European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

GINSENG
(Extension of use)

SUMMARY REPORT (2)

1. Ginseng (synonyms: *Panax quinquefolius*, *Panaxg ginseng*, Five fingers) is a plant of the family *Araliaceae* widely distributed in the shady forests of East Asia. Different kinds of standardised ginseng extracts are available prepared from ginseng roots. The content in ginsenoides depends on the plant age and the preservation methos, for this reason the extracts are standardised to assure the content of ginsenosides. In veterinary homeopathy ginseng is used as mother tincture of the dried roots of ginseng according to homeopathic pharmacopoeias, and dilutions thereof. Constituents of the ginseng roots are: triterpenoic saponins, and ginsenosides (up to 6%). The amount of ginsenosides in the root is dependent on the age of the plant and increases continuously with each year of growth of the plant. The major ginsenoside in the root is Rg_1. Further constituents are essential oils (0.05%), sesquiterpens e.g. β-elemene, eremophilene, polyacetylene, panaxydol (falcarinol), panaxan, and polysaccharides.

2. Ginseng was previously assessed by the CVMP in respect to its use as homeopathic veterinary medicinal product.

   Currently, ginseng is included in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Ginseng	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

   An application has now been submitted to include ginseng extract in Annex II of Council Regulation (EEC) 2377/90 to allow for its use as an immunomodulator in vaccines. In swine the proposed recommended dose is 4 mg ginseng extract per dose intramuscularly. For the intended indication a *Panax ginseng* dry extract is used. It contains saponins equivalent to 27 to 30% of ginsenoside Rg1 calculated with reference to the dried substance, with not less than 20% of ginsenosides: propopanaxtriol ginsenosides (Rg1, Rf, Re), expressed as ginsenoside Rg1 and protopanaxtriol ginsenosides (Rc, Rd, Rb2, Rb1) expressed as ginsenoide Rb1.

3. From several scientific published papers, it can be concluded that ginseng extracts seem to induce several pharmacological effects in laboratory animals and in humans according to the tested extracts or ginsenosides, none of these effects is considered to be of concern for consumer safety taking into account the intended use of ginseng in animals. The exact mechanism of action for ginseng remains unclear.

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4. From the pharmacokinetic data provided in laboratory animals (mice, rat, rabbit) it seems that absorption is very limited following the oral administration.

5. The acute toxicity of a ginseng-extract from a publicly available report on a study in minipigs and rats was reported. Oral applications up to 4 g/kg induced no toxic effects. Intraperitoneal LD_{50} values of various pure ginsenosides on mice were: Rg_1: 1250 mg/kg; Rf: 1340 mg/kg; Re: 405 mg/kg; Rd: 324 mg/kg; Rc: 410 mg/kg; Rb_1: 1110 mg/kg; Rb_2: 305 mg/kg.

6. No toxic effects were reported in a publicly available report on an oral 90-day study conducted in 32 Beagle dogs (0, 1.5, 5 and 15 mg G115 (standardized ginseng extract) kg/day, or 0, 066, 0.2, 0.6 mg ginsenoside/kg/day), in an oral 20-day toxicity study in rats (4000 mg G115 (standardized ginseng extract)/kg/day, or 160 mg ginsenoside/kg/day) or in an oral 33-week toxicity study in 1730 male and female rats (0, 1.5, 5, 10 mg G115 (standardized ginseng extract)/kg/day).

7. Ginseng extract as 100 mg root daily administered to rats for 5 days induced no toxic effects. However, because of deficiencies of these studies, it was not possible to retain a NOEL.

8. No data on the tolerance in the target species were provided. Nevertheless ginseng has been used for homeopatic use (including parenteral use) in animal for some time, so such data was not considered necessary.

9. In a well-documented 33-week 2-generation study, rats received orally 0, 1.5, 5 or 15 mg/kg/day G115 (standardized ginseng extract), equivalent to 0, 0.006, 0.2 and 0.6 mg/kg/day ginsenosides. No general treatment related effects in parent males and females were observed. There were no significant differences in reproductive parameters between treated and control group. G115 (standardized ginseng extract) had no effect on reproductive male and female performances. No effects on pups were observed.

   G115 (standardized ginseng extract) is neither maternotoxic nor embryo/foetotoxic in rats given oral doses of up to 15 mg/kg/day, equivalent to 0.6 mg/kg/day ginsenoside.

10. Results of 2 teratology studies were provided from a scientific publication. Female Wistar rats were orally given 40 mg/kg/day of G115 from day 1 to day 15 of gestation. Caesarian section was performed on day 21 of gestation. Female New Zealand rabbits orally received 20 mg/kg/day G115 (standardized ginseng extract) from day 6 to day 18 of gestation. Caesarian section was performed on day 25 of gestation. Both studies deviated from current OECD guidelines as only one dose was tested *versus* 3 doses. The number of pregnant females was lower than that recommended with 10 and 6 impregnated rats and rabbits, respectively, *versus* 20 pregnant females. Due to the deviation from guidelines, no final conclusion on foetotoxic and teratogenic potential of ginseng can be drawn from the studies. Nevertheless, there was no evidence from these studies that ginseng itself had any significant teratology activity.

11. From the scientific literature provided there were a number of reported studies (two Ames test, one chromosome aberration assay and one antitumor promotional effect study) mainly investigating the potential of ginseng to inhibit mutagenic activity of other substances. There was no evidence from these studies that ginseng itself had any significant mutagenic activity.

12. No carcinogenicity study was conducted. Ginseng shows no structure-activity relationship indicating a close chemical analogy with known carcinogens. It has been suggested that ginsenoside extracts from root and/or rhizome of *Panax ginseng* possesses preventive activity against cancer and/or anti-carcinogenic activity, in different organs. The mechanisms of these activities have not been explained.

13. No immunotoxicity studies were provided. It was considered that these were not required for the current application. In humans, ginseng is used as a dietary complement: 0.6 to 3 g, one to 3 times a day and to be taken from 3 weeks to 3 months. Suggested daily doses for therapeutic use: 1 to 2 g of root, in infusion, 3 to 4 times per day for 3 to 4 weeks. Ginseng is also used in food, as flavour in several products (beverages, ice cream, candy, chewing gum), in a range of 20 to 50 μg/kg, and it is added to some cosmetics.

    A possible interaction with warfarin has been suggested. No explanation has been provided. Possible estrogenic effects (vaginal mucosal changes, bleeding, mastalgia with diffuse nodules) have been reported in postmenopausal women. An interaction between ginseng saponins and hormone receptor has also been suggested.

    From publicly available literature, ginseng (200 mg *Panax ginseng*/subject/day for 28 days) appeared to have effects on electrocardiographic parameters (increasing corrected QT interval and decreasing blood pressure).

14. No neurotoxicity studies have been performed with ginseng.

    Brief abstracts and one full publication reported a neuroprotective effect of ginseng against substance-induced neurotoxicity and in rodent models of Parkinson disease.

15. Taking into account the information available, the characteristics of the substance and its use in humans, it was considered that no further information was required.

16. No residue studies were provided.

Conclusions and recommendation:

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

- ginseng did not indicate specific pharmacological or toxicological concern at the concentrations expected to be used in veterinary medicine,
- ginseng is a normal component of the diet in humans and is generally recognised as safe for humans,
- the substance and constituents thereof do not give rise to specific consumer health concern which may result from its use in veterinary medicine;

the Committee for Medicinal Products for Veterinary Use recommends the inclusion of ginseng extract in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Ginseng, standardised extracts and preparations thereof	All food producing species	