The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NAFCILLIN

SUMMARY REPORT (1)

1. Nafcillin is a derivative of 6-amidinopenicillanic acid, i.e. a semisynthetic penicillinase-resistant penicillin; other members of the family include methicillin and the isoxazolyl penicillins, e.g. oxacillin, cloxacillin, and dicloxacillin. The compound is an active ingredient in intramammary preparations intended for treatment of subclinical mastitis and prevention of mastitis in cows during the dry period (single treatment) and for treatment of mastitis in lactating cows (recommended treatment regimen: one dose per affected quarter per day for three successive days). The products currently marketed contain nafcillin (100 mg) as the sodium monohydrate salt, penicillin (300.000 IU) and dihydrostreptomycin (100 mg) per dose of 3 grams.

2. Nafcillin is active against various Gram positive species, e.g. staphylococci, streptococci and pneumococci. Like the other penicillinase-resistant penicillins, it shows little or no activity against Gram negative microbes. The antibacterial spectrum and the potency of nafcillin, oxacillin and cloxacillin against bovine mastitis pathogens are comparable. On a weight-to-weight basis nafcillin is 4-8 times more bactericidal than methicillin.

3. Administered intravenously to dogs in doses from 250 to 500 mg/kg nafcillin produced hypotension and bradycardia without affecting the pressor responses induced by epinephrine or norepinephrine. Doses of 500-1000 mg/kg caused irreversible cardiovascular collapse in some animals, while 1000 mg/kg was 100% lethal. Cats were somewhat more sensitive to the pharmacological effects of nafcillin than dogs. Methicillin in comparable doses showed less pharmacological activity than nafcillin.

4. In dogs, absorption following oral administration tends to be poor. Maximum concentration in serum is reached within 30 minutes following intramuscular administration. At similar oral doses peak serum levels are lower and plasma levels are less persistent than observed for methicillin and penicillin G. In contrast to methicillin and especially penicillin G, the liver is the main excretory pathway for nafcillin, the 0-24 hour bile accounting for 97%, 56% and 30% of the total dose following intravenous-, intramuscular-, and oral administration, respectively. Corresponding figures for methicillin and penicillin G following intravenous administration are 22% and 9%, respectively. Concentrations of nafcillin in organs/tissues tended to be higher and more persistent following parenteral administration than is the case for methicillin and penicillin G, apparently due to enterohepatic recirculation for nafcillin.

5. No data on the biotransformation of nafcillin have been provided. However, the fact that all determinations of nafcillin in the kinetic studies were carried out by means of microbiologically based methods coupled with the observed relatively high 0-24 hours excretion rates via the liver makes it seem plausible that, like most other penicillins, the substance undergoes biotransformation only to a small extent.

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6. The presence of detectable levels in plasma and urine of treated cows shows that nafcillin is absorbed systemically following intramammary administration. After intramammary use in lactating cows the major part of the nafcillin is excreted in the milk, while a higher proportion is absorbed from the udder when nafcillin is administered at drying off. Obviously, systemic absorption in connection with intramammary administration depends on time of treatment as well as product formulation. The proportions of the doses actually absorbed systemically remain unknown, as does to some extent the fate of systemically absorbed nafcillin.

7. Like other penicillins nafcillin is of low toxicity in laboratory animals by single administration. In laboratory rodents the minimum oral lethal dosis was above 5000 mg/kg; the LD_{50} following intramuscular administration was 2800 mg/kg, and the intraperitoneal LD_{50} was 1200 mg/kg. The intravenous LD_{50} was 1100 mg/kg, which is less than reported for penicillin G (2200 mg/kg), but in the same order of magnitude as reported for oxacillin (1500 mg/kg). In dogs the LD_{50} following intravenous administration was 600 mg/kg. For all routes signs of toxicity occurred near the LD_{50} and included occasional mild convulsion followed by depression, loss of muscle tone and dyspnea.

8. As nafcillin belongs to a group of substances with a well known toxicological profile that, apart from their allergenic potential, does not include significant adverse effects in connection with repeated exposure and as there are no indications that nafcillin exhibits a different repeated dose toxicity profile than the other penicillins, no specific data for nafcillin concerning repeated-dose toxicity are considered necessary.

9. The bovine lactating udder showed acceptable tolerance to the currently marketed intramammary products containing nafcillin.

10. Reproductive studies in mice and rats employing doses up to 2000 and 4000 mg/kg/day, respectively, provided no evidence of foetal toxicity, including teratogenicity, and no negative effects were observed on postnatal development in the pups. Considering the class of compounds to which nafcillin belongs plus the fact that no teratogenic or other effects of reproductive_toxicity of nafcillin were seen in the studies carried out, no additional reproductive toxicity studies are considered necessary.

11. Since nafcillin belongs to a class of compounds considered to be devoid of mutagenic and carcinogenic potential no specific studies on these endpoints for nafcillin are considered necessary.

12. No data on immunotoxicity have been provided. A claim that the allergic potential of nafcillin is less than that of penicillin, because the structure of nafcillin was designed specifically to prevent opening of the beta-lactam ring, has not been documented. The same applies to a claim that nafcillin and oxacillin are comparable with respect to allergic potential.

13. No studies have been carried out concerning the effect of nafcillin on the human gut flora**.** In general, the activity of nafcillin and similar penicillins against anaerobic Gram negative bacteria is small in comparison with their activity on Gram positive organisms (*Streptococcus* spp. *Staphylococcus* spp. etc.). A claim that nafcillin and oxacillin are comparable with respect to antimicrobial effect on the human gut flora has not been documented.

14. The acidifying activity of three commercially available and widely used yoghurt cultures was significantly affected only at concentrations of nafcillin above 0.075 µg/ml. However, significant effects on cell morphology were observed at lower concentrations. At concentrations above 0.02 µg/ml *Lactobacillus bulgaricus* grew in long thin filaments. At concentrations above 0.05 µg/ml *Streptococcus thermophilus* were swollen and irregular. At concentrations in excess of 0.15 µg/ml only growth of *Lactobacillus bulgaricus* was observed. The effects of oxacillin and nafcillin on yoghurt cultures were qualitatively and quantitatively similar.

15. Nafcillin was originally developed for use in humans. Since the late 1960s the substance has been employed in the treatment of serious infections caused by penicillinase-producing staphylococci, e.g. endocarditis, septicemia, osteomyelitis and pneumonia. The recommended daily dose is 1 g administered intramuscularly; in the case of severe infections up to 6-18 g/day may be given in divided doses. The compound is highly bound to serum protein (about 90%). Although formulations for oral administration are available the oral route is not recommended due to irregular absorption. Data concerning adverse effects reported in connection with clinical use in humans have not been presented. Reports have been published associating the development of interstitial nephritis with clinical use of nafcillin. Cases have occurred mainly in patients exhibiting other signs of an allergic reaction concurrent with deteriorating renal function.

16. Depletion studies carried out in connection with treatment at drying off show that for animals with a dry period greater than or equal to 19 days the residues in all edible tissues were below 300 µg/kg at 24-72 hours after calving. The studies also show that with a dry period greater than or equal to 30 days, the residues in milk were below 30 µg/l at the 2nd milking after calving. Similarly, the depletion studies carried out in connection with treatment of lactating cows show that residues in all edible tissues were below 300 µg/kg at 72 hours after cessation of treatment and that residues in milk were below 30 µg/l from the 4th milking onwards, after cessation of treatment.

17. The analytical method submitted by the applicant is microbiologically based and therefore does not meet the requirements specified in Volume VI of the Rules Governing Medicinal Products in the European Community with respect to specificity. An HPLC method for determination of nafcillin is currently being developed.

Conclusions and recommendation

Having considered that :

- nafcillin is intended to be for intrammary administration only,
- the MRLs established for oxacillin, cloxacillin and dicloxacillin are based on their antimicrobial effect on the human gut flora and their effects on starter cultures employed in the dairy industry;

notwithstanding the fact that the toxicological profile for nafcillin appears to differ somewhat from those of the oxacillin, cloxacillin and dicloxacillin, namely with respect to the influence of nafcillin on the renal function, the Committee considered that MRLs for nafcillin should in principle also be based on the same effects of those three substances and recommends the inclusion of nafcillin into Annex III of Council Regulation (EEC) No 2377/90 in accordance with the following table :

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Nafcillin	Nafcillin	Bovine	300 µg/kg	Muscle, fat, liver and kidney	For intrammary use only
			30 µg/kg	Milk	Provisional MRLs expire on 01.01.1999

A final decision on nafcillin can only be considered after clarification of the points included in the list of questions.

LIST OF QUESTIONS

1. The substance must be properly identified i.e. in accordance with the specifications of Volume VI of the Rules Governing Medicinal Products in the European Community.

2. The sensitisation potential of nafcillin must be evaluated, preferably in comparison with other penicillinase-resistant penicillins.

3. Similarity between the antimicrobial activity of nafcillin and other penicillinase-restistant penicillins on the normal human gut flora must be documented.

4. Data concerning adverse effects observed in connection with clinical use of nafcillin in humans must be provided, especially as regards the effect of the substance on renal function.

5. A confirmatory analytic method must be provided. The method must be validated for all relevant bovine tissues in accordance with Volume VI of the Rules Governing Medicinal Products in the European Community. The description of the method should be provided in an internationally recognised format (e.g. the ISO 78/2)

6. The missing pages in Annex II.a.5 (p. 13-16) must be supplied.