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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Tulinovet (EMEA/V/C/005076/0000)

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 V.M.D. N.V. submitted on 21 June 2019 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Tulinovet 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

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. Tulinovet 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 Tulinovet is tulathromycin, a semi-synthetic macrolide antimicrobial agent, which is a bacteriostatic acting antibiotic and 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.

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

The applicant is registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC.

The rapporteur appointed is Leona Nepejchalová and the co-rapporteur is Sylvie Louet.

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 16 July 2020, the CVMP adopted an opinion and CVMP assessment report.

On 16 September 2020, the European Commission adopted a Commission Decision granting the marketing authorisation for Tulinovet.

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 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 at a site in the EEA. The site has a manufacturing authorisation issued by the French Agency for veterinary medicinal products. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture of such veterinary dosage form, has been provided.

Batch release within the EU take place at Laboratoires Biové (Arques, France) and V.M.D. n.v. (Arendonk, Belgium). Both hold appropriate manufacturing authorisations.

GMP certification, which confirms the date of the last inspection and shows that the sites are authorised for the batch release of such veterinary dosage form, has been provided for both sites.

A GMP declaration for the active substance manufacturing sites was provided from the Qualified Person (QP) at V.M.D. n.v. on behalf of the QPs of both batch release sites. The declaration was based on an on-site audit by the manufacturing site responsible for batch release.

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, hydrochloric acid dilute, sodium hydroxide, propylene glycol and water for injections. Nitrogen purging is used for filling of the headspace of the vials. The complete composition table for the applied formulation of Tulinovet is provided including all ingredients included in the formulation.

The product is available in clear type I glass vials of 25 ml, 50 ml, 100 ml and 250 ml, closed with uncoated chlorobutyl and coated bromobutyl rubber stoppers and sealed with an aluminium cap. The vials are further individually packed in outer cardboard boxes.

Initially the applicant applied for 50 ml, 100 ml and 250 ml presentations. The 25 ml vial was added by the applicant during the assessment as recommended by CVMP.

Containers

An overview of the packaging material for the active substance is provided in an acceptable form. More details are referred in the ASMF open part of both manufacturers.

The description of the finished product primary packaging, *i.e.* type I clear glass vials closed with uncoated chlorobutyl rubber stoppers for the 25, 50 and 100 ml vials, and coated bromobutyl rubber stoppers for the 250 ml vials sealed with aluminium caps, has been provided. The glass vials are compliant with European Pharmacopoeia (Ph. Eur.) requirements. Results of stopper tests for fragmentation, penetrability and self-sealing properties for uncoated chlorobutyl and coated bromobutyl rubber stopper material using the different needle lumen that are foreseen during animal treatment have been provided. Results for fragmentation test comply with the Ph. Eur. requirement for 20 mm uncoated chlorobutyl rubber stopper.

Vials and stoppers are sterilised by moist heat at the finished product manufacturing site.

Development pharmaceutics

The target is a generic veterinary medicinal product that closely resembles the reference product Draxxin 100 mg/ml which contains tulathromycin as active substance at a concentration of 100 mg/ml. The applicant used publicly available information (patent application, SPC and scientific discussion of the reference product) as well as laboratory deformulation to achieve this.

A comparison between the reference product (4 batches) and the candidate product at release is provided including results comparing the impurity profile and tulathromycin B content between both products.

Tulinovet is a parenteral product for subcutaneous or intramuscular use.

Critical process parameters were identified during development.

The temperature setting and its duration during preparation of the tulathromycin solution as well as mixing speeds have been justified. The impact of the scale-up on the equilibrated mixture of tulathromycin A and B has been appropriately discussed. The choice of the sterilisation method has been satisfactorily justified according to the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015).

Two laboratory scale batches were placed in stability studies under accelerated, long-term and intermediate conditions. One batch was manufactured without flushing the headspace with nitrogen, the other batch was prepared flushing the headspace with nitrogen. A significant decrease on monothioglycerol content was observed under the three stability conditions when no nitrogen was used and therefore, nitrogen headspace was used for the manufacture of larger scale batches and proposed for commercial batches. Both batches were manufactured without significant heating which had an impact on tulathromycin B isomer and tulathromycin A+B contents.

Method of manufacture

The manufacturing process for the applied formulation is described in an adequate form containing the main process steps. A flow chart is provided which shows all process steps from the narrative description including the in-process controls (IPCs).

The VMP is manufactured by a process of sequential addition and mixing of the active substance and the excipients. The bulk solution is pre-filtered (clarifying filtration) followed by sterilising filtration and filling in pre-sterilised containers.

The manufacturing process is considered non-standard in accordance with the Guideline on process validation for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1) as the product is sterilised by filtration followed by aseptic processing.

Satisfactory process validation data from three production batches and 4 smaller batches were provided.

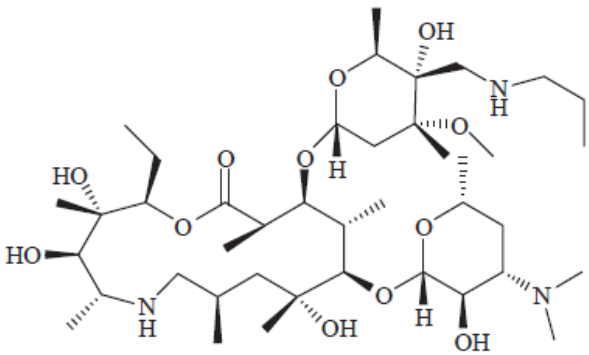
For the validation of the manufacturing process with the production scale batch, a bracketing approach with respect to the filling of different vial sizes has been proposed based on the headspace to total volume ratio. This was considered acceptable.

The batches of finished product used for process validation have been manufactured in accordance with the proposed manufacturing process for commercial batches and using active substance batches from the proposed suppliers.

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. Two manufacturing sites are proposed for the active substance Assessment of the ASMFs is contained in separate documents.

The active substance specification from the manufacturer of the veterinary medicinal product includes tests for appearance, identity, optical rotation, assay, impurities, residual solvents, water content, sulphated ash, microbiological quality and endotoxins. 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 sufficiently 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-NF standards in the case of monothioglycerol.

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.

Control tests on the finished product

The specifications proposed at release are appropriate to control the quality of the finished product and include appearance including colour, clarity and visible particles, filling volume, pH, density, tulathromycin and monothioglycerol identification and assay, isomer B percentage, related substances 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 and impurities testing has been presented.

Batch results of four pilot batches and one production batch were presented. Results are acceptable meeting the specification requirements.

Stability

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

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

Four bulk batches manufactured according to the process proposed for commercial batches were tested at long-term, accelerated and intermediate conditions and filled in 50, 100 and 250 ml vials. The stoppers used for the vials in stability studies were either those proposed for commercialisation or

of equivalent quality which is considered acceptable. Active substance from both manufacturers was used in the manufacture of the finished product bulk solution.

Initially, compliant 12 months stability data at long-term conditions were presented for all vial sizes stored in inverted position. Significant changes were observed in 2 batches under accelerated conditions but no significant changes were found in the intermediate and long term studies.

Updated long-term and intermediate stability data up to 18 months were provided. Results are compliant with specifications.

Based on the stability data provided, a shelf-life of 2 years with the storage precaution 'do not store above 30°C' can be granted.

A self-preserving efficacy test has been performed demonstrating the self-preserving effect of the solution for 28 days where log reduction (log CFU/ml) could be detected. Ph. Eur. compliance criteria A is met.

In-use stability studies performed on each vial size after 3 months and 12 months storage at 25 °C or at 30 °C, support the proposed shelf-life of 28 days after broaching.

Photostability of the finished product was tested as per the VICH GL5 and results confirm that the product is considered photostable in the primary packaging and needs no further protection, other than the vial itself.

Regarding stability the applicant has indicated that they will undertake and complete additional or ongoing studies (long-term, accelerated, in-use at the end of shelf-life).

The CVMP has agreed with the approach proposed by the applicant.

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.

The applicant has indicated that it will undertake and complete additional or ongoing studies (long-term, accelerated, in-use at the end of shelf-life).

Part 3 – Safety

Safety documentation

The product Tulinovet 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, authorised by the Commission through a centralised procedure in 2003, has been chosen as reference product.

Given that the requirements of Directive 2001/82/EC, Article 13(1), relating to generic medicinal products, are fulfilled (see Part 4 – Bioequivalence), and that the omission of bioequivalence studies is adequately justified, results of toxicological, pharmacological or clinical tests are not required.

User safety

Tulinovet 100 mg/ml is bioequivalent to Draxxin 100 mg/ml and the products are of the same pharmaceutical form and contain the same concentration of the active substance. The dose, route of administration and target animals are the same as for the reference product. As such, the tasks and situations that lead to exposure and the exposure scenarios will be the same. All excipients of Tulinovet 100 mg/ml (monothioglycerol, propylene glycol, citric acid, hydrochloric acid and sodium hydroxide) have been widely used in pharmaceutical preparations and, in the USA, are Generally Recognized As Safe (GRAS) substances. Therefore, the qualitative and quantitative risk to the user as a result of Tulinovet 100 mg/ml exposure can be considered to be the same as that of the reference product.

Therefore, the same warnings as those included in the SPC of the reference product 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 Concentrations for soil were 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-Corr., 2016).

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 both scenarios, intensively reared animals (cattle and pigs) and pasture animals (cattle and sheep), were less than 100 µg/kg.

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

Residues documentation

MRLs

The MRL status of the active substance of Tulinovet 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-	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	Muscle Skin and fat in natural		

	trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopent-decan-15-one expressed as tulathromycin equivalents		4000 µg/kg 8000 µg/kg	proportions Liver Kidney		

All constituents of the intended product Tulinovet 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 Regulation (EC) No 470/2009.

Residue studies

No residue studies were provided in support of the current application

Tulinovet 100 mg/ml has been developed as generic a product according to Article 13(1) of Directive 2001/82/EC.

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 product. The candidate product has the same qualitative and quantitative composition in active substance. 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 for use in the same species as the reference products. Based on these considerations the depletion of residues at the injection site is expected to be the same as that of the reference product and no additional 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

The application has been submitted in accordance with Article 13 (1) of Directive 2001/82/EC. Therefore, results of toxicological, pharmacological or clinical tests are not required. As this product has identical qualitative and quantitative composition in active substance and the same excipients in similar amounts as the reference veterinary medicinal product and furthermore, the target species, the route of administration, the dose and the indications are the same as for the reference product, the same warnings as those included in in section 4.5. ii) of the SPC of the reference product are considered sufficient to prevent the user's exposure and manage the associated risks.

A Phase I Environmental Risk Assessment (ERA) has been performed. Predicted Environmental Concentrations in soil ($PEC_{soil\ initial}$) for tulathromycin were below the trigger value of 100 µg/kg for all categories of target species both intensively reared animals (cattle except dairy cows, and pigs) and pasture animals (cattle except dairy cows, and sheep). It can be concluded that Tulinovet 100 mg/ml is not expected to pose a risk for the environment when used according to the SPC.

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

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

Tulinovet 100 mg/ml has been developed as a generic product according to Article 13(1) of Directive 2001/82/EC. The reference product is Draxxin 100 mg/ml 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 has provided comparative analytical data to demonstrate the similarity of both formulations. 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 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, Tulinovet has the same

pharmaceutical form, 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 Tulinovet and the reference product Draxxin can be accepted.

Development of resistance

The applicant has provided data on the resistance situation to tulathromycin obtained from published literature and from surveillance programs of individual European Member States as well as industry (Vetpath, Mycopath). Data obtained from isolates collected during the last 5 years are limited for *Mycoplasma bovis, M. hyopneumoniae, B. bronchiseptica* and *H. parasuis*. Data for the following bacterial species cover the last 5 years: *M. haemolytica, P. multocida, H. somni, A. pleuropneumoniae*. No data is available for *Dichelobacter nodosus.* No data has been submitted on the resistance of *Moraxella bovis*. However, taking into account all the information submitted, there is no evidence that the resistance situation has changed for target pathogens since the renewal of the reference product Draxxin in 2008.

The risk for resistance development appears acceptable, provided that the prudent use warnings and responsible use of the product will be followed in practice. Based on data submitted and considering that the reference and candidate products are bioequivalent, it is not expected that the risks of resistance development will differ after the use of reference and generic products.

The product information of Tulinovet contains appropriate information regarding the responsible use of the product, 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 introduced 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

No clinical data has been provided by the applicant. As bioequivalence between the proposed generic product and the reference product is considered established, the efficacy is expected to be the same for both products when administered by the same routes and at the same dose. 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 (i.e. a generic application). The generic product, Tulinovet 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 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. The efficacy and safety profiles for the generic and reference products are expected to be the same at the same posology.

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 current QRD vet template (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

Tulinovet 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. Tulinovet 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 Tulinovet is considered established on the basis of bioequivalence to the reference product. Therefore, the direct therapeutic benefits for Tulinovet 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 been accepted, the products are expected to have the same safety profiles in the target animals when administered according to the same posology. Administration of Tulinovet 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. Same safety advice as for the reference product is included in the SPC.

Risk for the environment:

Tulinovet 100 mg/ml 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 target species and food commodities concerned under this application. All constituents of the intended product 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 Regulation (EC) No 470/2009.

Tulinovet is not expected to pose a risk to the consumer of meat and offal derived from treated animals when it is used according to the proposed SPC recommendations. The withdrawal periods approved under section 4.11 of the SPC of the reference product will also apply to the candidate 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.

Antimicrobial resistance:

The risk for resistance development appears acceptable provided that the prudent use warnings and responsible use of the product will be followed in practice. Based on data submitted and considering that the reference and candidate products are bioequivalent, it is not expected that the risks of resistance development will differ after the use of reference and generic products.

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 Tulinovet 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.