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

EMEA/MRL/697/99-FINAL
October 1999

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PHENOXYMETHYLPENICILLIN

SUMMARY REPORT

1. Phenoxymethylpenicillin (CAS Number 87-08-1, synonym: penicillin V), the phenoxymethyl derivative of 6-aminopenicillanic acid, is a beta-lactam antibiotic produced by certain strains of *Penicillium notatum* or related fungi on culture media containing appropriate precursors.

   The potassium salt of phenoxymethylpenicillin is the active ingredient in a 10% oral powder approved for use in pigs for treatment and control of streptococcal meningitis and septicaemia caused by *Streptococcus suis*, and for treatment and control of pleuropneumonia caused by *Actinobacillus pleuropneumoniae* and of secondary pneumonia caused by *Pasteurella multocida*. The product is administered via the feed at a rate of 200 mg active substance/kg feed for 2 to 6 weeks, equivalent to a daily dose of 10 mg phenoxymethylpenicillin/kg bw.

2. Phenoxymethylpenicillin shares many characteristics with benzylpenicillin (the benzyl derivative of 6-aminopenicillanic acid) including antibacterial spectrum. It shows good activity against Gram positive aerobic and anaerobic species, but, with few exceptions, has little effect on Gram negative species, at least not in the usual therapeutic concentrations. Rupture of the beta-lactam ring results in loss of antibacterial activity. Like benzylpenicillin it is sensitive to penicillinases/beta-lactamases.

   Phenoxymethylpenicillin is relatively resistant to acidic degradation and therefore better absorbed from the gastrointestinal tract than benzylpenicillin. On an equivalent oral dose basis, the compound yields plasma concentrations in human adults 2 to 5 times greater than those of benzylpenicillin. Peak plasma concentrations of 3 to 5 µg/ml are reached within 30 to 60 minutes after an oral dose of 500 mg potassium phenoxymethylpenicillin. Once absorbed phenoxymethylpenicillin kinetically behaves in essentially the same way as benzylpenicillin.

3. No experimental data on single dose toxicity, repeated-dose toxicity, tolerance in the target species, reproductive toxicity, mutagenicity or carcinogenicity have been submitted. It is, however, well established that penicillins have a minimal direct toxicity to animals and man. The therapeutic index is more than 100, and toxic effects of non-allergic nature (bone-marrow depression, granulocytopenia and hepatitis) have only been observed after extremely high doses. Although non-allergic acute toxic effects are occasionally reported in animals and humans, many of these are the result of toxic effects of the compounds with which the penicillins are associated in the medicinal products (procaine, potassium). No teratogenic effects have been recorded for penicillins. The group is regarded as being devoid of mutagenic and carcinogenic potential.

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

4. No studies concerning the immunotoxic potential of phenoxymethylpenicillin have been submitted. For the penicillins, as a group, hypersensitivity reactions are by far the most common adverse effects noted, and penicillins are assumed to be the most common cause of drug allergy in humans. There is no convincing evidence that a single penicillin differs from the group in its potential for causing true allergic reactions, i.e. all penicillins are assumed to be cross-sensitizing and cross-reacting. The incidence of allergic reactions in connection with penicillin therapy varies from 0.7% to 10% in different studies. The major adverse effects of penicillins are acute anaphylaxis and collapse. Their incidence is thought to be 0.015 to 0.04% in humans treated with penicillin. Milder hypersensitivity reactions (urticaria, fever, angioneurotic edema) are more common. The overall prevalence of penicillin allergy in humans has been estimated to be between 3% and 10%.

   No evidence of sensitization caused by benzylpenicillin residues in food has been found. As regards the capacity of penicillins to elicit an allergic reaction in sensitized humans the overwhelming majority of penicillin preparations causing reactions were administered parenterally. However, the open literature contains 4 cases in which ingestion of less than 40 µg caused hypersensitivity reaction.

5. No experimental data have been presented demonstrating the activity of phenoxymethylpenicillin on the human gut flora. However, it is well known that changes in the intestinal flora occur in all individuals treated orally with penicillin. The degree of alteration is related directly to the quantity administered. This effect is usually of no clinical significance and the normal microflora is re-established shortly after therapy is stopped. Occasionally *supra*-infection results from the changes in the flora.

6. Phenoxymethylpenicillin has been widely used in human medicine for several decades. The recommended dosage for adults is 1000 to 3000 mg per day divided in 2 to 4 doses, for children 30 to 70 mg/kg bw divided in 2 to 3 doses. Phenoxymethylpenicillin is generally well tolerated but may occasionally cause transient nausea, diarrhoea and allergic reactions. True anaphylactic reactions are extremely rare in connection with oral administration.

7. The CVMP previously assessed benzylpenicillin and concluded that allergy was the determining factor in the safety evaluation of residues in food commodities. Because no adequate experimental data were available to establish a NOEL for allergic effects, human clinical data were used for estimating a safe level. No evidence was found of sensitization in humans caused by benzylpenicillin residues in food. It was therefore decided to base a safe level in food commodities on the ability of benzylpenicillin to provoke an allergic reaction in already sensitized humans. Although it has been reported that as little as 10 units (6 µg) of benzylpenicillin has occasionally provoked an allergic reaction the CVMP concluded that the risk to the consumer associated with oral doses up to approximately 50 units (30 µg) would be insignificant.

   At its 36th meeting in 1990 the Joint FAO/WHO Expert Committee on Food Additives (JECFA) used the same approach as the CVMP in the safety evaluation of benzylpenicillin. In the absence of adequate data to establish a NOEL, the JECFA did not, however, establish any MRL's for the compound, but instead recommended that the daily intake of benzylpenicillin from food be kept as low as practicable, and in any case below 30 µg.

   The situation for phenoxymethylpenicillin is identical to that previously encountered for benzylpenicillin, i.e. no adequate experimental data are available to establish a NOEL on which to base an ADI. In their absence it appears reasonable to evaluate phenoxymethylpenicillin in a manner identical to that employed for benzylpenicillin because of the close similarity of the two penicillins in all relevant aspects, i.e. the conclusions previously made regarding the safety to the consumer of residues of benzylpenicillin in food commodities of animal origin equally apply to phenoxymethylpenicillin as regards residues in porcine tissues.

8. Six 9-week old pigs were fed a diet containing 200 mg phenoxymethylpenicillin/kg feed corresponding to a daily dose of 10 mg phenoxymethylpenicillin/kg bw, divided in 2 doses (feedings) of 5 mg/kg bw, for 2 weeks. Blood was sampled at days 1, 3, 6, 10 and 14 of treatment.

Blood serum was assayed for phenoxymethylpenicillin by means of a microbiological method. Maximum concentrations in the range of 0.1 to 0.175 µg/ml occurred 2 hours after feeding.

A radiolabelled study in pigs with oral administration of 10 mg/day for up to 14 days showed rapid metabolism and formation of 8 metabolites. The extraction of radioactivity from tissues expressed as percent of total radioactivity was lowest in fat (16.5 to 20.5%) and ranged from 32.5 to 58.1% in other edible tissues. Profiling of tissue radioactivity in the depletion period (2 and 24 hours after final dose) revealed that the proposed marker residue (phenoxymethylpenicillin) represented 12 to 13% of total extractable radioactivity in liver and kidney, respectively. Residues (marker residue) were below the limit of quantification in fat and muscle.

In a residue depletion study 40 weaner pigs were fed a diet containing 200 mg phenoxymethylpenicillin/kg feed, intended to provide a daily dose of 10 mg active ingredient/kg bw, for 6 weeks starting at 4 weeks of age. Groups of 6 animals were sacrificed immediately after the end of treatment (day 0), and at days 1, 5 and 7 after treatment. Contents of phenoxymethylpenicillin in samples of skeletal muscle, liver, kidney and fat + skin were assayed by means of a microbiologically based method (limit of detection 50 µg/kg). At day 0 contents of phenoxymethylpenicillin were detected in kidney samples from 4 of 6 animals (up to 62 µg/kg) while samples from other tissues were negative as were all samples collected at later time points.

9. A validated analytical method based on HPLC and detection with a mass spectrometer, described in ISO 78/2 format is available. The limit of detection is 2.5 µg/kg, and the limit of quantification is 25 µg/kg for all edible tissues.

Conclusions and recommendation

Having considered that:

- the maximum permitted daily intake of 30 µg per person, agreed for penicillins in relation to the prevention of allergic reactions, also applies to phenoxymethylpenicillin due to its close similarity to benzylpenicillin,
- phenoxymethylpenicillin is rapidly metabolised and excreted,
- phenoxymethylpenicillin was identified as the marker of residue in porcine edible tissues,
- residues were below the limit of quantification for all tissues at all times, except for kidney where only negligible quantities were detected 24 hours after treatment,
- the marker residue in liver and kidney represents 12 and 13% of total residues,
- the contribution of the residues in muscle and fat to the total residue intake was considered negligible,
- the MRLs for the kidney, liver and muscle are based on the limit of quantification of the proposed routine analytical method,
- a validated routine analytical method is available for monitoring residues in edible porcine tissues;

the Committee recommends the inclusion of phenoxymethylpenicillin in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissue	Other provisions
Phenoxymethyl-penicillin	Phenoxymethyl-penicillin	Porcine	25 µg/kg 25 µg/kg 25 µg/kg	Muscle Liver Kidney	

Based on the MRL for kidney (the only tissue in which residue concentrations above the limit of quantification can be detected) and the residue depletion profile, the daily intake of phenoxymethylpenicillin residues will not exceed 30 µg/person.