European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

PHENOXYMETHYLPENICILLIN
(Extension to poultry)

SUMMARY REPORT (2)

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 to pigs 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. Benzylpenicillin was considered by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at its 36th meeting in 1990. Several cases of allergic reactions in humans following the ingestion of food containing penicillin residues were reviewed. Reports of further cases, which were not available to JECFA, had also been reported in the published literature. It was evident that penicillin residues have caused allergic reactions in consumers and that some of these reactions have been serious.

   In setting MRLs for the penicillins, the CVMP adopted the same approach as JECFA. Being aware of cases of allergic reactions at very low doses, JECFA recommended that the daily intake of benzylpenicillin from food be kept as low as practicable, and in any case below 30 µg parent drug per person. The CVMP set MRLs such that consumer intake from all foods would not exceed this 30 µg threshold. Thus, the MRLs established by the CVMP for benzylpenicillin were 50 µg/kg for edible tissues.

   In view of the close similarity of the two penicillins in all relevant aspects the conclusions previously made regarding the safety to the consumer of residues of benzylpenicillin in food commodities of animal origin were retained when the CVMP considered the use of phenoxymethylpenicillin for pigs in 1999. In this case, phenoxymethylpenicillin was identified as the marker residue in porcine tissues. The marker residue represented 12 and 13% of total residues in liver and kidney, respectively. MRLs for liver, kidney and muscle were based on the limit of quantification of the routine analytical method (25 µg/kg).

3. Currently, phenoxymethylpenicillin is included 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	

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An application has now been submitted for the extension of the existing MRLs for phenoxymethylpenicillin to poultry. The proposed indication for poultry is the treatment and control of clostridium enteritis. The proposed recommended dose is 10 to 20 mg/kg bw/day for 5 days in drinking water. The product is not intended for use in animals laying eggs for human consumption.

4. A GLP compliant pharmacokinetic study was performed in chickens after intravenous and oral administration of 15 mg phenoxymethylpenicillin potassium/kg bw. A two-compartment elimination model described the plasma concentration time-curve after intravenous administration. After oral administration, a one-compartment elimination model with first-order absorption described the plasma concentration time curves. After intravenous administration, maximum plasma concentrations obtained were around 10 mg/l, plasma clearance was calculated to be 7.1 l/h/kg and the elimination half-life was 0.58 hours. Plasma concentrations after oral administration of 15 mg phenoxymethylpenicillin/kg were above 0.1 mg/l for more than 5 hours with a maximum plasma concentration of 0.40 mg/l after 1.7 hours. Good absorption was obtained after oral administration with an absorption half-life of 0.6 hours and a calculated bioavailability of 69%.

5. A GLP compliant radiolabelled metabolism and residue depletion study was performed in 16 chickens administered orally 20 mg phenoxymethylpenicillin/kg bw for five days. Animals were slaughtered 3, 6, 12 and 24 hours after last administered dose and tissues were examined. Concentrations of phenoxymethylpenicillin in edible tissue were assayed by an HPLC/MS/MS method. Mean concentrations after 24 hours were 346 µg/kg in liver, 428 µg/kg in kidney, 122 µg/kg in skin+fat, 59 µg/kg in breast muscle, 64 µg/kg in thigh muscle and 68 µg/g in abdominal fat. The only compound that was identified in the study was parent phenoxymethylpenicillin, which was selected as marker residue due to its presence in all tissues. The ratio of marker to total residues was estimated to be 17% in muscle, 21% in abdominal fat, 14% in skin+fat, 11% in liver and 15% in kidney at 12 hours after treatment.

6. A GLP compliant non-radiolabelled residue depletion study was performed in 30 chickens administered orally 10 to 20 mg phenoxymethylpenicillin/kg bw/day for five days. Animals were sacrificed at 24, 48, 72 and 96 hours after the end of the treatment and tissues were examined with a validated LC/MS/MS method. Phenoxymethylpenicillin concentrations were lower than 25 µg/kg at any time point.

   Although the results of the radiolabelled and non-radiolabelled studies cannot be directly compared due to the differences in the time points investigated it can be concluded from the metabolite profiling of the radiolabelled study that the concentrations of the parent compound are in the same magnitude.

7. A routine analytical method was provided for chicken tissues (muscle, liver, kidney and skin with adhering fat). A comparative study using chicken and turkey (muscle, liver, kidney and skin with adhering fat) was provided to demonstrate the applicability of the chicken tissue method to turkey tissues. The study demonstrated that the method is valid for turkey muscle in terms of accuracy and repeatability. The method was based on LC/MS/MS and was developed for the determination of extractable phenoxymethylpenicillin residues. The method was described in an international recognised format, i. e. ISO 78/2 format according to the requirements of Volume 8 of the Rules Governing Medicinal Products in the European Union. The limits of quantification for phenoxymethylpenicillin in chicken tissues are 11.6 µg/kg (for muscle, liver, kidney and skin with adhering fat) and 11.2 µg/kg for turkey tissue (muscle, liver, kidney and skin with adhering fat). For chicken the limits of detection were 0.0006 µg/kg for muscle, 0.0007 µg/kg for kidney, 0.001 µg/kg for liver and 0.0009 µg/kg for skin adhered to fat. The specificity of the analytical method was investigated with regard to other antibiotics and is specific towards potential metabolites of phenoxymethylpenicillin.

Conclusions and recommendation

Having considered that:

- the maximum permitted daily intake of 30 µg parent compound 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 residue in chicken edible tissues,
- phenoxymethylpenicillin residues were below 25 µg/kg for all tissues at all time points after 24 hours,
- a validated analytical method for residue monitoring purposes in chicken tissues, and applicable to turkeys is available;

the Committee for Veterinary Medicinal Products recommends the inclusion of phenoxymethylpenicillin for poultry 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	Poultry	25 µg/kg 25 µg/kg 25 µg/kg 25 µg/kg	Muscle Skin + fat Liver Kidney	Not for use in animals from which eggs are produced for human consumption

Based on these MRL values the daily intake will represent about 42 % of the ADI.