



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CVMP/796083/2010
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Phenoxymethylpenicillin (eggs)

On 1 February 2012 the European Commission adopted a Regulation¹ establishing maximum residue limits for phenoxymethylpenicillin in eggs, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Phenoxymethylpenicillin is intended for use in poultry for the treatment and control of clostridium enteritis and administered via the drinking water.

Phenoxymethylpenicillin had maximum residue limits already established for pigs² and poultry³.

Dopharma Research B.V. submitted the application for the extension of maximum residue limits to the European Medicines Agency, on 28 September 2010.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 14 July 2011 the establishment of maximum residue limits for phenoxymethylpenicillin in eggs.

Subsequently the Commission recommended on 1 December 2011 that maximum residue limits in eggs are established. This recommendation was confirmed on 22 December 2011 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 1 February 2012.

¹ Commission Regulation (EU) No 84/2012, O.J. L30, of 02.02.2012

² Commission Regulation (EC) No 1286/2000, O.J. L145, of 20.06.2000

³ Commission Regulation (EC) No 1299/2005, O.J. L206, of 09.08.2005



Summary of the scientific discussion for the establishment of MRLs

Substance name:	Phenoxymethylpenicillin
Therapeutic class:	Anti-infectious agents/Antibiotics
Procedure number:	EU/10/181/DOP
Applicant:	Dopharma Research B.V.
Target species:	Chicken (eggs)
Intended therapeutic indication:	Necrotic enteritis caused by <i>Clostridium perfringens</i>
Route(s) of administration:	Oral via drinking water

1. Introduction

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.

In pigs phenoxymethylpenicillin is administered via the feed 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*. In poultry the substance is administered via the drinking water for the treatment and control of clostridium enteritis.

The CVMP has previously assessed the consumer safety of phenoxymethylpenicillin and concluded that similarly to the evaluation of benzylpenicillin the intake of residues from food should be kept as low as practicable, and in any case below 30 µg of parent compound per person per day.

Currently phenoxymethylpenicillin is included in table 1 of the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009 in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Phenoxymethylpenicillin	Phenoxymethylpenicillin	Porcine	25 µg/kg 25 µg/kg 25 µg/kg	Muscle Liver Kidney	NO ENTRY	Anti-infectious agents/Antibiotics
		Poultry	25 µg/kg 25 µg/kg 25 µg/kg 25 µg/kg	Muscle Skin and fat Liver Kidney	Not for use in animals from which eggs are produced for human consumption	

An application has now been submitted for the extension of the MRLs for phenoxymethylpenicillin to eggs. The proposed indication for chickens and laying hens is necrotic enteritis caused by *Clostridium perfringens*. The proposed recommended doses are 13.5 to 20 mg/kg bw/day for five days administered via the drinking water.

2. Scientific risk assessment

2.1. Safety assessment

Phenoxymethylpenicillin was previously assessed by the CVMP and in view of the close similarities between benzylpenicillin and phenoxymethylpenicillin the conclusions of the CVMP regarding the safety of the consumer of residues of benzylpenicillin in food commodities of animal origin were retained with regard to phenoxymethylpenicillin. In line with the Joint FAO/WHO Committee on Food Additives (JECFA) evaluation the conclusions were based on the potential for allergic reactions and recommended that the daily intake of residues from food should be kept as low as practicable, and in any case below 30 µg of parent compound.

Therefore, no further assessment regarding the safety of the substance is required for the purpose of this extension application.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

A GLP compliant pharmacokinetic study was available 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%.

2.2.2. Residue depletion studies

A GLP-compliant residue study in eggs was performed using 48 laying hens administered a single dose of 100 mg/kg phenoxymethylpenicillin orally by drenching. Eggs were collected daily from all animals until slaughter. Animals were slaughtered in groups of six, following 6, 24, 48, 72, 96, 168, 192 and 216 hours after drug administration. Egg follicles and eggs in the oviduct were in addition collected from slaughtered animals. Albumen (egg white) and egg yolk from collected eggs were examined, as well as the three largest growing follicles from each slaughtered animal and eggs sampled from the oviduct separated into white and yolk.

The analytical method used was LC-MS/MS with a limit of quantification (LOQ) in yolk and albumen of 2.6 µg/kg. The residues in the yolk and albumen were analysed separately with two different analytical procedures, which have been validated according to the levels seen in the depletion studies and a lower range than applied for the routine testing.

The fastest absorption and depletion was found in the albumin of collected eggs where concentrations from 2.8 to 37 µg/kg were found in eggs collected one day after drug administration. Detectable phenoxymethylpenicillin concentrations in albumin were only found in one egg collected at day two. In yolk of collected eggs, concentrations above the limit of quantification were only detected in two eggs at day one but were measured in almost all eggs at day two from 4.2 to 26.2 µg/kg, which was the day with maximum concentrations. At day five, all eggs collected had concentrations below the limit of quantification in yolk. Similar distribution pattern was found in eggs collected in the oviduct of slaughtered animals, but at higher concentrations because sampling times were earlier than in collected eggs (hours instead of days). Highest overall concentrations were found in follicles collected six hours after drug administration with concentrations up to 320 µg/kg. Concentrations then rapidly depleted below the limit of quantification at 96 hours.

Another GLP-compliant study was performed using 16 laying hens administered phenoxymethylpenicillin in drinking water during five consecutive days at a daily dose of 20 mg/kg. Eggs were collected daily from first day of medication until seven days after the end of medication. Phenoxymethylpenicillin concentrations in yolk and albumen were measured separately using the same method as above.

Highest concentrations of phenoxymethylpenicillin were found in egg albumen during drug administration and were present at quantifiable concentrations from the second day of drug administration. After the end of drug administration residues depleted very fast and were only sporadically detected above the limit of quantification in a few eggs. Concentrations in yolk were low during phenoxymethylpenicillin administration and were first detected at day 4 during phenoxymethylpenicillin administration. Also here, residues depleted fast and were mostly below the limit of quantification in the next seven days after the end of drug administration.

None of the measured samples from either albumen or yolk had concentrations above 25 µg/kg.

Phenoxymethylpenicillin was identified as the marker residue in poultry tissues and was also retained as the marker residue in eggs.

No radiolabelled study in eggs was available and therefore the ratio of marker to total residues cannot be established. Similar to the approach taken for the evaluation of phenoxymethylpenicillin in pigs and poultry tissues, the metabolites were not considered relevant for the evaluation of the safety of the consumer, and therefore the absence of a radiolabelled study is accepted.

2.2.3. Monitoring or exposure data

No data available.

2.2.4. Analytical method for monitoring of residues

A method for routine analysis of phenoxymethylpenicillin residues in whole eggs was provided. The principle of the method applied for whole eggs is similar to the two methods applied for the analysis of yolk and albumen used for the depletion study. The analytical method is based on a solid phase extraction followed by injection on a HPLC column with MS/MS detector. The analytical method for routine testing has been validated according to the requirements of Volume 8 of the Rules Governing Medicinal Products in the European Union.

The validated concentration range of the routine method includes 5, 25 and 100 µg/kg (20% up to 400% of the proposed MRL of 25 µg/kg).

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2.2.5. Findings of EU or international scientific bodies

No data available.

3. Risk management considerations

3.1. Potential effects on the microorganisms used for industrial food processing, if relevant

No data were provided in relation to the potential effects on the microorganisms used for industrial food with this application for the extension of the existing MRLs to eggs. Such effects on microorganisms are not considered relevant for processing of eggs.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits, if relevant

None.

3.3. Elaboration of MRLs

In the residue depletion study performed according to the recommended dose, residues of phenoxymethylpenicillin in eggs depleted rapidly, and were below the limit of quantification of the analytical method (2.6 µg/kg) in most eggs within seven days after the end of treatment and below the suggested MRL value of 25 µg/kg at all times.

The same MRL value as established in tissues of pigs and poultry of 25 µg/kg can be proposed for eggs.

Taking into account the existing MRLs for tissues and the proposed MRL for eggs the theoretical daily intake of residues would be as follows:

Edible tissue or products	Daily consumption (kg)	MRL proposal (µg/kg)	Amount per edible tissue or product (µg)
Muscle	0.30	25	7.5
Skin and fat	0.09	25	2.25
Liver	0.10	25	2.5
Kidney	0.01	25	0.25
Eggs	0.10	25	2.5
Total			15

Based on these MRLs the theoretical maximum daily intake from poultry tissues plus eggs is 15 µg phenoxymethylpenicillin, which would account for 50% of the established maximum permitted daily intake for the substance of 30 µg/person/day.

3.4. Considerations on possible extrapolation of MRLs

Article 5 of Regulation (EU) No 470/2009 specifies that:

“With a view to ensuring the availability of authorised veterinary medicinal products for conditions affecting food-producing animals, the Agency, while ensuring a high level of protection of human health, shall, when carrying out scientific risk assessments and when drawing up risk management recommendations, consider using maximum residue limits established for a pharmacologically active substance in a particular foodstuff for another foodstuff derived from the same species, or maximum residue limits established for a pharmacologically active substance in one or more species for other species”.

In line with the above article the CVMP considered the possibility of using the maximum residue limits established for phenoxymethylpenicillin in pigs and poultry in other species/food commodities.

However, no pharmacokinetic or residue data were provided for ruminant tissues or milk, horses, rabbits, fish or honey. In the absence of these data no scientific grounds were identified on which to base a conclusion that the pharmacokinetic behaviour of the substance in these species/food commodities will be similar to that seen in pigs and poultry. Consequently no conclusions could be drawn on safe MRLs to be established in these species/food commodities and therefore no extrapolation of the MRLs is recommended.

3.5. Conclusions and recommendation for the establishment of maximum residue limits

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 retained as the marker residue for eggs,
- A validated analytical method is available for monitoring the marker residue in whole eggs,

The Committee for Veterinary Medicinal Products for Veterinary Use recommends the establishment of a maximum residue limit for phenoxymethylpenicillin in eggs and the modification of the current entry for phenoxymethylpenicillin in table 1 of the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009, in accordance with the following table:

Pharmaco- logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Phenoxymethyl- penicillin	Phenoxymethyl- penicillin	Porcine	25 µg/kg 25 µg/kg 25 µg/kg	Muscle Liver Kidney	NO ENTRY	Anti-infectious agents/ Antibiotics
		Poultry	25 µg/kg 25 µg/kg 25 µg/kg 25 µg/kg 25 µg/kg	Muscle Skin and fat Liver Kidney Eggs		

4. Background information on the procedure

Submission of the dossier 28 September 2010

Steps taken for assessment of the substance

Application validated:	12 October 2010
Clock started:	13 October 2010
List of questions adopted:	9 February 2011
Consolidated response to list of questions submitted:	15 April 2011
Clock re-started:	16 April 2011
CVMP opinion adopted:	14 July 2011