkgo extract used in human phytotherapy (ginkgolic acid content of less than 5 mg/kg). Ginkgols and ginkgolic acids are reported to provoke severe allergic reactions. These allergens belong to the class of alkylphenols of the urshiol-type, a class which is known to contain some the strongest contact allergens in nature. Cross-reactivity between ginkgo fruit pulp and several *Rhus*-species (*Anacardiaceae*) as well as cross reactivity between ginkgo fruit pulp and cashew nut shell oil has been demonstrated. In patients, treated with ginkgo leaf extracts, severe circulatory disturbances including anaphylactic shock have been reported.

5. Due to the high content of ginkgolic acids (600 to 1500 mg/kg) in the homeopathic mother tincture, *Ginkgo biloba* may give rise to consumer health concerns due to possible allergic reactions. Data on pharmacokinetics and residues in treated animals were not available, and therefore risk assessment was based on worst case estimations. It was calculated that the maximum homeopathic dose (10 ml given intravenously to a 500 kg bw animal) of a 1:10 plant dilution (an approximate 1:3 dilution of the mother tincture) could lead to 2000 to 5000 ng of ginkgolic acids in the 500 g standard edible meat portion (assuming no detoxification and excretion). This estmated maximum intake still exceeds the doses tolerated in human therapy (600 to 1200 ng/daily dose) by a factor 3 and therefore an additional 100-fold safety factor (i.e. higher dilution) was considered necessary to ensure consumer safety.

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 taking into consideration that:

- *Ginkgo biloba* is intended for use as the mother tincture which was found to contain up to 1500 mg/kg of ginkgolic acids,
- there is evidence that *Ginkgo biloba* constituents such as ginkgolic acids can provoke severe allergic reactions,
- no pharmacokinetic and residue data were available allowing to estimate actual exposure of humans to residues of *Ginkgo biloba*, in particular ginkgolic acids, whilst a worst case estimation indicates that the amount of those substances in products from animals treated with a homeopathic 1:10 dilution could still exceed the amount tolerated in human therapy,
- the content of ginkgolic acids in foodstuffs derived from treated animals should be well below any amounts arising from the use of *Ginkgo biloba* extracts in human therapy;

the Committee for Veterinary Medicinal Products concluded that only adequately diluted preparations of *Ginkgo biloba* are suitable for use in in veterinary homeopathy and recommends the includsion of *Ginkgo biloba* in Annex II to Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Ginkgo biloba	All food producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias in the products not exceeding one part per thousand only