The European Agency for the Evaluation of Medicinal Products

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

JUNIPERI FRUCTUS

SUMMARY REPORT

1. *Juniperi fructus* is the dried berry-like cones of *Juniperus communis*.

   Juniperi fructus contains the following constituents:

   - volatile oil (0.2 to 3.4%) containing monoterpenes, among others α- and β-pinene, β-myrcen, limonen, terpinen-4-ol and sabinene. The composition of commercially available volatile oils from juniper berries is varies considerably. The proportion of terpinen-4-ol to a+β-pinene can vary from 1:4 to 1:55. The content of a-pinene varies from 10 to 76%. The oil from the berries contains appreciable amounts of sabinene (1 to 28%) but sabinylacetate, which is responsible for the abortive properties of the oil of *Juniperus sabina*, was not found. One report gives the following quantitative data: a-pinene 18 to 58% of the oil, myrcene 7 to 23%, cadinene 5 to 13%, sabinene more than 1%, caryophyllene, β-elemene and terpinen-4-ol together approximately 3%;
   - proanthocyanidines: gallocatechin and epigalloatechin;
   - flavonoids in small amounts;
   - the lignan desoxypodophyllotoxin and its isomer desoxypicropodophyllotoxin;
   - diterpene acids and sesquiterpenes such as caryophyllene and cadinene.

   Juniperi fructus is contained in a concentration of 10% (w/w) as one of 14 active ingredients in a powder for oral administration to cattle, horses, pigs, sheep and goats used for the induction of heat and rut. The doses are 50 g/animal twice a day on two consecutive days for cattle and horses, and 10 to 20 g/animal twice a day on 3 to 4 consecutive days for sheep, goats and pigs.

   In man *Juniperi fructus* is stated to have diuretic, antiseptic, stomachic and antirheumatic properties. Traditional use include cystitis, flatulence and colic. Topical application for rheumatic pains in joints or muscles is also reported. The usual doses are 2 to 10 g of the crude drug or 20 to 100 mg of the volatile oil.

2. Pharmacological actions are primarily associated with the volatile oil components. A diuretic activity is attributed to terpinen-4-ol of the oil. Increase of the glomerular filtration rate is induced.

   An antiviral effect against *Herpes simplex* type I is attributed to desoxypodyphyllotoxin and, partly, to the flavonoid amentoflavone.

   An anti-inflammatory activity has been reported for an extract of the crude drug. No mention is made of the solvent used or the drug/extract ratio. The oral dose used in rats was 100 mg/kg bw.

   A transient hypertensive effect, followed by a more prolonged hypotensive effect was observed at an intravenous dose of 25 mg/kg bw to rats. No records of the solvent or drug/extract ratio are made.

   A hypoglycaemic effect of an aqueous decoction in rats after oral administration is reported.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8447
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

A uterine stimulant activity is reported for the volatile oil. An ethanol extract contracted the isolated mouse ileum in concentrations in the organ bath corresponding to 0.2 to 0.4 g/100 ml of the crude drug. Concentrations corresponding to 0.2 to 0.5 g crude drug/100 ml organ bath increased the contractions of the isolated mouse uterus. An emulsion of the volatile oil decreased the contractions of the mouse-ileum but increased the tonus. On the isolated rat uterus an emulsion of the volatile oil decreased the contractions but increased the tonus of the uterus. The concentration is not possible to deduct from the description of the experiment, only that 2 to 6 drops of the emulsion in 200 ml organ bath caused increased tonus. The effects of the fluid extract prepared according to the Swiss Pharmacopoeia were ambiguous.

3. It has been reported that the volatile oil applied to the skin of a rabbit could be detected in the expired air after one hour following application. After 4 hours traces of the oil could be detected. Human beings were bathed for 20 minutes in water with 1 mg/l each of α-pinene, β-pinene and camphene. Fifty to 75 minutes following the bath, 7 to 8 ng/ml of the terpenes could be detected in the blood. One day following the treatment only 0.5% of the maximum value was present. The uptake of the terpenes is calculated to result from inhalation (10 to 20%) and from percutanous absorption (80 to 90%).

4. The intraperitoneal LD_{50} of a lyophilised aqueous extract in mice is 3 g/kg bw. The oral LD_{50} of the volatile oil is 6.28 g/kg bw in the rat. The acute dermal LD_{50} value was greater than 5 g/kg bw in rabbits.

   The oil is slightly irritating to human and animal skin.

   There are contradictory reports concerning kidney irritation caused by excessive doses (no figures) of terpinen-4-ol. Dermal, allergic, reactions are reported. According to a recent evaluation of the literature, the nephrotoxic effects attributed to the juniper berry and the volatile oil of juniper berries depend on much too high doses and that conclusions have erroneously been drawn from pathological protein values in the urine which are due to acute kidney infections. Another explanation can be the falsification of juniper oil with turpentine oil. The nephrotoxic effects have not been substantiated for almost one century.

   A study on the possible nephrotoxic effect of the volatile oil of the juniper berries has been published very recently. The ratio of terpinen-4-ol to α + β-pinene of the two investigated batches of oil were 1:3 and 1:5, respectively. No nephrotoxic effect were detected in rats even at daily doses of 1 g/kg bw for 28 days. Also terpinen-4-ol at a daily dose of 400 mg/kg bw had no nephrotoxic effect. No other toxic manifestations were detected.

5. A daily oral dose to rats of 2.5 g/kg bw for 7 days of an aqueous ethanol extract of *Juniperi fructus* was tolerated with no mortalities or side effects. The drug to extract ratio was 1:3. The dose corresponds to 0.8 g crude drug or 8 mg volatile oil. At 3 g/kg bw hypothermia and mild diarrhoea were reported for 10 to 30% of the animals. A daily dose (duration of treatment not stated) of 20 g/kg bw of a not defined extract was lethal to guinea pigs. Rabbits can tolerate daily doses up to 40 g extract per animal (time period not reported). No further information on long-term toxicity was provided.

6. No information on repeated dose toxicity was provided.

7. An anti-fertility effect has been reported for oral doses of 300 and 500 mg/kg bw of a 50% ethanol extract (no information on drug/extract ratio) to rats on days 1 to 7 of pregnancy. An abortifacient effect was also noted at both dose levels when the extract was administered on days 14 to 16. Anti-implantation activity has been reported as 60 to 70% and as dose dependent. Reports on anti-fertility effects are contradictory.

8. No information was provided on teratogenic, mutagenic and carcinogenic effects of *Juniperi fructus*.

9. No information was provided on immunotoxic effects of *Juniperi fructus*. Contact dermatitis, however, is a known reaction to this plant. Application of a preparation containing 5% of the oil did not cause dermatitis in humans.

10. It was reported that kidney damage can occur on continued use or overdose, however no data were given. Juniper berry products should not be used without medical advice for more than 4 weeks and they are contraindicated in nephritis and pyelitis. The monoterpene hydrocarbons in the volatile oil are reported to have kidney irritating or injuring effect (no details given). The British Herbal Pharmacopoeia and the German Commission on Herbal Remedies for use in humans, indicate that juniper berries should be avoided in renal disease. However, in a recently performed evaluation of the literature and a modern investigation in rats, reviewed in paragraph 4, no nephrotoxic effects were found.

11. *Juniperi fructus* is used for flavouring food and alcoholic beverages (maximum level 0.006% in beverages). In the United States of America the oil is given GRAS (generally recognised as safe)-status by the Flavouring Extract Manufacturers Association (FEMA) and is approved by the Food and Drug Administration (FDA) for food use. Juniper berry is included in the Council of Europe's list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product (limitation not yet determined).

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:

- *Juniperi fructus* is of low acute oral toxicity,
- *Juniperi fructus* is used as a spice in human food,
- *Juniperi fructus* is used only in a small number of individual animals, for infrequent or 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 *Juniperi fructus* 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
Juniperi fructus	All food producing species	