7 October 2020
EMA/557847/2020
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Rexxolide (EMEA/V/C/005384/0000)

INN: tulathromycin

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Introduction

The applicant Dechra Regulatory B.V. submitted on 4 December 2019 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Rexxolide 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 22 May 2019 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

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

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. Rexxolide should only be used if pigs are expected to develop the disease within 2-3 days.

Sheep

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

The active substance of Rexxolide 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.

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

The rapporteur appointed is Sylvie Louet and the co-rapporteur is Jeremiah Gabriel Beechinor.

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 7 October 2020, the CVMP adopted an opinion and CVMP assessment report.

On 3 December 2020, the European Commission adopted a Commission Decision granting the marketing authorisation for Rexxolide.

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 5 February 2019) 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 within the EU. The site has a manufacturing authorisation issued on 2 April 2019 by the corresponding EU competent authority. GMP certification, which confirms the date of the last inspection conducted in November 2016, shows that the site is authorised for the manufacture of such veterinary dosage forms, has been provided in the dossier. A GMP certificate issued by an EU competent authority based on an audit carried out on 5 November 2019 is available on the EudraGMP database and indicates that the site is appropriately authorised for the manufacture of sterile veterinary medicinal products, both aseptically prepared and terminally sterilised.

Batch release takes place at Eurovet Animal B.V., Handelsweg 25, 5531AE Bladel, The Netherlands. The manufacturing authorisation and current GMP certificate shows that the site is authorised for batch release of this dosage form.

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 which has taken into consideration the GMP certificate available for the active substance site issued based on the Chinese Good Manufacturing Practices for Animal Drugs and by the Finnish medicines Agency.

Overall conclusions on administrative particulars

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

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

Part 2 - Quality

Composition

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

Other ingredients are monothioglycerol, citric acid, propylene glycol, water for injections, hydrochloric acid dilute and sodium hydroxide.Nitrogen is sparged during the whole manufacturing process. The product is a clear colourless to slightly yellow solution.

The product is available in multidose vials containing 50 ml, 100 ml and 250 ml, as described in section 6.5 of the SPC. The vials are further individually packed in outer cardboard boxes.

Containers

The primary packaging is type I clear glass vials closed with fluoropolymer coated rubber stoppers of 20 mm or 32 mm diameter and sealed with aluminium caps. The materials comply with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. As the medicinal product is presented in a multidose container with rubber closures intended to be pierced by a hypodermic needle, penetrability, self-sealing and fragmentation of the rubber closures have been tested according to the Ph. Eur. monograph 3.2.9. A restriction on the number of punctures has been included in section 4.9 of the SPC. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The methods of sterilisation of the different parts of the primary packaging have been described.

The proposed pack sizes were properly justified based on the target species, the dosage regimen and duration of use. However, one package should not be larger than necessary to allow the full course of the treatment of one single animal of average size (in line with the 'Question and Answer' on the CVMP guideline on the SPC for antimicrobial products). The applicant is thus recommended to develop a small vial of 20 ml (also available for the reference product) for the treatment of individual animals or group of light/small animals.

Development pharmaceutics

The objective was to develop a generic of Draxxin 100 mg/ml solution for injection for cattle, pigs and sheep. The applicant established the composition by analysis of samples of the reference product, on patents published and public information on EMA website on the reference product.

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. This ratio is achieved by means of an equilibration step during the manufacturing process of the veterinary medicinal product (VMP).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. and USP standards. The manufacturing process development was based on the identification of the product critical quality attributes (CQAs) and critical process parameters and on a risk assessment of the impact of the manufacturing process steps on the product CQAs identified previously. Critical steps have been appropriately studied and discussed. The process steps identified as impacting the CQAs were further optimised.

The selection of the sterilisation method has been made according to the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container EMA/CHMP/CVMP/QWP/850374/2015, on the basis of analysis results of batches sterilised by terminal heat sterilisation under different conditions. The compatibility of the filter with the medicinal product as well as the filter integrity and bacterial retention have been adequately demonstrated and supported by data and validation reports.

Method of manufacture

The process consists of obtaining the bulk solution, sterile filtration, filling and visual inspections of the filled vials. The solution is obtained by sequential addition of ingredients with control of their dissolution.

The manufacturing process has been appropriately described, including target pH, quantities of the different ingredients, speed and mixing duration.

Taking the considerable experience of the manufacturer with sterilisation via sterile filtration into account, the manufacturing process can be considered standard albeit that it includes a non-standard sterile filtration process. The proposed process validation plan is appropriate. It includes the size and number of validation batches, CQAs, critical process parameters (CPPs), a manufacturing description, in-process controls (IPCs), acceptance criteria and validated analytical methods. The manufacturing process has been validated on 3 industrial batches and the efficiency of the sterile filtration has been demonstrated by a challenge test.

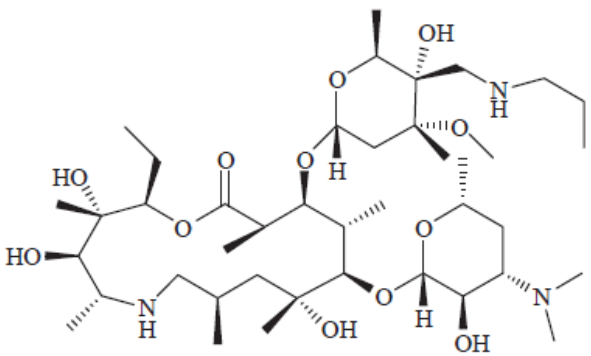
The IPCs are adequate for this type of manufacturing process and pharmaceutical form. The isomerisation process has been thoroughly studied and is appropriately controlled by inclusion of an IPC. The bioburden is appropriately controlled before the filtration step, and the specifications are in line with the Note for guidance on manufacture of the finished dosage form EMEA/CVMP/126/95. The method used for bioburden testing of the bulk solution has been adequately validated.

The bulk solution batch is split in two parts prior to filtration and filling in order to be able to fill different vial sizes. In line with the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container EMA/CHMP/CVMP/QWP/850374/2015, the maximum time between the start of bulk solution preparation and sterile filtration has been determined on the basis of data from three industrial batches, bioburden testing of the bulk solution is performed immediately before the start of sterile filtration and the filtration time will not be longer than 24 hours. The maximum holding time for the sterile filtered solution proposed by the applicant was supported by data from media fill simulations.

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 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 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 VMP includes tests for appearance, identity, specific rotation, assay, impurities, residual solvents, water content, residue on ignition and microbiological quality. The suitability of the microbiological test method for use with tulathromycin has been demonstrated. Limits for total and individual impurities and assay are identical to the specifications set by the active substance manufacturer. The specified impurities from the manufacturer of active substance are included in the specifications. The omission of the bacterial endotoxins control is justified according to Ph. Eur. 0520 on the basis of the posology of the veterinary medicinal product.

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

Batch analysis data from the finished dosage form manufacturer have been provided for two batches of tulathromycin. The results are within the specifications and consistent from batch to batch.

Full stability data, long-term and accelerated conditions, were provided by the ASMF holder to establish a re-test period of the active substance. According to the results provided, a retest period of 24 months is considered acceptable. More details can be found in the applicant's part of the ASMF.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or USP standards. As the use of aseptic processing provides the lowest guarantee of sterility assurance (decision tree for sterilisation choices for aqueous products EMA/CHMP/CVMP/QWP/850374/2015) and as testing of a product cannot ultimately guarantee its sterility, all measures must be taken throughout the manufacturing process to ensure sterility. Therefore, the microbiological quality of relevant excipients is controlled.

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 quality of nitrogen used to sparge the solution during the manufacturing process is adequate.

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

Declarations stating compliance of all ingredients 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), were 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, colour, extractable volume, visible particles, density, pH, tulathromycin

identification, tulathromycin assay, monothioglycerol identification and assay, isomer B ratio, degradation products, sterility and closure integrity. The omission to control the bacterial endotoxins level on the medicinal product has been adequately justified. The analytical methods have been described and appropriately validated in accordance with the VICH guidelines.

Satisfactory information regarding the reference standards used for assay, degradation products and antioxidant testing has been presented. Appropriate information on the method used to certify the primary standard of tulathromycin has been provided.

Batch analysis results are provided for two bulk batches at commercial scale sub-divided in the three proposed vial sizes, 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 and a freeze/thaw study.

The specifications proposed at the end of shelf-life are the same as those proposed at release except for extractable volume which is not tested during shelf-life. The differences between release and end of shelf-life acceptance criteria have been appropriately justified.

The stability testing program was performed on two batches for each pack size of the product Rexxolide 100 mg/ml solution for injection, stored under long term conditions up to 12 months at 25 ºC/60% RH and 30 ºC/65% RH and under accelerated conditions at 40 ºC/75% RH for 6 months according to the VICH GL3. They were packed in the primary packaging proposed for marketing and placed in both upright and inverted positions. In addition, one batch was subjected to freeze/thaw cycles and the formulation is considered stable. A photostability study has been performed according to VICH GL5. The analytical procedures are the same as described to control the product at release.

No significant changes have been observed in the stability data provided. The tulathromycin B ratio decreases slightly during storage with a slight increase in total tulathromycin impurities but remaining well within the limits of specifications.

The proposed shelf-life of 2 years without any special storage conditions as stated in the SPC is acceptable.

Data submitted on in-use stability studies, with one recent batch filled in 50 ml vial size, is considered appropriate to support the proposed shelf-life of 28 days after broaching. The in-use test design has been detailed and appropriately justified, as reflecting the worst-case scenario of the maximum number of plausible punctures to still leave enough volume for testing on day 28. The study will be repeated post-approval on two batches of respectively 100 ml and 250 ml pack size, close to expiry.

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.

In addition, the applicant is recommended to develop a small vial of 20 ml (also available for the reference product) for the treatment of individual animals or group of light/small animals. See 'Containers' section above.

Part 3 – Safety

Rexxolide 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.

This application has been submitted in accordance with Article 13 (1) of Directive 2001/82/EC (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), authorised by the European Commission through the centralised procedure in 2003, was chosen as the reference product.

No *in vivo* bioequivalence studies were conducted. The applicant claims exemption from the requirement for bioequivalence studies in accordance with Section 7.1.b of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3). From the results provided in Part 2, it is accepted that the criteria set out in section 7.1.b of the CVMP bioequivalence guideline have been satisfied; that is, the candidate formulation is of the same type of solution, contains the same concentration of active substance and comparable excipients in similar amounts as the reference product and that any differences in their concentrations will have no influence on the rate and/or extent of absorption of the active substance.

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 accepted, the safety profile of the reference product can be assumed and only information on ecotoxicity is required.

User safety

The applicant has presented a user safety risk assessment in accordance with 'EMEA/CVMP/543/03-Rev.1. Guideline on User Safety for Pharmaceutical Veterinary Medicinal Products.'

Since this is a generic application, and since bioequivalence with the veterinary reference product has been established, there are no requirements to provide additional toxicological data. Therefore, cross-reference is made to data from the summary report of tulathromycin (EMEA/MRL/894/04-Final, January 2004) and from the summary discussion from the EMA (2003) for the reference product Draxxin with regards to user safety studies of tulathromycin. No further studies regarding user safety were conducted with the product.

Both the reference and generic veterinary medicinal products will be administered at the same dose, by the same route of administration and for the same indications for use in the same species as the reference product. Furthermore, Rexxolide has the same qualitative and quantitative composition in active substance and contain the same excipients in similar amounts as the reference veterinary medicinal product. Therefore, the hazards and risks from use of Rexxolide will be the same as those for Draxxin 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.

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 as the initial predicted environmental concentrations in soil (PECsoil) for intensively reared animals (cattle and pigs) and pasture animals (cattle and sheep), were below the trigger value of 100 µg/kg.

Rexxolide 100 mg/ml is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

The MRL status of the active ingredient of Rexxolide 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-(dimethylamino)-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 proportions Liver Kidney		

All constituents of the intended product Rexxolide 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 as Rexxolide 100 mg/ml was developed as a generic product according to Article 13(1) of Directive 2001/82/EC. It can be accepted that the candidate formulation is sufficiently similar to the reference product formulation 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

Title III of the Directive 2009/9/EC (amending Directive 2001/82/EC) 'Requirements for Specific Marketing Authorization Applications', notes that 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. The formulations 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 product is intended to be administered by the same route of administration at the same dose and for the same indications in the same species as the reference product. Based on these data the depletion of residues at the injection site is expected to be the same as that of the reference product and no injection site depletion studies for cattle, pig or sheep are required.

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

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

Rexxolide 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 profile of the candidate product 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.

A Phase I ERA has been performed. For intensively reared animals (cattle and pigs) and pasture animals (cattle and sheep), PECsoil values for tulathromycin were below the trigger value of 100 µg/kg. Thus, in accordance with current guidelines the environmental risk assessment 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 injection site depletion studies for cattle, pig or sheep are required. The withdrawal periods of the reference product can be also applied to the generic.

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

This application is for a generic product, submitted in accordance with 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 CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3) and also indicated compliance with requirements for a biowaiver in accordance with section 7.1.d) of the aforementioned guideline, i.e. identical composition and manufacturing process between generic and reference product. CVMP agrees 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 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, Rexxolide is to be used in the same target species at the same dose, by the same route of administration and for the same therapeutic indications as the reference product.

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

Development of resistance

No data on resistance has been provided. Given the legal basis of this application, the fact that bioequivalence with the reference product is considered to have been suitably supported and the candidate formulation is to be administered to the same target species for the same indications at the same posology using the same routes of administration as the reference product, the potential for resistance development is not expected to differ between the candidate and reference products.

The applicant proposes to state in the SPC the same text as in the SPC of the reference product regarding the resistance section, which is considered acceptable.

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

No data on target animal tolerance has been provided. Bioequivalence is considered established between the candidate 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 is the same. The omission of tolerance data is considered acceptable.

Clinical field trials

No clinical data has been provided. 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 a generic application based on Article 13(1) of Directive 2001/82/EC. The generic product, Rexxolide (100 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/016/2000-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 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.

The risk for the development of resistance can be considered as low as for the reference product.

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

Rexxolide is a solution for injection containing 100 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

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

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

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 Rexxolide is considered established on the basis of bioequivalence to the reference product. The direct therapeutic benefits for Rexxolide 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 animals when administered according to the same posology is expected. Administration of Rexxolide in accordance with SPC recommendations is generally well tolerated. The main 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. 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:

Rexxolide 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. Rexxolide 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 withdrawal periods, 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) concluded that the application for Rexxolide 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.