



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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EMA/CVMP/350415/2014  
Committee for Medicinal Products for Veterinary Use

## European public MRL assessment report (EPMAR) Gamithromycin (porcine)

On 30 January 2015 the European Commission adopted a Regulation<sup>1</sup> establishing maximum residue limits for gamithromycin in porcine, 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.

Gamithromycin is used in non-lactating cattle for the treatment of bovine respiratory disease (BRD), caused by the bacteria *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. In porcine species gamithromycin is intended for intramuscular use in the treatment of respiratory disease.

Gamithromycin had maximum residue limits already established<sup>2</sup> for bovine species.

MERIAL submitted the application for the extension of maximum residue limits to the European Medicines Agency, on 09 July 2013.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 10 July 2014 the extension of maximum residue limits for gamithromycin to porcine species.

Subsequently the Commission recommended on 15 November 2014 that maximum residue limits in porcine are established. This recommendation was confirmed on 6 December 2014 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 30 January 2015.

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<sup>1</sup> Commission Implementing Regulation (EU) No 2015/150, O.J.L26, of 31.01.2015

<sup>2</sup> Commission Implementing Regulation (EU) No 581/2009, O.J. L175, of 04.07.2009



# Summary of the scientific discussion for the establishment of MRLs

Substance name:	Gamithromycin
Therapeutic class:	Anti-infectious agents / Antibiotics
Procedure number:	EMA/V/MRL/003158/EXTN/0002
Applicant:	Merial
Target species:	Porcine
Intended therapeutic indication:	Swine respiratory disease
Route(s) of administration:	Intramuscular

## 1. Introduction

Gamithromycin is a semi-synthetic macrolide (CAS No 145435-72-9) prepared by fermentation followed by organic synthesis. The substance is a member of the azalide subclass of macrolide antibiotics consisting of a 15-membered macrocyclic lactone ring.

Gamithromycin is used in non-lactating cattle for the treatment of bovine respiratory disease (BRD), caused by the bacteria *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.

Gamithromycin is not used in human medicine.

Gamithromycin was previously assessed by the CVMP and an ADI of 10 µg/kg bw, i.e 600 µg/person was established.

Currently, gamithromycin 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:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Gamithromycin	Gamithromycin	Bovine	20 µg/kg 200 µg/kg 100 µg/kg	Fat Liver Kidney	Not for use in animals producing milk for human consumption	Anti-infectious / Antibiotics

Merial submitted the application for the extension of maximum residue limits to porcine species to the European Medicines Agency, on 9 July 2013. The substance is proposed for use in pigs at a dose of 6 mg/kg bw, administered intramuscularly, for the treatment of swine respiratory disease.

## 2. Scientific risk assessment

### 2.1. Safety assessment

The CVMP has previously assessed the consumer safety of gamithromycin and established a toxicological ADI of 10 µg/kg bw, i.e 600 µg/person, based on the NOEL of 1 mg/kg bw/day from a 52-week repeated dose toxicity study in dogs and applying a safety factor of 100.

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

## **2.2. Residues assessment**

### **2.2.1. Pharmacokinetics in target species**

In a preliminary study the pharmacokinetic profile of gamithromycin was examined after intravenous, intramuscular and subcutaneous administration of the recommended dose of 6 mg/kg bw.

Gamithromycin was absorbed rapidly and completely after intramuscular administration but to a lesser extent after subcutaneous administration. The substance was distributed widely to tissues with a volume of distribution of 38 l/kg bw and was eliminated slowly with a half-life of proximately 25 hours.

In a pivotal pharmacokinetic study gamithromycin was examined in 40-55 kg pigs after a single intravenous dose (6 mg/kg bw) or a single intramuscular dose (3, 6, or 12 mg/kg bw). Based on the results of this study, gamithromycin administered once to swine by the intramuscular route demonstrated fast absorption, high bioavailability, approximate dose proportionality of  $AUC_{inf}$ , rapid and extensive distribution to tissues, and a rather slow elimination rate with a terminal half-life of 76-94 hours. The longer half-life noted in this study compared to in the preliminary study was considered to reflect the different sampling protocols used in the two studies – the pivotal study included sampling at later time points and so allowed derivation of the terminal half-life.

### **2.2.2. Residue depletion studies**

The depletion of residues was examined in two studies. In the first study the depletion of gamithromycin residues was examined in pigs following an intramuscular injection of 6 mg/kg bw of 6-<sup>3</sup>H gamithromycin. Eleven barrows (castrated animals) and 11 gilts (females) were administered the radiolabelled drug and groups of pigs were slaughtered at 1, 2, 3, 5, 7, 10 and 15 days after treatment with samples of bile, plasma, liver, kidney, muscle, skin, fat and injection site (inner and outer perimeter) collected.

Quantitative collection of faeces and urine was performed in two barrows. Most of the radioactivity was found in faeces (45-51% of dose) with the remainder in urine (11-16% of dose). Over 90% of excreted radioactivity was obtained by day 6 after drug administration. The low recovery of <sup>3</sup>H-gamithromycin in excreta may have been due to incomplete collection of urine and faeces and/or the long half-life of gamithromycin.

At the earlier sampling points, extremely high concentrations of gamithromycin were found in bile showing that biliary excretion is an important route of elimination. This also explains the high concentration of gamithromycin and associated radioactivity found in faeces. As in cattle, the major component in tissues was the parent compound. The main metabolites were declid (the metabolite formed by the loss of the dideoxy sugar moiety, cladinose) and the translactone derivative of gamithromycin, with smaller quantities of minor metabolites.

Drug residues (total residues) rapidly depleted in all tissues and bile. Kidney was the target tissue with the highest initial drug concentration. Total residues in kidney were 1.02, 0.33 and 0.24 µg equivalents/g at 7, 10 and 15 days after administration and parent compound concentrations in kidney at these time points were 0.57, 0.14 and 0.04 µg/g, leading to parent to total ratios between 0.15 and 0.55. In liver the figures for total residues at 7, 10 and 15 days after administration were 0.71, 0.20 and 0.28 µg equivalents/g and for parent compound the figures were 0.275, 0.05 and less than 0.010 µg/g. In muscle

tissue, total residues concentrations were 0.06, 0.03 and 0.02 µg/g at 7, 10 and 15 days respectively, whereas parent compound concentrations were 0.04 at day 7 days and below limit of quantification thereafter. Similar levels were seen in the fat tissue. Total injection site residues were 0.98, 0.52 and 0.23 µg /g on day 7, 10 and 15 respectively. All residues in the injection site were parent compound.

The ratio of marker to total residue at day 7 was 0.56 in kidney, 0.39 in liver, 1 in muscle 1 in skin and fat and 1 in injection site muscle.

The second study was conducted with the commercial injectable formulation (15% gamithromycin w/v) at a dose of 6 mg/kg bw and was performed in line with VICH GL 48 on marker residue depletion studies to establish product withdrawal periods. Fifty pigs (25 castrated males, 25 female) were included in the study. The animals were approximately 3.5 months old and weighed between 40.2 and 56.2 kg. Animals were sacrificed at 1, 2, 4, 7, 10, 15, 22 and 30 days after administration and samples of liver, kidney, muscle and skin and fat were collected. The processed tissues were analysed for gamithromycin using a validated LC-MS/MS method with a limit of quantification of 50 µg/kg tissue. Data showed that gamithromycin concentrations were below the limit of quantification in all animals for muscle from day 7, for skin and fat from day 10, for liver and kidneys from day 15 and, for injection site ring from day 22 on, and were below limit of quantification for core injection site on day 30. The gamithromycin concentrations in edible tissues of treated swine followed a similar pattern to that reported in the radio-residue metabolism study.

### **Selection of marker residue and ratio of marker to total residues**

From the results of the radiolabelled study it was concluded that gamithromycin should be retained as the marker residue.

Marker to total residues ratios were based on residue levels seen at day 7 after administration. The ratios are 0.56 in kidney, 0.39 in liver, 1.0 in muscle, 1.0 in skin and fat and 1.0 in injection site muscle.

### **2.2.3. Monitoring or exposure data**

No monitoring or exposure data other than that described elsewhere in this report were available.

### **2.2.4. Analytical method for monitoring of residues**

The analytical method for analysis of gamithromycin residues in swine liver, kidney, heart, skin and fat (in natural proportions), and muscle is well described in an internationally recognised format. The method is based on extraction from tissue via homogenization with phosphate buffer, followed by hexane partition and solid phase extraction. The sample extracts are analysed by LC-MS/MS using an internal standard (deuterated (D5) gamithromycin). The method has been validated over the concentration range of 50–10,000 µg/kg for liver, kidney, heart, and muscle including the injection site and 50–2,500 µg/kg for skin with fat. The limit of quantification is 50 µg/kg.

The method has been validated in line with the requirement of Volume 8 of The rules governing medicinal products in the European Union and VICH GL 49 on validation of analytical methods used in residue depletion studies.

The relevant European Reference Laboratory has reviewed the proposed analytical methods and is in agreement with the above conclusions.

### 2.2.5. Findings of EU or international scientific bodies

No relevant reports relating to residues of gamithromycin in porcine species were identified.

## 3. Risk management considerations

### 3.1. Potential effects on the microorganisms used for industrial food processing

The substance is not intended for use in dairy animals and therefore potential effects in dairy products were not investigated.

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

Residue depletion data demonstrate that gamithromycin levels in carcass tissues (i.e. fat and muscle) other than injection site muscle were low compared to levels in liver and kidney. Residues in muscle depleted to below the limit of quantification within a few days. However, in order to enable residue control of meat when only lean cuts of muscle are available a MRL for muscle is required. For this substance the approach described in the CVMP revised reflection paper on injection site residues: consideration for risk assessment and residue surveillance (EMA/CVMP/520190/2007-Rev.1) was considered appropriate for derivation of the muscle MRL.

### 3.3. Elaboration of MRLs

According to the non-radiolabelled residue depletion study tissue concentrations (except non-injectable muscle) can be quantified up to 7 days after drug administration in all tissues except muscle. Based on residues observed at this timepoint and taking the ADI of 600 µg/person into account, the following MRLs are proposed, with the MRL for muscle set based on twice the limit of quantification of the analytical method.

Tissue	MRL (µg/kg)
Muscle	100
Skin and fat	100
Liver	100
Kidney	300

In line with the approach described in the CVMP revised reflection paper on injection site residues, and in light of the slow depletion of residues from the injection site, an "Injection Site Residue Reference Value" (ISRRV), which specifies the level of residues at the injection site that can be considered as safe, of 1700 µg/kg is established. This value is not intended for use in routine residue surveillance but provides a value to be used by competent authorities when setting withdrawal periods for gamithromycin containing products.

Withdrawal periods for injectable gamithromycin products should ensure that residue levels present in non-injection tissues do not exceed the MRLs for muscle, liver, kidney and skin and fat, respectively, and that residue levels present in injection site muscle do not exceed the ISRRV of 1700 µg/kg.

### Calculation of residues intake

Edible tissue or products	Daily consumption (kg)	MRL proposal µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product (µg)
Muscle	0.30	100	1	30
Fat and skin in natural proportions	0.05	100	1	5
Liver	0.10	100	0.39	25.6
Kidney	0.05	300	0.56	26.8
Total				87.4

Based on the above figures the maximum theoretical consumer intake represents 15 % of the ADI (of 600 µg/person). When the calculation is performed taking into account the ISRRV of 1700 µg/kg, the consumer intake represents 94.6% of the ADI.

### 3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No 470/2009 the CVMP considered the possibility of extrapolating its recommendation on maximum residue limits for gamithromycin to other food producing species and commodities. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

Animal species/ food commodities	Extrapolation possible (Yes/No)	Justification
Sheep	No	<p>Existing data indicate that the pattern of metabolites seen in rats, dogs, cattle and pigs is similar and it can be expected that the parent compound would be a suitable marker residue in sheep tissues. However, no specific pharmacokinetic or residue data were available for sheep and therefore the assumption that the parent compound would be a suitable marker residue could not be confirmed and the marker to total residues ratios could not be derived.</p> <p>Sheep meat is consumed on a regular basis and in large quantities. Species specific data are therefore considered necessary to allow adequate evaluation of the risk to consumer safety proposed by residues in sheep tissues.</p> <p>No data are available to demonstrate that the analytical method used for monitoring of residues in pigs or cattle tissues is applicable for monitoring of residues in sheep tissues.</p>
Goats	No	<p>Existing data indicate that the pattern of metabolites seen in rats, dogs, cattle and pigs is similar and it can be expected that the parent compound would be a suitable marker residue in goat tissues. However, no specific pharmacokinetic or</p>

		<p>residue data were available for goat and therefore the assumption that the parent compound would be a suitable marker residue could not be confirmed.</p> <p>No data are available to demonstrate that the analytical method used for monitoring of residues in pigs or cattle tissues is applicable for monitoring of residues in goat tissues.</p> <p>The numerical MRLs established for cattle and pigs are different and there are no data to demonstrate which values would be most appropriate for sheep.</p>
Milk	No	<p>No data are available that would allow conclusions to be drawn on the appropriate marker residue or marker to total residues ratio to use in milk. Milk is consumed on a regular basis and in large quantities and consequently data on residues in this commodity are considered necessary in order to allow adequate evaluation of the risk to consumer safety posed by residues in milk.</p> <p>No analytical method for monitoring of residues in milk was available for evaluation.</p>
Poultry (including eggs)	No	<p>Metabolism can be significantly different in poultry compared to pigs. Consequently species specific metabolism and residue data are considered necessary to allow adequate evaluation of the risk to consumer safety posed by residues in poultry-derived food commodities.</p> <p>No analytical method for monitoring of residues in poultry tissues (or eggs) was available for evaluation.</p>
Horses	No	<p>Existing data indicate that the pattern of metabolites seen in rats, dogs, cattle and pigs is similar and it can be expected that the parent compound would be a suitable marker residue in horse tissues. However, no specific pharmacokinetic or residue data were available for horses and therefore the assumption that the parent compound would be a suitable marker residue could not be confirmed.</p> <p>No data are available to demonstrate that the analytical method used for monitoring of residues in pigs or cattle tissues is applicable for monitoring of residues in horse tissues.</p> <p>The numerical MRLs established for cattle and pigs are different and there are no data to demonstrate which values would be most appropriate for horses.</p>
Rabbits	No	<p>Existing data indicate that the pattern of metabolites seen in rats, dogs, cattle and pigs is similar and it can be expected that the parent compound would be a suitable marker residue in rabbit tissues. However, no specific pharmacokinetic or</p>

		<p>residue data were available for rabbits and therefore the assumption that the parent compound would be a suitable marker residue could not be confirmed.</p> <p>No data are available to demonstrate that the analytical method used for monitoring of residues in pigs or cattle tissues is applicable for monitoring of residues in rabbit tissues.</p> <p>The numerical MRLs established for cattle and pigs are different and there are no data to demonstrate which values would be most appropriate for rabbits.</p>
Fin fish	No	<p>Metabolism is generally less complicated in fish than in mammals. Consequently, as the marker residue is the parent compound in pigs it can be assumed that gamithromycin would also be a suitable marker for fish meat. However, no analytical method for monitoring of residues in fish meat was available for evaluation.</p>
Honey	No	<p>Residue depletion in honey does not occur through metabolism and consequently conclusions drawn from data in other food products cannot be extrapolated to honey. Honey specific data are required in order to allow adequate evaluation of the risk to consumer safety posed by residues in honey.</p> <p>No data are available to demonstrate that the analytical method used for monitoring of residues is applicable for monitoring of residues in honey.</p>

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

Having considered that:

- the toxicological ADI of 10 µg/kg bw (i.e. 600 µg/person) was established as the overall ADI for gamithromycin,
- the parent compound was retained as the marker residue,
- the ratios of marker to total residues calculated at 7 days were 1 in muscle, 1 in skin and fat, 0.39 in liver, 0.56 in kidney and 1 in injection site muscle,
- residue concentrations in fat and muscle depleted rapidly; the MRL for muscle was set at twice the limit of quantification,
- an injection site residues reference value (ISRRV) of 1700 µg/kg was established for porcine species,
- a validated analytical method for the monitoring of residues of gamithromycin in edible porcine tissues (liver, kidney, muscle and skin and fat) is available,
- for the purpose of monitoring of residues of gamithromycin it is recommended that, where the entire carcass is available, liver or kidney should be sampled in preference to muscle or skin and fat as



residues in liver and kidney deplete more slowly than residues in muscle and skin and fat and so will provide a better basis for verifying compliance with the withdrawal period;

the Committee recommends the establishment of maximum residue limits for gamithromycin in porcine species accordance with the following table:

Pharmaco- logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Gamithromycin	Gamithromycin	Porcine	100 µg/kg 100 µg/kg  100 µg/kg 300 µg/kg	Muscle Skin and fat in natural proportions  Liver Kidney	NO ENTRY	Anti-infectious agents / Antibiotics

## Background information on the procedure

Submission of the dossier	9 July 2013
Steps taken for assessment of the substance	
Application validated:	14 August 2013
Clock started:	15 August 2013
List of questions adopted:	12 December 2013
Consolidated response to list of questions submitted:	4 April 2014
Clock re-started:	12 April 2014
CVMP opinion adopted:	10 July 2014