10 December 2015
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for ZACTRAN for pigs (EMEA/V/C/000129/X/0027)

International non-proprietary name: gamithromycin

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Product profile

Invented name:	ZACTRAN
Active Substances:	Gamithromycin
Target Species:	Cattle and Pigs
Pharmaceutical Form:	Solution for injection
Strength:	150 mg/ml
Therapeutic Indication:	Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. The presence of the disease in the herd should be established before metaphylactic use. Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Haemophilus parasuis*.
ATCvet code:	QJ01FA95
Pharmacotherapeutic group:	Antiinfectives for systemic use
Applicant:	Merial

Introduction

On 19 August 2014, the applicant Merial submitted an application for an extension to the marketing authorisation to the European Medicines Agency (the Agency), in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I point 3 thereof.

ZACTRAN (active substance gamithromycin) was first authorised in the Community on 24 July 2008, and is available as a solution for injection for cattle (subcutaneous use) for the treatment and prevention of respiratory disease. This extension application is for a new food-producing target species, pigs.

The rapporteur appointed is Christian Friis and the co-rapporteur is Jeremiah Gabriel Beechinor.

The indication for the new target species, pigs, is: "Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Haemophilus parasuis*." The route of administration is intramuscular for a single dose of 6 mg/kg bw, and the withdrawal period for pig meat and offal is 16 days.

On 10 December 2015, the CVMP adopted an opinion and CVMP assessment report.

On 10 February 2016, the European Commission adopted a Commission Decision for granting an extension to the marketing authorisation for ZACTRAN.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (RA-SOP-060 v.6; date: 14 April 2014) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country. There are no outstanding issues.

Manufacturing authorisations and inspection status

The active substance and the finished product are manufactured in the European Economic Area (EEA).

A valid GMP certificate for the dosage form manufacturing site and a GMP declaration for the active substance manufacturing sites are provided. Hence, no GMP inspections are deemed necessary within the scope of this application.

The last audit of a manufacturing site of the active substance was on 19 November 2009 and exceeds 3 years; however, no batch of gamithromycin has been manufactured at that site since July 2012. Merial

stated that should any batch of gamithromycin be manufactured at this site, an audit of the site will be performed by the site responsible for batch release (Merial, Toulouse, France).

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certificates of the manufacturing sites were considered in line with legal requirements.

Part 2 - Quality

This is an application for an extension to the existing ZACTRAN marketing authorisation to add a new target species (pigs).

There are no changes to the quality of the product as the strength, pharmaceutical form (solution for injection) and presentations remain exactly the same as already authorised for cattle. The dosage (6 mg/kg bodyweight) also remains the same. Therefore this application does not affect the quality part of the dossier. Cross-reference has been made to data that have already been submitted and accepted for this product.

Although the dose volumes used for treating pigs and piglets will be considerably smaller than the dose volumes used for treating cattle, data have been provided which demonstrate the suitability of the closures to withstand the possible increased number of punctures to the stopper.

Part 3 – Safety

No new safety studies in addition to those already reviewed for the cattle presentation have been conducted with regards to single dose toxicity, repeat dose toxicity, reproductive toxicity, genotoxicity, carcinogenicity or special studies, and cross-reference is made to data that have already been submitted and accepted for previous application(s). Given the scope of this application, this was considered acceptable.

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Tolerance in the target species of animal

See part 4.

User safety

No new data on user safety have become evident since the original user safety assessment was prepared to support the initial application for ZACTRAN in cattle. However, since then, the CVMP Guideline on user

safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/2003-Rev.1) has been revised and, consequently, a new user risk assessment has been provided in compliance with the revised guideline. The safety warnings in the product literature were confirmed at renewal of the marketing authorisation for ZACTRAN in 2013.

The product is intended to be used parenterally in pigs (intramuscular use) as well as in the authorised target species cattle (subcutaneous use), and at the same dosage (mg/kg) and the same treatment duration as for cattle. Therefore, user exposure to the formulation when used in pigs is not expected to be greater than user exposure associated with use in cattle. Consequently, the existing user safety statements that were agreed in relation to use in cattle are equally applicable to use in pigs. The CVMP concluded that the extension does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the VICH GL 6. Predicted environmental values in soil for intensive reared groups of pigs are all below 100 µg/kg. Consequently no further studies are required.

Based on the data provided the ERA can stop at Phase I. ZACTRAN is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Cross-reference has been made to toxicity, genotoxicity, carcinogenicity and special studies, which have been submitted and assessed as part of previous applications for the product, which is considered acceptable.

A user risk assessment report in line with current guidance was provided, and the extension does not pose an unacceptable risk to the user when used in accordance with the SPC.

A new Phase I environmental risk assessment (ERA) was provided and the extension for pigs is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

In the pivotal studies the final formulation of ZACTRAN has been used. ZACTRAN contains 150 mg gamithromycin/ml and is recommended to be used in pigs at a single dose of 6 mg/kg bw intramuscularly.

Pharmacokinetics

In a pivotal pharmacokinetic study gamithromycin was administered to pigs (40–55 kg bw) as a single intravenous dose (6 mg/kg bw) or as a single intramuscular dose (3, 6, or 12 mg/kg bw) of gamithromycin. Based on the results of this study, gamithromycin administered once to swine by the intramuscular route demonstrated rapid 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 74– 94 hours.

Depletion of residues

The depletion of residues has been examined in two studies.

In the first study the depletion of residues of gamithromycin was examined in pigs using an intramuscular injection of 6 mg/kg bw of 6-^{3}H gamithromycin. Eleven barrows (castrated animals) and 11 females received radiolabelled gamithromycin. Group of pigs were slaughtered at 1, 2, 3, 5, 7, 10 and 15 days post treatment, and samples of bile and plasma, liver, kidney, muscle, skin, fat and injection site (inner and outer perimeter) were 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).

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.

Gamithromycin was identified as the marker residue. Drug residues (total residues) rapidly depleted in all tissues and bile. Kidney was the target tissue with the highest initial concentration. Total residues in kidney was 1.02, 0.33 and 0.24 µg equivalents/g at 7, 10 and 15 days post treatment and for parent compound 0.57, 0.14 and 0.04 µg/g, leading to marker to total ratios between 0.15–0.55 µg/g. In liver the figures for total residue were 0.71, 0.20 and 0.28 µg equivalents/g and for parent compound 0.275, 0.05 and less than 0.010 µg/g. In muscle tissue, total residues were 0.06, 0.03 and 0.02 µg/g at 7, 10 and 15 days respectively whereas the parent compound was 0.04 µg/g at day 7 days and below limit of quantification thereafter. Similar figures occurred 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/fat and 1 in injection site muscle.

The second study was conducted in 50 pigs (25 castrated males, 25 females, approximately 3.5 months old, weight between 40 and 56 kg) using an intramuscular injection of gamithromycin at the dose of 6 mg/kg bw. Animals were sacrificed at 1, 2, 4, 7, 10, 15, 22 and 30 days after dosing and samples of liver, kidney, muscle and skin/fat were collected. The processed tissues were analysed for gamithromycin using a validated LC-MS/MS PKDM method with a limit of quantification of 50 ng/g tissue. Data showed that gamithromycin concentrations were below the limit of quantitation in all animals for muscle from Day 7, for skin/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 the similar order as reported in the radio-residue metabolism study.

MRLs

The MRL status of the constituents is as follows:

On 10 July 2014, the CVMP recommended the extension of the entry for gamithromycin in table 1 of the annex to Commission Regulation (EU) No 37/2010 to porcine species, in accordance with the table below. The Commission Implementing Regulation (EU) 2015/150 was published in the Official Journal of the European Union on 30 January 2015.

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

The CVMP established an injection site residues reference value (ISRRV) of 1700 µg/kg for porcine species.

The excipients listed in section 6.1 of the SPC (i.e. monothioglycerol, succinic acid and glycerol formal) are allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required when used as in this product.

Analytical method

The analytical method for monitoring of residues for gamithromycin in pig tissues has been evaluated during the MRL evaluation and reviewed by the relevant European reference laboratory. The method was considered validated and adequate for monitoring of residues.

Withdrawal periods

For calculating the withdrawal period for liver, kidney, fat and muscle, the "statistical method" was used; however, the withdrawal period for the injection site was calculated using the "alternative approach" method. The use of the "alternative approach" for determination of the injection site withdrawal period was justified on the basis that application of the "statistical approach" would not be valid for this data set (homogeneity of variances assumption not satisfied, which may be due to a large variation in residues at day 4 and day 15). Injection site residues in all animals slaughtered at Day 10 were below the injection site residue reference value (ISRRV) of 1700 µg/kg. A 30% safety span was proposed, resulting in a withdrawal period for injection site of 13 days.

However, in line with the CVMP Note for guidance: Approach towards harmonisation of withdrawal periods (EMA/CVMP/036/95), CVMP was of the opinion that the statistical method for the determination of the withdrawal period can be used in cases where the statistical analysis supports a (log-)linear regression of the data. When one or more of the statistical tests fail, careful consideration should be given to the reasons for this, and an informed decision should be taken on the applicability of the statistical method. Therefore, the statistical method should not be rejected automatically in such cases.

In this application the homogeneity of variances was not satisfied with either Bartlett or Cochran tests which required $p>0.05$. However, in Cochran test the p-value was $0.01<p<0.05$. Considering the injection site residue data it appears that the statistical method gives a more thorough picture of the depletion than the alternative approach. The CVMP, therefore, agreed to follow the statistical approach methodology, which results in a withdrawal time for pig meat and offal of 16 days.

Overall conclusions on the residues documentation

A well-conducted residue study which has been assessed in the MRL procedure was presented. Data shows the gamithromycin is the marker substance. Based on the MRLs for pigs, a withdrawal period of 16 days for pig meat and offal has been established.

Part 4 – Efficacy

Pharmacodynamics

Gamithromycin is a semisynthetic azalide which has a 15-membered semisynthetic lactone ring with a uniquely positioned alkylated nitrogen atom at the 7a-position. Azalides, in common with other macrolides, disrupt protein synthesis by reversibly binding to 50S subunits of the ribosome, thereby inhibiting the transpeptidation and translocation process and causing premature detachment of incomplete polypeptide chains. Macrolides are generally bacteriostatic agents but they may also be bactericidal. Gamithromycin acts in a bactericidal manner.

The bacterial isolates (*P. multocida, A. pleuropneumoniae*, *B. bronchiseptica* and *H. parasuis* isolated between 2010 and 2012*)* were appropriately selected and considered to be current representatives of swine respiratory pathogens in Europe. MICs were determined in compliance with the current CVMP Guideline on the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01).

MIC data for relevant swine respiratory pathogens, including *P. multocida (n=100), A. pleuropneumoniae (n=100), B. bronchiseptica (n=91)* and *H. parasuis (n=67*) was provided*.* The MIC values obtained show that gamithromycin exhibits a high level of in vitro activity against swine respiratory pathogens. Respective MIC_{50} and MIC_{90} values were 0.5 and 1 (range: 0.25-2) µg/ml for *P. multocida;* 4 and 4 (range 2-16) µg/ml for *A. pleuropneumoniae;* 1 and 2 (range 1-4) µg/ml for *B. bronchiseptica,* and 0.25 and 0.5 (range 0.06-4) µg/ml for *H. parasuis.*

Since MBC values were close to the MIC values for each species gamithromycin is considered to act in a bactericidal manner. Both the MBC data and the kill curves indicate that *A. pleuropneumoniae* is likely to be the limiting pathogen in eradicating the bacteria in vivo.

Development of resistance

Gamithromycin belongs to the macrolide class of antimicrobials which cover a number of molecules. All appear to act via the same mechanism and there is no reason to expect a much higher selection pressure against bacterial pathogens than already present. Development of resistance for gamithromycin in bovine respiratory pathogens has been fully assessed in the initial Marketing Authorisation (2007–2008) and at renewal in 2013 and has been supported and well documented in the renewal file. The CVMP concluded at that time that resistance prevalence of bovine respiratory pathogens to gamithromycin in Europe remains very low, and that there has not been a major shift in susceptibility to the target pathogens.

Regarding the risk to public health, available data suggest that the use of gamithromycin since its first approval in 2008 for the treatment of bovine respiratory disease has not compromised the use of macrolides for the treatment of infection in man. Accordingly, it is considered unlikely that the use of gamithromycin in the treatment of swine respiratory disease will prejudice the use of macrolides, in the limited cases where they are used, nor other drug classes, for the treatment of human infections.

Pharmacokinetics

In support of the application for the new target species, two pivotal pharmacokinetic GLP studies were submitted, both have already been assessed during the swine MRL application.

In the first study gamithromycin was administered to healthy pigs (40–55 kg bw) as a single intravenous dose (6 mg/kg bw) or as a single intramuscular dose (3, 6, or 12 mg/kg bw), 6 or 8 animals per group. The study demonstrated that gamithromycin in pigs is rapidly absorbed, and showed 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 74–94 hours.

A second study examining the distribution of gamithromycin to lung tissue compartments has been provided, i.e. the tissues relevant for the proposed indication. Gamithromycin was administered at a dose of 6 mg/kg intramuscularly to 4 month old pigs. Three animals each were necropsied at 10 time points from 0.5 hours to 10 days after administration. The concentration of gamithromycin in plasma, pulmonary epithelial lining fluid (PELF), lung tissue homogenate and bronchoalveolar lavage (BAL) cells was analysed using an LC-MS/MS method. Gamithromycin was quickly absorbed and a maximal plasma concentration of 0.44 µg/ml was observed 2 hours after treatment. Gamithromycin rapidly distributed to lung tissue reaching a peak concentration of 7.3 µg/g in lung homogenate by 8 hours after treatment. Peak gamithromycin concentrations of 1.1 µg/ml and 21 µg/ml were observed in PELF and BAL cells, respectively, at 24 hours after treatment. The terminal half-life of the drug in PELF (115 hours) was longer than that in lung homogenate (48.4 hours), plasma, or BAL cells (87.1 hours). The order of mean residence time (MRT_{last}) follows BAL cells > PELF > lung > plasma.

These distribution data should be interpreted with caution. The extent to which these data can be relied on for PK/PD analyses is probably limited. However, it is accepted that the data presented suggest that the concentrations of gamithromycin achieved in relevant matrices (site of infection) are greater than the concentrations achieved in plasma (consistent with the distribution seen for gamithromycin in cattle and what has been shown for other macrolides). That said, while the peak concentrations achieved in lung homogenate and BAL cells exceeds the MIC_{90} for all target pathogens (based on the MIC data presented), it is noted that the peak concentrations achieved in PELF (1130 ng/ml) did not exceed the MIC_{90} for all target pathogens.

In summary, based on the data presented, it is accepted that gamithromycin in pigs is absorbed rapidly, distributed quickly to the lung (site of infection) and that concentrations remain high (relative to plasma) for an extended period. However, given the uncertainties with the measurements in the various lung matrices, the concentrations of gamithromycin to which target pathogens will be exposed are not precisely known.

Dose determination/justification

Three GCP compliant studies were performed to provide data on dose determination, including the two pivotal challenge studies with *A. pleuropneumoniae* performed in 2005 and 2007 in the USA, and a third study under field-like conditions performed in 2014 in the EU, which was only considered supportive.

Since *A. pleuropneumoniae* is considered to be the limiting bacteria according to MIC screening, this species was chosen as the test organism for the laboratory challenge studies.

In the first study in 2005, respiratory disease was induced in 8 weeks old pigs by seeder-pig-challenge infection using *A. pleuropneumoniae* (MIC=2 µg/ml). Pigs were treated with a single dose of saline or gamithromycin at 3, 4.5 or 6 mg/kg (n=20 pigs per group) by intramuscular (IM) injection. Animals were

observed daily up to 7 days. All doses evaluated exhibited treatment efficacy and there were no significant differences between treatments.

A second study in 2014 was conducted in 7 weeks old pigs, which were artificially challenged with a defined dose of *A. pleuropneumoniae* (7×10^8 CFU). Animals were allocated to three groups: a single dose of saline control, 3 or 6 mg/kg bw gamithromycin. Treatments were administered 4-8 hours after challenge when clinical symptoms were present. Pigs were observed up to 4 days after challenge. Results showed that a single treatment with gamithromycin was efficacious compared to the saline control group in an *A. pleuropneumoniae* challenge model at all time points except for Day 1, and the dose of 6 mg/kg bw was significantly more effective than a dose of 3 mg/kg bw for the treatment of SRD associated with *A. pleuropneumoniae*.

Based on these results, the dose of 6 mg/kg was selected, although the 4.5 mg/kg dose used in the first dose-titration study was not tested further.

The CVMP considered that only the two dose determination studies that used the *A. pleuropneumoniae* challenge infection would be considered as pivotal studies because they included a comprehensive evaluation at necropsy (lung lesions and bacteriological cure). The Committee also accepted that the results from the *A. pleuropneumoniae* challenge infections could be extrapolated to *P. multocida* and *H. parasuis.* However, extrapolation to infections caused by *B. bronchiseptica,* were questioned taking into consideration the differences in the pathogenesis of the related diseases and differences in the locations of the organisms within the respiratory tract environment. CVMP accepted that both challenge studies provide clear evidence of an effect of gamithromycin (relative to control) in animals with SRD due to challenge with *A. pleuropneumoniae*. While there were no significant differences detected between gamithromycin dose groups in one of the studies, the dose of 6.0 mg/kg was clearly superior to a dose of 3.0 mg/kg in the other study.

Although none of the dose finding studies included doses greater than 6.0 mg/kg, no differences were detected in a study (conducted under field conditions) between the 4.5 and the 6.0 mg/kg dose groups in terms of treatment success. Further, a higher dose is unlikely to offer a significant clinical efficacy advantage over 6.0 mg/kg. Consequently, a dose of 6 mg/kg bw intramuscularly was used for the clinical field studies.

Target animal tolerance

Target animal tolerance was evaluated in a GLP-compliant target animal safety study, and in the clinical field studies.

The target animal tolerance study was conducted in 2010 in the USA, in accordance with the VICH GL 43 on target animal safety. Forty pigs were allocated in 4 treatment groups received either saline or 1x, 3x and 5x the recommended use level of 6 mg/kg bw gamithromycin on 3 occasions (Days 0, 5 and 10) representing up to 30 mg/kg of gamithromycin. The maximum volume was of 5 ml per injection site (IJS). The pigs were approximately 6 weeks of age and weighed 9.1 kg–11.8 kg on Day 0. The injection sites were observed for reactions following treatment on Days 1, 5 and 10 and prior to necropsy on Day 11. Histopathological changes were present at the injection site (musculature of right dorsal neck) and were considered consistent with mechanical trauma of the intramuscular injection and/or local tissue irritation. The local reaction was transient and typically resolved within 2 days. All other observations were considered to be biological variation.

In the field trials a total of 541 pigs have been treated with the recommended dose of 6 mg/kg gamithromycin, and 162 with alternative doses (3 and 4.5 mg/kg bw) and there have been no reports of

systematic toxicity. Approximately 1 in 20 pigs treated with 6 mg/kg gamithromycin experienced mild to moderate injection site swelling consistent with inflammation and/or mechanical trauma. This transient local tissue reaction at the injection site typically resolved within 2 days.

In the majority of studies only very young pigs weighing 15-40 kg were enrolled and were treated with a small injection volume 1-2 ml. Although SRD predominantly is associated with growing animals, sows will also be included in the target animal population. Sows weighing 200 kg require a dose of 1200 mg, equivalent to 10 ml ZACTRAN. In section 4.9 of the proposed SPC it is indicated that the volume at one injection site should not exceed 5 ml. In a SRD outbreak it is expected that a low number of sows will be treated and taking into account the low prevalence of the injection reaction, it is very unlikely that a local reaction in sows would be a concern.

It is noted that the safety of the product was not investigated in pigs intended for breeding or pregnant/lactating animals. As a consequence, section 4.7 of the SPC, originally agreed for cattle, is retained: "*Based on laboratory animal data, gamithromycin has not produced any evidence of selective developmental or reproductive effects. The safety of gamithromycin during pregnancy and lactation has not been evaluated in target species. Use only according to the risk/benefit assessment by the responsible veterinarian.*"

Field trials

Two pivotal EU studies were provided and two studies, performed in Japan, which were considered supportive.

The first EU study was GCP-compliant and conducted in 2013 at 6 sites in Europe (Spain, France, Germany) and involved 420 crossbreed pigs of either sex, aged 11–18 weeks. Pigs treated with gamithromycin (6 mg/kg IM) were compared with pigs treated with a positive control product, containing tulathromycin (2.5 mg/kg IM). To qualify the sites, the first three pigs meeting the enrolment criteria were used to confirm outbreak of SRD in the herd. The animals were sampled by nasal swab or collection of bronchoalveolar lavage fluid (BAL) for bacterial culturing and PCR, and were necropsied and swabbed (lungs) for gross pathology and additional bacterial culturing. Animals were observed daily for respiratory and depression scoring. On Day 10, final evaluation was performed by clinical observation and rectal body temperature was measured.

At inclusion *A. pleuropneumoniae* was only isolated in 6.4% of the sentinel animals, whereas *P. multocida* was the dominating pathogen, suggesting that the outbreaks were rather mild. Based on the primary variables (Depression Score ≤1 AND Respiratory Score ≤1 AND Rectal Temperature <40.0 °C on Day 10), the proportion of treatment success was 70% in the gamithromycin group and 80% in the tulathromycin group; however, the criteria for statistical non-inferiority were not met. Individual analysis of data showed that "rectal temperature" did not support the hypothesis that the gamithromycin group was comparable to the tulathromycin group. A *post hoc* analysis confirmed that a subpopulation of pigs with a rectal temperature of 40.0 °C and no respiratory/depression signs of SRD was considered as a treatment failure according to the definition of success. Given that non-inferiority to tulathromycin has not been confirmed based on the pre-specified primary efficacy end-point, CVMP did not accept gamithromycin as non inferior to tulathromycin in this trial, and considered the trial as insufficient to demonstrate the efficacy of ZACTRAN in the treatment of SRD.

In the second, pivotal European field study the clinical efficacy of gamithromycin for the treatment of SRD in pigs was compared to tildipirosin. From a total of 6 sites located in France, Germany and Spain, 305 growing pigs were enrolled based on clinical signs of SRD (Depression score ≥ 2, Respiratory score ≥ 2 and rectal temperature ≥ 40.0 °C). Pigs were 11 to 18 weeks old and weighed 20.5–86.0 kg. Three

animals at each site meeting the inclusion criteria (Sentinel pigs) were euthanised and necropsied prior to treatment to obtain samples for detection of pathogens and site qualification. Then the other eligible animals were randomly assigned to be treated with gamithromycin at 6.0 mg/kg bodyweight or tildipirosin at 4.0 mg/kg bodyweight intramuscularly once on Day 0. From Day 1 to Day 10 each animal was clinically assessed for Depression and Respiratory scores, and rectal temperature was measured. Beginning on Day 2, animals with at least one score of 3 and with rectal temperature ≥40.0 °C were removed from the study, euthanized and necropsied for confirmation of SRD. For assessment of local tolerance, the injection site was observed approximately 1 hour post-treatment of the last animal on Day 0 and at the end of the study (Day 10 or on the Day of removal). Nasal swabs or bronchoalveolar lavages were collected on Day 0 prior to treatment and at the end of the study (Day 10 or on the Day of removal) and SRD target pathogen identified. All of the sentinels presented macroscopic lesions of the lung indicative for SRD and/or SRD-associated bacteria identified after culture and/or through PCR of lung tissue, bronchial and/or nasal swabs. *Actinobacillus pleuropneumoniae*, *P. multocida*, *B. bronchiseptica, H. parasuis* and/or *M. hyopneumoniae* were isolated from the sentinels and enrolled animals at the various study sites.

Of the 301 cases included in the efficacy analysis, 292 animals completed the study. From Day 2 to Day 8, 9 animals (4 in the gamithromycin group and 5 in the tildipirosin group) were removed from the study due to SRD. The proportion of treatment success was 97% in the gamithromycin group and 93% in the tildipirosin group. When comparing the two groups based on this criteria, treatment success of gamithromycin was demonstrated not inferior (non-inferiority margin 10%) to tildipirosin. Individual analysis of Respiratory score, Depression score and Rectal Temperature for 'Success' (i.e., Depression Score ≤1, Respiratory Score ≤1 or Rectal Temperature <40.0 °C, respectively) revealed that for all the parameters, the data supported that the gamithromycin group was comparable to the tildipirosin group (Depression Success 95% in the two groups, Respiratory Success 93% in the gamithromycin group and 94% in the tildipirosin group and temperature Success 93% in the gamithromycin group and 91% in the tildipirosin group).

The success criteria defined in the 2nd field trial have been modified compared to the 1st trial. It was argued that this has been designed to avoid false treatment failure assignments using a definition of failure which was weighted more towards the clinical signs of SRD including at least one clinical score ≥ 1 concomitant with hyperthermia. The adapted criteria allow for animals to be categorised as a success both when displaying clinical signs of respiratory disease in the absence of hyperthermia and when presenting with hyperthermia in the absence of clinical signs of respiratory disease. It is clear that when using the adapted criteria, a larger proportion of test animals are categorized as a success compared to when applying the success criteria used in the first European field study. Given that rectal temperature offers an objective measure of infectious disease (more so than the other clinical parameters), it is considered that the chosen success criteria should have required a normalization of temperature. That said, it is noted that, in addition to the per protocol analysis, the data for the second EU field study have been re-evaluated using the definition of treatment success used in the first field study. Non-inferiority was confirmed both when the study data were analysed per protocol and when re-analysed applying the definition of treatment success used in the first EU field study.

Following injection, local reactions were observed in six out of the 153 animals of the gamithromycin group and 10 out of the 152 animals of the tildipirosin group. These visible reactions resolved rapidly within one day.

Treatment with gamithromycin showed a clear reduction in *Actinobacillus pleuropneumoniae* and in *Pasteurella multocida* in both the 1st and 2nd EU field study whereas *Haemophilus parasuis* only was reduced in the 2nd study. A reduction in *B. bronchiseptica* isolation post-treatment was not seen in either

study. Although clinical cure is not always reflected in a bacteriological cure the data on *B. bronchiseptica* suggest very little effect on this species. To support the *B. bronchiseptica* claim the applicant has calculated the clinical cure of *B. bronchiseptica*-positive SRD animals that were negative for the other bacteria in the EU field studies and found treatment success in 18 out of 22 in the 2nd field study and 9 out of 11 in the 1st field study. However, *B. bronchiseptica* could still be isolated in 14 (2nd field study) and 4 cases (1st field study) classified as cured animals. No change was seen for *B. bronchiseptica* and *M. hyopneumoniae*. CVMP was therefore of the opinion that the data for these pathogens were not sufficiently robust, and that the ZACTRAN claim for SRD should only include *Actinobacillus, Pasteurella* and *Haemophilus.*

In addition to the European studies, two field studies performed in Japan were submitted, indicating that treatment success rate for gamithromycin was non-inferior to danofloxacin. However, these studies were considered supportive only, due to the fact that they include a limited number of animals, and the inclusion criteria allowed for the inclusion of mildly diseased animals. In addition, the studies were conducted outside the EU.

Overall conclusion on efficacy

Pharmacodynamics:

The MIC values obtained show that gamithromycin exhibits a high level of in vitro activity against swine respiratory pathogens (*A. pleuropneumoniae*, *P. multocida*, *H. parasuis*, and *B. bronchiseptica)*.

Resistance development:

There has not been a major shift in susceptibility in bovine respiratory pathogens, and it is not expected that the use of ZACTRAN in pigs will result in an increased selection pressure against bovine or porcine bacterial pathogens. Likewise, it is considered unlikely that the use of gamithromycin in pigs will prejudice the use of macrolides for the treatment of human infections.

Pharmacokinetics:

Gamithromycin in pigs is absorbed rapidly, distributed quickly to the lung (site of infection) and concentrations remain high (relative to plasma) for an extended period.

Dose determination/justification:

Three dose titration studies using an *A. pleuropneumoniae* infection as model were presented. Two of these have been conducted in US and did not show difference between 3, 4.5 mg/kg and the recommended 6 mg/kg dose. The third study has been conducted in 2014 in Europe and demonstrated a higher cure rate of the 6 mg/kg bw than the 3 mg/kg bw. Consequently 6 mg/kg was chosen as an appropriate dose.

Target animal safety:

At the recommended dose of 6 mg/kg bw, the product did not show any systemic reactions; common local reactions (1 in 20 piglets) were mild to moderate tissue reactions at the injection site, which typically resolved within 2 days. Data in sows receiving larger volumes of the product were not provided but it is very unlikely that a local reaction in sows would be a concern.

The safety of the product was not investigated in pigs intended for breeding or pregnant/lactating animals. As a consequence, the product should only be used according to the risk/benefit assessment by the responsible veterinarian.

Clinical studies:

Two pivotal EU field studies and two supportive studies, performed in Japan, were presented.

The first EU study failed to demonstrate non-inferiority to tulathromycin based on respiratory and depression scores and body temperature. In the second EU field study, gamithromycin showed non-inferiority to tildipirosin in the treatment of SRD. Treatment with gamithromycin showed a clear reduction in *A. pleuropneumoniae* and in *P. multocida* in both the 1st and the 2nd EU field study whereas *H. parasuis* was only reduced in the 2nd study. No change was seen for *B. bronchiseptica* and *M. hyopneumoniae.* Since the only favourable data on *B. bronchiseptica* were preclinical MIC values, and pathogenesis and localisation of this commensal bacterium is considered different from *A. pleuropneumoniae,* the CVMP considered the data insufficient to support a claim for this pathogen.

Part 5 – Benefit-risk assessment

Introduction

ZACTRAN (active substance gamithromycin) was first authorised in the Community on 24 July 2008, and is available as a solution for injection for cattle for the treatment and prevention of respiratory disease by subcutaneous use.

This extension application is to add a new food-producing target species, pigs.

The proposed new indication is: "Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida* and *Haemophilus parasuis*." The route of administration is intramuscular use for a single dose of 6 mg/kg bw. The withdrawal period for pig meat and offal is 16 days.

Benefit assessment

Direct therapeutic benefit

The benefit of ZACTRAN 150 mg/ml solution for injection for pigs is its efficacy in the treatment of swine respiratory disease, associated with *A. pleuropneumoniae, P. multocida,* and *H. parasuis*.

Microbiological studies showed that gamithromycin exhibits a high level of in vitro activity against relevant swine respiratory pathogens (*A. pleuropneumoniae, P. multocida*, *H. parasuis*, and *B. bronchiseptica).*

A single dose of 6 mg gamithromycin/kg bw (intramuscular) is efficacious in the treatment of experimentally induced infections with *A. pleuropneumoniae,* the pathogen involved in the development of SRD considered to be the most difficult to treat.

Although an initial European multicentre field study failed to demonstrate efficacy by non-inferiority to the comparator tulathromycin, a second European field study demonstrated the efficacy of ZACTRAN at a single dose of 6 mg gamithromycin/kg bw (intramuscular) in the treatment of swine respiratory disease associated with *A. pleuropneumoniae, P. multocida,* and *H. parasuis* by non-inferiority to the comparator, tildipirosin.

However, the clinical documentation in relation to *B. bronchiseptica* was considered insufficient to support a claim for this pathogen.

Risk assessment

Main potential risks have been identified as follows:

Quality:

The strength, pharmaceutical form and presentations are the same as already authorised for cattle, and cross-reference was made to data that have already been submitted and assessed as satisfactory for the product.

For the target species, user and the environment:

In general, ZACTRAN is well tolerated by pigs, with only mild to moderate tissue reactions at the injection site, which typically resolved within 2 days.

ZACTRAN for pigs is not expected to pose a risk to the user or the environment when used as recommended in the SPC.

For the consumer:

A withdrawal period of 16 days for pig meat and offal has been established.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user and the environment and to provide advice on how to prevent or reduce these risks.

Since the application concerns a new target animal species, the CVMP also recommended that the PSUR cycle for ZACTRAN should be re-started to ensure more frequent pharmacovigilance monitoring. The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 31 July 2016.

Evaluation of the benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary data presented at the CVMP concluded that the quality, safety and efficacy of ZACTRAN 150 mg/ml solution for injection for pigs are considered to be in accordance with the requirements of Directive 2001/82/EC. The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the extension of the marketing authorisation for ZACTRAN to add a new target species, pigs, for ZACTRAN 150 mg/ml solution for injection.