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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Tulissin (EMEA/V/C/005073/0000)

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 Virbac S.A. submitted on 7 January 2019 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Tulissin 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 25 May 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. Tulissin 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 Tulissin 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 Tulissin 100 mg/ml and pigs only for Tulissin 25 mg/ml.

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

Tulissin 25 mg/ml is presented in packs containing 1 vial of 20 ml, 50 ml, 100 ml or 250 ml.

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

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 Tulissin.

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 on 5 December 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 EU. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture of the proposed veterinary dosage form, has been provided.

Batch release takes place at Fareva Amboise (Pocé-sur-Cisse, France) and Virbac S.A. (1ère Avenue 2065m, Carros Cedex, France), which hold a manufacturing authorisation and GMP compliance was confirmed by the Competent Authority of France.

GMP declarations for the active substance manufacturing sites were provided from the Qualified Person (QP) at the EU batch release site Virbac on behalf of both batch release sites (Virbac and Fareva Amboise). The declarations were based on an on-site audit by the manufacturing site responsible for batch release, Virbac.

Overall conclusions on administrative particulars

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

The GMP status of both 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 solution for injection containing 100 mg/ml or 25 mg/ml of tulathromycin as active substance.

Other ingredients are monothioglycerol, anhydrous citric acid, hydrochloric acid concentrated, sodium hydroxide, propylene glycol and water for injections. The product is a clear colourless to slightly coloured solution.

The solution for injection is filled into 20, 50, 100, 250 and 500 ml clear type I glass vials, sealed

with a fluoropolymer coated stopper and aluminium flip-off seal cap. The 500 ml vial is only presented for the 100 mg/ml formulation. The vials are further individually packed in outer cardboard boxes.

The composition is appropriately stated.

Containers

The primary packaging is clear type I glass vials, sealed with a fluoropolymer coated stopper and aluminium flip-off seal cap. The materials comply with the relevant European Pharmacopoeia (Ph. Eur.) monograph. The choice of container and its closure system has been validated by stability data and is adequate for the intended use of the product. A rubber protective sleeve can be included in the 250 ml and 500 ml glass vials to provide protection against breakage by the end user.

Glass vials of 20, 50, 100, 250 and 500 ml of solution 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 was to develop a generic of Draxxin, a medicinal product marketed by Zoetis, which was authorised via the centralised procedure in 2003. The applicant has made use of available information in Draxxin Summary of Product Characteristics (SPC), European Public Assessment Report (EPAR) and labelling.

The active substance, tulathromycin, is a semi-synthetic macrolide antibiotic that presents a combination of two regio-isomers (A and B). 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 means of an equilibration step during the manufacturing process of the veterinary medicinal product. Concerning this equilibration step, sufficient information has been provided.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or USP standards in the absence of a specific Ph. Eur. monograph, which 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.

Preliminary stability studies have been performed in order to assess the stability of the formulation and the compatibility with the container and its closure system. Different stability studies have been carried out: at 5 ºC, 40 ºC/75% RH, freeze-thaw cycles, photostability and in-use. Acceptable results are obtained. According to the results obtained on the fragmentation and self-sealing tests, a restriction on the number of punctures has been included in section 4.9 of the SPC.

A comparison of the content of related substances and degradation products of tulathromycin in the candidate and reference product has been provided. Both products show a similar profile.

Method of manufacture

The solution for injection is manufactured in a process involving sequential addition and dissolution of the product constituents in water for injections. Preparation of the solution takes place under nitrogen atmosphere.

The bulk solution is prepared by addition of all ingredients to water for injections to the manufacturing vessel. The bulk solution is then sterilised by filtration and filled into previously sterilised containers. The process is considered a non-standard manufacturing process. The

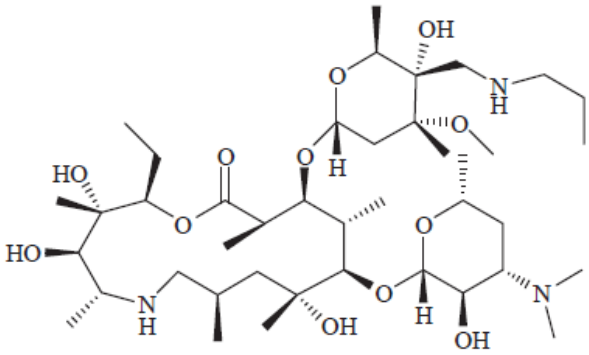
selection of the sterilisation method of the product is considered appropriately justified and the method of sterilisation of vials and stoppers has been detailed.

The process is considered satisfactorily validated with 3 commercial batches of each strength.

Control of starting materials

Active substance

The chemical 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 the substance 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 by specific optical rotation.

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 product, particle size and polymorphism 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. Two manufacturing sites are proposed for the active substance.

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

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.

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

Full stability data, long-term and accelerated conditions, have been provided from both manufacturers in order to establish a re-test period of the active substance. According to the results provided, a retest period of 24 months is considered acceptable for both suppliers. More details can be found in the applicant's part of both ASMFs.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or USP. 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

A declaration stating compliance with the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, (EMA/410/01 rev. 3), 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, extractable volume, particulate contamination, density, pH, tulathromycin and monothioglycerol identification and assay, isomer B ratio, degradation products and sterility.

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.

Batch analysis results are provided for 3 commercial batches sub-divided in 3 different vial sizes (small, medium and large), for each strength (100 mg/ml and 25 mg/ml), confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability studies are performed under VICH conditions and comprise the primary stability study, an in-use stability study, a freeze-thaw stability study and a photostability study.

The specifications proposed at the end of shelf-life have been adequately justified.

Stability data for 3 bulk batches of commercial scale, sub-divided in 2 different vial sizes (small and large), for each strength (100 mg/ml and 25 mg/ml) of finished product stored under long term conditions for 18 months at 30 ºC/65% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH GL3 on stability were provided. The absence of stability studies under long-term conditions at 25 ºC/60% RH has been justified. The batches of product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, one batch of each strength was exposed to light as defined in the VICH GL5 on photostability testing and the formulation is considered stable when the content of antioxidant is in the range proposed. Two batches per strength have been used for a freeze-thaw study showing stable behaviour.

The proposed shelf-life of 30 months without any special storage conditions as stated in the SPC is considered acceptable, since data up to 18 months at long term conditions are provided.

Data submitted from in-use stability studies, with 2 recent sub-batches of the largest vial size for each strength, are considered appropriate to support the proposed shelf-life of 28 days after broaching. Two aged sub-batches of 100 ml per strength will be added to the in-use stability study when they are available.

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

Safety documentation

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

Tulissin 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 in 2003 and 2014, respectively, have been chosen as reference products.

The applicant claims that the products intended to be registered are qualitatively and quantitatively identical in terms of composition and pharmaceutical form to the reference product and that specific studies demonstrating bioequivalence with the reference medicinal product are not required since, according to section 7.1.d) of the Guideline on the conduct of bioequivalence studies (EMA/CVMP/016/2000-Rev.3), no studies on bioequivalence need to be conducted when *the formulations are identical (identical active substances and excipients as well as physicochemical properties [e.g. identical concentration, dissolution profile, crystalline form, pharmaceutical form and particle size distribution with identical manufacturing process]).*

However, the CVMP considers that the absence of bioequivalence studies should be based on condition 7.1 b) of the guideline mentioned above (see part 4).

Given that the requirements of Directive 2001/82/EC, article 13(1), relating to generic medicinal products, are fulfilled, and that the omission of bioequivalence studies is acceptable, the safety profile of the reference product can be assumed and only information on ecotoxicity is required.

User safety

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 the reference product Draxxin are considered appropriate to prevent the user's exposure and manage the associated risks.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines. The Predicted Environmental Concentration (PEC) for soil was calculated in accordance with VICH GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the initial predicted environmental concentrations in soil for intensively reared animals (cattle and pigs) and pasture animals (cattle and sheep), were below the trigger value of 100 µg/kg.

Residues documentation

MRLs

The MRL status of the constituents of Tulissin 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 Tulissin 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 when used as in this product.

Residue studies

No residue studies were provided in support of the current application. Tulissin 25 mg/ml and Tulissin 100 mg/ml have been developed as generic products according to Article 13(1) of Directive 2001/82/EC. It can be accepted that the candidate formulations are sufficiently similar to the reference product formulations, and thus specific studies demonstrating bioequivalence with the reference medicinal product are not required. 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/016/2000-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. They 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

Tulissin has been submitted in accordance with Article 13(1) of Directive 2001/82/EC.

Given that the omission of bioequivalence studies is accepted, results of toxicological and pharmacological tests are not required.

The safety profiles of the candidate products are expected to be the same as those of the reference products and hence no additional user risk assessment needs to be submitted. The same risk mitigation measures as those of the reference product have been included in section 4.5. ii) of the SPC.

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.

A Phase I environmental risk assessment (ERA) has been performed. For intensively reared animals (cattle and pigs) and pasture animals (cattle and sheep), values of PEC_{soil} initial of tulathromycin were below the trigger value of 100 µg/kg. Thus, in accordance with current guidelines the environmental risk assessment for both products may stop in phase I. It can be concluded that the product does not entail any risk for the environment when used as recommended in the SPC.

The depletion of residues is expected to occur at the same rate as that of the reference product and no additional meat depletion studies for cattle, pig or sheep are required. The withdrawal periods of the reference products can be also applied to the generic.

Part 4 – Efficacy

The application is for a generic product, submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended. 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.d) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3). This exemption requires demonstration of identical qualitative and quantitative composition in active substance and excipients and identical physicochemical properties (including manufacturing process) as those of the reference product. However, it is noted that the product meets the requirements set in section 7.1.b) of the guideline since both the generic and the reference products are aqueous solutions to be administered by the subcutaneous or intramuscular route and they have the same qualitative and quantitative composition in terms of active substance and the same qualitative composition in terms of excipients. 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.

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

Development of resistance

As this is a generic product, the applicant proposes to include in the SPC the same information on resistance as the reference product.

However, as the current resistance situation might have changed since the last renewal of the marketing authorisation of the reference product in 2008, the applicant has provided data to document the current situation based on literature and recent MIC testing data.

A literature search was conducted to ascertain whether there have been any recent reports of resistance to tulathromycin in all claimed bacteria. Only 3 articles with susceptibility data on the claimed bacterial species isolated in Europe during the last 5 years in cattle, pigs or sheep were identified. These articles were related to *Mycoplasma bovis* in cattle and *Haemophilus parasuis* and *Actinobacillus pleuropneumoniae* in pigs. The results (MIC data or resistance percentage) are consistent with those obtained at the time when the reference product Draxxin was authorised (2003).

In addition, data from two European monitoring programs on antimicrobial resistance vigilance in target pathogens were provided. These data originated from different European countries representing a major part of the animal production in the EU. The MIC testing was performed at a central laboratory using broth microdilution method according to CLSI standards. The resistance rates were calculated taking into account CLSI breakpoints (VET08, 2018).

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 data difficult in some cases. Furthermore, very little information is available on the susceptibility of *Moraxella bovis* and *Dichelobacter nodosus*.

Taking into account all the available data, together with the characteristics of the application (generic product) and the product (solution to be injected to individual animals), the CVMP considers that the information provided is sufficient to document the current situation on resistance. Based on the data provided, the risk of resistance development seems unlikely in the target pathogens. It should also be noted that the product information contains appropriate sentences regarding 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 responsible use of the veterinary medicinal product has been inserted 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 test and the reference product. These products have the same qualitative and quantitative composition in active substance and the same excipients in similar amounts. Both products are 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 proposed generic product and the reference product is considered established and they are administered by the same routes and at the same dose, the same level of efficacy is expected for both products. As such, omission of clinical data is acceptable.

Overall conclusion on efficacy

This is an application based on Article 13(1) of Directive 2001/82/EC (a generic application). The generic product, Tulissin, 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/016/2000-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 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 on resistance to tulathromycin in most of the 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

Tulissin 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 (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 Tulissin is considered established on the basis of bioequivalence to the reference product. The direct therapeutic benefits for Tulissin 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 same safety profile in the target animal when administered according to the same posology is expected. Administration of Tulissin 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 safety profile of the generic is expected to be the same as that of the reference product, and hence no additional user risk assessment needs to be submitted. The same risk mitigation measures as those of the reference product have been included in section 4.5. ii) of the SPC.
The user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment:

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

Risk for the consumer:

Tulathromycin has been evaluated previously in respect to the safety of residues and MRLs limits have been established for the target species and food commodities concerned under this application. Tulissin 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 withdrawal periods approved under section 4.11 of the SPC of the reference product will also apply to the generic product, namely:

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 Tulissin 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.