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Committee for Medicinal Products for Veterinary Use

Withdrawal assessment report for Tulatrixx (EMEA/V/C/005364/0000)

Pharmaceuticals

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Introduction

The applicant Emdoka BVBA submitted on 4 October 2019 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Tulatrixx through the centralised procedure under Article 3(3) of Regulation (EC) No 726/2004 (generic).

The eligibility to the centralised procedure was agreed 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 (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 (25 mg/ml and 100 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. Tulatrixx 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 Tulatrixx 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 for Tulatrixx 100 mg/ml and pigs only for Tulatrixx 25 mg/ml.

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

Tulatrixx 25 mg/ml is presented in packs containing 1 vial of 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 dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC – a generic application.

On 1 April 2020, Emdoka BVBA communicated the withdrawal of the marketing authorisation application at day 120 of the procedure to the Agency.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 – Administrative particulars

Detailed description of the pharmacovigilance system

The applicant 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 and batch release takes place in the EEA. The site has a manufacturing authorisation issued by the corresponding competent authority. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided.

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

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 clear colourless to slightly yellow solution for injection containing 25 mg tulathromycin/ml or 100 mg tulathromycin/ml as active substance. Tulathromycin is a macrolide antibiotic that consists of two isomers, tulathromycin A and tulathromycin B.

Other ingredients are: monothioglycerol, propylene glycol, citric acid monohydrate, hydrochloric acid (diluted), sodium hydroxide and water for injections.

The product would have been available in type I glass vials with a fluoropolymer coated bromobutyl stopper and an aluminium overseal as described in section 6.5 of the proposed SPC.

Containers

The primary packaging proposed was type I glass vials of 50 ml, 100 ml or 250 ml with fluoropolymer coated bromobutyl stoppers. The material complied with the relevant European Pharmacopoeia (Ph. Eur.)

requirements. The choice of the container closure system was validated by stability data however further data was requested by CVMP.

The glass vials were proposed to be packed in outer cardboard boxes containing one vial of the solution for injection.

Certificates of analysis for the primary packaging were supplied demonstrating compliance with the proposed specifications.

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). Also, 'the quantity prescribed and supplied shall be restricted to the minimum amount required for the treatment or therapy concerned' as stated in article 67 of Directive 2001/82/EC.

The applicant was recommended to develop a small vial of 20 ml for the 100 mg/ml strength (also available for the reference product) for the treatment of individual animals or group of light/small animals.

Development pharmaceutics

Tulatrixx 25 mg/ml solution for injection and Tulatrixx 100 mg/ml solution for injection were submitted as a generic application under Article 13(1) of Directive 2001/82/EC. The applicant applied for a waiver from bioequivalence study requirements referencing data presented in Part 2A of the dossier and citing section 7.1.d of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/00-Rev.2).

Formulation development for the generic products is based on the formulations of the reference products Draxxin 25 mg/ml solution for injection and Draxxin 100 mg/ml solution for injection. To this end, the applicant utilised available information for the reference product from a number of sources in the public domain.

Information on the reference product SPC allowed the applicant to determine the quantitative composition of the reference product with respect to the active substance i.e. 25 mg tulathromycin/ml or 100 mg tulathromycin /ml, monothioglycerol (5 mg/ml) and its full qualitative composition with respect to excipients. Further analysis of Draxxin batches was carried out in order to determine the quantitative composition of both strengths of the reference product with respect to excipients. The quantities of these excipients included in the generic product are based on this data. At the time of withdrawal of the marketing authorisation application, further information on the quantitative composition of the generic products had been requested. Physico-chemical characteristics of the Draxxin batches were also determined in these studies as was the content of the reference product batches in terms of tulathromycin isomer ratio.

In terms of the manufacturing process development, reference is made to publicly available information which includes the information that tulathromycin dissolved in water exists as two isomers, tulathromycin A and tulathromycin B, which are in equilibrium with each other as a function of time, the pH of the solution and other components in the mixture. Tulathromycin A is usually present in excess with the formation of tulathromycin B occurring slowly. The use of heat reduces the time required to achieve an equilibrated mixture of the two isomers during production. Additional studies to optimise the manufacturing process were carried out during development so that the generic product would have the same ratio of tulathromycin A and tulathromycin B isomers as is present in the reference product. Based

on the data provided on the manufacturing process development, the CVMP is of the opinion that the manufacturing process was appropriately optimised.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or in-house specifications (linked to US-NF standards). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the proposed SPC.

As part of pharmaceutical development, studies were also carried out to establish the most appropriate method of sterilisation of the product. Based on the results of these studies, the applicant proposed to sterilise the product by filtration as terminal sterilisation led to excessive formation of impurities and was therefore not considered appropriate. The applicant's approach to establishing the most appropriate method of sterilisation for the finished product is not in line with the decision tree for sterilisation choices for aqueous products (EMA/CHMP/CVMP/QWP/850374/2015). Additional data were requested to demonstrate that the decision tree for sterilisation choices was followed faithfully. CVMP considered that filtration as the proposed method of sterilisation of Tulatrixx was not adequately justified at the time of withdrawal of the marketing authorisation application.

With respect to the biowaiver, although the applicant cited section 7.1.d of the previous version of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/00-Rev.2) in support of omitting *in-vivo* bioequivalence study data, the CVMP is of the opinion, subject to satisfactory resolution of clarification requested regarding the quantitative composition of the VMP, that an exemption from the requirement to demonstrate *in-vivo* bioequivalence could be supported 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) which states:

'For products intended for intramuscular, subcutaneous or systemically acting topical administration, bioequivalence studies are not required in cases when the product is of the same type of solution, contains the same concentration of the active substance and comparable excipients in similar amounts as the reference veterinary medicinal product, if it can be adequately justified that the difference(s) in the excipient(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance.'

Method of manufacture

The finished product is a solution for injection, which is manufactured in a process involving sequential addition and dissolution of the product ingredients with mixing between each addition. A batch size range as proposed by the applicant could be accepted but the commercial batch size should also be described by the number of vials. The bulk solution is sterilised by filtration through a sterilising filter and the vials are filled under aseptic conditions.

The manufacturing process was developed based on work carried out by the applicant and also with reference to information in the public domain. However, the description of the manufacturing process as presented in the dossier was too brief and gave rise to a number of questions.

In-process controls were defined for the process and were generally appropriate for this type of manufacturing process however, a number of questions arose on the information presented in this section.

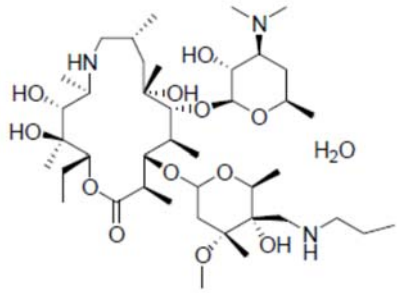
Process validation was conducted on three production scale batches of each strength, which were filled into the container closure system proposed for marketing. The process validation batches were manufactured without the heating step for isomer equilibration and as such, have not been manufactured in accordance with the proposed process. The applicant provided an explanation for this which was not

accepted by CVMP and therefore remained unsolved at the time of withdrawal of the marketing authorisation application.

Control of starting materials

Active substance

The active substance tulathromycin is a semi-synthetic macrolide antimicrobial agent. In aqueous environments it exists as two isomers, tulathromycin A and tulathromycin B, with the A isomer present in excess. The tulathromycin A isomer has the following structure:



The active substance is a crystalline powder that exhibits slight hygroscopicity and is freely soluble in methanol, acetone and ethyl acetate and soluble in ethanol. Enantiomeric purity is controlled routinely by specific optical rotation.

The applicant's specification for tulathromycin was provided in the dossier and was generally acceptable but some questions arose concerning tightening, revision and addition of some limits for the various parameters.

Batch data for the active substance was provided in the dossier however the provision of further batch data was requested.

The information on the active substance was provided according to the Active Substance Master File (ASMF) procedure and two sources of the material were proposed. For both sources, commercially available well defined starting materials were used. The level of detail provided for the active substance manufacturing process was sufficient.

The ASMF holders' specifications for the active substance were generally acceptable but some questions remained unsolved at the time of withdrawal concerning the revision (tightening) of some of the limits. Test methods were well described and were validated in accordance with VICH GL2: *Validation of analytical procedures: methodology*. Satisfactory batch analysis data was included in each ASMF for three industrial scale batches of the active substance. The results were within the specifications and consistent from batch to batch.

The characterisation of the active substance and its impurities were in accordance with the Guideline on the chemistry of active substances for veterinary medicinal products (EMA/CVMP/QWP/707366/2017). Potential and actual impurities were well discussed with regards to their origin and characterisation.

Questions on control of residual solvents, genotoxic and DNA reactive impurities remained unsolved by the time of withdrawal of the marketing authorisation application.

Adequate in-process controls were applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents were presented.

Detailed information on the manufacturing of the active substance was provided in the restricted part of the ASMFs and, while the data presented is considered generally satisfactory, a number of questions arose on the data presented in the ASMF restricted parts.

Stability data on 3 industrial scale batches of active substance from the each of the proposed manufacturers stored either in the commercial packaging or in simulated packaging was provided. The analytical methods used are the same as for the active substance specification and are stability indicating.

For one of the active substance suppliers, 6 months data at both 25 °C/60% RH and 40 °C/75% RH were provided. The retest period proposed was not supported by the data presented and additional stability data for further time points was requested. For the other active substance supplier, 24 months data at 30 °C/65%RH and 6 months data at 40 °C/75% RH were provided and the stability results justify the proposed retest period in the proposed container. Results for stress test studies under the conditions acid, alkali, oxidation, high temperature, high humidity and light stress conditions were also provided in studies carried out on a single batch from each source.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or acceptable in-house specification (linked to US-NF). There are no novel excipients used in the finished product formulation. The list of excipients was included in section 6.1 of the proposed SPC. Some issues remained unsolved on the specifications of the excipients.

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

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

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

Control tests on the finished product

Specifications were provided for both strengths of the product which were generally acceptable and included relevant test parameters for the dosage form however, some issues remained unsolved at the time of withdrawal of the marketing authorisation application.

Analytical methods were well described and were validated in accordance with VICH GL2: *Validation of analytical procedures: methodology*. Some clarifications and further data were requested by CVMP.

Satisfactory information regarding the reference standards used for assay and impurities testing was presented.

Batch analysis results were provided for three production scale batches of each product strength however, as these batches had not been manufactured in accordance with the proposed process, the results were not considered acceptable.

Stability

Primary stability study

Stability data was presented for studies carried out on three production scale batches of each product strength, manufactured at the proposed dosage form manufacturing site. The stability batches were the same batches used in the process validation study which were not manufactured in accordance with the proposed manufacturing process. The stability batches were packaged in the intended commercial packaging and all vial sizes proposed.

The batches were placed on stability at VICH long-term, intermediate and accelerated conditions. The applicant has presented 12 months data for product stored at 25 °C/60% RH and at 30 °C/65% RH, and 6 months data for product stored at 40 °C/75% RH according to VICH GL4 Stability testing for new veterinary dosage forms.

With the exception of results for one test, results for all parameters were within the proposed shelf life specifications.

The shelf life for the veterinary medicinal product as packaged for sale proposed by the applicant could not be agreed by CVMP as the batches used in the stability study were not manufactured in accordance with the proposed process for commercial batches and did not comply with the full shelf life specification on stability.

In-use stability

In-use stability testing was carried out for all three batches of each product strength using product filled in all container sizes. Details of the product sampling and storage for the in-use test were provided and differ for each container size although no specific rationale for the design of the in-use study was provided. As seen in the primary stability study, all results were within specification with the exception of one test. The results for preservative efficacy indicated that the product meets the Ph. Eur. 5.1.3 A criteria for parenteral preparations.

Overall conclusions on quality

Tulatrixx solution for injection provides 25 mg/ml or 100 mg/ml of tulathromycin as the active substance. Tulathromycin is a macrolide antibiotic that consists of two isomers , tulathromycin A and tulathromycin B. The application for Tulatrixx was submitted as a generic application under Article 13(1) of Directive 2001/82/EC. The product is an aqueous solution and was to be packaged in Type I glass vials of 50 ml, 100 ml or 250 ml which are closed with fluoropolymer coated bromobutyl rubber stoppers.

In the development pharmaceutics the applicant provided satisfactory detail on the development of the formulation and the development of the manufacturing process. Information was also included on the selection of the sterilisation method for the finished product however, based on the data presented, the proposal to sterilise the product by filtration was not considered to have been adequately justified at the time of withdrawal of the marketing authorisation application.

The solution for injection is manufactured in a process involving sequential mixing and dissolution of the product constituents in water for injections. The product is sterilised by filtration and filled into sterile packaging. Issues were pending on the description of the manufacturing process and the in-process controls. Process validation for three production scale batches of each product strength was provided in the dossier however, the batches included in the process validation study were not manufactured following the manufacturing process proposed for commercial batches. As the batches were not manufactured in accordance with the proposed process, the process was considered to be inappropriately validated.

Information on the control of starting materials was provided. The active substance tulathromycin is not monographed in a pharmacopoeia and is sourced from two suppliers who have supporting ASMFs. Several queries arose on the ASMFs. The dosage form manufacturer provided a specification for the active substance which was generally acceptable albeit that some revisions to the limits proposed were requested. Active substance batch data was provided however, updated batch data demonstrating compliance with the revised active substance specification was requested.

The product excipients are supplied to either Ph. Eur. grade or an acceptable in-house specification linked to US-NF standards. The finished product container closure system needed some updated supporting information and additional data was requested.

The finished product specification at time of release controlled those parameters appropriate for the dosage form; however, some questions arose including questions on the tightening of limits. Analytical methods were well described and validation was provided, however, a number of minor questions arose on the validation data. Batch data for three batches of each product strength were provided however, as the batches were not manufactured in accordance with the proposed manufacturing process, the batch data did not confirm compliance with the proposed release specification.

Stability data for the active substance from both proposed suppliers was provided. The data was sufficient to allow a retest period to be agreed for material from one of the suppliers but not for the other.

A finished product shelf-life specification was provided but needed some updating. In terms of dosage form stability, the batches placed on stability were not manufactured in accordance with the proposed manufacturing process and the CVMP could not agree a shelf life for the finished product based on the data presented. With respect to the in-use stability study, no information on the rationale for the design of the study was provided. An in-use shelf life could therefore not be agreed.

The product quality was not approvable at the time of withdrawal of the marketing authorisation application. A list of questions was adopted by CVMP at Day 120 of the procedure

The applicant was recommended to develop a small vial of 20 ml for the 100 mg/ml strength (also available for the reference product) for the treatment of individual animals or group of light/small animals, see details in ‘containers’ section above.

Part 3 – Safety

Safety documentation

The application is for an injectable formulation containing tulathromycin as the active substance, for use in cattle, pigs and sheep. This application was submitted in accordance with Article 13(1) of Directive 2001/82/EC (a generic veterinary medicinal product). The reference product Draxxin 25 and 100 mg/ml solution for injection has been authorised in the European Community for more than 10 years and was accepted as a valid reference product (originally authorised on 11 November 2003).

The applicant claimed that the quantitative and qualitative composition of the candidate formulation is identical to the reference product and that both candidate and reference products have the same pharmaceutical form.

In Part 2 of the application dossier, the applicant cited section 7.1.d of the previous version of the CVMP ‘Guideline on the conduct of bioequivalence studies for veterinary medicinal products’ (EMA/CVMP/016/00-Rev.2) in support of omitting *in vivo* bioequivalence study data and claimed that the

candidate formulation contains the same active substance and excipients in the same concentrations and has the same physico-chemical properties as the reference product.

However, the CVMP noted that the waiver cited by the applicant requires that the formulations are identical (identical active substance and excipients as well as physico-chemical properties (e.g. identical concentration, dissolution profile, crystalline form, pharmaceutical form and particle size distribution with identical manufacturing process), that is, the exemption cited goes beyond demonstration of the same physico-chemical properties compared by the applicant and includes identical manufacturing process.

Given that the product is intended to be administered subcutaneously to cattle and intramuscularly to pigs and sheep, and for the same indications and posology as the reference product the CVMP concluded that an exemption from the requirement to demonstrate *in vivo* bioequivalence could be supported 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).

Accordingly, given that bioequivalence has been claimed and it is argued that the test product is a generic of the reference product, cross-reference to the safety and efficacy parts of the dossier of reference product was considered appropriate. Therefore, results of toxicological, pharmacological or clinical tests were not required.

It was accepted that the toxicological profile of the generic product will be the same as that of the reference product.

User safety

The applicant did not provide a user safety risk assessment.

Based on the information presented in Part 2, it could be reasonably concluded that no difference in terms of risk to the user is to be expected between candidate and reference formulations and consequently, the provision of user safety data is unnecessary in this instance. Furthermore, the product was intended to be administered to the same target species, using the same routes of administration at the same dose rate as already approved for the reference product. The proposed user safety warnings were identical to those approved for the reference product. Consequently, the proposed user safety warnings were considered acceptable.

It was accepted that the candidate formulation will not present an unacceptable risk to the user when stored, handled, administered and disposed of in accordance with the recommendations included in the proposed SPC.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the relevant CVMP/VICH guidelines.

The environmental assessment can conclude at Phase I, question 17, as the $PEC_{soil\ initial}$ value is below the Phase II trigger value of 100 µg/kg. The omission of a Phase II assessment can be accepted.

The standard disposal statement proposed by the applicant for inclusion in SPC section 6.6 is the same as that previously agreed by the CVMP for the reference products and can therefore be applied to the candidate products.

The CVMP concluded that the candidate formulation will not present an unacceptable risk for the environment when handled, used, stored and disposed of in accordance with the recommendations included in the proposed SPC.

Residues documentation

MRLs

The active substance in Tulatrixx is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

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		

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Residue studies

The applicant did not provide any residue depletion studies. However, based on the information presented in Part 2, it can be accepted that the applicant has suitably demonstrated 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 substances 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.

Further, the applicant has compared the physico-chemical characteristics of the candidate and reference formulations and concluded that they are similar. Based on the data provided, the CVMP accepted that depletion of residues of tulathromycin from the subcutaneous injection site in cattle and the intramuscular injection site in pigs and sheep is not expected to differ between candidate and reference formulations.

On account of this and given that the candidate formulation is to be administered to the same target species, using the same route of administration and the same posology as already approved for the reference product, the CVMP accepted that studies investigating the depletion of residues from the

injection site are not required in this instance. 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. The candidate products have 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 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 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 (a generic veterinary medicinal product).

Based upon the results of comparative studies presented in Part 2 of the dossier, the applicant claimed that the candidate formulation and the reference formulation:

- have the same qualitative and quantitative composition of active substance and excipients;
- have the same indications for use in the same species;
- will be administered by the same route of administration at the same dose.

Based on the data provided in Part 2, the CVMP accepts that the criteria set out in section 7.1.b of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products

(EMA/CVMP/016/2000-Rev.3) have been satisfied, that is; the candidate formulation is of the same type of solution, contains the same concentration of active substances 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. Consequently, bioequivalence between candidate and reference formulations can be assumed.

Further, as the test product is intended to be administered to the same target species, using the same routes of administration at the same dose rate as already approved for the reference product, the omission of the results of safety tests can be accepted.

No user safety risk assessment has been provided. The proposed user safety warnings are identical to those approved for the reference product and are considered acceptable. It may be concluded that the candidate formulation will not present an unacceptable risk for the user when handled, used, stored and disposed of in accordance with the recommendations included in the proposed SPC.

An environmental risk assessment has been provided by the applicant. It may be concluded that the candidate formulation will not present an unacceptable risk for the environment when handled, used, stored and disposed of in accordance with the recommendations included in the proposed SPC.

No residue depletion studies were provided. The depletion of residues is expected to be the same 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 product can be also applied to the generic.

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.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 Tulatrixx and the reference product Draxxin can be accepted.

Development of resistance

No data were 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 formulations.

The applicant proposed including the same warning statements in relation to the development of resistance in sections 4.5i and 5.1 as approved by the CVMP for the reference product. However, in line with current guidelines, the CVMP proposed to include additional standard warnings to section 4.5(i) in relation to the development of resistance to antibiotics.

Target animal tolerance

No data were provided.

Based on the information presented in Part 2, it was accepted that the applicant suitably demonstrated that the candidate formulation is sufficiently similar to the reference formulation; thus, bioequivalence between the candidate and reference formulations can be assumed.

Given that the candidate product was to be administered to the same target species for the same indications at the same posology using the same routes of administration, the tolerance profile of the candidate formulation is expected to be the same as that of the reference product.

Consequently, information included in sections 4.6 and 4.10 of the SPC approved for the reference product can be applied to the test product. It is noted that the warnings included in section 4.3 and 4.7 of the proposed SPC are in line with those that appear on the SPC of the reference product.

Clinical field trials

No clinical study data were provided.

Given the legal basis of this application, the fact that bioequivalence with the reference product was considered to have been suitably supported and the candidate product is intended to be administered to the same target species, using the same routes of administration at the same dose rate as already approved for the reference product, it was accepted that the clinical efficacy profile of the candidate formulation would be the same as that of the reference formulation. As such, the omission of results of pre-clinical and clinical trials can be accepted and the proposal to indicate use of the generic product for the same indications as already approved for the reference product using the same posology was considered acceptable.

Overall conclusion on efficacy

The application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (generic veterinary medicinal product).

Based upon the results of comparative studies presented in Part 2 of the dossier, it was accepted that the applicant suitably demonstrated that the candidate formulation is sufficiently similar to the reference formulation.

Further, it was accepted that the criteria set out in section 7.1.b of the CVMP bioequivalence guideline were satisfied, that is; the candidate formulation is of the same type of solution, contains the same concentration of active substances 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.

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.

However, notwithstanding the legal basis of this generic application, minor amendments to the SPC were proposed. 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 (EMA/CVMP/SAGAM/383441/2005).

Part 5 – Benefit-risk assessment

Introduction

Tulatrixx 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* 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. Tulatrixx 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 Tulatrixx is considered established on the basis of bioequivalence to the reference product. The direct therapeutic benefits for Tulatrixx are expected to be the same as those for the reference product, Draxxin, i.e. efficacy for the proposed indications.

Additional benefits

No additional benefits for this generic veterinary medicinal product have been identified, other than the availability of an alternative product on the marketplace.

Risk assessment

Given that bioequivalence with the reference product has been accepted, the risks associated with the use of the product are expected to be the same as those of the reference product. Therefore, the product is not expected to present an unacceptable risk to the target animal, the user or the environment when used as recommended.

As possible risks to the user and the potential for adverse effects at the site of administration are identified in the SPC of the reference product, suitable risk mitigation measures and advice have been included in the proposed SPC (in line with what has been approved for the reference product) and this is considered adequate to mitigate the potential risks.

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

Tulathromycin has been evaluated previously in respect to the safety of residues and MRLs have been established in table 1 of the Annex to Regulation (EU) No 37/2010 for the target species food commodities concerned under this application. Tulatrixx is not expected to pose a risk to the consumer of meat and offal derived from treated animals when used according to the proposed SPC recommendations. The withdrawal periods established to ensure depletion of residues below the MRLs in meat and offal are the same as those of the reference product and are accepted. Tulathromycin is not for use in animals from which milk is produced for human consumption and suitable advice has been included in the proposed SPC.

As with all antibacterials, use of the product may select for resistance and suitable risk mitigation measures and advice have been included in the proposed SPC and this is considered adequate to mitigate the potential risks.

Risk management or mitigation measures

Since bioequivalence between candidate and reference formulations has been accepted, it is considered appropriate that the warnings and risk mitigation measures proposed for inclusion in the SPC reflect those approved for the reference product. It is accepted that, for the risks identified in the SPC approved for the reference product, the same appropriate risk mitigation measures have been proposed for this generic product.

Evaluation of the benefit-risk balance

In the presence of major and other concerns, no conclusions could be taken on the benefit-risk balance of the application.

Conclusion

Based on the original data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) considered that the application for Tulatrixx was not approvable at Day 120 since ‘major objections’ and ‘other concerns’ were identified which preclude a recommendation for marketing authorisation. The details of the outstanding issues were provided in the list of questions. On 1 April 2020, during the clock-stop, Emdoka BVBA communicated the withdrawal of the marketing authorisation application to the Agency.