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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Lydaxx (EMEA/V/C/005199/0000)

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 Vetoquinol submitted on 27 February 2019 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Lydaxx 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 11 October 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. Lydaxx 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 Lydaxx is tulathromycin, a semi-synthetic macrolide antimicrobial agent, which is a bacteriostatic acting antibiotic that inhibits essential protein biosynthesis by virtue of its selective binding to bacterial ribosomal RNA. It stimulates the dissociation of peptidyl-tRNA from the ribosome during the translocation process. The target species are cattle, pigs and sheep.

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

The rapporteur appointed is Sylvie Louet and the co-rapporteur is Cristina Muñoz Madero.

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 18 March 2020, the CVMP adopted an opinion and CVMP assessment report.

On 18 May 2020, the European Commission adopted a Commission Decision granting the marketing authorisation for Lydaxx.

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 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 Vetoquinol, Lure in France. The site has a manufacturing authorisation issued by the ANMV–ANSES, the French Agency for veterinary medicinal products - French Agency for food, environmental and occupational health safety. 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.

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

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 is in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as a multidose solution for injection containing 100 mg/ml 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 during manufacturing and as head space. The product is a clear colourless to slightly yellow solution.

The product is available in multidose vials containing 50 ml, 100 ml, 250 ml and 500 ml, as described in section 6.5 of the SPC. The vials are further individually packed in outer cardboard boxes.

Containers

The primary packaging is type I clear glass vials closed with chlorobutyl rubber stoppers coated with ethylene tetrafluoroethylene (ETFE) and sealed with aluminum flip-off caps. The materials comply with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. Rubber stoppers comply with the Ph. Eur. fragmentation test adapted to the field use. A restriction on the number of punctures (maximum of 30) has been included in section 4.9 of the SPC.

Vials are washed and depyrogenised and rubber stoppers are sterilised by suppliers. As conditions of the Ph. Eur. monograph 5.1.1. are used, no validation data were needed.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The proposed pack sizes were properly justified based on the target species, the dose 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 is thus recommended to develop a small vial of 20 ml (also available for the reference product) for the treatment of individual animals or group of light/small animals.

Development pharmaceutics

The objective was to develop a generic of Draxxin, medicinal product marketed by Zoetis, which was authorised via the centralised procedure in 2003. The applicant has made use of available information in Draxxin Summary of Product Characteristics (SPC), European Public Assessment Report (EPAR), patent applications and has carried out an analysis and submitted data comparing the formulations of the reference and generic products.

The active substance, tulathromycin, is a semi-synthetic macrolide antibiotic that presents a combination of two regio-isomers (A and B). The content of isomer B in tulathromycin active substance is different to that in tulathromycin solution for injection. The adequate ratio in the finished product is achieved by means of an equilibration step during the manufacturing process of the veterinary medicinal product. Concerning this equilibration step, sufficient information has been provided.

Quality by design approach was followed during the development of the manufacturing process. The aim was to gain product and process knowledge, to understand the impact of critical process parameters, to design the optimised process at laboratory and pilot scale and finally to confirm the process parameters at pilot scale and full-scale batches.

The list of drug product's Critical Quality Attributes (CQAs) was established from the Quality Target Product Profile (QTPP) objectives and is considered satisfactory. They correspond to elements or parameters which are studied during a classical pharmaceutics development.

A Preliminary Hazard Analysis (PHA) was carried out to present unit operations likely to have an impact on the drug product CQAs. The applicant focused on the medium and high-risk areas, where material attributes and/or process parameters may affect CQAs during the preparation of the bulk sterile solution. The aim was to identify the steps with those risks and to reduce them to low risk level. Critical manufacturing steps were identified.

The selection of the sterilisation method of the product has been appropriately justified. The bioburden level of the bulk solution before sterilisation has been set according to the guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015).

Bulk manufacture scale-up is expected to be at low risk considering the design of the equipment to manufacture the bulk solution and the physico-chemical properties of the raw materials.

Critical Material Attributes (CMAs) related to the raw materials, likely to impact the processability and/or the final CQAs, were studied and support the proposed specifications.

Established Conditions (i.e. parameters for which a variation should be submitted in case of change) and Non-established conditions (i.e. changes controlled under the Pharmaceutical Quality System) were clearly described. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur., USP standards or in-house monograph. Data on microbiological contamination of the excipients were provided and no further control was deemed necessary. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

Preliminary stability studies have been performed in order to assess the stability of the formulation and the compatibility with the container closure system. Different stability studies have been carried out: at 25 ºC/ 60% RH, 40 ºC/75% RH, photostability and in-use. Results confirm the stability of the formulation and the compatibility with the container closure system.

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 in different grade areas and nitrogen bubbling is used at certain steps.

There are appropriate controls in place to monitor the critical process parameters and intermediate attributes.

The bulk solution is then sterilised by filtration and filled into glass vials which have been previously sterilised, stoppered with sterilised rubber closures and sealed with aluminium flip-off caps.

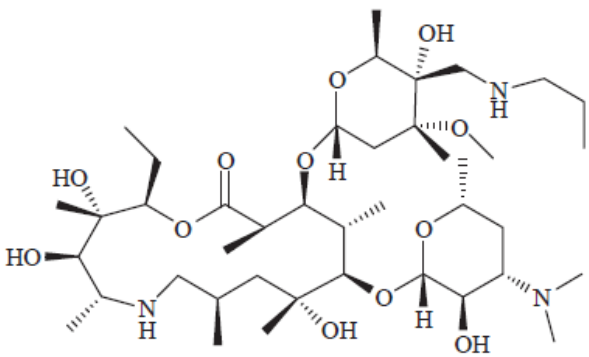
The methods of sterilisation of vials and stoppers are detailed and comply with the Ph. Eur. monograph 5.1.1.

The process has been validated with 4 pilot scale batches. Based on the information provided, the manufacturing process can be considered standard for this manufacturer and the provision of pilot scale validation data is considered acceptable. Summary of the validation data and the full validation report have been given and confirm the in-process controls and the Critical Process Parameters. The protocol to validate the process on full scale batches is the same as the one used for validation of pilot scale batches.

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 VMP includes tests for appearance, identity, specific rotation, assay, impurities, residual solvents, water content, heavy metals, residue on ignition and microbiological quality. The specification for the active substance proposed by the finished product manufacturer is acceptable and is in line with the specifications set by both active substance manufacturers.

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

Batch analysis data (3 batches from each active substance manufacturer) of tulathromycin 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

All excipients are well known pharmaceutical ingredients, their quality is compliant with Ph. Eur., USP standards or in-house monograph.

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

Declarations stating compliance of the active substance with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*, (EMA/410/01 rev. 3), were provided.

Control tests on the finished product

The specifications proposed at release are appropriate to control the quality of the finished product and include tests for appearance including clarity and visible particles, pH, relative density, extractable volume, sterility, bacterial endotoxins, tulathromycin and monothioglycerol identification and assay, isomer B percentage and degradation products.

The analytical methods used have been adequately described and appropriately validated in

accordance with the VICH guidelines. Information regarding the reference standards used for assay testing of active substance and antioxidant were presented.

Batch analysis results are provided for three batches of each proposed vial sizes, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

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

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

Stability data were provided for three pilot batches for each vial size of finished product stored under long term conditions for 18 months (vials in upright position) and for 9 months (vials in inverted position), at 25 ºC/60%RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH GL3. The batches of product were manufactured at the proposed manufacturing site and using both sources of active substance. They were packed in the primary packaging proposed for marketing and placed in both up-right and upside-down positions.

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 18 months reported.

In addition, one batch was exposed to light as defined in the VICH GL5 and the formulation is considered stable when the content of antioxidant is at the proposed range.

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

In-use stability studies, with 2 recent bulk batches filled in each vial size, and according to an appropriate design support the proposed shelf-life of 28 days after broaching. The study will be repeated post-approval on batches close to expiry.

Overall conclusions on quality

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

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

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

Part 3 – Safety

Safety documentation

Lydaxx 100 mg/ml is a solution for injection, which contains tulathromycin as active substance,

intended to be administered by subcutaneous route in cattle and by intramuscular route in pigs and sheep.

This application has been submitted in accordance with Article 13 (1) of Directive 2001/82/EC (generic product) thus, the results of pharmacological and toxicological tests are not required, as long as bioequivalence with the reference product is demonstrated.

Draxxin 100 mg/ml (EU/2/03/041/001-005), authorised by the European Commission through the centralised procedure in 2003, 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 properly justified, the safety profile of the reference product can be assumed and only information on ecotoxicity is required.

User safety

The candidate product has the same qualitative and quantitative composition in active substance and a very similar composition in excipients and the same pharmaceutical form as the reference product. 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 product. Therefore, the risk for the user is expected to be the same as that of the reference product.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines. The Predicted Environmental Concentration 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 concentration in soil is less than 100 g/kg for all categories of target species.

Lydaxx 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 constituents of Lydaxx is as follows:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Tulathromycin	(2R,3S,4R, 5R,8R,10R, 11R,12S, 13S,14R)-2-ethyl-3,4,10,13-tetra-hydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy- 3-(dimethy-lamino)-ß-D-xylo-hexopyranosyl] oxy]-1-oxa-6-azacyclopent-decan-15-one expressed as tulathromycin equivalents	Ovine, Caprine	450 µg/kg 250 µg/kg 5400 µg/kg 1800 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption	Anti-infectious agents/ Antibiotics
		Bovine	300 µg/kg 200 µg/kg 4500 µg/kg 3000 µg/kg	Muscle Fat Liver Kidney		
		Porcine	800 µg/kg 300 µg/kg 4000 µg/kg 8000 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney		

All constituents of the intended product Lydaxx 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. Lydaxx 100 mg/ml has been developed as a generic product according to Article 13(1) of Directive 2001/82/EC. It can be accepted that the candidate formulation is sufficiently similar to the reference product formulation and thus specific studies demonstrating bioequivalence with the reference medicinal product are not required, as justified by the fulfilment of condition 7.1 b) of the 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/00-Rev.3). 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 Authorisation 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/016/00-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 product has the same qualitative and quantitative composition in active substance, the same excipients and pharmaceutical form. The differences in the amount of excipients, if any, are not expected to affect the rate of residue depletion.

Moreover, the candidate product is intended to be administered by the same route of administration at the same dose and for the same indications for use in the same species as the reference product. Based on these data the depletion of residues at the injection site is expected to be the same as that of the reference product and no 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

Lydaxx has been submitted in accordance with Article 13 (1) of Directive 2001/82/EC. Given that the omission of bioequivalence studies is justified, results of toxicological and pharmacological tests are not required.

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

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

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

The depletion of residues is expected to 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, as amended. The reference product is Draxxin solution for injection for cattle, pigs and sheep, which was authorised by the European Commission on 11 November 2003.

Bioequivalence

In vivo bioequivalence studies were not conducted. Instead, the applicant claimed an exemption from such studies based on section 7.1.b) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.3) and has conducted a chemo-equivalence study to demonstrate the similarity of formulations. The product meets the requirements set in section 7.1.b) of the guideline since both the generic and the reference product are aqueous solutions to be administered by the subcutaneous or intramuscular route and they have the same qualitative composition in terms of active substance and excipients and the same concentration of active substance. The differences in the amount of excipients, if any, are not expected to affect the rate and/or extent of absorption of the active substance.

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

Development of resistance

As this is a generic product, the applicant proposes to state in the SPC the same text as in the SPC of the reference product regarding the resistance section.

However, since the current resistance situation might have changed since the introduction of tulathromycin in the European Union in 2003, the applicant has provided data to document the current situation in different European countries in bovine and porcine target pathogens. Data are based on published literature and on European surveillance programs. No such data are available for *Dichelobacter nodosus* or *Moraxella bovis*.

Data indicate that resistance is not frequent among the major respiratory tract pathogens isolated from diseased cattle and pigs; also, no evidence for a shift in the susceptibility that would raise a concern has been observed for the target pathogens, where breakpoints are available.

It is noted that no clinical breakpoints are available for *Mycoplasma bovis*, *M. hyopneumoniae*, *Haemophilus parasuis*, *Moraxella bovis* and *Dichelobacter nodosus* and that makes the data difficult to evaluate.

The CVMP considers that the information provided is sufficient to document the current situation on resistance. It should also be noted that the product information contains appropriate information regarding the correct use of the product in the context of antimicrobial resistance, in line with the information included in the SPC of the reference product.

However, notwithstanding the legal basis of this generic application, an additional phrase to ensure responsible use of the veterinary medicinal product has been inserted in section 4.5 of the SPC in line with the revised guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005).

Target animal tolerance

Bioequivalence is considered demonstrated between the test and the reference product. These products have the same qualitative and quantitative composition in active substance and the same excipients in similar amounts. Both products are to be used at the same dose and by administration routes. Thus, the expected tolerance profile in the target species would be the same. The omission of tolerance data is considered acceptable.

Clinical field trials

As bioequivalence between the proposed generic product and the reference product is accepted, 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, Lydaxx, 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/016/00-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 the same and are present in similar amounts 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 pre-clinical and clinical studies is acceptable. The efficacy and safety profiles for the generic and reference product are expected to be the same at the same posology.

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 (EMA/CVMP/ SAGAM/383441/2005).

Part 5 – Benefit-risk assessment

Introduction

Lydaxx is a solution for injection containing 100 mg tulathromycin/ml.

The active substance, tulathromycin, is a well-known semi-synthetic macrolide antimicrobial agent, which is a bacteriostatic acting antibiotic that inhibits essential protein biosynthesis by virtue of its selective binding to bacterial ribosomal RNA. The product is intended for use in cattle, pigs and sheep for:

Cattle

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

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

Pigs

Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica* susceptible to tulathromycin. The presence of the disease in the herd should be established before metaphylactic treatment. The product should only be used if pigs are expected to develop the disease within 2-3 days.

Sheep

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

The proposed effective dose of 2.5 mg tulathromycin/kg bodyweight as a subcutaneous (cattle) or intramuscular (pigs and sheep) injection has been confirmed.

The application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (abridged application (generic)). The reference product is Draxxin solution for injection for cattle, pigs and sheep.

Benefit assessment

Direct therapeutic benefit

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

Risk for the user:

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

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

Risk for the environment:

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

Risk for the consumer:

Tulathromycin has been evaluated previously in respect to the safety of residues and MRLs have been established for target species and food commodities concerned under this application. Lydaxx 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 product is not authorised for use in animals producing milk for human consumption. The withdrawal periods approved under section 4.11 of the SPC of the reference product will also apply to the candidate product, namely:

Cattle (meat and offal): 22 days.
Pigs (meat and offal): 13 days.
Sheep (meat and offal): 16 days.

The product is not authorised for use in animals producing milk for human consumption.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, environment and consumer and to provide advice on how to prevent or reduce these risks.

To ensure comprehensive adverse event surveillance, PSUR submissions and surveillance of EVVet data should be synchronised with the reference product.

Evaluation of the benefit-risk balance

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures, including the same withdrawal periods as for the reference product, have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for Lydaxx 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.