EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 June 2012
EMA/CVMP/323019/2012
Veterinary Medicines and Product Data Management

Withdrawal variation assessment report

DRAXXIN 100 mg/ml Solution for injection for cattle and pigs

International non-proprietary name: Tulathromycin

(EMEA/V/C/000077/II/0023)

EU/2/03/041/001-005

Type II variation to add the indication for *Bordetella bronchiseptica* to the existing list of claims for the treatment and prevention of swine respiratory disease (SRD).

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

Withdrawal at day 91

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

Introduction

The applicant applied on 2 December 2011 to vary the marketing authorisation of DRAXXIN for the treatment and prevention of swine respiratory disease (SRD) by including the target pathogen *Bordetella bronchiseptica*. This claim has inter alia already been applied for in 2008 within a previous variation application (EMEA/V/C/077/II/017). It was however not supported by CVMP, because the data provided were considered inadequate.

In the current application, the applicant provided three new Minimum Inhibitory Concentration (MIC) studies on the respective organism isolated in Europe and North America to support the additionally claimed target pathogen. Furthermore, seven clinical field studies in pigs were submitted, performed in North America (n=4) and Europe (n=3). It is noted that the European studies have already been submitted to support the previous variation procedure (EMEA/V/C/077/II/017). The studies were critically reviewed in a Pre-clinical and Clinical Expert Report by the applicant's expert. The studies are summarised in the following.

The application was validated on 9 December 2011 and the assessment was carried out by the CVMP in line with its normal timetable. At Day 90 of the procedure, the CVMP considered on the basis of quality, safety and efficacy data submitted, that the variation was not approvable, since major objections had been identified, which precluded a recommendation for a variation to the marketing authorisation. The concerns were mainly in relation to efficacy of the additional indication applied for. The clock was stopped and the applicant was given an opportunity to submit supplementary information.

On 11 May 2012, Pfizer Limited withdrew the application at Day 91 of the procedure.

Summary of preclinical part

MIC studies:

One pivotal European MIC study and two supportive MIC studies were provided. Due to outstanding questions it is at present not possible to conclude on MIC values and on the representativeness of the European data set. As a consequence no final conclusions can be drawn on the comparibilty of MICs for tulathromycin against *B. bronchiseptica* isolated from pigs with respiratory disease between USA/Canada and Europe. Additional MIC data may be necessary.

PK/PD analysis:

No PK/PD analysis for *B. bronchiseptica* was provided and its omission was not discussed by the Clinical Expert. However, MIC data suggest that *B. bronchiseptica* presumably will have no higher MIC_{90} value compared to highest MIC_{90} of already authorised target pathogens (i.e. *Actinobacillus pleuropneumoniae*) in SRD. From a PK/PD perspective *B. bronchiseptica* is not supposed to be the dose limiting pathogen and should be covered sufficiently by tulathromycin plasma/tissue levels.

Breakpoints:

The CLSI established MIC Breakpoints for tulathromycin and target pathogens in BRD and SRD. According to this all tested *B. bronchiseptica* strains have MIC values ≤16 µg/ml and hence are sensitive to tulathromycin.

Resistance

No additional information on resistance was submitted. Adding of a new target pathogen is not expected to have any further impact on potential development on resistance than for the already

existing indication of treatment and prevention of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Mycoplasma hyopneumoniae* and *Haemophilus parasuis* sensitive to tulathromycin.

Summary of clinical part

The CVMP noted the statement of the Pre-clinical and Clinical Expert Report reading

"The data available in the dossier on efficacy specifically against SRD associated with *Bordetella bronchiseptica* are limited. However, this is a reflection of the relatively low prevalence of this pathogen in SRD compared with other more common respiratory pathogens such as *P. multocida* and *A. pleuropneumoniae*. It can be extremely difficult to obtain field efficacy data specifically for SRD associated with *Bordetella bronchiseptica*".

Nevertheless, even when taking into account this statement, the CVMP concluded that the overall clinical data is too limited to justify the claim in *Bordetella bronchiseptica* for the following reasons:

- The European clinical field studies have been provided with the previous variation application EMEA/V/C/077/II/017. At that time, the claim of *Bordetella bronchiseptica* was not supported because the presence of *Bordetella bronchiseptica* was demonstrated in a small number of pigs only. Thus the clinical data had been considered insufficient with respect to SRD associated with this bacteria species.
- Two out of the three North American clinical field studies failed to demonstrate efficacy of tulathromycin in pigs suffering from SRD (treatment claim). In these studies the incidence of *Bordetella bronchiseptica* was 42.9% and 29.3%.
- One North American study demonstrates efficacy of tulathromycin in pigs suffering from SRD (treatment claim). *Bordetella bronchiseptica* was found in 24.3% of sampled pigs, which was the lowest incidence of the three North American studies. In line with the previous assessment of the European studies, this incidence of *Bordetella bronchiseptica* is deemed too low as basis for a respective claim. Apart from that, the contradictory results of the studies do not allow any clear conclusion. Thus, it would be hardly possible to justify a claim based on these studies.
- One North American clinical field study presented to prove the prevention claim has major shortcomings: i) The study report does not allow to discriminate between treatment success after therapeutic treatment of sick animals and preventive treatment of in contact animals; ii) *Bordetella bronchiseptica* has been isolated from a number of lung samples which is considered too low to justify that claim; iii) the observation period of 7 days is deemed too short to conclude on a preventive treatment claim; iv) treatment success rate after treatment with tulathromycin is considered low for an antimicrobial of that class indicating questionable internal study validity. The present study does, therefore, on its own not allow concluding on the efficacy of DRAXXIN in preventing SRD associated with *Bordetella bronchiseptica*. It is noted that according to FDA FOI this study served to approve in 2008 DRAXXIN "For the control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed".

The CVMP concluded that the data presented, i.e.

i) one favourable North American study with a too low incidence of *Bordetella bronchiseptica*,

ii) two unfavourable North American studies,

iii) one favourable North American study with major shortcomings, and

iv) the previously assessed unfavourable European studies

do not support the inclusion of the additional claim against *Bordetella bronchiseptica* for this product.

Benefit-risk assessment

Introduction

DRAXXIN 100 mg/ml solution for injection for cattle and pigs is a long-acting formulation containing tulathromycin, which is a semi-synthetic macrolide antimicrobial agent. It is presented as a solution for injection in cardboard boxes containing one vial. Vial sizes are 20 ml, 50 ml, 100 ml, 250 ml and 500 ml.

Benefit assessment

The benefit of DRAXXIN is that Swine Respiratory Disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Mycoplasma hyopneumoniae* and *Haemophilus parasuis* sensitive to tulathromycin can effectively be treated and prevented with one single intramuscular injection of 2.5 mg/kg body weight. This represents an advantage in terms of compliance. The presence of the disease in the herd should be established before preventative treatment. DRAXXIN should only be used if pigs are expected to develop the disease within 2-3 days.

A type II variation was submitted to add the indication for *Bordetella bronchiseptica* to the existing list of claims for the treatment and prevention of SRD.

Previous submissions have discussed the manner in which tulathromycin concentrates in the lung, particularly in neutrophils and alveolar macrophages, and other tissues of pigs. From a PK/PD perspective *B. bronchiseptica* is not supposed to be the dose limiting pathogen compared to already authorizised target pathogens and should be covered sufficiently by tulathromycin plasma/tissue levels.

The use of DRAXXIN against SRD associated with *Bordetella bronchiseptica* is not yet properly confirmed by data. The data presented i.e. i) one favourable North American study with a too low incidence of *Bordetella bronchiseptica*, ii) two unfavourable North American studies, iii) one favourable North American study with major shortcomings, and iv) the previously assessed unfavourable European studies are considered inadequate to support this claim.

Efficacy

Due to outstanding questions it is at present not possible to conclude on MIC values and on the representativeness of the European data set. As a consequence no final conclusions can be drawn on the comparibilty of MICs for tulathromycin against *B. bronchiseptica* isolated from pigs with respiratory disease between USA/Canada and Europe. Additional MIC data may be necessary.

The efficacy of DRAXXIN at the recommended dosage in treatment and prevention of swine respiratory disease associated with *Bordetella bronchiseptica* was not reliably proven.

Risk assessment

Resistance

Adding of a new target pathogen is not expected to have any further impact on potential development on resistance than for the already existing indication of treatment and prevention of SRD associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Mycoplasma hyopneumoniae* and *Haemophilus parasuis* sensitive to tulathromycin.

Target animal safety

Target animal tolerance had previously been demonstrated. Adverse effects, warnings and precautions in order to warrant proper use are included in the product literature. There is no change envisaged.

No change to the impact on the environment is envisaged.

Evaluation of the benefit-risk balance

The proposed variation to the marketing authorisation of DRAXXIN for the treatment and prevention of swine respiratory disease (SRD) by including the target pathogen *Bordetella bronchiseptica* did not demonstrate to have a positive benefit risk balance as regards the new indication of use.

Overall conclusions of the evaluation and recommendations

The CVMP considers that this variation, accompanied by the submitted documentation is not approvable since 'major objections' have been identified which preclude a recommendation for approval.