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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NONIVAMIDE

SUMMARY REPORT

1. Nonivamide (CAS 2444-46-4), synonyms N-nonanoyl vanillylamide, vanillylnonanamide, is a synthetic analogue of capsaicin (8-methyl N-vanillyl-6-nonenamide), a vanillyl fatty acid amide which is the predominant pungent constituent of fruits of the *Capsicum* family (e.g. chilli, red pepper, paprika). The structures of capsaicin and nonivamide differ only slightly with respect to the fatty acid moiety of the side chain (8-methyl nonenoic acid versus nonanoic acid). In veterinary medicine nonivamide is used in combination with nicoboxil as rubefacient in liniment products for topical treatment of locomotor disorders, oedemas or haematomas. This application relates to the topical use of nonivamide in horses. The daily dose is approximately 3.4 mg/horse corresponding to about 6 to 9 µg/kg bw as single dose. The treatment can be repeated over several days.

   A combination product of nicoboxil and nonivamide is also used as local rubefacient in human medicine.

2. Nonivamide like other capsaicinoids acts on the vanilloid receptors of peripheral afferent nerve fibres exhibiting short-lasting irritant and algesic properties. Applied dermally these substances act by stimulating sensitive chemoreceptors of the skin and by reflex cause hyperaemia and local increase in temperature. After repeated administration capsaicinoids have been reported to produce desensitisation to nociceptive stimuli possibly by long-lasting depletion of peptide neurotransmitters (substance P) from peripheral sensory neurons. Capsicinoids may alter smooth muscle tone (in bladder, bronchus etc.). Intravenous injection of nonivamide to rats (10 µg/kg bw) was found to lead to bradycardia and a triphasic blood pressure response. The cardiovascular effects are partly explained by substance P release. Nonivamide given to rats subcutaneously (1 mg/kg bw) was found to cause body temperature decrease, vasodilatation and salivation. Capsaicinoids were found to evoke bronchospastic effects in guinea pigs. Capsaicin and analogues were reported to increase barbiturate sleeping time in rats by interacting with hepatic metabolising enzymes. Data on other pharmacological effects of nonivamide were not available.

3. Studies on dermal absorption of nonivamide in laboratory animal or target species were not provided. Some information on absorption of capsaicinoids including nonivamide derived from published literature indicated however, that the substances of this class are able to penetrate skin in various animal species and man.

   Limited information was available on pharmacokinetics and metabolism of nonivamide. For the closely related capsaicin and other capsaicinoids gastrointestinal absorption was found to be rapid and nearly complete in rats (oral dose of about 10 to 15 mg/kg bw of combined capsaicin and dihydrocapsaicin) with about 85% of the dose absorbed within 3 hours. Both substances were reported to undergo first pass metabolism and partly already metabolized at the site of absorption.

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

Following intravenous administration of capsaicin (2 mg/kg bw) to rats the concentration of capsaicin was 5 times higher in the brain and the spinal cord and 3 times higher in the liver than in the blood. Ten minutes after application the concentration in the blood and the liver is strongly reduced while capsaicin can still be detected in the brain and spinal cord.

Major routes of metabolism of capsaicinoids have been found to be hydrolysis of the acid amide bond, beta or omega-oxidation of the alkyl side chain, phenyl ring hydroxylation and conjugation of the phenolic group. The elimination of intraperitoneally administered capsaicin in rats (1 mg/kg bw) was found to be short with a half-life of about 7 minutes. Elimination half-life data for other routes of administration were not available for any capsaicinoids. No informations on repeated dose pharmacokinetics are available.

4. Nonivamide appears to be of low acute toxicity. The oral LD_{50} in rats was reported with 5110 mg/kg bw and the dermal LD_{50} in rabbits was greater than 10 000 mg/kg bw. Given intraperitoneally, the LD_{50} in rats was established at about 90 mg/kg bw. In combination with nicoboxil, the acute dermal toxicity was found to be increased. Toxic signs (depression, laboured respiration, diarrhoea) were seen at doses as low as 32 mg/kg bw nonivamide plus 200 mg nicoboxil/kg bw.

5. Repeated dose toxicity was studied in rabbits for a combination of nicoboxil and nonivamide using dermal administration of a paraffin containing cream aerosol at dose levels of 0.25 and 1 mg nicoboxil/kg bw and 0.38 and 1.5 mg nonivamide/kg bw (3 animals/sex/dose). The dose was administered over 3 weeks for about 8 hours daily on 6 days a week. Observed effects were a dose dependent decrease in leukocyte cell count in treated animals and lowered red blood cell parameters in one female of the highest dose group. The toxicological significance of this effect was not clear. Besides slight skin irritation in the highest group no other changes were noted. Oral repeated dose toxicity studies were not provided. Admixture of 5% of red pepper or 0.015% of capsaicin to the standard diet of rats for a period of 8 weeks caused reduction of body weight and lipogenic enzymes. Fructose-induced increase of serum triglycerides was also diminished. Oral administration of 1 mg/kg bw of capsaicin (ethanol solution) to rats for 3 to 9 months caused lesions of the mucous layer of the stomach. Rats receiving 50 mg/kg bw/day of capsaicin were reported to suffer from significant reduction of body weight (time period of treatment not given).

6. Reproduction toxicity or teratogenicity studies were not provided for nonivamide nor was any published literature concerning these issues available for nonivamide or other capsaicinoids.

7. No mutagenicity studies or any published data on mutagenic activity of nonivamide were available. Few data have been found in published literature on mutagenic properties of capsaicinoid containing fractions of chilli extracts and capsaicin. Capsaicin was not mutagenic in the *Salmonella typhimurium* assay without metabolic activation. Contradictory results were reported for capsaicin and chilli extracts in the *Salmonella typhimurium* assay in the presence of metabolic activation and in *in vitro* mutagenicity assays using mammalian cells (V79 cells). Capsaicin itself was positive in the mouse bone marrow micronucleus test near the LD_{50} dose of 7.5 mg/kg but not at 1.8 mg/kg bw. No dominant-lethal mutations were observed in mice during an 8-week sequential mating schedule of males treated intraperitoneally with capsaicin at 1.6 mg/kg bw daily over 5 days. Capsaicin was also reported to form possibly mutagenic nitrophenols under physiological pH and nitrite content of the stomach. Though there was some indication from published articles that capsaicinoid constituents of chilli or capsaicin itself could have mutagenic properties, the overall database was too limited and inconsistent to draw clear conclusions regarding genotoxicity of capsaicin or to make any extrapolations concerning mutagenic risks of the synthetic analogue nonivamide.

8. No information on carcinogenic properties of nonivamide was available. Tumorigenic properties have been reported in literature for capsaicin or chilli. Capsaicin was found to induce adenocarcinomas of the duodenum in mice when present in the diet at levels of 0.0625 to 1% and liver tumours in rats feed

diets containing 10% chilli pepper. Other authors reported that chilli or capsaicin may act as co-carcinogens or tumour promoters for stomach and liver carcinogenesis.

9. No specific studies on immunotoxicity were provided. Allergic reactions in humans following administration of capsaicin or capsicum extracts were reported to be rare

10. No data on antimicrobial activity or effects on human gut flora were available but these are not considered necessary for the type of compound.

11. No adverse side effects were reported in humans after therapeutic use of the combination of nicoboxil/nonivamide. In a study using dermal application of a combination of nicoboxil/nonivamide in over 1000 patients allergic reaction were not observed.

12. Residue studies in horses were not available, but are not considered necessary as pharmacokinetic data indicate rapid metabolism and elimination of capsaicinoids.

Conclusions and recommendation

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

- nonivamide is used only for topical treatment of individual animals at very low doses,
- animals are unlikely to be sent for slaughter during or immediately after treatment,
- like its natural anologue capsaicin and other capsaicinoids, the bioavailable fraction of the dose is expected to be readily metabolised and eliminated,
- nonivamide is of low oral acute toxicity;

the Committee concluded that there is no need to establish MRLs for nonivamide and recommends inclusion of the substance into Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Nonivamide	Equidae	For topical use only