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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Lexylan (EMEA/V/C/006103/0000)

INN: Cefalexin

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

Introduction

The applicant Emdoka submitted on 6 September 2022 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Lexylan, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on 13 April 2022.

At the time of submission, the applicant applied for the following indications:

Treatment of diseases caused by cefalexin susceptible micro-organisms at well accessible infection sites, within the limits of effective cefalexin concentrations.

Cattle:

Metritis, interdigital dermatitis, wounds and abcesses, treatment of septicemic mastitis in addition of an intramammary therapy.

Dogs:

Infections of the respiratory tract, the uro-genital system, the skin, soft tissues and the gastro-intestinal system.

Cats:

Infections of the respiratory tract, the uro-genital system, the skin and soft tissues.

The active substance of Lexylan is cefalexin, a cephalosporin antibiotic. The bactericidal effect of cefalexin is based on interference with the cell membrane synthesis by inactivation of transpeptidase. The target species are cats, cattle and dogs.

Lexylan suspension for injection contains 180 mg/ml of cefalexin and is presented in vials containing 100 ml or 250 ml.

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

The rapporteur appointed is Sylvie Louet and the co-rapporteur is Els Dewaele.

The dossier has been submitted in line with the requirements for submissions under Article 18 of Regulation (EU) 2019/6 – a generic application.

On 14 February 2024, the CVMP adopted an opinion and CVMP assessment report.

On 8 April 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for Lexylan.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has put in place a pharmacovigilance system master file (PSMF) with reference number PSMF-EMDOKA, has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

A GMP certificate issued by the competent authority of Italy is presented for the site responsible for the manufacture, micronisation, quality control testing, packaging and storage of the active substance.

Manufacture of the intermediate cefalexin monohydrate takes place within the EU. A QP declaration for the intermediate manufacturing site was provided from the Qualified Person (QP) at WDT in Germany, the site responsible for batch release of the finished product. The declaration was based on an onsite audit which has taken into consideration the GMP certificate available for the active substance site issued by Italian competent authority following an inspection.

Manufacture, micronisation, quality control testing chemical/physical, microbiological, primary packaging, secondary packaging, storage of active substance of the active substance cefalexin sodium take place outside the EEA. A QP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at WDT in Germany, the site responsible for batch release of the finished product. The declaration was based on an onsite audit which has taken into consideration the GMP certificate available for the active substance site issued by Italian competent authority following inspection.

A QP declaration for the active substance manufacturing sites was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by a third party for the active substance manufacturer and for the active substance intermediate manufacturer.

Sterilisation of the active substance cefalexin sodium takes place outside the EEA. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the activities indicated above, has been provided.

Finished product

Batch release take place at Wirtschaftsgenossenschaft Deutscher Tierärtze eG (WDT) in Germany. The site has a manufacturing authorisation issued on 9 June 2021 by the German Authority, Trade and Industry Inspection Agency of State of Lower Saxony, agency Hannover). GMP certification, which confirms the date of the last inspection (26th February 2021) and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as a multidose suspension for injection containing 180 mg/ml of cefalexin (as cefalexin sodium) as active substance.

Other ingredients are hydrogenated castor oil and medium-chain triglycerides. The product is manufactured under nitrogen. The product is a white to slightly yellow suspension.

The product is available in multidose glass vials containing 100 ml and 250 ml, as described in section 5.4 of the SPC. The vials are further individually packed in outer carton.

Containers and closure system

The primary packaging is type II clear glass vials closed with fluorinated bromobutyl rubber stoppers and sealed with aluminium caps (with or without flip-off caps) as stated in section 5.4 of the SPC. The materials comply with the relevant monographs of the European Pharmacopoeia (Ph. Eur.). Rubber stoppers comply with the Ph. Eur. fragmentation test adapted to the field use. A restriction on the number of punctures (maximum of 25 for the 100 ml vial and maximum 50 for the 250 ml vials) has been included in section 3.9 of the SPC.

Glass vials are sterilized by the manufacturer of the finished product. The conditions retained for the depyrogenation of the vials are clearly specified. Rubber stoppers are sterilised by the manufacturer of the finished product. As conditions of the Ph. Eur. are adhered to, no validation data were needed.

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

The larger packaging size was justified according to the dose regimen and duration of use. Considering the smaller target species which can be treated and the nature of the active substance (antibiotic), it is recommended that the applicant develops a smaller packaging. Certificates of analysis have been supplied demonstrating compliance with the proposed specifications.

Product development

The present drug formulation is based on the existing Cefalexin 180mg/mL suspension for injection marketed by Intervet International 'Ceporex 180mg/mL', authorised in the Union since 1988.

The active substance is Cefalexin (as Cefalexin sodium), an antibacterial drug of the cephalosporin family.

Several studies on the reference product were conducted to check the chemical composition. The results lead to a concentration of castor oil, hydrogenated in fractionated coconut oil to obtain the most similar viscosity of the reference product. Further studies carried out by the applicant led them to set an amount of the hydrogenated castor oil to be used in the product. The applicant argued that, if a small difference in the final amount of hydrogenated castor oil / fractionated castor oil between the reference and the candidature products is found, it could be considered negligible as a variation within batch to batch can be obtained for hydrogenated castor oil.

Physicochemical properties of the candidate and the reference products were compared, including a control of density, viscosity, related substances, size and shape of particles, syringeability and

polymorphism.

It was concluded that the proposed and reference products have the same qualitative and quantitative composition in active substance and the same excipients in very similar amounts and that the two products have comparable physicochemical properties.

The selection of the sterilisation method of the product has been appropriately justified.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. The list of excipients is included in section 2 of the SPC.

Description of the manufacturing method

The manufacturing process consists of 3 steps: mixing and sterilisation of the excipients, addition of sterile active pharmaceutical ingredient (API) and homogenisation and filling into sterile primary packaging.

The process is considered to be a non-standard manufacturing process (aseptic processing). The aseptic processing was satisfactorily justified considering the high sensitivity of the active substance to heat.

Manufacturing formulas were presented covering the range of proposed commercial sizes.

The manufacturing process is considered well described and information on the maximum storage time applied during the process provided.

The oily base (mixture of both excipients) is satisfactorily sterilised according to a standard method. Bioburden is included as standard in-process controls with a satisfactory limit. The methods used to sterilise the different parts of the packaging are included in the description of the manufacturing process.

The methods of sterilisation of vials and stoppers are also detailed in part 2c3. According to part 2c3, the sterilisation method used for rubber stoppers complies with the Ph. Eur.

Several steps were identified as critical. The in-process controls are adequate for this manufacturing process.

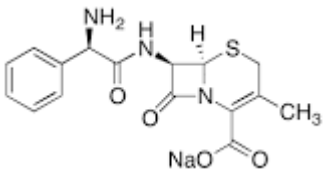
A holding time (from the sterilisation of the excipients until the end of filling) is proposed and validated.

The process has been validated with 2 industrial scale batches. The validation report has been given, including results of in-process controls and validation parameters. Physical parameters of the suspension were also tested. Results of media fill are provided for both industrial batches. According 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, Corr.1), validation data should be completed by data on another batch. The applicant justified the absence of validation on a 3rd industrial batch in the dossier. However, it committed to validate the manufacturing process on a 3rd industrial batch before the end of 2024 and to release no batch before the completion of the validation process.

Control of starting materials

Active substance

The chemical name of cefalexin sodium is (6R,7R)-7-[[(2R)-2-Amino-2-phenylacetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct -2-ene-2-carboxylic acid sodium salt and has the following structure:



Cefalexin sodium is a semi-synthetic antibacterial drug of the cephalosporin family.

The active substance is a white or almost white, crystalline powder. Since the active ingredient is not solubilised in the product, particle size and polymorphism considerations are considered critical for the quality of the finished product.

Cefalexin sodium is not described in any pharmacopoeia. Supporting data for the active substance has been provided in the form of an ASMF. One manufacturing site is proposed for the active substance. Assessment of the ASMF is contained in separate documents.

The active substance specification from the manufacturer of the VMP includes tests for appearance, microscopic appearance, solubility, pH, specific optical rotation, identity sodium, identity, particle size, water content, related substances, assay, sterility, residual solvents and are in accordance with the specifications proposed by the active substance supplier.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines.

Batch analysis data 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 in order to establish a re-test period years for the active substance. According to the results provided, an agreed retest period, with the following storage precaution "Do not store above 25°C" is considered acceptable.

Excipients

All excipients are well known pharmaceutical ingredients, their quality is compliant with Ph. Eur. A control of microbiological contamination is included in their specifications and nitrogen is sterilised on-site.

No certificate of analysis is presented for the excipients.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 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.

Declaration stating compliance of the finished product 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), is provided.

A valid TSE certificate of suitability for cefalexin sodium (sterile bulk) from the stated manufacturer was provided.

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 at release are appropriate to control the quality of the finished product and include tests for appearance, particle size, relative density, extractable volume, sedimentation, syringeability, resuspendability, sterility, cefalexin identification and assay 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.

A risk assessment on the presence of elemental impurities was provided.

Batch analysis results are provided for 2 industrial scale batches and 2 laboratory batches, 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 stability study before use and an in-use stability study. A photostability study was performed and confirms that no storage precaution for the light is necessary.

The specifications proposed at the end of shelf-life are the same as those proposed at release.

Stability data of 2 industrial scale batches of finished product and 2 laboratory scale batches packaged in 100 mL and 250 mL stored under long term conditions for 18 months (vials in upright position) and for 6 months (vials in upside down position), at 25 ºC/60%RH, for 12 months in intermediate conditions at 30°C/65% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH (in both positions, upright and upside down) according to the VICH GL3 were provided. All the studies were performed protected from light. The industrial batches of product were manufactured at the proposed manufacturing site. 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 36 months reported, except for resuspendability. The applicant performed sterility test at the end of the proposed shelf-life (36 months).

Based on the more recent available stability data, the proposed shelf-life of 36 months without the storage precaution "Do not store above 30°C" as stated in the SPC is accepted.

In-use stability studies, with recent and aged industrial batches filled in each vial size, and according to an appropriate design support the proposed shelf-life of 28 days after broaching.

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 documentation (Safety and residues tests)

Lexylan 180 mg/ml is a suspension for injection, which contains cefalexin as active substance, intended to be administered by intramuscular or subcutaneous routes in cattle, dogs and cats.

The dossier has been submitted in line with the requirements for submissions under Article 18 of Regulation (EU) 2019/6 – a generic application.

The reference veterinary product referred to for the scientific data and for the expiry of the 10-year data protection period is "Ceporex Injection, 180 mg/ml, suspension for injection", a VMP that was authorized in the Union by the National Procedure (Authorisation Holder: Intervet International; Date of first authorization in Belgium: 21/06/1988; SPC: see Annex I).

Safety tests

The dossier has been submitted in line with the requirements for submissions under Article 18 of Regulation (EU) 2019/6 – a generic application.

In accordance with Regulation (EU) 2019/6, a generic application may rely on the results of the appropriate safety, residue, pre-clinical and clinical studies for the reference product as approved in the Union when the conditions in Article 18(1) are fulfilled. As bioequivalence with the reference veterinary medicinal product is accepted, the applicant is exempt from providing proprietary safety data. The applicant has provided a full user safety assessment (part III.A.5) and an environmental risk assessment (part III.A.6).

Pharmacology

See Part 4.

Toxicology

The active substance cefalexin was previously assessed by the CVMP in the context of the establishment of MRLs and the key findings of the toxicity studies evaluated are summarised in the European Public MRL Assessment Report (EMEA/MRL/627/99-FINAL).

Excipients

The excipients of the product are currently used in veterinary medicines and do not raise any safety concern.

User safety

In accordance with the legal basis of this application, this generic veterinary medicinal product may rely on the results of the reference product when the conditions in Article 18(1) are fulfilled. The risks for the user handling this veterinary medicinal product are expected to be the same as those of the reference product and the warnings in the product information for the reference product can be considered adequate as regards the potential risks. However, the applicant has presented a user risk assessment which has been conducted in accordance with CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1).

The hazard identification and characterisation of the active substance is based on data presented in the cefalexin EMA MRL summary report (EMEA/MRL/627/99-FINAL, July 1999). From the overall set of data on different species, the overall NOEL for repeated dose toxicity was defined at 160 mg/kg bw/day, based on a 3-month oral (gavage) repeated dose study in dogs (slight effects were found on blood biochemistry at higher doses). Cefalexin is not teratogenic up to doses of at least 400 mg/kg bw/day in mice but could elicit maternal and foetotoxicity at all tested dose levels, the lowest of which was 100 mg/kg bw/day in mice. Since cefalexin is not considered to be mutagenic, since no evidence for pre-neoplastic changes were found in the repeated dose toxicity studies and since the cefalexin molecule does not contain structural alerts, carcinogenicity studies were not considered necessary.

Veterinary professionals may be exposed to the whole product and the routes of exposure could be oral, dermal, ocular or parenteral. The most likely way of exposure is inadvertent spilling of the product on clothes, hands or eyes or accidental self-injection during administration of the product to the animal or during disposal of the syringe. The exposure and risk associated is considered to be minimal as the product will be administered to the patient by professionals.

For accidental self-injection, according to the data available about the consequences of injection of oil-based antibiotics in humans, appropriate risk communication is proposed in the product information (e.g. section 3.5, special precautions to be taken by the person administering the veterinary medicinal product to animals).

The warnings proposed are identical to those presented in the SPC of the reference veterinary medicinal product and are adequate as regards the potential risks. This is consistent with the legal basis of this application.

Environmental risk assessment

An environmental risk assessment was performed for Lexylan suspension for injection in accordance with VICH GL6 (Ecotoxicity Phase I, CVMP/VICH/592/98-FINAL) 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 product is an injectable antibiotic (not used to treat respiratory disease in cattle) that will only be used to treat a small number of animals in a flock or herd.

Lexylan 180 mg/ml is not expected to pose an unacceptable risk for the environment when used according to the SPC.

Residue tests

MRLs status

The active substance in Lexylan 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
Cefalexin	Cefalexin	Bovine	200 µg/kg 200 µg/kg 200 µg/kg 1000 µg/kg 100 µg/kg	Muscle Fat Liver Kidney Milk	NO ENTRY	Anti-infectious agents/antibiotics

The excipients listed in section 2 of the SPC are either allowed substances for which Table 1 of the Annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Depletion of residues

A depletion study in cattle has been performed by the applicant.

Withdrawal periods

The Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4) states that bioequivalence or waivers cannot be used for extrapolation of withdrawal periods between products with a potential to leave local residues. In such cases, information on the behaviour of residues at the site of administration needs to be assessed before the withdrawal period is extrapolated. A residue study was performed in 16 cattle weighing between 510-540 kg after intramuscular administration at 7 mg cephalexin (CEF) per kg bodyweight (corresponding to 1 mL of the veterinary medicinal products per 25 kg body weight) once a day for 5 days, which corresponds to the maximum dose. Maximum injection volumes were 20 ml/injection site.

In muscle, fat and liver residues were below the LOQ at all slaughter points.

In kidney, residues were above the LOQ and below MRL 1 day post treatment, and below the LOQ for the other slaughter points.

In the injection site (core), residues were below the muscle MRL from 7 days post treatment and below the LOQ from 15 days post treatment in all animals.

Altogether, 7 days after the last injection, all residues are below the respective MRLs.

Based on the depletion of residues from the injection site, a statistical withdrawal period of 12 days was calculated. Thus, a meat and offal withdrawal period of 12 days with a maximum volume per injection site of 20 ml is retained.

Based on the accepted bioequivalence, the withdrawal period for cattle milk can be extrapolated from the reference product and is set at 'zero hours'.

Overall conclusions on the safety documentation: safety and residues tests

Lexylan 180 mg/ml has been submitted in line with the requirements for submissions under Article 18 of Regulation (EU) 2019/6 – a generic application. In accordance with Regulation (EU) 2019/6, generic applications may rely on the results of the appropriate safety studies for the reference product as approved in the Union. As bioequivalence is accepted the applicant is exempt from providing proprietary toxicology data.

User safety:

The applicant has presented a user risk assessment, which has been conducted in accordance with CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1). According to the data available, warnings proposed, which are identical of those presented in the SPC of the reference product, are adequate as regards to the potential risks.

Environmental risk assessment:

An appropriate environmental risk assessment was provided. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

Residue tests:

A tissue residue depletion study has been performed in cattle after intramuscular administration of the candidate product at the maximum recommended dose and the maximum duration of treatment leading to a withdrawal period of 12 days with a maximum volume of 20 ml per injection site. The withdrawal period for cattle milk is set at 'zero hours', in line with the reference product.

Part 4 – Efficacy

Lexylan is a suspension for injection containing 180 mg cefalexin/ml, which is intended for use in cattle, dogs and cats by intramuscular or subcutaneous route.

The application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 - a generic application.

Pre-clinical studies

Pharmacology

Pharmacodynamics

No pharmacodynamic studies were presented, as bioequivalence with the reference product has been claimed. The omission of pharmacodynamic data is considered acceptable given the legal basis of the application.

The pharmacodynamic properties of the active substance are detailed in section 4.2 of the SPC and are identical to those approved for the reference product. This is considered acceptable.

Pharmacokinetics

No pharmacokinetic studies were presented, as bioequivalence with the reference product has been

claimed. The omission of pharmacokinetic data is considered acceptable given the legal basis of the application.

The pharmacokinetic properties of the active substance are detailed in section 4.3 of the SPC and are identical to those approved for the reference product. This is considered acceptable.

Bioequivalence studies

Cattle:

An *in vivo* bioequivalence study in cattle after intramuscular administration of the candidate (Lexylan) and the reference product (Ceporex Injection, 180 mg/ml, suspension for injection) has been provided. The study was well conducted and in accordance with the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4). The study was performed as a randomised, two-period, two-sequence single dose crossover design with 12 animals per group. The 90% confidence intervals for the ratio of population means (test/reference) for C_{max} (86.9-108.9%) and AUC_{last} (95.8-103.1%) fell within the bioequivalence acceptance limits of 80 to 125%. Therefore, bioequivalence is considered to have been demonstrated between the candidate and the reference product following intramuscular administration in cattle after a single dose of 7 mg/kg bodyweight in cattle.

Dogs and cats:

No *in vivo* bioequivalence studies have been provided.

While the proposed and reference products have the same qualitative and quantitative composition in active substance and the same excipients in very similar amounts, and the two products have comparable physicochemical properties (viscosity, density, related substances, size and shape of particles, syringeability and polymorphism), these quality data, on their own, would not be considered sufficient to justify a biowaiver in accordance with section 7 of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4). However, the combination of these data with the demonstration of *in vivo* bioequivalence in cattle support the argument that the existing small differences between the two formulations do not impact on bioavailability. Consequently, considering the totality of the data, the products are considered to be bioequivalent in dogs and cats (as well as in cattle).

Development of resistance and related risks in animals

The applicant has provided a summary of the epidemiological situation based on bibliographical information and surveillance data in relation to resistance to cephalexin (or other representative substance) in relevant target bacteria per target animal species. From the data available, the level of resistance to cephalexin is considered generally low within the EU with the exception of *E. coli* isolates in different target animal species. Indeed, according to national surveillance data, in bovine, resistance proportion is around 20% in *E. coli* isolates from intra-mammary and digestive tract infections. In cats and dogs, the proportion of strains resistant to cephalexin can be considered moderate to high notably in isolates from urinary tract, skin/soft tissues infections and otitis. These findings are appropriately reflected in the product information.

Dose determination and confirmation

No data has been presented.

This application is made in accordance with Article 18 of Regulation (EU) 2019/6 (a generic application). Therefore, given that bioequivalence with the reference product is considered to have been demonstrated, the omission of dose determination/confirmation data can be accepted.

Tolerance in the target animal species

No data has been presented.

The proposed and reference products have the same qualitative and quantitative composition in active substance and the same excipients in very similar amounts. Both products are to be used at the same dose and by the same administration routes in the same target animal species. Thus, the expected tolerance profile in the target animal species is considered to be the same and the omission of tolerance data is acceptable since bioequivalence between the two products has been demonstrated.

Clinical trials

No clinical trials have been conducted.

Since bioequivalence between the proposed generic product and the reference product is accepted, the efficacy is considered the same for both products when administered by the same routes and at the same dose in the same target animal species. As such, omission of clinical data is acceptable.

Overall conclusions on efficacy

This is an application submitted under Article 18 of Regulation (EU) 2019/6 (i.e. a generic application).

Bioequivalence between Lexylan and the reference product has been demonstrated in cattle by means of an *in vivo* bioequivalence study after intramuscular administration.

No *in vivo* bioequivalence studies have been conducted in dogs and cats. Nevertheless, bioequivalence is accepted based on qualitative and quantitative formulation data, physico-chemical properties and one bioequivalence study in another species (bovine).

Given that bioequivalence between the candidate and reference products is considered to have been demonstrated, the omission of pre-clinical studies and clinical trials is acceptable. The expected tolerance profile in the target animal species is considered to be the same.

Part 5 – Benefit-risk assessment

Introduction

Lexylan is a suspension for injection containing cefalexin an active substance, which is well-known.

The active substance, cefalexin, is a cephalosporin antibiotic. The bactericidal effect of cefalexin is based on interference with the cell membrane synthesis by inactivation of transpeptidase.

The product is intended for use in cattle, dogs and cats for the treatment of diseases caused by cefalexin susceptible micro-organisms at well accessible infection sites, within the limits of effective cefalexin concentrations.

Cattle:

Metritis, interdigital dermatitis, wounds and abscesses, treatment of septicaemic mastitis in addition of an intramammary therapy.

Dogs:

Infections of the respiratory tract, the uro-genital system, the skin, soft tissues and the gastro-intestinal system.

Cats:

Infections of the respiratory tract, the uro-genital system, the skin and soft tissues.

For cats and dogs, the proposed dose of 10 mg cefalexin/kg subcutaneously or intramuscularly once a day for 5 days has been confirmed.

For cattle, the proposed dose of 7 mg cefalexin/kg intramuscularly once a day for 5 days has been confirmed.

The application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 - generic application.

Benefit assessment

Direct benefit

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

Bioequivalence in cattle, dogs and cats is accepted.

Additional benefits

Not applicable.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented, generally, 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:

The proposed product and the reference product 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 administration routes in the same target animal species. Thus, the expected tolerance profile in the target species is considered to be the same and the omission of tolerance data is acceptable as bioequivalence between the two products has been demonstrated.

Risk for the user:

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1). The safety profile of the product to be authorised is expected to be the same as that of the reference product. The same risk mitigation measures as those of the reference product have been included in the SPC.

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

Risk for the environment:

Lexylan is not expected to pose an unacceptable risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk for the consumer:

Lexylan is not expected to pose an unacceptable risk to the consumer of foodstuffs derived from treated animals when Lexylan is used according to the SPC recommendations. The withdrawal period established in meat and offal to ensure depletion of residues below the MRLs is 12 days with a maximum volume of 20 ml per injection site. The withdrawal period in milk is set at 'zero hours', in line with the reference product.

Resistance

The applicant has provided a summary of the epidemiological situation based on bibliographical information. The information illustrates the EU resistance situation for some target pathogens from target animal species.

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.

Evaluation of the benefit-risk balance

Based on the data presented to date, the overall benefit-risk balance is considered positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Lexylan is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) No 2019/6).

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.