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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for Zeleris (EMEA/V/C/004099/VRA/0005/G)

INN: florfenicol / meloxicam

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

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Table of contents

1. Introduction

1.1. Submission of the variation application

In accordance with Article 62 of Regulation (EU) 2019/6, the marketing authorisation holder, CEVA Santé Animale (the applicant), submitted to the European Medicines Agency (the Agency) on 2 May 2022 an application for a group of variations requiring assessment for Zeleris.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one
G.I.18	One-off alignment of the product information with version 9.0 of the QRD templates i.e. major update of the QRD templates in accordance with Regulation (EU) 2019/6, for veterinary medicinal products placed on the market in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004

The group of variations is to add a new therapeutic indication for the treatment of bovine respiratory disease associated with pyrexia due to *Mycoplasma bovis* and to align the product information with version 9.0 of the QRD template.

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. Limited market status

Not applicable.

2. Scientific Overview

On 2 May 2022, the marketing authorisation holder CEVA Santé Animale submitted an application for a group of variations requiring assessment for Zeleris to add a new therapeutic indication and to align the product information with version 9.0 of the QRD template.

2.1. New therapeutic indication: for the treatment of bovine respiratory disease associated with pyrexia due to Mycoplasma bovis

Zeleris was authorised by centralized procedure on 15th of May 2017 for the treatment of bovine respiratory disease (BRD) associated with pyrexia due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* susceptible to florfenicol. The product is a fixed combination of florfenicol (400 mg/ml) and meloxicam (5 mg/ml). With the current variation application, the applicant intends to add "treatment of bovine respiratory disease (BRD) associated with pyrexia due to *Mycoplasma bovis*" to the list of indications.

No changes concerning the target species, posology or withdrawal period have been proposed. The quality remains also unaffected by this variation.

The applicant provided data and explanations on pharmacology (MIC data) and development of resistance. Furthermore, a clinical field trial was conducted and results were presented in order to demonstrate efficacy.

2.1.1. Pharmacology

Zeleris is already authorised for the intended target species cattle, by the same route of administration and with the same dosing regimen as for the proposed indication. Thus, no additional study data related to pharmacology were submitted; however, a literature review on the efficacy of florfenicol + flunixin against *M. bovis* was provided by the applicant.

Furthermore, MIC data on the susceptibility of *M. bovis* isolated from bovine respiratory diseases (BRD) between 2018 and 2021 were presented, with a distribution of florfenicol MICs against 272 *M. bovis* strains between 0.25 and 16 µg/ml. The study showed that 50% of all tested isolates were susceptible to 2.74 µg/ml, while 90% of susceptible isolates were susceptible to 5.39 µg/ml.

Additionally, the applicant referred to data on the susceptibility of *M. bovis* isolated from bovine respiratory diseases (BRD) between 2009 and 2021 in European countries. Those *M. bovis* strains were susceptible to florfenicol with lowest and highest MIC_{90} values of 3.27 µg/ml (2011) and 7.34 µg/ml (2014-2015), respectively. Regarding individual MIC values, a shift of the median value from 2 to 4 µg/ml has been observed from 2015.

MIC determination for field isolates obtained as part of the pivotal clinical field trial submitted with the current application revealed MIC values for all field strains of *M. bovis* between 2 and 4 µg/ml.

With regard to the applicability of the index T>MIC, the applicant reasonably explains that $T>MIC_{90}$ does not correlate with clinical efficacy observed in the field as there is a lack of clear PK/PD relationship for *M. bovis*, and applying a PK/PD model bears too many uncertainties. This statement is underlined by a publication from Foster *et al*. (2016) showing that the lung concentrations of florfenicol after treatment with a veterinary medicinal product containing florfenicol and flunixin were more than 200% of the plasma concentrations. The plasmatic C_{max} and AUC were at 3.42 µg/ml and 142.90 hours*µg/ml, respectively, in plasma versus 7.52 µg/ml and 342.27 hours*µg/ml, respectively, in pulmonary epithelial fluid (PELF). Therefore, it can be assumed that the florfenicol concentration at the site of action of the BRD treatment is higher than the MIC_{90} (5.39 µg/ml, determined on *M. bovis* CEESA isolates collected between 2018 and 2021 for *M. bovis* (Foster *et al.*, 2016)).

2.1.2. Development of resistance

Regarding the development of resistance for *Mycoplasma*, the applicant cited several publications, which are summarised below.

Three mutation sites in the rRNA have been associated with phenicol resistance in *Mycoplasma* spp. (Pereye and Tardy, 2021). According to the authors, there have been several studies indicating that *M. bovis* has developed multiple antimicrobial resistances but depending on the study the outcome on susceptibility and range of MICs is highly variable (Pereye and Tardy, 2021).

Gautier-Bouchardon reported no differences in MIC values for gamithromycin, tildipirosin, florfenicol and valnemulin (MIC_{50} of 128, 128, 8, <0.03 µg/ml, respectively) comparing isolates from BRD outbreaks obtained in 1978-1979 and in 2010-2012, whereas an increase for tylosin, tilmicosin, tulathromycin and spectinomycin (from 2 to >64, 2 to >128, 16 to 128 and 4 to >64 µg/ml,

respectively) could be observed (Gautier-Bouchardon *et al*., 2014). This statement is supported by more recent data from Klein *et al*. (2019), who reported MIC_{50} and MIC_{90} values of 4 respective 8 µg/ml for florfenicol and both MIC_{50} and MIC_{90} values of >64 µg/ml for tulathromycin of *M. bovis* isolates from different European countries collected between 2014-2016.

Moreover, a recent Danish study reports that older isolates seemed to be less susceptible to florfenicol than more recent ones while comparing *M. bovis* isolates collected between 1981 and 2016 (Tardy *et al*., 2020).

In the absence of official criteria to assess breakpoints or epidemiological cut off values, Bokma *et al*. conducted own studies to estimate cut-off values for *M. bovis* for various antibiotics using different methods (visual, NRI and ECOFFinder). The authors also included percentages of isolates belonging to the wild type and non-wild type population and determined the epidemiological cut-off for florfenicol to be 16 µg/ml, with only four isolates showing acquired resistance (MIC 32 µg/ml) (Bokma *et al*., 2020).

Whole genome sequencing of a *M. bovis* isolate from a farm facing a natural outbreak of BRD allowed strain classification to the Belgian genomic cluster IV. The genome was screened for previously described mutations in *M. bovis* involved in antimicrobial resistance as described elsewhere. No mutations directly associated with florfenicol resistance were detected. However, known mutations for other antimicrobials such as macrolides were observed (Jourquin *et al*., 2022).

In a recent assessment report published by the European Food Safety Authority (EFSA) panel on Animal Health and Welfare (AHAW), based on information collected by a worldwide conducted extensive literature review and an expert judgement on the collected data, it was concluded that "*M. bovis* is not a relevant antimicrobial-resistant cattle pathogen in the EU even though it is a frequent reason for group medication, and has limited therapeutic options". Low mean levels of resistance to florfenicol and fluoroquinolones were reported, whereas resistance to both macrolides and tetracyclines was much more pronounced (EFSA panel on animal health and welfare, 2021).

2.1.3. Dose determination and confirmation

The applicant has proposed the same dosing regimen for the treatment of *M. bovis* as is already authorised for Zeleris for the treatment of BRD associated with pyrexia due to *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. Thus, no additional data on dose determination or confirmation were provided, but the applicant demonstrated clinical equivalence with a positive control product for the intended indication in the clinical field trial.

2.1.4. Tolerance in the target animal species

As Zeleris is already authorised for the target species cattle by the same route of administration and using the same dosing regimen, no additional data related to the target animal safety were provided by the applicant. This is considered acceptable.

2.1.5. Clinical trials

The efficacy of Zeleris regarding the new indication against *Mycoplasma bovis* was investigated in one clinical trial conducted in Europe (Hungary, Netherlands and Germany).

The purpose of this clinical trial as stated by the applicant was to evaluate the efficacy and safety of a single subcutaneous injection of Zeleris for the treatment and reduction of associated clinical signs of acute respiratory tract infections in bovines associated with pyrexia due to *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis*, in comparison with one subcutaneous

injection of a positive control product authorised for the treatment of BRD and containing a fixed combination of florfenicol (40 mg/kg bw) and flunixin (2.2 mg/kg bw).

A number of 406 calves (Full analysis set population) were included in the study, with 203 calves being allocated to the treatment group (Zeleris) and 203 calves to the positive control group. Per-protocol population consisted of 403 calves.

Calves showing BRD-related symptoms such as pyrexia, presence of coughing and/or nasal/ocular discharge and changes of behaviour/demeanour based on a clinical examination by a veterinarian on Day 0 were included in the study.

In order to demonstrate efficacy against infections of *M. bovis*, analysis was made in the per-protocol population of animals with a positive PCR or bronchoalveolar lavage (BAL) culture on D0 (n=166).

The primary endpoint for treatment efficacy was the percentage of calves cured on Day 7 with cure defined by a behavioural and respiratory score and a rectal temperature ≤39.5°C. Secondary efficacy criteria included reduction of rectal temperature 12±1 hours post treatment, percentages of calves cured on Day 14, percentages of calves cured on Day 28±1, percentages of calves cured without recurrence of signs of BRD on days 1 to 14, percentage of calves showing a relapse between day 8 and day 14, percentages of calves showing a new infection between Day 15 and Day 28±1, evolutions of clinical scores (respiratory and behavioural scores) and rectal temperature from Day 0 to Day 14 and Day 28±1, percentages of calves with rectal temperature ≤39.5°C 24 and 48 hours post treatment, mean average daily bodyweight gains from Day 0 to Day 28±1, percentages of mortality from Day 0 to Day 28±1, time to first clinical cure from Day 0 to Day 14.

For primary efficacy evaluation, non-inferiority against the positive control product was tested using a non-inferiority margin of 15%, a statistical power of 80%, and a confidence level of one-sided 97.5% on Day 7.

Zeleris was confirmed to be non-inferior to the positive control product regarding clinical cure at Day 7 and with comparable efficacy on all other clinical criteria, except for rectal temperature at Day 0+12 hours, where a slight statistically significant effect, with on average 0.1°C lower values in the positive control product compared to Zeleris, was noted.

It is however pointed out that only 2 out of 166 calves were found to be infected on Day 0 with *M. bovis* solely. All the other infections were caused by multiple BRD-related pathogens, especially mixed infections with those bacteria Zeleris is already authorised for and for which efficacy was demonstrated in the past.

Additionally, 114 out of the 403 animals included in the study were withdrawn, 112 due to BRD-related reasons. 93 out of those 112 animals were infected with *M. bovis* at the time of withdrawal, albeit only 49 had been positive at D0. Nevertheless, the statistical models did not present a significant relationship between withdrawal and *M. bovis* infection on D0. Furthermore, the prevalence of *M. bovis* was comparable in the withdrawal groups of both Zeleris and positive control product.

During the field trial 15 animals (7.4%) treated with Zeleris and 18 animals (8.9%) treated with the positive control product presented adverse events. Among these, four animals (2.0%) treated with Zeleris presented a serious adverse event. One and three animals died related and unrelated to BRD, respectively. One serious adverse event was also recorded in an animal (0.5%) treated with the positive control product (death unrelated to BRD).

In conclusion, it was demonstrated in the clinical field trial that Zeleris was non-inferior to the positive control product in the clinical cure at Day 7 against BRD-related mixed infections and with comparable efficacy on all other clinical criteria related to BRD, except for rectal temperature at Day 0+12 hours.

Based on the results of this study, a comparable efficacy against *Mycoplasma bovis* (in mixed infections) as the positive control product, which is indicated for the treatment of *M. bovis*, can be assumed. Therefore, the new indication for the treatment of bovine respiratory disease due to *Mycoplasma bovis* associated with pyrexia can be accepted.

2.2. Alignment of the product information with version 9.0 of the QRD template

In order to align the product information of Zeleris with version 9.0 of the QRD template, mostly editorial changes have been made. Additionally, to bring the product information in line with the 'Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/383441/2005-Rev.1)', some further changes have been proposed. Those changes especially concern the addition of special precautions for safe use in the target species (SPC section 3.4) and amendments of SPC section 3.6. Outdated CLSI breakpoints in SPC section 4.2 have been updated.

3. Benefit-risk assessment of the proposed change

Zeleris is authorised for the treatment of bovine respiratory disease associated with pyrexia due to *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* susceptible to florfenicol in cattle. The active substances are florfenicol, a synthetic broad-spectrum antibiotic, and meloxicam, a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. The product is available as solution for injection to be used subcutaneously at a dosage of 40 mg florfenicol/kg bodyweight and 0.5 mg meloxicam/kg bodyweight. The withdrawal period is 56 days for meat and offal; the product is not authorised for use in animals producing milk for human consumption.

The proposed grouped variation is to add a new therapeutic indication for the treatment of bovine respiratory disease associated with pyrexia due to *M. bovis* and to align the product information with version 9.0 of the QRD templates.

The proposed dose for this new indication is the same as for the already authorised indications.

3.1. Benefit assessment

Direct therapeutic benefit

The benefits of the product concerning the treatment of bovine respiratory disease associated with pyrexia due to *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* remain unaffected by this variation. However, the change in indication proposed in this application infer new benefits of the product by the addition of *Mycoplasma bovis* to the list of target pathogens.

3.2. Risk assessment

Quality:

The quality remains unaffected by this variation.

Safety:

The user, consumer, environmental and target animal safety remains unaffected by this variation. Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Administration of Zeleris in accordance with SPC recommendations is generally well tolerated. The adverse reactions reported in the field efficacy and safety trial provided with this application do not deviate from those already known from the initial marketing authorisation.

The potential for mild and transient adverse effects such as swelling at the injection site cannot be excluded.

Risk for the user:

The CVMP previously concluded that user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment:

Zeleris is not expected to pose a risk for the environment when used according to the SPC recommendations.

Risk for the consumer:

Based on the data provided and taking into account a sufficient safety span, a withdrawal period of 56 days for meat and offal was previously considered acceptable for the use of Zeleris in the target species cattle.

Resistance:

Concerns have been raised relating to the potential for resistance emergence as it cannot be excluded that there might be an increased risk of resistance in the target pathogen *M. bovis* against florfenicol.

The fact that no standard MIC determination method and no validated criteria to assess breakpoints or epidemiological cut off values of *M. bovis* isolates are available should be noted and makes the data comparison between laboratories and time periods difficult, especially when referring to published data. Also, the lack of clear PK/PD relationship for this pathogen should be taken into consideration when interpreting MIC data. Thus, a definite conclusion on development of resistance in recent years is not considered possible by the data available.

Appropriate warnings regarding responsible use of antimicrobials in line with the 'Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances' (EMA/CVMP/383441/2005-Rev.1) have been included in the product information.

3.3. Risk management or mitigation measures

Appropriate information to inform on the potential risks of this product relevant to the target animal and the development of resistance has been included in the SPC and other product information.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged regarding the addition of *Mycoplasma bovis* to the list of indications on the following aspects: quality, user safety, environmental safety, consumer safety.

The product has been shown to be efficacious for the treatment of bovine respiratory disease due to *Mycoplasma bovis* associated with pyrexia.

The product is well tolerated by the target animals and presents an acceptable risk for the target animals, when used as recommended.

Appropriate precautionary measures have been included in the SPC and other product information.

Based on the data presented, the overall benefit-risk is deemed positive.

4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Zeleris can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows: to add a new therapeutic indication for the treatment of bovine respiratory disease due to *Mycoplasma bovis* associated with pyrexia and to align the product information with version 9.0 of the QRD template.

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, II, IIIA and IIIB.

As a consequence of these variations, sections 2, 3, 4, 5, 6, 7, 8, 9 and 10 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.