16 July 2020
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Increxxa (EMEA/V/C/005305/0000)

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 Elanco GmbH submitted on 3 October 2019 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Increxxa 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 21 February 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. Increxxa 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 Increxxa 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 Increxxa 100 mg/ml and pigs only for Increxxa 25 mg/ml.

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

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

The rapporteur appointed is Andrea Golombiewski and the co-rapporteur is Katarina Straus.

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 Increxxa.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the pharmacovigilance system (dated October 2018) and an additional commitment document. Taking this into account, a statement signed by the applicant and the qualified person for pharmacovigilance, indicating that 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, has been provided.

The CVMP considers that the pharmacovigilance system as described by the applicant in addition to the submitted commitment document fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

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

Batch release takes place at Fareva Amboise (Zone Industrielle, 29 route des Industries, 37530 Poce-sur-Cisse, France). The site has a manufacturing authorisation issued by the competent authority in France. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the batch release of such veterinary dosage forms, has been provided.

GMP declarations for the active substance manufacturing sites were provided from the Qualified Person (QP) at the EU batch release site. The declarations were based on an on-site audit by Elanco.

Overall conclusions on administrative particulars

Together with the submitted commitment document the detailed description of the pharmacovigilance system was considered in line with legal requirements of Directive 2001/82/EC.

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

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

The 25 mg/ml strength will be presented in 50 ml, 100 ml and 250 ml colourless glass vials. The 100 mg/ml strength is filled in 20 ml, 50 ml, 100 ml, 250 ml and 500 ml colourless glass vials. Vials of all presentations are closed with fluoropolymer coated chlorobutyl stopper as described in section 6.5 of the SPC.

Containers

The primary packaging is a type I glass vial with a fluoropolymer coated chlorobutyl stopper and an aluminium overseal. The material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Fragmentation and self-sealing has been proven for a maximum of 40 punctures as described in the SPC.

For the 25 mg/ml strength the following pack sizes are proposed: 50 ml, 100 ml and 250 ml.

For the 100 mg/ml strength the following pack sizes are proposed: 20 ml, 50 ml, 100 ml, 250 ml and 500 ml.

Each cardboard box contains one vial.

The pack sizes are consistent with the dosage regimen and duration of use.

Development pharmaceutics

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

The generic was developed to be as close as possible to the originator regarding qualitative and quantitative aspects. The applicant used available information as the Summary of Product Characteristics (SPC), patent applications, EPAR Scientific discussion (CVMP/0968/03) as well as laboratory deformulation to achieve this.

Tulathromycin is a semi-synthetic macrolide antibiotic that presents a combination of two regio-isomers (A and B). The content of isomer B in tulathromycin active substance is different to that in tulathromycin solution for injection. The adequate ratio in the finished product is achieved by means of an isomerisation step during the manufacturing process. The applicant discussed the individual parameters and supported the results with laboratory data.

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

The manufacturing development and the sterilisation method have been satisfactorily described. The selection of the sterilisation method was performed following the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015).

Preliminary stability studies have been performed in order to assess the stability of the formulation and the compatibility with the container closure system under long-term and accelerated conditions for 12 and 6 months. Acceptable results are obtained. Leachables and extractables studies were not conducted and are not deemed necessary.

Method of manufacture

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

The 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. However, the applicant claims that considering the extensive experience of the manufacturer the manufacturing process can be regarded as standard for the manufacturer. Process validation has been performed on two consecutive commercial size batches per strength. Several parameters throughout the manufacturing process have been tested in order to prove the process as being robust and reproducible. It has been adequately justified and it is accepted that the process is considered standard for this manufacturer.

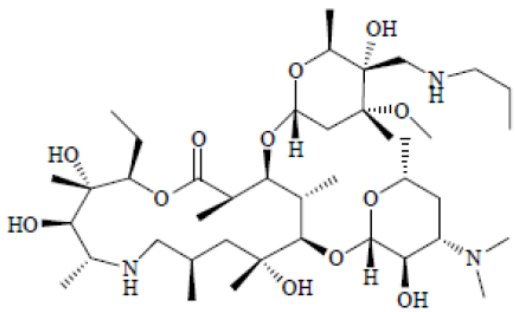
A bracketing approach has been proposed for the validation plan. Batches of the active substance purchased from both manufacturers were used for the process validation. Further validation of the process with all the commercial scales will be performed prior to releasing product to the market which is accepted.

Control of starting materials

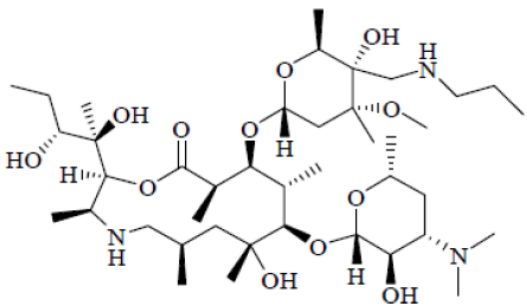
Active substance

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

Tulathromycin A:



Tulathromycin B:



Tulathromycin is a white to off-white powder, slightly hygroscopic, practically insoluble in water and freely soluble in dichloromethane and methanol. It exhibits stereoisomerism due to the presence of 18 chiral centres. Polymorphism has not been observed. Since the active ingredient is solubilised in the finished

product, particle size and polymorphism considerations are not considered critical for the quality of the finished product.

Tulathromycin is not described in any pharmacopoeia. Supporting data for the active substance is provided according to the Active Substance Master File (ASMF) procedure. Two manufacturing sites are proposed for the active substance.

The active substance specification from the manufacturer of the veterinary medicinal product (VMP) includes tests for appearance, identity, optical rotation, water content, sulfated ash, assay, related substances, residual solvents, bacterial endotoxins and microbiological quality. For impurities and residual solvents separate specifications depending on the manufacturer of the active substance are provided. A harmonised active substance specification has been provided by the applicant.

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

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

Full stability data, long-term and accelerated conditions, have been provided from both manufacturers in order to establish a re-test period for the active substance. According to the results provided, a retest period of 24 months is considered acceptable for both suppliers.

Excipients

The excipients propylene glycol, citric acid, hydrochloric acid (dilute), sodium hydroxide, water for injections and nitrogen are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. The excipient monothioglycerol is compliant with USP standards which is considered acceptable as there is no Ph. Eur. monograph for this substance. 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 for release are in general considered appropriate to control the quality of the finished product and include tests for appearance, extractable volume, visible particles, density, pH, tulathromycin identification, tulathromycin assay, monothioglycerol identification and assay, isomer B ratio, degradation products, sterility and bacterial endotoxins.

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

Batch analysis results are provided for two commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture the VMP in line with the intended product specification.

Stability

Stability studies are performed under the conditions described in the Guideline on stability testing: stability testing of existing active substances and related finished products (EMEA/CVMP/QWP/846/99-Rev. 1) and comprise the primary stability study, a photostability study, a freeze-thaw stability study and an in-use stability study.

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

Stability data of two commercial scale batches of finished product per strength stored under long term conditions for 12 months at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the guideline above were provided. A bracketing approach in accordance with VICH GL45 was applied. The composition and the primary packaging of the batches used in stability studies were identical to those proposed for marketing.

Samples were tested for the proposed specifications and the analytical procedures are the same as described to control the product at release. No significant changes have been observed up to the 12 months reported. Data provided for upright and inverted storage show similar results. No sorption processes of the ingredients into the stopper during storage are assumed.

In addition, one batch per strength was exposed to light as defined in the VICH GL5 on photostability testing of new veterinary drug substances and medicinal products. One batch per strength was tested for the behaviour under freeze-thaw conditions over 6 days and further samples of this batch have been tested for in-use stability. Results of the microbiological testing at the end of the proposed in-use shelf life of 28 days have been presented and show a stable behaviour. One further batch per strength will be tested for in-use stability at the end of the proposed shelf life.

Based on the available data the proposed shelf-life of 2 years without any special storage conditions as stated in the SPC is considered acceptable.

Overall conclusions on quality

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

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

Part 3 – Safety

Safety documentation

Increxxa 100 mg/ml is a ready-to-use solution for injection, containing 100 mg tulathromycin/ml as active substance, and is intended to be administered by injection in cattle (subcutaneous injection), pigs and sheep (both intramuscular injection).

Increxxa 25 mg/ml is a ready-to-use solution for injection, containing 25 mg tulathromycin/ml as active substance, and is intended to be administered by intramuscular injection in pigs.

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) and Draxxin 25 mg/ml (EU/2/03/041/006-008), authorised by the European Commission in 2003 and 2014, respectively, have been chosen as reference products.

In vivo bioequivalence studies were not conducted, but the absence of bioequivalence studies can be accepted as the condition 7.1 b) of the 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/2000-Rev.3) are fulfilled. See part 4 for more details. Bioequivalence between Increxxa 25 mg/ml, Increxxa 100 mg/ml and the respective reference products Draxxin 25 mg/ml and Draxxin 100 mg/ml can be accepted.

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

User safety

This application has been submitted in accordance with Article 13 (1) of Directive 2001/82/EC (generic product) and both 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 products. Furthermore, Increxxa 25 mg/ml and Increxxa 100 mg/ml have the same qualitative and quantitative composition in active substance and contain the same excipients in similar amounts as the respective reference veterinary medicinal products. Therefore, the hazards and risks from use of Increxxa 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

An environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

The predicted environmental concentration (PEC) for soil was calculated in accordance with VICH GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the initial predicted environmental concentrations in soil for all animal species and conditions are less than the trigger value of 100 µg/kg.

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

Residues documentation

MRLs

The active substance in Increxxa 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-	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	Anti-infectious agents/Antibiotics

	tetra-hydroxy3,5,8,10,12,14- hexamethyl-11- [[3,4,6-trideoxy3-(dimethylamino)-ß-Dxylo-hexopyranosyl]oxy]-1- oxa-6-azacyclopentdecan-15-one expressed as tulathromycin equivalents				produced for human consumption	
		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 Increxxa are included in Table 1 of Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin or are considered as not falling within the scope of Council Regulation 470/2009.

Residue studies

No residue studies were provided in support of the current application. Increxxa 100 mg/ml and Increxxa 25 mg/ml have been developed as generic products according to Article 13(1) of Directive 2001/82/EC. It can be accepted that the candidate formulations are sufficiently similar to the reference product formulations, and thus specific studies demonstrating bioequivalence with the reference medicinal product are not required. Since this application fulfils the requirements of Directive 2001/82/EC for generics, the applicant is exempt from providing the results of proprietary residues studies and analytical methods for the detection of residues in part 3.B.

Withdrawal periods

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

However, according to section 4.4 of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3), for formulations (i.e. active substance plus all excipients) that are qualitatively and quantitatively identical, a justification for the absence of residues data is acceptable.

The applicant has carried out an analysis and submitted data comparing the formulations of the reference and generic 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 products are 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 products. Based on these considerations 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 proposed withdrawal periods are:

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

Increxxa 100 mg/ml is a ready-to-use solution for injection, containing 100 mg/ml tulathromycin as active substance, and is intended to be administered by injection in cattle (subcutaneous injection), pigs and sheep (both intramuscular injection).

Increxxa 25 mg/ml is a ready-to-use solution for injection, containing 25 mg/ml tulathromycin as active substance, and is intended to be administered by intramuscular injection in pigs.

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.

In vivo bioequivalence studies were not conducted, but their absence was sufficiently justified in accordance with the CVMP guideline on bioequivalence (EMA/CVMP/016/2000-Rev.3). Bioequivalence to the reference products Draxxin 100 mg/ml (EU/2/03/041/001-005) and Draxxin 25 mg/ml (EU/2/03/041/006-008) can be accepted.

Increxxa 25 mg/ml and Increxxa 100 mg/ml will be administered at the same dose, by the same route of administration and for the same indications in the same species as the reference products. Furthermore, they have the same qualitative and quantitative composition in active substance and contain the same excipients in similar amounts as the respective reference veterinary medicinal products. Therefore, the hazards and risks from use of Increxxa 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.

An appropriate environmental risk assessment was provided. The product 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 meat depletion studies for cattle, pig or sheep are required. The withdrawal periods of the reference products can be also applied to the generics.

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

Part 4 – Efficacy

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

Bioequivalence

In vivo bioequivalence studies were not conducted. Instead, the applicant claimed an exemption from such studies based on section 7.1.b) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3).

Increxxa and the reference product contain the same active substance and have the same pharmaceutical form. 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, Increxxa 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 Increxxa and the reference product Draxxin can be accepted.

Development of resistance

No data has been provided by the applicant which is considered acceptable for this type of application. As this is a generic application and bioequivalence between the candidate and the reference product can be accepted, and the candidate product is used in the same target animal species, for the same indications, at the same doses and in the same treatment regimen as the reference product, the resistance profile of the target pathogens against the candidate product will be the same as for the reference product. The risk for the development of resistance can be considered as low as for the reference product.

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

Overall conclusion on efficacy

This is a generic application based on Article 13(1) of Directive 2001/82/EC. The generic product, Increxxa (100 mg/ml and 25 mg/ml), is considered to be bioequivalent to the reference product, Draxxin,

in accordance with section 7.1.b) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-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. 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 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

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

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

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

Cattle (100 mg/ml)

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

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

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

Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Mycoplasma hyopneumoniae*, *Haemophilus parasuis* and *Bordetella bronchiseptica* susceptible to tulathromycin. The presence of the disease in the herd should be established before metaphylactic treatment. Increxxa 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 Increxxa is considered established on the basis of bioequivalence to the reference product. Therefore, the direct therapeutic benefits for Increxxa are expected to be the same as those for the reference product Draxxin, i.e. efficacy for the proposed indications.

Additional benefits

Not applicable.

Risk assessment

Quality:

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

Safety:

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

Risks for the target animal:

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

Risk for the user:

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

Risk for the environment:

Increxxa is not expected to pose a risk for the environment when used according to the SPC recommendations. The 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. Increxxa 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 products will also apply for the candidate products, 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 animals, 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) concluded that the application for Increxxa 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.