16 February 2022
EMA/138154/2022
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Chanaxin (EMEA/V/C/005606/0000)

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 Chanelle Pharmaceuticals Manufacturing Ltd submitted on 1 October 2020 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Chanaxin 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 24 April 2020 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. Chanaxin 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 Chanaxin 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.

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

The rapporteur appointed is Mary O'Grady and the co-rapporteur is Katarina Štraus.

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 February 2022, the CVMP adopted an opinion and CVMP assessment report.

On 19 April 2022, the European Commission adopted a Commission Decision granting the marketing authorisation for Chanaxin.

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 EU. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacturing activities above, has been provided.

Batch release takes place at Chanelle Pharmaceuticals Manufacturing Ltd., Dublin Road, Loughrea, Co. Galway, Ireland. The site has a manufacturing authorisation issued on 22 August 2020 by the Irish competent authority. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for batch release, has been provided.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the batch release site. The declaration was based on an on-site audit.

No additional inspection prior to grant of a marketing authorisation is required.

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 yellow solution for injection containing 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, sodium hydroxide and water for injections (solvent). The inclusion of monothioglycerol is justified with reference to the publicly available information on the composition of the reference product.

The product is available in Type I colourless glass vials with a fluoropolymer coated chlorobutyl rubber stopper and an aluminium cap as described in section 6.5 of the SPC.

Containers

The primary packaging is Type I glass vials of 20 ml, 50 ml, 100 ml or 250 ml with fluoropolymer

coated chlorobutyl rubber stoppers. The material complies with the relevant European Pharmacopoeia (Ph. Eur.) requirements. The choice of the container closure system has been validated by stability data. The dossier includes a study in which the integrity of the rubber closures was evaluated following 40 broachings of the stopper. With reference to the posology described in the SPC, this does not represent testing under worst case in-use conditions however, it is proposed to include the statement 'The stopper may be safely punctured up to 40 times' in SPC Section 4.9 which is acceptable as the stopper complies with acceptance criteria for the fragmentation test as per Ph. Eur. 3.2.9 after 40 broachings.

The glass vials are packaged in outer cardboard cartons containing one vial per carton of the solution for injection. With respect to the proposed pack sizes, all are consistent with the available packaging for the reference product, however, an additional 500 ml presentation is authorised for the reference product.

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

Development pharmaceutics

Chanaxin 100 mg/ml solution for injection has been submitted as a generic application under Article 13(1) of Directive 2001/82/EC as amended. The applicant has applied for a waiver from bioequivalence study requirements citing section 7.1.b of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/2000-Rev.3-corr*).

Formulation development for the generic product is based on the formulation of the reference product Draxxin 100 mg/ml solution for injection. To this end, the applicant utilises publicly available information for the reference product from a number of sources e.g. the SPC and the European Public Assessment Report (EPAR) for Draxxin as published on the EMA website. In addition, results of analysis of batches of the reference product sourced in the EU have also been utilised in formulation development.

In terms of manufacturing process development, studies described in the development section evaluated the effect on the tulathromycin isomer ratio of the temperature applied during dispersion of tulathromycin in the solution during manufacture. These studies determined the appropriate temperature and stirring time for tulathromycin dispersion in the formulation. An acceptable process validation protocol for industrial scale batches has been provided in Part 2.B.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or USNF standards. There are no novel excipients used in the finished product formulation. The applicant adequately demonstrated that the formulation is self-preserving, the test for efficacy of antimicrobial preservation was carried out in accordance with Ph. Eur. 5.1.3 and the product was found to meet the A criteria for parenteral preparations. The preservative efficacy test according to Ph. Eur. 5.1.3 will be conducted for batches at the end of shelf life.

The primary packaging materials i.e. clear Type I glass vials with a fluoropolymer coated chlorobutyl rubber stopper have been chosen with reference to the packaging declared for the reference product in the EPAR for Draxxin and relevant Ph. Eur. chapters. To demonstrate compatibility between formulation and the packaging, a pre-stability stress test on laboratory batch was performed. Due to known inertness of the proposed primary packaging materials and their similarity between proposed and reference product no additional sorption studies or elaboration of leachables or extractables are requested. Photostability studies have been performed and the product has been found to be photostable.

The integrity of the rubber closures was evaluated and complied with Ph. Eur. criteria following 40 broachings of the stopper.

With respect to the biowaiver, the applicant cites section 7.1.b of the 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/2000-Rev.3-corr.*) 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."

It is accepted that the product is intended to be administered subcutaneously to cattle and intramuscularly to pigs and sheep, is of the same type of solution (aqueous), includes the same concentration of active substance and includes the same excipients. Further, based upon the SPC of the reference product as authorised in the EU, it can be accepted that Chanaxin includes the same concentration of the excipient monothioglycerol.

The applicant has carried out an analysis and submitted data comparing the formulations of the reference and generic products. They have the same qualitative and quantitative composition in active substance, the same excipients and pharmaceutical form. The differences in the amounts of excipients, if any, are not expected to affect the rate and/or extent of absorption of tulathromycin, local tolerance or depletion of residues of tulathromycin from the injection site.

Method of manufacture

The manufacturing process has been well described. The product is a solution for injection which is manufactured in a process involving sequential addition of product ingredients with stirring to achieve dissolution. The bulk solution is sterilised by filtration through a sterilising grade filter and the vials are filled under aseptic conditions into sterile primary packaging. The manufacturing process is conducted in its entirety under nitrogen bubbling and the headspace of filled vials is flushed with nitrogen.

In-process controls (IPCs) are defined for the process and are generally appropriate for the manufacture of a sterile solution according to the proposed manufacturing process. Process validation was conducted on two pilot scale batches which were filled into the container closure system proposed for marketing. A process validation protocol for the manufacture of 3 industrial scale batches has been provided. The protocol includes the information detailed in Annex I to the Guideline on process validation for finished products – information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1). As sterile filtration is considered a non-standard process in line with the guideline on process validation EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev.1, the applicant has provided justification with respect to why the process can be considered standard at the proposed finished product manufacturing site. The basis for the justification is the manufacturer's experience in the manufacture of sterile products produced using sterile filtration with aseptic processing which is considered acceptable.

The process validation report includes data/results for different stages of the manufacturing process i.e. the process parameters monitored during main solution preparation, the in-process controls, the filtration process and data for the bulk solution pre and post filtration, the filling process and full finished product analysis of the filled product. All results comply with specifications with the exception of results for pre-filtration bioburden which do not meet the specified limit of ≤10 cfu/100 ml as per the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary

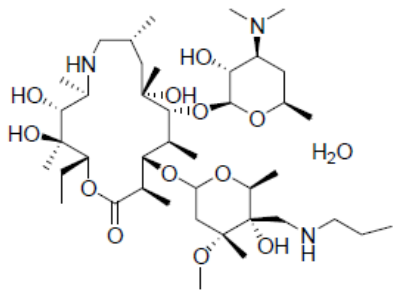
container (EMA/CHMP/CVMP/QWP/850374/2015). To address queries raised on these results, the applicant commenced root cause investigations and also conducted a comprehensive risk assessment in order to identify potential sources of the high bioburden. The root cause investigations identified issues the sample size and the length of time before its analysis as the cause of the results rather than being indicative of a high bioburden in the product itself. Arising from the root cause investigations and the risk assessment the applicant is implementing corrective and preventive actions (CAPAs) to improve sample management. The CAPAs are considered to be appropriate, and the sample size and bioburden test method have been amended. A satisfactory protocol for the method suitability test for the bioburden method has been provided. In addition, a process validation protocol for industrial scale batches has been provided which specifies a limit of ≤10 cfu/100 ml for prefiltration bioburden. Further supporting information has been provided in the form of a declaration from the qualified person at the finished product manufacturing site which highlights the significant experience of the site in the manufacture of sterile products according to aseptic processes. The root cause investigation has also demonstrated that there is no systemic issue with respect to control of bioburden at the manufacturing site. In addition, the high retention capacity of the sterilising filter has been demonstrated and data has been provided which confirms that the sterilising filter has the capacity to retain a bioburden in the solution at the level of 8 cfu/ml, albeit that this result is not considered to be representative of the microbiological load of the solution.

While the responses provided to queries on the bioburden issue are noted and provide assurance that the observed non-compliant bioburden results represent a sample processing issue rather than a manufacturing issue, no data has been presented which demonstrates that the product complies with a pre-filtration bioburden limit of ≤10 cfu/100 ml. To address this, prior to marketing the product, the marketing authorisation holder must provide validation of the pre-filtration bioburden test method and data from 2 batches of at least pilot scale tested using the validated method, demonstrating compliance with the pre-filtration bioburden limit of ≤10 cfu/100 ml. The data must be submitted as a variation requiring assessment.

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. One supplier is proposed for the active substance. Assessment of the ASMF is contained in separate documents.

The applicant's specification for tulathromycin is provided in the dossier and is acceptable, it is the same as the specification presented in the ASMF. Tests for character (i.e. appearance), identification, water content, specific rotation, sulfated ash, assay, related substances, residual solvents, bacterial endotoxins and microbiological quality are included.

Satisfactory batch data for three batches of the active substance has been provided in the dossier. Batch details of the reference standards used by the applicant for the control of the active substance have also been provided.

Full stability data, long-term and accelerated conditions were provided by the ASMF holder in order to establish a re-test period of the active substance. Long-term stability data up to 24 months were provided and a re-test period of 2 years is proposed when stored below 25 °C, in an airtight container and protected from light. According to the results provided, a retest period of 24 months is considered acceptable.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. (propylene glycol, citric acid monohydrate, hydrochloric acid, dilute, sodium hydroxide, water for injections) or USNF (monothioglycerol) standards. There are no novel excipients used in the finished product formulation. Control of microbiological quality is included on the specifications for relevant excipients in line with Ph. Eur. 5.1.4. 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.

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.

Control tests on the finished product

The specifications proposed for use at release include relevant test parameters for the dosage form and are appropriate to control the quality of the finished product. The specification includes tests for appearance, clarity, colour, visible particles, pH, density, extractable volume, identification and assay of tulathromycin, identification and assay of monothioglycerol, tulathromycin A assay, tulathromycin B assay, related substances and sterility.

Analytical methods are well described and have been validated, where relevant, in accordance with VICH GL2: Validation of analytical procedures: methodology. A forced degradation study which demonstrates that the related substances method is stability indicating has been carried out.

Satisfactory information regarding the reference standards used for assay, antioxidant and related substances determination has been presented.

Batch analysis results are provided for two pilot scale batches. All of the results comply with the limits as per the release specification with the exception of the result for tulathromycin A and B isomers in one batch packaged in the 50 ml vial. The applicant will evaluate a different stirring time for isomer equilibration during manufacture of industrial batches. Overall the finished product batch data exhibits a high level of intra- and inter-batch comparability.

Stability

Primary stability study

Stability data is presented for studies carried out on two pilot scale batches manufactured at the proposed dosage form manufacturing site. These are the same batches which were used in process validation however, for finished product stability studies, the applicant has applied a bracketing design whereby only the smallest and largest pack sizes of each batch have been included in the stability study i.e. the 20 ml and 250 ml vials. The bracketing design proposed is acceptable.

The specifications proposed at the end of shelf-life are the same as those proposed at release except for monothioglycerol content. The difference between release and end of shelf-life limits have been appropriately justified.

For both batches, 18 months data has been presented for product stored at long-term and intermediate storage conditions and 6 months data for product stored at accelerated conditions, according to VICH GL3, Stability testing for new veterinary drug substances and medicinal products. The study included vials stored in both upright and inverted orientations. The parameters monitored on stability are appearance (including colour, clarity and visible particles), condition of packaging, pH, density, tulathromycin assay, tulathromycin A isomer content, tulathromycin B isomer content, monothioglycerol assay, related substances and sterility. The studies under long-term and intermediate conditions are to continue to 36 months while the accelerated study is complete. The test for sterility is to be carried out at the initial time point and at the end of the study.

Results for all parameters are within the proposed shelf life specifications. .

A shelf-life of 3 years is proposed however, based on the available stability data, a maximum shelf-life of 30 months can be approved by extrapolation.

In-use stability

The product has been evaluated for in-use stability according to an acceptable in-use stability protocol. Data for one batch has been provided and an in-use shelf life of 28 days is proposed which is considered to be supported by the data. A second batch will be tested at the end of shelf life.

Photostability

The photostability of the finished product was evaluated as part of the forced degradation study presented in the dossier. The product was found to be photo-stable with no degradation observed. Based on the data, it is considered acceptable that the SPC does not include any special warning to protect the product from light.

Overall conclusions on quality

The application for Chanaxin has been submitted as a generic application under Article 13(1) of Directive 2001/82/EC.

The finished product is presented as a clear, colourless to yellow solution for injection containing the

active substance tulathromycin at 100 mg/ml. Tulathromycin is a macrolide antibiotic that consists of two isomers, tulathromycin A and tulathromycin B. The formulation is an aqueous solution for injection containing monothioglycerol, propylene glycol, citric acid monohydrate, hydrochloric acid, sodium hydroxide and water for injections. The product is available in clear Type I glass vials of 20 ml, 50 ml, 100 ml and 250 ml, with a fluoropolymer coated chlorobutyl rubber stopper and an aluminium cap.

In the development pharmaceutics the applicant provides information on the development of the formulation and the development of the manufacturing process with respect to the tulathromycin isomerisation process and the filtration process. Information is also included on the selection of the sterilisation method for the finished product. Based on the data presented, the proposal to sterilise the product by filtration is considered acceptable.

The solution for injection is manufactured in a process involving sequential mixing and dissolution of the product constituents in water for injections. The finished product is sterilised by filtration and the product is filled into sterilised primary packaging. The manufacturing process has been well described. Process validation data for 2 pilot scale batches and a process validation protocol for 3 industrial scale batches have been provided. The level of process validation data provided in the dossier is acceptable as the applicant has provided an acceptable justification to consider this manufacturing process standard for this specific manufacturer.

The process validation results indicate that the batches do not meet the specified limit of ≤10 cfu/100 ml for pre-filtration bioburden. The applicant has undertaken root cause investigation and carried out a risk assessment in order to identify potential sources of the high bioburden. The bioburden issue is deemed to relate to the sample and its analysis as opposed to being indicative of a high bioburden in the product itself. Appropriate CAPAs are to be introduced on foot of the root cause investigation and risk assessment. In addressing the bioburden issue, the significant experience of the dosage form manufacturing site in the manufacture of sterile products according to aseptic processes has been highlighted and it was also demonstrated that there is no systemic issue with respect to control of bioburden at the site. While the information provided by the applicant in relation to the bioburden issue is noted and provide assurance that the observed non-compliant bioburden results represent a sample processing issue rather than a manufacturing issue, no data has been presented which demonstrates that the product complies with a pre-filtration bioburden limit of ≤10 cfu/100 ml. To address this, prior to marketing the product, the MAH must provide validation of the pre-filtration bioburden test method and data from 2 batches of at least pilot scale tested using the validated method, demonstrating compliance with the pre-filtration bioburden limit of ≤10 cfu/100 ml. These data must be submitted as a variation requiring assessment.

Information on the control of starting materials has been provided. The active substance tulathromycin is not monographed in a pharmacopoeia and data on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Assessment reports for the applicant's and restricted parts of the ASMF are provided separately. The dosage form manufacturer has provided a specification for the active substance. It is the same as the specification presented in the applicant's part of the ASMF. Satisfactory batch analysis data for three batches of the active substance has been provided.

All of the product excipients are supplied to either Ph. Eur. or USNF grade. Control of microbiological quality is included on the specifications for relevant excipients in line with Ph. Eur. 5.1.4. The finished product container closure system is considered to be appropriate and the required supporting information is included in the dossier.

The finished product specification at time of release controls those parameters appropriate for the dosage form. Analytical methods for determination of active substance assay, tulathromycin isomer ratio, related substances and monothioglycerol assay have been provided. The methods are well

described and validation has been provided in line with VICH GL2: *Validation of analytical procedures: methodology*. The test for sterility is carried out by membrane filtration and has been satisfactorily validated. Batch data for two pilot scale batches of the finished product has been provided.

In terms of dosage form stability, 18 months data has been presented for product stored at long-term and intermediate storage conditions and 6 months data for product stored at accelerated conditions. No differences were observed for data from inverted vials when compared with data for upright vials. The applicant has requested a shelf life of 3 years. The data presented is sufficient to allow a shelf life of 30 months to be approved, by extrapolation.

An in-use stability study protocol and in-use data for one batch has been provided. A second batch of product will be tested for in-use stability at the end of shelf life. The design of the study is considered to be appropriate.

The photostability of the finished product was evaluated as part of the forced degradation study and the product was found to be photostable.

Part 3 – Safety

Safety documentation

This application is for Chanaxin 100 mg/ml, an injectable solution containing tulathromycin as the active substance, for use in cattle, pigs and sheep. This application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (a generic product).

The reference product Draxxin 100 mg/ml solution for injection for cattle, pigs and sheep (EU/2/03/041/001-005) has been authorised in the European Union for not less than 10 years based on a full dossier and can be accepted as a valid reference product (originally authorised on 11 November 2003).

According to Article 13(1) of Directive 2001/82/EC, the applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if they can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 5 for not less than eight years in a Member State or the Community.

The applicant has claimed an exemption from the requirement to conduct *in-vivo* bioequivalence studies in accordance with section 7.1.b of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3-corr.*).

According to section 7.1.b, for products intended for intramuscular or subcutaneous administration, studies to compare the rate and extent of absorption between two formulations or products containing identical active substances are generally 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.

Chanaxin is proposed for the same indications using the same administration routes at the same posology in the same target species as the reference product. The product is the same type of solution (aqueous), includes the same concentration of active substance and includes the same excipients as the reference product. Further, based upon the SPC of the reference product as authorised in the EU, it can be accepted that Chanaxin includes the same concentration of the excipient monothioglycerol.

In addition, the applicant has provided the results of comparative analyses which indicates that the concentrations of the excipients propylene glycol, citric acid monohydrate, sodium hydroxide and

hydrochloric acid are similar. 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.

It can be concluded that the criteria set out in section 7.1.b of the aforementioned CVMP bioequivalence guideline have been satisfied and the omission of *in-vivo* bioequivalence study data can be accepted. The applicant has not submitted a complete safety file which is considered acceptable.

User safety

The applicant has provided a user risk assessment which has been conducted broadly in accordance with the CVMP guideline on user safety (EMA/CVMP/543/03-Rev.1).

Although a quantitative risk assessment has not been carried out by the applicant, given the legal basis of this application (generic) and the fact that the candidate formulation is claimed to be qualitatively and quantitatively the same as that of the reference product, no difference in user exposure is anticipated.

It can be accepted that the candidate formulation is intended to be administered by the same routes of administration at the same dose rate and for the same indications in the same species as already approved for the reference product. Consequently, injection volumes and therefore risk of exposure are considered to be the same.

Given the above and notwithstanding the absence of a quantitative user safety assessment and calculation of margins of exposure, given that no greater risk to the user is anticipated following use of the candidate formulation than that which already exists for the reference product, no further user safety data are required.

The proposed user safety warnings are identical to those approved for the reference product which are considered acceptable.

It may be concluded 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 product and can therefore be applied to the candidate product.

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

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

All constituents of the intended product Chanaxin are included in Table 1 of Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin or are considered as not falling within the scope of Council Regulation 470/2009 when used as in this product.

Residue studies

No residue depletion studies were provided. The applicant claims 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 (pH, density, appearance) of the candidate and reference formulations and concluded that they are similar.

Consequently, it can be concluded that the rate of depletion of residues from the injection site will be the same for Chanaxin as for the reference product.

Withdrawal periods

The applicant proposes the same withdrawal periods for the candidate formulation as already approved for the reference product, namely;

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.

According to the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3-corr.*; Chapter 4.4):

"It should be noted that bioequivalence or waivers cannot be used for extrapolation of withdrawal periods between products with a potential to leave local residues (for example intramuscular and subcutaneous injectables, dermal and transdermal applications). In this case, information on the behaviour of residues at the site of administration needs to be assessed before the withdrawal period is extrapolated. It should also be noted that for formulations (i.e. active substance plus all excipients) that are qualitatively and quantitatively identical, a justification for the absence of residues data would be acceptable."

Further, Commission Directive 2009/9/EC states:

"For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:

— evidence to demonstrate equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies,"

Consequently, data to investigate the depletion of residues from the injection site would normally be expected for a generic application.

According to the CVMP 'Guideline on determination of withdrawal periods for edible tissues' (EMA/CVMP/SWP/735325/2012), it is stated that *"in the case of products administered subcutaneously or intramuscularly, small differences in composition may have significant effects on injection site depletion which may not be detected in the standard blood level bioequivalence studies. Therefore, for such formulations, in addition to bioequivalence studies, equivalent (or faster) depletion of residue from the injection site should be demonstrated, in order that the withdrawal period established for the reference product can be adopted."*

The applicant has provided the results of comparative analyses which indicates that the concentrations of the excipients propylene glycol, citric acid monohydrate, sodium hydroxide and hydrochloric acid are similar. The differences in the amount of excipients, if any, are not expected to affect the rate of residue depletion.

Consequently, it can be concluded that the rate of depletion of residues from the injection site will be the same for Chanaxin as for the reference product and therefore the proposed withdrawal periods are adequate.

The withdrawal periods approved for the reference product may be applied to Chanaxin.

Overall conclusions on the safety and residues documentation

Chanaxin has been submitted in accordance with Article 13(1) of Directive 2001/82/EC.

Given that the omission of bioequivalence studies is accepted, results of toxicological and pharmacological tests are not required.

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

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

The environmental assessment can conclude at Phase I as the PECsoil initial value is below the Phase II trigger value of 100 µg/kg. The omission of a Phase II assessment can be accepted. It can be concluded that the product does not entail any risk for the environment when used as recommended in the SPC.

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

Part 4 – Efficacy

This application is for a generic product, submitted in accordance with Article 13(1) of Directive 2001/82/EC. The reference product is Draxxin solution for injection for cattle, pigs and sheep, which was authorised by the European Commission on 11 November 2003.

Bioequivalence

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

Chanaxin is to be indicated for the same indications using the same administration routes at the same posology in the same target species as the reference product.

Chanaxin is intended to be administered subcutaneously to cattle and intramuscularly to pigs and sheep, is of the same type of solution (aqueous), includes the same concentration of active substance and includes the same excipients as the reference product. Further, based upon the SPC of the reference product as authorised in the EU, it can be accepted that Chanaxin includes the same concentration of the excipient monothioglycerol.

In addition, the applicant has provided the results of comparative analyses which indicate that the concentrations of the excipients propylene glycol, citric acid monohydrate, sodium hydroxide and hydrochloric acid are similar. 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.

It can be concluded that the criteria set out in section 7.1.b of the aforementioned CVMP bioequivalence guideline have been satisfied and the omission of pre-clinical and clinical data can be accepted.

Development of resistance

No data on resistance has been provided.

This application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (a generic veterinary medicinal product). The omission of *in-vivo* bioequivalence studies is claimed in accordance with section 7.1.b of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products'.

It can be accepted that Chanaxin is qualitatively the same as the reference product and is quantitatively the same in respect of the active substance (tulathromycin) and the excipient monothioglycerol. Further, both products are to be administered at the same dose rates by the same routes of administration to the same target species. Consequently, the risk for resistance

development is expected to be the same as that of the reference product.

The applicant has included 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 and this is considered acceptable.

Target animal tolerance

No data on target animal tolerance has been provided.

The applicant claims that it has suitably demonstrated that the candidate formulation is sufficiently similar to the reference formulation to be considered the same and 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.

Commission Directive 2009/9/EC states:

"For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:

— evidence to demonstrate target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies."

The applicant has provided the results of comparative analyses which indicate that the concentrations of the excipients propylene glycol, citric acid monohydrate, sodium hydroxide and hydrochloric acid are similar hence it is the opinion of the CVMP that tolerance at the injection site is not expected to differ between Chanaxin and the reference product and, consequently, the information proposed for inclusion in sections 4.6 and 4.10 of the SPC approved for the reference product can be applied to Chanaxin.

Clinical field trials

No clinical study data has been provided.

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

Based on the data provided, bioequivalence with the reference product can be accepted, as well as the omission of clinical study data for the candidate formulation.

Overall conclusion on efficacy

This is a generic application based on Article 13(1) of Directive 2001/82/EC and the applicant has claimed bioequivalence with 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-corr.).

No data on resistance, target animal tolerance or clinical studies have been provided.

Chanaxin is qualitatively the same as the reference product and is quantitatively the same in respect of the active substance (tulathromycin) and the excipient monothioglycerol. The applicant has provided the results of comparative analyses which indicate that the concentrations of the excipients propylene

glycol, citric acid, sodium hydroxide and hydrochloric acid are similar, hence bioequivalence with the reference product can be accepted, as well as the omission of target animal tolerance and clinical study data for the candidate formulation.

The risk for the development of resistance can be considered the same as for the reference product. Further, safety warnings in line with the SPC for the reference product are included and are acceptable.

Part 5 – Benefit-risk assessment

Introduction

Chanaxin 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 group must be established before the product is used.

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 group must be established before the product is used. The veterinary medicinal 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 is the same as that of the reference product and can be accepted.

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 Chanaxin is considered established on the basis of bioequivalence to the reference product. The direct therapeutic benefits for Chanaxin 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

Quality

Information on development, manufacture and control of the active substance and finished product has been presented. 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. However, no data has been presented which demonstrates that the product complies with a pre-filtration bioburden limit of ≤10 cfu/100 ml. To address this, prior to marketing the product, the MAH must provide validation of the pre-filtration bioburden test method and data from 2 batches of at least pilot scale tested using the validated method, demonstrating compliance with the pre-filtration bioburden limit of ≤10 cfu/100 ml. These data must be submitted as a variation requiring assessment.

Safety

Bioequivalence with the reference product is accepted 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-corr.).

Chanaxin is not expected to pose a risk for the target animal, the consumer, the user or the environment when used according to the SPC recommendations.

Risk management or mitigation measures

In view of non-compliant bioburden results seen in samples collected during manufacturing, the MAH must provide validation of the pre-filtration bioburden test method as well as data from 2 batches of at least pilot scale tested using the validated method, demonstrating compliance with the pre-filtration bioburden limit. These data are to be provided prior to marketing of the product.

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.

Evaluation of the benefit-risk balance

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures, including withdrawal period, 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 Veterinary Medicinal Products (CVMP) concluded that the application for Chanaxin 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. However, the CVMP recommends a condition for marketing authorisation.