COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PENETHAMATE (extension to pigs)

SUMMARY REPORT (3)

1. Penethamate is the diethylaminoethyl ester of benzylpenicillin. In formulations intended for veterinary use the compound is incorporated as the hydroiodide. Penethamate hydroiodide is used in intramammary products for treatment of mastitis in cows and as an injectable solution for treatment of bacterial infections in swine, cattle, horse, goat and sheep.

Currently, penethamate is included in Annex I and Annex III of Council Regulation (EEC) No 2377/90 in accordance with the following tables:

<table>
<thead>
<tr>
<th>Pharmacologically active substance(s)</th>
<th>Marker residue</th>
<th>Animal Species</th>
<th>MRLs</th>
<th>Target tissues</th>
<th>Other provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penethamate</td>
<td>Benzylpenicillin</td>
<td>Bovine</td>
<td>50 µg/kg</td>
<td>Muscle Fat Liver Kidney Milk</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 µg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 µg/kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional data in support the establishment of final MRLs concerning porcine species only have now been provided, while the use of the substance in sheep, goats and horses is no longer defended.

2. Penethamate is a prodrug from which benzylpenicillin and diethylaminoethanol are released by hydrolysis. Antimicrobial activity of the compound is exclusively related to benzylpenicillin.

3. Penethamate and procaine benzylpenicillin have similar profiles with respect to pharmacological properties. Penethamate possesses local anaesthetic activity, an effect also observed with other esters of diethylaminoethanol. In experimental animals rapid intravenous administration gives rise to anticholinergic (atropine-like) and cardiac depressing effects. These effects are not observed in connection with intramuscular injection.
4. Penethamate is a base with a pK_a of 8.4 at room temperature. At pH 7.2, 8% of the drug will be present as the uncharged molecule, while 92% will be in the cationic state.

5. Penethamate is rapidly converted into benzylpenicillin. At 37°C and pH 7.3 (physiological conditions) the half-life of penethamate in aqueous solution is 23 minutes. In tissue homogenate at 32°C half of the penethamate was hydrolysed within two hours and at 20 hours no penethamate remained.

6. Benzylpenicillin itself is of low toxicity. Consequently, the toxic effects of the penicillin esters will depend on the alcohol released by hydrolysis. Since procaine penicillin and penethamate hydroiodide both contain an esterified diethylaminoethanol group, which is released by hydrolysis, the two compounds have similar toxicological profiles.

7. In laboratory animals the LD_{50} of penethamate hydroiodide is 2000 mg/kg bw following oral or subcutaneous administration, 300 to 1650 mg/kg following intraperitoneal administration, and 30 to 90 mg/kg bw in connection with intravenous administration.

   The oral LD_{50} of diethylaminoethanol in rats is 1300 to 5600 mg/kg bw. The LD_{50} following intraperitoneal administration is 1220 mg/kg bw. Like several other aliphatic amines diethylaminoethanol is an ocular and mucous membrane irritant. The small amounts of diethylaminoethanol released by hydrolysis of penethamate make any toxicological risk from this compound appear unlikely.

8. In repeated-dose toxicity studies subcutaneous administration of penethamate hydroiodide at a dose of 200 mg/kg bw daily for 7 weeks to rats did not affect growth rate or give rise to significant changes in haematological parameters. Nor were any treatment-related abnormalities detected at autopsy at the end of the study period. Similar results were seen in a study in rabbits treated by intramuscular injection with a daily dose of 25 or 50 mg/kg bw for 20 to 36 days.

9. No formal studies have been carried out regarding reproductive toxicity, mutagenic and carcinogenic potential, immunotoxicity, and antimicrobial properties of residues in animals treated with penethamate. Since penethamate is quickly hydrolysed to benzylpenicillin within the body, there is little reason to assume penethamate to act significantly different from benzylpenicillin. Benzylpenicillin belongs to a group of substances with a long history of safe use, which, apart from their allergenic potential, does not include significant adverse effects in connection with repeated exposure.

11. No residue depletion studies were submitted as penethamate is rapidly converted into benzylpenicillin.

12. More than 400 persons have received penethamate hydroiodide in studies. From these, it appears that the toxicity of penethamate hydroiodide is low and comparable to that of procaine penicillin. Penethamate has been authorised for human use in several European countries and in the United States of America.

13. A fully validated HPLC-MS method for determination of penethamate (determined as benzylpenicillin) in porcine tissues, described in ISO 78/2 format is available. The limit of quantification is 25 µg/kg for porcine liver, kidney, muscle and fat. The limit of detection is 4.5 µg/kg in fat, 9.5 µg/kg in muscle, 6.3 µg/kg in liver and 8.3 µg/kg in kidney.
Conclusions and recommendation

Having considered that:

- penethamate is a β-lactam antibiotic which has a long history of safe use in food-producing animals and is thus a well-known substance,
- like the other penicillins, penethamate is of very low oral toxicity,
- penethamate is rapidly and completely hydrolysed to benzylpenicillin for which MRLs have been established with benzylpenicillin itself as marker residue,
- due to the rapid hydrolysis of penethamate benzylpenicillin was chosen as the marker residue for penethamate;

the Committee for Veterinary Medicinal Products recommends the inclusion of penethamate for pigs in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

<table>
<thead>
<tr>
<th>Pharmacologically active substance(s)</th>
<th>Marker residue</th>
<th>Animal species</th>
<th>MRLs</th>
<th>Target tissues</th>
<th>Other provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penethamate</td>
<td>Benzylpenicillin</td>
<td>Porcine</td>
<td>50 µg/kg 50 µg/kg</td>
<td>Muscle Fat Liver Kidney</td>
<td></td>
</tr>
</tbody>
</table>