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

EMEA/MRL/400/98-FINAL
April 1998

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

OXIDATION PRODUCTS OF TEREBINTHINAE OLEUM

SUMMARY REPORT

1. The oxidation products of *Terebinthinae oleum* are obtained by oxidation of the turpentine oil obtained from *Pinus pinaster* Sol.; turpentine oil is the oil distilled from the oleoresin collected from this tree.

   Limited information on the composition of the oxidation products of *Terebinthinae oleum* has been provided, however the pharmacologically and toxicologically relevant components of the turpentine oil are α- and β-pinene (ratio 2:1) contained at approximately 98%.

   Because of its poor solubility in water, turpentine oil is oxidised in order to increase the diffusion in vivo of its active components through membranes and mucous membranes. Thus, the oxidation products of *Terebinthinae oleum* are more soluble and effective than the non-oxidised products.

2. In veterinary medicine the oxidation products of *Terebinthinae oleum* are used as adjuvant treatment of broncho-pulmonary disorders. In combination with two other active ingredients they are indicated for subcutaneous, intramuscular and intravenous injection to bovine, ovine, caprine and porcine at a dose of 0.18 to 0.45 mg/kg bw/day. The duration of treatment is 4 to 7 days.

   The oxidation products of *Terebinthinae oleum* are also used in human medicine following parenteral, oral or rectal administration at doses of 40 to 280 mg/day (0.5 to 3 mg/kg bw).

3. The oxidation products of *Terebinthinae oleum* regulate tracheo-bronchial secretion and are useful adjuncts in the clearance in obstruction of lung disease. Furthermore, they cause a significant reduction in respiratory resistance to airflow.

   In vitro effects of the oxidation products of *Terebinthinae oleum* are reported to be decrease of surface tension of natural and artificial surfactants by changing the visco-elastic properties of the surfactant.

   In vivo effects of the oxidation products of *Terebinthinae oleum* in rats, rabbits and hamsters are reported to be increases of ciliary beat frequency, mucus production and velocity of mucus transport, mild bronchodilator activity.

   The bronchodilator activity was confirmed *in vivo* in Guinea pigs treated orally with 5, 10 or 20 mg/kg bw of the oxidation products of *Terebinthinae oleum* and *in vitro* in Guinea pig lung and tracheal spiral preparations, while turpentine oil itself, tested at the same doses and concentrations, remained without effect.

4. No information on absorption, distribution, metabolism and excretion for oxidation products of *Terebinthinae oleum* has been provided. The following information was presented for turpentine oil obtained from *Pinus* spp.

   Analogous to other volatile oils, turpentine oil undergoes rapid renal, biliary and pulmonary excretion.

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

5. In view of the very limited use of the oxidation products of *Terebinthinae oleum* in veterinary medicine and the long history of safe use of both the oxidation products of *Terebinthinae oleum* and the related more toxic substance turpentine oil, no further data on repeated dose toxicity, reproduction toxicity and teratogenicity, mutagenicity and carcinogenicity were considered necessary.

6. No information on the effects of the oxidation products of *Terebinthinae oleum* in humans has been provided.

   For turpentine oil obtained from *Pinus* spp. the following summary information was available but not supported by data. Acute toxic episodes have been reported after poisoning with turpentine oil, toxic signs being local burning and gastro-intestinal upset, coughing and choking, pulmonary oedema, excitement, coma, fever, tachycardia, liver damage, haematuria, albuminuria and cutaneous efflorescence such as erythema, papule and urticaria. Neurotoxic effects have also been reported following treatment of large areas of skin with turpentine oil.

   Sensitisation due to exposure to turpentine oil has been reported.

7. No data on microbiological properties of residues of the oxidation products of *Terebinthinae oleum* are available.

   For turpentine oil obtained from *Pinus* spp. the following information was available. Turpentine oil is reported to show antimicrobial activity in dilution and agar diffusion tests against *Streptococcus* spp., *Staphylococcus* spp., *Escherichia coli*, *Bacillus* spp. and *Vibrio cholerae*. However as residues are only expected at very low concentrations such information is not considered relevant for the oxidation products of *Terebinthinae oleum*.

   In view of the very limited use of the oxidation products of *Terebinthinae oleum* in veterinary medicine residues are only expected at very low concentrations and no further information was considered necessary.

Conclusions and recommendation

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

- the oxidation products of *Terebinthinae oleum* have a long history of safe use in traditional human medicine,
- the oxidation products of *Terebinthinae oleum* are used only for infrequent and non-regular treatment of individual animals
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- the oxidation products of *Terebinthinae oleum* are likely to be rapidly absorbed and excreted;

the Committee concludes that there is no need to establish an MRL for the oxidation products of *Terebinthinae oleum* and recommends their 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
Oxidation products of *Terebinthinae oleum*	Bovine, ovine, caprine, porcine	