EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use (CVMP)

# CVMP assessment report for type II variation for ZACTRAN (EMEA/V/C/000129/II/0036)

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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# 1. Introduction

## *1.1. Submission of the variation application*

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, MERIAL (the applicant) submitted to the European Medicines Agency (the Agency) on 24 August 2017 an application for a type II variation for ZACTRAN.

## *1.2. Scope of the variation*

| **Variation(s) requested** | | **Type** |
|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |

This variation is to add a new therapeutic indication: *Bordetella bronchiseptica* - new pathogen for the approved indication: treatment of swine respiratory disease (SRD).

**Current**

**SPC**

**Section 4.2 Indications for use, specifying the target species**

Pigs:

Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida* and *Haemophilus parasuis*.

**Section 5.1 Pharmacodynamic properties**

……The broad spectrum antimicrobial activity of gamithromycin includes *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, *Actinobacillus pleuropneumoniae,* and *Haemophilus parasuis,* the bacterial pathogens most commonly associated with BRD and SRD, and also *Fusobacterium necrophorum* and *Dichelobacter nodosus*……

| Pigs | $MIC_{90s}$ | $MBC_{90s}$ |
|---|---|---|
| | µg/ml | |
| *Actinobacillus pleuropneumoniae* | 4 | 4 |
| *Pasteurella multocida* | 1 | 2 |
| *Haemophilus parasuis* | 0.5 | 0.5 |

**Proposed**

**SPC**

**Section 4.2 Indications for use, specifying the target species**

Pigs:

Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida*, ~~and~~ *Haemophilus parasuis* and *Bordetella bronchiseptica*.

**Section 5.1 Pharmacodynamic properties**

……The broad spectrum antimicrobial activity of gamithromycin includes *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, *Actinobacillus pleuropneumoniae,* ~~and~~ *Haemophilus parasuis and Bordetella bronchiseptica,* the bacterial pathogens most commonly associated with BRD and SRD, and also *Fusobacterium necrophorum* and *Dichelobacter nodosus*……

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| *Actinobacillus pleuropneumoniae* | 4 | 4 |
| *Pasteurella multocida* | 1 | 2 |
| *Haemophilus parasuis* | 0.5 | 0.5 |
| *Bordetella bronchiseptica* | 2 | 4 |

| | |
|---|---|
| **PACKAGE LEAFLET**<br><br>**Section 4. Indication(s)**<br><br>Pigs:<br><br>Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida* and *Haemophilus parasuis.* | **PACKAGE leaflet**<br><br>**Section 4. Indication(s)**<br><br>Pigs:<br><br>Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida,* ~~and~~ *Haemophilus parasuis* and *Bordetella bronchiseptica.* |

### *1.3. Changes to the dossier held by the European Medicines Agency*

This application relates to the following sections of the current dossier held by the Agency:

Part 1 and Part 4

### *1.4. Scientific advice*

Not applicable.

### *1.5. MUMS/limited market status*

Not applicable.

## 2. Scientific Overview

ZACTRAN currently has the following indication for swine: 'Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Haemophilus parasuis*.'

This variation is to add a new therapeutic indication: *Bordetella bronchiseptica* - new pathogen for the approved indication treatment of swine respiratory disease (SRD).

Following assessment of the original efficacy data package submitted in support of the swine respiratory disease indication, the CVMP stated that the clinical documentation in relation to *Bordetella bronchiseptica* was insufficient to support a claim for this pathogen.

To support the addition of *B. bronchiseptica* to the swine respiratory disease indication, the applicant has extracted the MIC/MBC data and PK/PD data relevant for *B. bronchiseptica* previously presented in the original application (EMEA/V/C/000129/X/0027) and assessed by CVMP. The *B. bronchiseptica* isolates included in the MIC study were collected from 8 European countries (VetPath III) and included 91 isolates whereof 33 originate from 2012, i.e. isolates within 5 years prior to submission of the application as required in the *Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances* EMA/CVMP/627/2001-Rev.1). The isolates were harvested from clinically sick animals, pigs aged from 3 weeks to 6 months and showing depression, hyperthermia (>39.8°C), with one or more of these respiratory signs: polypnoea, dyspnoea, cough, sneezing. *B. bronchiseptica* strains did not demonstrate a susceptibility shift in isolates from 2010, 2011 and 2012. Half of the isolates were randomly selected to characterize the MBCs. The MBC data for *B. bronchiseptica* were ≤1 doubling dilution for the vast majority of isolates showing that gamithromycin acts in a bactericidal manner against *B. bronchiseptica*.

In an attempt to conduct a PK/PD relationship analysis, the *B. bronchiseptica* $MIC_{90}$ may be compared with the concentration of gamithromycin in the targeted tissues (BAL cells, PELF and lung homogenate), considering that these concentrations are representative of the exposure of *B. bronchiseptica* to the active in the case of SRD. Although the preferential location of the bacteria is the epithelial cells lining the nasal mucosa and trachea, in case of SRD the upper respiratory tract is colonized by the bacteria and *B. bronchiseptica* may colonize the entire respiratory tract. Considering that the purpose of the treatment is to treat SRD typically associated with pulmonary lesions and with the presence of the target bacteria in the respiratory tract, comparing the concentration in the lung with the $MIC_{90}$ is relevant. The results showed that only the concentration of gamithromycin in BAL cells and lung tissue homogenates exceeded the $MIC_{90}$.

In order to add *B. bronchiseptica* to the swine respiratory disease indication, the applicant has provided three new experimental studies, including development of a *B. bronchiseptica* model and a dose confirmation study based on the new model.

The objective of the first study was to determine the MIC of gamithromycin against two *B. bronchiseptica* isolates (one canine and one swine origin strains), which were used for the other two experimental studies. The two *B. bronchiseptica* isolates (plus quality control reference strain *Staphylococcus aureus* ATCC 29213) were tested to determine the MIC of gamithromycin according to the CLSI guideline M31-A3. All testing complied with the protocol and there were no deviations recorded; all tests results were deemed valid. It was noted that the pig isolate was obtained from France in 1983, which far exceeds the maximum time period in which isolates of the target bacteria to be tested should be collected (<5 years prior to the submission of the application as per *Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances* EMA/CVMP/627/2001-Rev.1). That said, based on the MIC results observed in this study, it was accepted that the two *B. bronchiseptica* isolates can be considered representative of the current field sensitivity of *B. bronchiseptica* in pigs. In addition, based on the findings of the challenge studies, it was clear that the isolate was capable of inducing clinical disease. The CVMP agreed that the selected test strains for *B. bronchiseptica* were representative of the isolates in respect to MICs.

The objectives of the second study were to compare the pathogenicity following experimental infection with a canine origin *B. bronchiseptica* strain (one infective dose) or with a swine origin *B. bronchiseptica* strain at two different infective doses, and identify the best strain/dose for further evaluation of gamithromycin. Twenty-eight healthy Large White pigs of approximately 5 weeks of age (n=16 females; n=12 males, weighing 5.4 to 10.9 kg on Day -5) were included. The animals were ranked by sex and bodyweight and were randomly allocated to one of the three groups: Group A inoculated with the canine *B. bronchiseptica* strain at $10^9$ CFU/ml (positive control); Group B inoculated with the swine origin strain at $10^8$ CFU/ml; Group C inoculated with the same swine origin strain at $10^9$ CFU/ml. The infective preparations were administered intranasally by 1 ml on Day 0, and pigs were observed once daily until Day 14 when euthanasia was performed. Clinical scores were recorded from Day 0 until the end of the study. Nasal swabs (Day 0 and Day 13), and tracheal swabs and lung samples (Day 14) were collected for quantitative PCR. Lung and tracheal samples were also collected on Day 14 for histology. The inoculation of *B. bronchiseptica* strains isolated from dog or swine induced clinical signs (dyspnoea, coughing) and increased temperature transiently correlating with tracheopulmonary inflammation characterized microscopically by minimal to severe subacute and/or pyogranulomatous pneumonia and/or minimal to mild subacute tracheitis. The inoculated agent *B. bronchiseptica* was isolated from the respiratory tract at the end of the study, 13 and 14 days after inoculation, suggesting that the tracheitis and pneumonia were secondary to the bacteria infection. The clinical signs, gross lesions and histopathological findings are consistent with the natural infection of *B. bronchiseptica* confirming the relevance of the experimental model to reproduce the disease in the laboratory. Although lesions and signs were globally observed among the groups, the occurrence and severity of lung gross lesions and

lung pyogranulomatous inflammation were markedly higher in group C inoculated with *B. bronchiseptica* strain from swine at $10^9$ CFU/ml. Hence, this strain formulated at $10^9$ CFU/ml was chosen for a future efficacy study.

The aim of the third study was to confirm the efficacy of a single intramuscular injection of 6.0 mg/kg gamithromycin (ZACTRAN) for the treatment of swine respiratory disease associated with *B. bronchiseptica* in experimentally infected piglets. Forty *B. bronchiseptica*-negative SPF piglets (n=20 males; n=20 females), 5.0 to 5.3 weeks of age on Day 3, and 4.5 to 12.7 kg bodyweight on Day -4, were included. On Day 0, all animals were inoculated with 2 ml of a *B. bronchiseptica* suspension by nasal route (swine origin strain at $10^9$ CFU/ml). Animals were blocked based on Day 1 – Day 3 SRD clinical scores and randomly allocated on Day 3 to one of two treatment groups: saline group (n=20) and ZACTRAN treated group (n=20). On Day 3, treatments were administered intramuscularly in the dorsal part of the neck at 1.0 ml/25 kg bodyweight for both groups. Nasal swabs were collected on Day -4, Day 3 and Day 13 and tracheal swabs were collected on Day 13. From Day -4 to the end of the study, the animals were observed once daily for health and SRD signs (rectal temperature, general condition, coughing, dyspnoea and other respiratory signs, e.g. sneezing) were recorded from Day -1 to Day 13. On Day 13, all animals were euthanized, necropsied and lungs were examined macroscopically for lesions. Lung samples including lesions, if any, and normal tissues with tracheal sample from each animal were collected for histology. The inoculation with *B. bronchiseptica* strain induced respiratory clinical signs (mostly coughing) and bacterial shedding at the nasal and tracheal levels in both groups, correlating with tracheo-pulmonary inflammation characterized microscopically by minimal to marked bronchio-alveolar and/or pyogranulomatous pneumonia and/or minimal to mild tracheitis. A single intramuscular injection of ZACTRAN administered at 6.0 mg gamithromycin/kg was demonstrated to be efficacious in the treatment of *B. bronchiseptica* respiratory disease as shown by the statistically significant reduction of the clinical signs, gross lung lesions and tracheal shedding in treated animals compared to the controls. However, an eradication of *B. bronchiseptica* from lung tissue could not be demonstrated since no bacteriology was conducted on lung sample.

In summary, the conditions of the experimental infection study were adequately representative of the field conditions in terms of the type of infection and the animals involved. In addition, the susceptibility pattern for the *B. bronchiseptica* infective strain used is relevant for the current field situation. The experimental infection model was successful as it caused characteristic respiratory clinical signs, bacterial shedding and pathology in the untreated control animals. ZACTRAN treatment at the intended dosage of 6 mg/kg as a single dose caused a statistically significant reduction of the clinical signs, gross lung lesions and tracheal shedding compared to placebo. Therefore, it can be expected that ZACTRAN offers an efficacy benefit for the treatment of SRD associated with *B. bronchiseptica*.

*B. bronchiseptica* may be involved as part of swine respiratory disease along with *Actinobacillus pleuropneumoniae, Pasteurella multocida* and *Haemophilus parasuis.* Gamithromycin has been documented to reduce the lesions caused by all these pathogens. The indication: 'Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Haemophilus parasuis and Bordetella bronchiseptica*' is supported at a dose of 6 mg gamithromycin/kg.

# 3. Benefit-risk assessment of the proposed change

In pigs, this product is authorised for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Haemophilus parasuis*. The active substance is gamithromycin, an azalide, 15-membered semisynthetic macrolide class antibiotic. The pharmaceutical form is solution for injection containing 150 mg gamithromycin/ml. The recommended

dose in pigs is 6 mg gamithromycin/kg body weight (equivalent to 1 ml/25 kg body weight) as a single dose. The withdrawal period in pigs for meat and offal is 16 days.

The proposed variation is to add a new therapeutic indication: *Bordetella bronchiseptica* - new pathogen for the approved indication: treatment of swine respiratory disease (SRD).

## *3.1. Benefit assessment*

**Direct therapeutic benefit**

The benefit of ZACTRAN is its efficacy in the treatment of SRD associated with *B. bronchiseptica*, which was established in well-designed experimental studies conducted to an acceptable standard.

The applicant has compared ZACTRAN at the recommended dosage of 6 mg gamithromycin/kg once by the intramuscular route with a placebo under controlled conditions for the treatment of SRD associated with *B. bronchiseptica.* It can be concluded that ZACTRAN offers an efficacy benefit for the treatment of SRD associated with *B. bronchiseptica*.

## *3.2. Risk assessment*

**Quality:**

Quality remains unaffected by this variation.

**Safety:**

As the product will be administered to the same target species at the same dose rate and at the same frequency as already approved for existing indications, no new risk is considered to arise in terms of user safety, environmental safety, consumer safety or target animal safety.

Antimicrobial resistance:

Evaluation of gamithromycin *in vitro* demonstrates that *B. bronchiseptica* is sensitive to gamithromycin and suggests that the risk of development of resistance in the target pathogens is low. Therefore, it is unlikely that the development of resistance presents a significant concern for clinical efficacy. The applicant has previously demonstrated that ZACTRAN has a high therapeutic index. The warnings, contraindications and precautions outlined in the current Summary of Product Characteristics remain appropriate.

## *3.3. Risk management or mitigation measures*

N/A

## *3.4. Evaluation of the benefit-risk balance*

ZACTRAN offers an efficacy benefit for the treatment of SRD associated with *B. bronchiseptica*. No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety, consumer safety and target animal safety.

The benefit-risk balance remains unchanged.

# 4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for ZACTRAN can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to add a new therapeutic indication: *Bordetella bronchiseptica* - new pathogen for the approved indication: treatment of swine respiratory disease (SRD).

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I and IIIB