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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ANISI AETHEROLEUM

SUMMARY REPORT

1. *Anisi aetheroleum* is the essential oil obtained by steam-distillation of the dried, ripe fruits of *Pimpinella anisum* L (synonym of the fruit: aniseed), in which it is contained in a concentration of up to 14%. The main components are *trans*-anethole (75 to 96%), *cis*-anethole (0.3 to 0.4%), methyl chavicol (1 to 4%), epoxipseudoisoeugenyl-2-methylbutyrate (0.1 to 0.5%), pseudo-isoeugenyl-2-methylbutyrate (1%), anisaldehyde (0.5 to 0.9%) and terpenes 1 to 2%.

2. *Anisi aetheroleum* is contained in a concentration of 1% (w/w) in one veterinary medicinal product in combination with 4 other active principles for use in all food producing species. The product is prescribed for treatment of flatulence and disturbances of the stomach and gut. The doses range from a few drops to 15 ml, depending on bodyweight. The maximal dose corresponds to 0.15 g of *Anisi aetheroleum*.

   Anisi aetheroleum is also used in humans as a carminative and expectorant and as a flavouring agent in food (baked goods, custards, meat and meat products) and sweets as well as drinks (liqueurs). *Anisi aetheroleum* is also used as a fragrance in cosmetics (creams, lotions and toothpaste etc.), perfumes (maximum concentrations of 0.25%) and to mask unpleasant odours in medicinal products.

   Aniseed is used extensively in the human diet as a spice.

3. Anethole anisaldehyde have mild insecticidal properties. *Anisi aetheroleum* has an expectorant effect in doses up to 50 mg/kg bw. In rabbits higher doses (0.7 to 6.5 g/kg bw) are tissue-damaging and fatal at the highest dose. Spasmolytic activity has been demonstrated *in vitro* but it is doubtful if this has any *in vivo* relevance, as the doses used are high. Old reports about estrogenic activity of *Anisi aetheroleum* have not been confirmed by modern investigations.

4. No information on the pharmacokinetics of *Anisi aetheroleum* is available. Summary information is available for its main constituent, anethole, however the study reports were not provided.

   In mice and rats, anethole is metabolised by *o*-demethylation and oxidative transformation of the C_3-side chain. In lower doses (0.05 to 5 mg/kg bw) *o*-demethylated metabolites prevail, while different oxidative metabolites are predominant after large doses (up to 1500 mg/kg bw).

   In humans, data observed after oral administration of 1 to 250 mg C^{14}-labelled *trans*-anethole per person indicate that *Anisi aetheroleum* is rapidly and extensively absorbed (70 to 85%). The oxidative metabolism is predominant even after an oral dose of 1 mg.

   After oral doses of 1.5 and 250 mg/person, 54 to 69% of the radioactivity were excreted in the urine independent of the dose. More than 90% of the urinary radioactivity is due to 4-methoxy hippuric acid. At least 13 to 17% are excreted by exhalation. However, due to loss of the radiolabel exhaled metabolites, produced by *o*-demethylation can not be detected. Excretion is almost complete within the first 8 hours. Faecal excretion has not been observed.

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5. The oral LD_{50} for *Anisi aetheroleum* in rats is 2.7 g/kg bw. For *trans*-anethole an intraperitoneal LD_{50} of 1 g/kg bw has been reported for mice. Oral LD_{50} values for *trans*-anethole of 1.8 to 5 g/kg bw in mice, 2 to 3 g/kg bw in rats and 2.1 g/kg bw in guinea pigs have been reported.

6. No information on the oral repeated dose toxicity of *Anisi aetheroleum* has been submitted. For the main pharmacological constituents the following information was available. No toxic effects were observed in rats given food containing 0.1% *trans*-anethole for a period of 90 days. Liver damage was observed with concentrations of 0.3%, 1% and 3%. In another experiment addition of 0.25% anethole to the feed given to rats for one year had no adverse effects on the liver. Anisaldehyde in a concentration of 1% in the feed given to rats for 15 weeks or in a concentration of 0.1% in the feed given for 28 weeks had no toxic effect. *Trans*-anethole given as addition to the feed in doses of 105 to 550 mg/kg bw/day had no adverse effects except a slight retardation of the bodyweight.

7. No information on the reproductive toxicity and teratogenicity of *Anisi aetheroleum* was provided.

8. *Anisi aetheroleum* and *trans*-anethole had mutagenic effect in Ames-test with *Salmonella typhimurum* TA 98 and TA 100 when high concentrations of 2 mg/plate were tested. Concentrations of 60, 90 and 120 µg/plate gave a dose-dependant effect but the number of mutants was not higher than twice that of the control. No mutagenicity was detected for anisaldehyde.

9. No information on the carcinogenicity of *Anisi aetheroleum* has been provided.

10. No information on the immunotoxicity of *Anisi aetheroleum* has been provided.

11. *Anisi aetheroleum* is used in humans as a carminative and expectorant at a dose of 0.05 to 0.2 ml three times daily. The daily dose of *Anisi aetheroleum* in human medicine amounts to 0.3 g/person. No cases of poisoning of humans with *Anisi aetheroleum* or *trans*-anethole are reported. Traditionally, due to the previously suspected estrogenic activity, aniseed, which contains *Anisi aetheroleum*, is reputed to be an abortifacient and to produce lactation. The safety of aniseed taken during pregnancy and lactation has not been established; however there are no concerns provided that doses taken do not greatly exceed the amounts used in foods. These statements are probably applicable also to the volatile oil. Contact dermatitis reactions to aniseed and anise oil have been attributed to anethole. The volatile oil and anethole have been stated to be both irritant and sensitising.

12. Aniseed is listed by the Council of Europe as a natural source of food flavouring (category N2, which indicates that the substance may be added to foodstuffs in small quantities with a possible limitation of the active principle). *Anisi aetheroleum* is listed as "Generally recognised as safe" in the USA. For *trans*-anethole, the main constituent of the oil, an ADI of 0.6 mg/kg bw has been established by the Joint FAO/WHO Expert Committee on Food Additives in 1991.

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:

- *Anisi aetheroleum* is contained in aniseed, which is a normal component of the human diet,
- trans-anethole, the main constituent of *Anisi aetheroleum* is rapidly and extensively metabolised and excreted,
- *Anisi aetheroleum* is used only for occasional treatment of individual animals,
- the animals are unlikely to be sent to slaughter immediately after treatment;

the Committee concludes that there is no need to establish an MRL for *Anisi aetheroleum* and recommends its inclusion in Annex II to Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Anisi aetheroleum	All food producing species	