20 February 2020
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Tulaven (EMEA/V/C/005153/0000)

INN: tulathromycin

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

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Introduction

The applicant CEVA Santé Animale submitted on 27 February 2019 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Tulaven through the centralised procedure under Article 3(3) of Regulation (EC) No 726/2004 (generic).

The eligibility to the centralised procedure was agreed upon by the CVMP on 14 September 2018 as the product would constitute a generic of a product authorised through the centralised procedure - Draxxin (reference product).

The applicant applied for the following indications:

Cattle (100 mg/ml)

Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* sensitive to tulathromycin. The presence of the disease in the herd should be established before metaphylactic treatment.

Treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis* sensitive to tulathromycin.

Pigs (100 mg/ml and 25 mg/ml)

Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica* sensitive to tulathromycin. The presence of the disease in the herd should be established before metaphylactic treatment. Tulaven should only be used if pigs are expected to develop the disease within 2-3 days.

Sheep (100 mg/ml)

Treatment of the early stages of infectious pododermatitis (foot rot) associated with virulent *Dichelobacter nodosus* requiring systemic treatment.

The active substance of Tulaven is tulathromycin, a semi-synthetic macrolide antimicrobial agent, which is a bacteriostatic acting antibiotic that inhibits essential protein biosynthesis by virtue of its selective binding to bacterial ribosomal RNA. It stimulates the dissociation of peptidyl-tRNA from the ribosome during the translocation process. The target species are cattle, pigs and sheep for Tulaven 100 mg/ml and pigs only for Tulaven 25 mg/ml.

Tulaven 100 mg/ml is presented in packs containing 1 vial of 20 ml, 50 ml, 100 ml, 250 ml or 500 ml.

Tulaven 25 mg/ml is presented in packs containing 1 vial of 50 ml, 100 ml or 250 ml.

The rapporteur appointed is Andrea Golombiewski and the co-rapporteur is Cristina Muñoz Madero.

The dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC – a generic application.

On 20 February 2020, the CVMP adopted an opinion and CVMP assessment report.

On 24 April 2020, the European Commission adopted a Commission Decision granting the marketing authorisation for Tulaven.

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 (dated June 2017) 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.

Manufacturing authorisations and inspection status

Manufacture of the dosage form takes place in the EEA. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture of such veterinary dosage forms, has been provided.

Batch release takes place at CEVA Santé Animale, 10 avenue de La Ballastiere, 33500 Libourne, France. The site has a manufacturing authorisation issued by the competent authority in France. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the batch release of such veterinary dosage forms, has been provided.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by a third party.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system is in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and is in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as a multidose aqueous solution for injection containing 100 mg/ml or 25 mg/ml of tulathromycin as active substance.

Other ingredients are monothioglycerol, citric acid anhydrous, propylene glycol, hydrochloric acid dilute, sodium hydroxide and water for injections.

The veterinary medicinal product (VMP) is filled in 20 ml glass vials or 50 ml, 100 ml, 250 ml or 500 ml plastic vials in the case of the 100 mg/ml strength. The 25 mg/ml strength will be presented in 50 ml, 100 ml and 250 ml plastic vials. All presentations are closed with bromobutyl stoppers coated with a fluoropolymer film as described in section 6.5 of the SPC.

Containers

The primary packaging is either colourless type I glass vials or multilayer translucent plastic vials, both sealed with a type I bromobutyl stopper coated with a fluoropolymer film and aluminium flip capsules. Compliance with Ph. Eur. monograph 3.1.6 'Polypropylenes for containers and closures for parenteral and ophthalmic preparations' and with Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come in contact with foodstuff has been declared for polypropylene (inner layer of the multi-layer plastic vials). Besides, compliance of glass vials and rubber stoppers with relevant monographs of Ph. Eur. has also been stated. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. In addition, the extraction and interaction studies have been performed with the plastic vials.

According to section 6.5 of the SPC the vials are packaged in outer cardboard cartons containing 1 vial. The pack sizes are consistent with the dosage regimen and duration of use.

Development pharmaceutics

The objective of pharmaceutical development was to develop a generic of Draxxin, authorised in November 2003 (100 mg/ml solution for injection in cattle, pigs and sheep) and July 2014 (25 mg/ml solution for injection in pigs) in the EU marketed by Zoetis.

The generic was developed to be as close as possible to the originator regarding qualitative and quantitative composition. The applicant used several available sources of information such as patent applications and CVMP scientific discussion (EPAR) as well as laboratory deformulation to achieve this.

Tulathromycin is a semi-synthetic macrolide antibiotic that has been shown to be active against respiratory pathogens of cattle and pigs (e.g. *Actinobacillus pleuropneumonia*, *Bordetella bronchiseptica*, *Haemophilus parasuis*, *Histophilus somni*, *Mannheimia haemolytica*, Mycoplasma bovis, *Mycoplasma hyopneumoniae* and *Pasteurella multocida*). Tulathromycin exhibits a high chirality with 18 stereocenters. The content of isomer B in tulathromycin active substance is different to that in tulathromycin solution for injection. The adequate ratio in the finished product is achieved by adding an isomerisation step to the manufacturing process. The applicant discussed the individual parameters and supported the conclusions with laboratory data.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur or USP NF standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

The applicant presented pre-stability as well as comparative stability data with the reference product to prove the suitability of the proposed manufacturing process and the intended container closure system.

Method of manufacture

The VMP is manufactured by a process of sequential addition and mixing of the active substance and the excipients, isomers equilibration, pH adjustment and sterilisation by filtration and filling in pre-sterilised containers.

The process is considered to be a non-standard manufacturing.

The isomerisation reaction marks the most critical step within the manufacturing process and is tightly controlled.

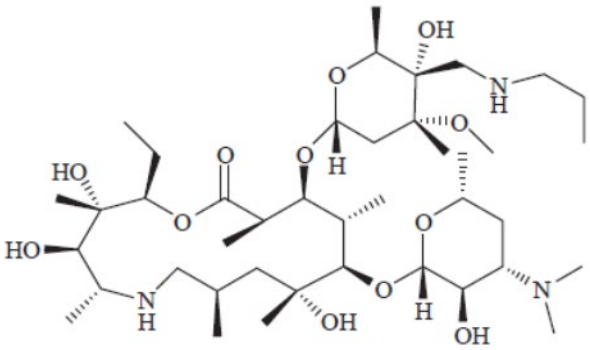
The manufacturing process has been validated using 4 commercial scale batches of Tulaven 100

mg/ml and 2 commercial scale batches of Tulaven 25 mg/ml. It has been demonstrated that the manufacturing process is capable of producing finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Control of starting materials

Active substance

The IUPAC name of tulathromycin is (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyranosyl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylohexopyranosyl]oxy]- 1-Oxa-6-azacyclopentadecan-15-one and has the following structure:



Tulathromycin is a semi-synthetic macrolide antibiotic that presents a combination of two regio-isomers: tulathromycin A and tulathromycin B. Tulathromycin A is the predominant isomer with low levels of tulathromycin B which is controlled as an impurity in the active substance. Enantiomeric purity is controlled routinely.

The active substance is a white or off-white powder, slightly hygroscopic, practically insoluble in water and freely soluble in dichloromethane and methanol. Since the active ingredient is solubilised in the finished product, particle size and polymorphism considerations are not considered critical for the quality of the finished product. Tulathromycin is not described in any pharmacopoeia. Supporting data for the active substance has been provided in the form of an ASMF.

The active substance specification from the manufacturer of the medicinal product includes tests for appearance, identity, sulfated ash, optical rotation, water content, assay, related substances, residual solvents and microbiological quality. The specification for the active substance proposed by the finished product manufacturer is acceptable and is in line with the specification set by the active substance manufacturer.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the CVMP Guideline on the chemistry of active substances for veterinary medicinal products

(EMA/CVMP/QWP/707366/2017). Potential and actual impurities were discussed with regards to their origin and characterised.

Batch analysis data for production-scale batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

The stability studies on tulathromycin have been conducted by the ASMF holder. Stability data on production-scale batches of active substance from the proposed manufacturer stored in the intended commercial package under long term conditions at 25 ºC/60% RH and under accelerated conditions at 40 ºC/75% RH according to the VICH guidelines were provided.

The following parameters were tested during stability studies: appearance, identification, water content, related substances and assay. The analytical methods used were the same as for the active substance specification and were stability indicating. All tested parameters were within the specification. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify a retest period of 24 months as requested.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or USP NF standards except the excipient sodium hydroxide which meets an in-house monograph. The proposed in-house specification is acceptable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The product does not contain any materials derived from human or animal origin.

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

A valid TSE declaration from the manufacturer of the finished product has been provided.

Control tests on the finished product

The specifications proposed at release are appropriate to control the quality of the finished product and include tests for appearance, identification and quantification of tulathromycin and monothioglycerol, quantification of isomers ratio, average volume, clarity, particulate contamination with visible particles, degree of coloration, pH, relative density and sterility. The results for tulathromycin assay, isomer ratio and total degradation products found in the finished product during shelf life are consistent with the set limits.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines. Satisfactory information regarding the reference standards used for assay testing of active substance and antioxidant has been presented.

Results of the 25 mg/ml strength batch analysis and the 100 mg/ml strength batch analysis confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification are provided.

Stability

The specifications proposed at the end of shelf-life have been adequately justified and include limits for degradation products.

Results of stability studies of both strengths of the products were carried out in line with the VICH GL3 were provided. The product was stored under long term or intermediate conditions at 25 ºC/60% RH and 30 ºC/75% RH and under accelerated conditions at 40 ºC/75% RH for up to 6 months. The batches of product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, clarity, degree of coloration, pH, tulathromycin assay, isomers ratio, monothioglycerol assay, degradation products, sterility and content of plastic additives. Limits for the parameter's particulate contamination with visible particles and for relative density have been included in the specifications. The analytical procedures are the same as those described to control the product at release. No significant changes have been observed up to the reported sampling points. In addition, each strength was exposed to light as defined in the VICH GL5 on photostability testing of new veterinary drug substances and medicinal products and the formulation is considered stable. A freeze-thaw stability study has been also provided and no significant evolution is observed for all the tests and on both presentations.

Based on the stability data available, the shelf-life is 2 years without any special storage conditions.

Data submitted on in-use stability studies, with one recently manufactured batch of the largest vial size for each strength, are considered appropriate to support the proposed shelf-life of 28 days after broaching. Confirmation is provided that the in-use stability study will be repeated with at least one batch per strength at the end of the shelf life.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way.

Part 3 – Safety

Tulaven 100 mg/ml is a solution for injection, which contains tulathromycin as active substance, intended to be administered by the subcutaneous route in cattle and by the intramuscular route in pigs and sheep.

Tulaven 25 mg/ml is a solution for injection, which contains tulathromycin as active substance, intended to be administered by intramuscular route in pigs.

This application has been submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended (generic product) thus, the results of pharmacological and toxicological tests are not required, as long as bioequivalence with the reference product is demonstrated.

Draxxin 100 mg/ml (EU/2/03/041/001-005) and Draxxin 25 mg/ml (EU/2/03/041/006-008), authorised by the Commission through a centralised procedure in 2003 and 2014, respectively, have

been chosen as reference products.

Tulaven 100 mg/ml and Tulaven 25 mg/ml will be administered at the same dose and by the same route of administration as the reference product. In addition, there are no differences in the composition of the candidate product compared to the reference product that would be expected to alter the absorption, rate and extent of distribution and persistence of tulathromycin.

Since this is a generic application submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended, and the omission of bioequivalence studies has been justified, results of toxicological, pharmacological or clinical tests are not required.

User safety

No user risk assessment has been submitted due to the legal basis of this application. It can be reasonably concluded that no difference in terms of risk to the user is to be expected between candidate and reference formulations and consequently, the provision of user safety data is unnecessary in this instance. The candidate products have the same qualitative and quantitative composition in active substance and the same excipients in similar amounts as the reference veterinary medicinal product. The candidate products are intended to be administered by the same route of administration at the same dose and for the same indications for use in the same species as the reference products. Therefore, the risk for the user is expected to be the same as that of the reference products and the same warnings as those included in the SPC of Draxxin are considered sufficient to prevent the user's exposure and manage the associated risks.

Based on the above risk assessment the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

The applicant has submitted Phase I calculations of the predicted environmental concentrations of tulathromycin in soil in both scenarios (intensively reared and pasture animals). The calculations were performed according to the guidelines on environmental impact assessment for veterinary medicinal products (Phase I - CVMP/VICH/392/98-FINAL as well as the guideline on environmental impact assessment for veterinary medicinal products in support of the VICH GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

For intensively reared animals (cattle and pigs) and pasture animals (cattle and sheep), values of PECsoil initial of tulathromycin were below the trigger value of 100 µg/kg. Thus, in accordance with current guidelines the Environmental Impact Assessment for both products can stop in phase I.

Based on the data provided Tulaven is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

MRLs

The MRL status of the constituents of Tulaven is as follows:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Tulathromycin	(2R,3S,4R, 5R,8R,10R, 11R,12S, 13S,14R)-2-ethyl-3,4,10,13-tetra-hydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethy-lamino)-ß-D-xylo-hexopyranosyl]oxy]-1- oxa-6-azacyclopent-decan-15-one expressed as tulathromycin equivalents	Ovine, Caprine	450 µg/kg 250 µg/kg 5400 µg/kg 1800 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption	Anti-infectious agents/Antibiotics
		Bovine	300 µg/kg 200 µg/kg 4500 µg/kg 3000 µg/kg	Muscle Fat Liver Kidney		
		Porcine	800 µg/kg 300 µg/kg 4000 µg/kg 8000 µg/kg	Muscle Skin and fat in natural proportion Liver Kidney		

All constituents of the intended product Tulaven are included in Table 1 of Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin or are considered as not falling within the scope of Council Regulation 470/2009.

Residue studies

No residue studies were provided in support of the current application. Tulaven 25 mg/ml and Tulaven 100 mg/ml have been developed as generic products according to Article 13(1) of Directive 2001/82/EC. The omission of bioequivalence studies is justified by the fulfilment of condition 7.1 b) of the 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' EMA/CVMP/016/00-Rev.3.Tulaven 25 mg/ml and Tulaven 100 mg/ml have the same qualitative and quantitative composition as Draxxin solution for injection in terms of active substance and the same pharmaceutical form. The qualitative composition in terms of excipients is also the same as that of the reference product. Differences in the amount of excipients, if any, are not expected to affect the rate and/or extent of absorption of the active substance. Moreover, these products are to be used at the same dose, using the same route of administration and are for the same therapeutic indications as the reference products. Since this application fulfils the requirements of Directive 2001/82/EC for generics, the applicant is exempt from providing the results of proprietary residues studies and analytical methods for the detection of residues in part 3.B.

Withdrawal periods

According to Title III of the Directive 2009/9/EC (amending Directive 2001/82/EC) 'Requirements for Specific Marketing Authorization Applications', the following additional data shall be provided for generic veterinary medicinal products intended to be administered by intramuscular (IM), subcutaneous (SC) or transdermal routes: 'Evidence to demonstrate equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies'.

However, according to section 4.4 of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.3), for formulations (i.e. active substance plus all excipients) that are qualitatively and quantitatively identical, a justification for the absence of residues data is acceptable.

The applicant has carried out an analysis and submitted data comparing the formulations of the reference and generic products. Both products have the same qualitative and quantitative composition in active substance, the same excipients and pharmaceutical form. The differences in the amount of excipients, if any, are not expected to affect the rate of residue depletion.

Moreover, the candidate products are intended to be administered by the same route of administration at the same dose and for the same indications for use in the same species as the reference products. Based on these data the depletion of residues at the injection site is expected to be the same as that of the reference products and no additional meat depletion studies for cattle, pig or sheep are required.

The withdrawal periods approved under section 4.11 of the SPC of the reference products will also apply for the candidate products:

Cattle (meat and offal): 22 days.

Pigs (meat and offal): 13 days.

Sheep (meat and offal): 16 days.

Not authorised for use in animals producing milk for human consumption. Do not use in pregnant animals, which are intended to produce milk for human consumption, within 2 months of expected parturition.

Overall conclusions on the safety and residues documentation

Since this is a generic application submitted in accordance with Article 13(1) of Directive 2001/82/EC, and the omission of bioequivalence studies has been justified, results of toxicological and pharmacological studies are not required.

The risk for the user is expected to be the same as that of the reference products, because the products have the same qualitative and quantitative composition in active substance and the same excipients in similar amounts as the reference veterinary medicinal products. Furthermore, the route of administration, the dose and the indications are the same as for the reference products. Therefore, the same warnings as those included in the SPC of Draxxin are considered sufficient to prevent the user's exposure and manage the associated risks.

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

Since the products intended to be authorised are qualitatively and quantitatively the same as the reference products in terms of active substance, since the differences in the amount of excipients, if any, are not expected to affect the rate of residue depletion and since the pharmaceutical form, target species, indications, dosage and route of administration are the same, the withdrawal periods of the reference products can be also applied to the generics.

To ensure comprehensive adverse event surveillance and to benefit from the possibility of aligning periodic safety update report (PSUR) submissions for generic products as foreseen in the legislation, PSUR submissions should be synchronised with the reference product, Draxxin. In addition, surveillance of the data in EudraVigilance Veterinary (EVVet) will also be synchronised for signal detection of the two products.

Part 4 – Efficacy

Tulaven 25 mg/ml and Tulaven 100 mg/ml have been developed as generic products according to Article 13(1) of Directive 2001/82/EC. The reference product is Draxxin solution for injection for cattle, pigs and sheep, which was authorised by the European Commission on 11 November 2003.

Bioequivalence

In vivo bioequivalence studies were not conducted. Instead, the applicant claimed an exemption from such studies based on section 7.1 b) of the 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/00-Rev.3).

Tulaven and Draxxin have the same qualitative composition in terms of active substance and excipients and the same concentration of active substance. The differences in the amount of excipients, if any, are not expected to affect the rate and/or extent of absorption of the active substance. Moreover, these products have the same pharmaceutical form, are to be used in the same target species at the same dose, using the same route of administration and the same therapeutic indications as the reference products.

Considering the above, bioequivalence between the candidate product Tulaven and the reference product Draxxin can be accepted.

Development of resistance

As this is a generic application and bioequivalence between the candidate and the reference product can be accepted, and the candidate product is used in the same target animal species, for the same indications, in the same doses and in the same treatment regimen as the reference product, the resistance profile of the target pathogens against the candidate product will be the same as for the reference product. Nevertheless, the applicant has conducted a comprehensive literature review on the situation and development of resistance of the target pathogens against tulathromycin comprising articles published since the approval of the reference product Draxxin.

Based on the data submitted, no evidence for a shift in the susceptibility that would raise a concern has been observed for the target pathogens, where breakpoints are available. It is noted that no clinical breakpoints are available for *Mycoplasma bovis*, *M. hyopneumoniae*, *Haemophilus parasuis*, *Moraxella bovis* and *Dichelobacter nodosus* and that makes the interpretation of the data difficult in some cases. Specifically, this was the case of *Mycoplasma bovis* in which high MICs were detected but no valid conclusion can be drawn due to the absence of a clinical breakpoint. Furthermore, very little information is available on the susceptibility of *Moraxella bovis* and *Dichelobacter nodosus* to tulathromycin.

Although only limited susceptibility data of the claimed target pathogens isolated in Europe during the last five years are published, it can be concluded from the entire data available that resistance development to tulathromycin is limited or not observed. Hence, the potential for resistance development appears to be low and it is not expected to differ between Tulaven and the reference product Draxxin.

The product information of Tulaven contains appropriate information on the correct use of the product in the context of antimicrobial resistance, in line with the information included in the SPC of the reference product. However, notwithstanding the legal basis of this generic application, an additional phrase to ensure prudent use of the veterinary medicinal product has been included in section 4.5 of the SPC in line with the revised guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005).

Target animal tolerance

Bioequivalence is considered demonstrated between the candidate and the reference product. The products have the same qualitative and quantitative composition in active substance and the same excipients in similar amounts. Both products are intended to be used at the same dose and administration routes. Thus, the expected tolerance profile in the target species would be the same. The omission of tolerance data is considered acceptable.

Clinical field trials

As bioequivalence between the generic product and the reference product is considered established and the candidate product is administered by the same routes and at the same dose, the same level of efficacy is expected as for the reference product. Therefore, omission of clinical data is accepted.

Overall conclusion on efficacy

This is a generic application based on Article 13(1) of Directive 2001/82/EC. The generic product, Tulaven (100 mg/ml and 25 mg/ml), is considered to be bioequivalent to the reference product, Draxxin, in accordance with section 7.1.b) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.3).

Both the reference and generic products are aqueous solutions to be administered by the subcutaneous or intramuscular route and both contain the same active substance (tulathromycin) at the same concentration. In addition, the excipients are qualitatively the same in both formulations. Differences in the amount of excipients, if any, are not expected to affect the rate and/or extent of absorption of the active substance. Therefore, the omission of *in vivo* bioequivalence studies or further pharmacological, toxicological and (pre-)clinical studies is acceptable. When the same posology is followed, the efficacy and safety profiles for the generic and reference products are expected to be the same.

A bibliographical search revealed no reports that would raise concern in relation to resistance to tulathromycin in relevant target pathogens, suggesting that the situation on resistance has not significantly changed since the last renewal of the marketing authorisation for the reference product Draxxin in 2008.

However, notwithstanding the legal basis of this generic application, minor amendments to the SPC have been introduced. These are in line with the QRD vet template at the time of CVMP opinion (Version 8.1, 01/2017) and the revised guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005).

Part 5 – Benefit-risk assessment

Introduction

Tulaven is a solution for injection containing 100 mg tulathromycin /ml or 25 mg tulathromycin/ml.

The active substance, tulathromycin, is a well-known semi-synthetic macrolide antimicrobial agent, which is a bacteriostatic acting antibiotic that inhibits essential protein biosynthesis by virtue of its selective binding to bacterial ribosomal RNA.

The product is intended for use in cattle, pigs and sheep for:

Cattle (100 mg/ml)

Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* susceptible to tulathromycin. The presence of the disease in the herd should be established before metaphylactic treatment.

Treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis* susceptible to tulathromycin.

Pigs (100 mg/ml and 25 mg/ml)

Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica* susceptible to tulathromycin. The presence of the disease in the herd should be established before metaphylactic treatment. The product should only be used if pigs are expected to develop the disease within 2-3 days.

Sheep (100 mg/ml)

Treatment of the early stages of infectious pododermatitis (foot rot) associated with virulent *Dichelobacter nodosus* requiring systemic treatment.

The proposed effective dose of 2.5 mg tulathromycin/kg bodyweight as a subcutaneous injection (cattle) or intramuscular (pigs and sheep) injection has been confirmed.

The application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (abridged application - generic). The reference product is Draxxin solution for injection for cattle, pigs and sheep.

Benefit assessment

Direct therapeutic benefit

The evidence for the direct therapeutic benefit of Tulaven 100 mg/ml and 25 mg/ml is considered established on the basis of bioequivalence to the reference product. Therefore, the direct therapeutic benefits for Tulaven are expected to be the same as those for the reference product, Draxxin, i.e. efficacy for the proposed indications.

Additional benefits

Not applicable.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Given that bioequivalence of the generic and reference products can be accepted, the products are

expected to have the same safety profiles in the target animal when administered according to the same posology. Administration of Tulaven in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions include very commonly transient pain reactions and local swellings at the injection site that can persist for up to 30 days after subcutaneous injection in cattle. Pathomorphological injection site reactions (including reversible changes of congestion, oedema, fibrosis and haemorrhage) are very common for approximately 30 days after injection in cattle and pigs. In sheep, transient signs of discomfort (head shaking, rubbing injection site, backing away) are very common after intramuscular injection. These signs resolve within a few minutes.

Risk for the user:

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

Risk for the environment:

Tulaven is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk for the consumer:

Tulathromycin has been evaluated previously in respect to the safety of residues and MRLs have been established for the target species and food commodities concerned under this application. Tulaven is not expected to pose a risk to the consumer of meat derived from treated animals when it is used according to the SPC recommendations. The product is not authorised for use in animals producing milk for human consumption. The withdrawal periods approved under section 4.11 of the SPC of the reference product will also apply to the generic product. The withdrawal periods are:

Cattle (meat and offal): 22 days.
Pigs (meat and offal): 13 days.
Sheep (meat and offal): 16 days.
The product is not authorised for use in animals producing milk for human consumption.

Risk management or mitigation measures

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

To ensure comprehensive adverse event surveillance, PSUR submissions and surveillance of EVVet data should be synchronised with the reference product.

Evaluation of the benefit-risk balance

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures, including the same withdrawal periods as for the reference product, have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the

Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for Tulaven is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.