DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

FINAL PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Draxxin Plus 100 mg/ml + 120 mg/ml solution for injection for cattle

Draxxin KP 100 mg/ml + 120 mg/ml solution for injection for cattle (FR)

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0352/001/DC
Name, strength and pharmaceutical form	Draxxin Plus 100 mg/ml + 120 mg/ml solution for injection for cattle Draxxin KP 100 mg/ml + 120 mg/ml solution for injection for cattle
Applicant	Zoetis Belgium SA Rue Laid Burniat 1 Louvain-la-Neuve 1348, Belgium
Active substance(s)	Tulathromycin/ Ketoprofen
ATCvet Code	QJ01FA99
Target species	Cattle
Indication for use	Treatment of bovine respiratory disease (BRD) associated with pyrexia due to *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* susceptible to tulathromycin.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13.b of Directive 2001/82/EC as amended (so called fixed combination application)
Date of completion of the original decentralised procedure	06/05/2020
Date product first authorised in the ReferenceMemberState (MRP only)	-
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, FR, DE, EE, EL, HR, HU, IE, IT, LT, LU, LV, NL, PL, PT, RO, SI, SK, UK

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains tulathromycin (100 mg/ml) and ketoprofen (120 mg/ml) as active substances and monothioglycerol, anhydrous citric acid, 2-pyrrolidone, hydrochloric acid, sodium hydroxide, propylene glycol and water for injections as excipients.

The medicinal product is packaged in 50, 100 and 250 ml type I amber glass vials sealed with a fluoropolymer coated chlorobutyl rubber stopper and an aluminium overseal.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

Ketoprofen is described in Ph. Eur. The information on the active substance is provided by presenting a copy of the Certificate of Suitability of the Ph. Eur. procedure (CEP) for that substance, granted by EDQM to the manufacturer.

The active substance, tulathromycin, is not described in a pharmacopoeia. The information on the active substance is provided as a full Part 2C.

The active substances are manufactured in accordance with the principles of good manufacturing practice.

Specifications of both active substances are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with these specifications have been provided.

Satisfactory TSE information has been provided in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

D. Control on intermediate products

Not applicable.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance tulathromycin have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A retest period is included in the CEP for ketoprofen.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (2 years) when stored under the approved conditions.

Data submitted on in-use stability studies are considered sufficient to support an in-use shelf life of 56 days after broaching.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that tulathromycin is a bacteriostatic acting antibiotic that inhibits essential protein biosynthesis by virtue of their selective binding to bacterial ribosomal RNA. It acts by stimulating the dissociation of peptidyl-tRNA from the ribosome during the translocation process. Tulathromycin presents *in vitro* activity against *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis*.

Ketoprofen has anti-inflammatory, analgesic and antipyretic properties. Effects are obtained partially by the inhibition of prostaglandin and leukotriene synthesis by ketoprofen, acting on cyclooxygenase and lipoxygenase respectively. The formation of bradykinin is also inhibited. Ketoprofen inhibits thrombocyte aggregation.

The applicant has also conducted studies which show that when subcutaneously co-administered in the combination formulation, the maximum tulathromycin concentration (Cmax) in plasma was achieved approximately 3 hours post-dosing (Tmax). Peak tulathromycin concentrations were followed by a slow decline in systemic exposure with an apparent elimination half-life (t1/2) of 85 hours in plasma.

Furthermore, after subcutaneous injection of the tulathromycin-ketoprofen combination, the AUC0-t of tulathromycin has been shown to be bioequivalent to the AUC0-t after subcutaneous injection of tulathromycin 100 mg/ml for cattle. The combination had a slightly lower tulathromycin Cmax and the rate of absorption was decreased in comparison with the administration of the compounds separately.

Regarding ketoprofen, following administration of the combination product, at 3 mg ketoprofen/kg body weight, the pharmacokinetics of ketoprofen are driven by flip-flop kinetics. The mean Cmax in plasma was achieved at 4 hours on average. The terminal half-life of ketoprofen is dominated by the slow absorption and was estimated at 6.8 hours.

Furthermore, after subcutaneous injection of the tulathromycin-ketoprofen combination, there was a delay in the absorption, with a lower ketoprofen peak concentration, and a longer elimination half-live, as compared with the compound alone.

Toxicological Studies

The applicant has performed extensive bibliographic research to characterize the toxicology of both active substances, tulathromycin and ketoprofen, of the veterinary medicinal product. Toxicity studies with the combination have been also conducted.

- Single Dose Toxicity

  The results of single dose studies in rats and dogs using oral and intravenous administration indicated low acute toxicity of tulathromycin by the oral route, and

intermediate toxicity by the intravenous route. Following oral administration, the lethal doses were estimated to be greater than 1000 mg/kg bw in dogs and greater than 2000 mg/kg bw in rats.

Ketoprofen, as with NSAIDs causes gastrointestinal disturbances. The LD_{50} by all routes (oral, subcutaneous, intraperitoneal) in mice, rabbits and dogs, was approximately 500 mg/kg bw.

The LD_{50} cut-off value of the combination was established in 500 mg/kg bw in an acute oral toxicity study in rats.

- Repeated Dose Toxicity

  The overall repeat-dose NOAEL for tulathromycin after oral administration in rats and dogs has been established in 5 mg/kg bw/day.

  For ketoprofen, a NOEL could be established in three one month-studies (rats in feed: 6 mg/kg/day; rats oral: 2 mg/kg/day; dogs oral: 2 mg/kg/day) and in one 6-month oral study in baboons (4.5 mg/kg bw/day).

  A NOAEL of 3.33/4 mg/kg for the combination has been obtained in a 14-day repeat dose toxicity study in rats.

- Reproductive Toxicity, including Teratogenicity:

  For tulathromycin, the overall NOEL for maternal and foetal effects was established in 15 mg/kg bw based on two studies performed in rats and rabbits after oral administration.

  Regarding ketoprofen, it was maternotoxic in rats at 9 mg/kg bw/day and the toxicological NOEL for teratogenicity was established at 2 mg/kg bw (rabbits, oral). In fertility studies in rats, effects of ketoprofen on male and female reproduction functions were observed at doses higher than 3 mg/kg/day.

- Mutagenicity

  Tulathromycin has not shown mutagenic effects in a comprehensive battery of mutagenicity tests both *in vitro* and *in vivo*.

  Ketoprofen and its main metabolite are not mutagenic, based on the set of mutagenic tests performed.

- Carcinogenicity

  The absence of carcinogenicity potential has been demonstrated for both substances.

Other Studies

Tulathromycin was evaluated for skin and ocular irritation in albino rabbits. The compound proved to be neither a corrosive material nor a skin irritant but the results indicated it is an ocular irritant in rabbits. The potential of tulathromycin to produce sensitisation following topical exposure was evaluated in guinea pigs indicating that it can be considered a contact sensitizer.

Ketoprofen was not an eye or skin irritant and was not a skin sensitizer or phototoxic to guinea pigs but photosensitization was identified as the underlying cause of ketoprofen dermal toxicity reported in humans.

In vitro/in chemico studies to evaluate the potential ocular and dermal hazards and skin sensitization with the veterinary medicinal product were conducted. The results concluded unexpectedly that the product is not an eye or skin irritant and not a skin sensitizer.

Observations in Humans

Since tulathromycin was developed for veterinary use only, no information in humans is available. Tulathromycin is chemically closely related to the macrolide azithromycin which is considered the parent compound of tulathromycin. Azithromycin is an antibiotic widely used in the treatment of human infections.

Bibliographical data provided by the applicant show that ketoprofen is widely used in the management of inflammatory and musculoskeletal conditions, pain and fever in children and adults.

Microbiological Studies

A microbiological ADI for disruption of colonisation barrier of 0.055 mg/kg bw (i.e.,3.29 mg/60 kg person) has been established for tulathromycin. This value is higher than the toxicological ADI of 3 mg/person. The toxicological ADI is accepted as the relevant overall ADI.

Ketoprofen and its residues do not have microbiological properties.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that this veterinary medicinal product is irritating to the eyes, may cause hypersensitivity and may produce adverse effects after dermal exposure and self-injection. Furthermore, NSAIDs, such as ketoprofen, may affect fertility and be harmful for the unborn child.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

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

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the initial predicted environmental concentration in soil (PEC_{soil} value, initial = 7.29 µg/kg for tulathromycin and 8.74 µg/kg for ketoprofen) is less than 100 µg/kg.

The use of the product in the conditions authorised in the SPC will not pose a risk for the environment.

III.B Residues documentation

Residue Studies

A residue depletion studies using the final formulation have been conducted in cattle. Samples of liver, kidney, muscle, injection site and fat were taken from animals at several time points. Results show that ketoprofen depletes much faster than tulathromycin and both substances deplete to below the MRL in all tissues before the end of the withdrawal period. Statistical analysis of the results was used to set the withdrawal period.

The bioananalytical method used for the determination of the active substances in bovine tissues was LC/MS/MS. The method has been sufficiently described and validated.

MRLs

The active substances tulathromycin and ketoprofen and the excipients contained in the veterinary medicinal product are allowed substances described in table 1 of the Annex to Commission Regulation (EU) No 37/2010:

MRLs are listed below:

Active substance	Animal species	MRL	Target tissues
Tulathromycin Marker residue: 2R,3S,4R,5R,8R,10R,11R,12S, 13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-Dxylo-hexopyranosyl]oxy]-	Bovine	300 µg/kg 200 µg/kg 4500 µg/kg 3000 µg/kg	Muscle Fat Liver Kidney

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Active substance	Animal species	MRL	Target tissues
1-oxa- 6-azacyclopentadecan-15-one expressed as tulathromycin equivalents			
Ketoprofen	Bovine Porcine Equidae	No MRL required	NOT APPLICABLE

It must be noted that according to the European public MRL assessment report (EPMAR) on tulathromycin (modification of the microbiological ADI and MRLs in bovine and porcine species) – after provisional maximum residue limits (EMA/CVMP/380257/2014) an **Injection Site Residue Reference Value (ISRRV) of 6000 µg/kg** is established for cattle and swine.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 50 days for meat and offal in cattle is justified. The use is not authorised in cattle producing milk for human consumption or in pregnant animals, which are intended to produce milk for human consumption, within 2 months of expected parturition. These withdrawal periods are adequate to guarantee consumers' safety.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant provided bibliographic references that explain the mechanism of action, and the most important Pharmacokinetic properties.

The applicant characterized the pharmacokinetic behaviour of the formulation in a series of studies. The main study was aimed to document the influence of each of the active substances on the PK behaviour of the other compound.
The rate absorption of ketoprofen was decreased to the extent that the C_{max} dropped by 80% and the slope of the terminal phase of the time-concentration profile became less steep. This phenomenon is called flip-flop kinetics as the slope reflects the slower rate of absorption instead of the rate of elimination. As a result, ketoprofen concentrations were sustained for longer, resulting in higher concentrations during the terminal phase despite the lower initial concentrations. The extent of absorption did not appear to be affected by coadministration.

On the other hand, for Tulathromycin the modelling approach described by *Toutain et al.* was used in which AUC_{0-24}/MIC cut-offs are taken into account.
Another two studies assessed dose proportionality and effects of repeated dosing. Repeated dosing of the fixed combination showed no accumulation in ketoprofen. It is to be noticed that ketoprofen had a terminal half-life of 7 hours. Tulathromycin had a longer terminal half-life (~90 hours) and repeated dosing resulted in some accumulation ≤15% with the 14-day dose interval. This is in accordance with the fact that the dosing interval was less than 5 terminal half-lives and also it has to be taken into account that the product is intended for single use.

Tolerance in the Target Species of Animals

One pivotal tolerance study (margin of safety study) was carried out. Additional supportive data originates from a second preliminary study (injection site tolerance).

Margin of safety study
Four groups (saline, 2.5-3, 7.5-9 and 12.5-15 mg/kg BW tulathromycin-ketoprofen) and 8 animals/group (4 males-4 females/group):
A maximum dose volume of 10 ml was administered per injection site.
Subcutaneous injection of cattle with tulathromycin-ketoprofen at a dose of 1X, 3X and 5X once every two weeks for three consecutive treatments was well tolerated. Subcutaneous administration caused very common transient pain reactions and local swellings at the injection site that could persist for up to 32 days. Pathomorphological injection site reactions (including reversible changes of congestion, oedema, fibrosis and haemorrhage) were present for approximately 32 days after injection. At dosages of three and five times the recommended dose transient signs of injection site swelling were observed, which in some instances lasted until day 32. Microscopic mucosal erosions of the pylorus of the abomasum were observed at 3 and 5 times the recommended dose.

Injection site tolerance
Two groups (saline, 2.5-3 mg/kg BW tulathromycin-ketoprofen). Subcutaneous injection of tulathromycin-ketoprofen at 2.5 / 3 mg/kg in beef cattle was associated with palpable injection site reactions. Three of five 1X treated animals had palpable L1 injection site swelling. Resolution of swelling was variable over the study period, with one animal persisting through necropsy. One animal at 1X dose had swelling on R1 on day 8. However, this swelling was not detected from day 9 onwards. Subcutaneous injection of saline into the left and right neck of beef cattle was associated with no swelling through 18-days post-injection.

Resistance

The applicant determined the tulathromycin MICs of strains of *M. haemolytica, P. multocida, H. somni and M. bovis.* obtained as part of the pivotal clinical trial. Resistance development to tulathromycin appears to remain low in this study and in Europe for pathogens associated with BRD pathogens *M. haemolytica, P. multocida and H. somni.* For *M. bovis* the MIC_{90} value of these strains was > 128 µg/ml. However, standardized methods do not exist to determine antimicrobial susceptibilities that enable determination of the relationship between clinical success and MIC values for Mycoplasma spp. For this reason, clinical success is the best approach to determine the suitability of tulathromycin to treat infections caused by *M. bovis*.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant conducted one study that assessed 3 doses of Ketoprofen and selected the targeted one, that is the same as usually contained in VMP containing Ketoprofen alone. This dose was later used in the field assay.

A second study was conducted in the USA to evaluate the effectiveness of a tulathromycin-ketoprofen fixed combination formulation in control of pyrexia in weaned calves using an LPS challenge model, in clinically healthy calves. From this study, it is to be noted that the antipyretic effect was sustained for longer with the combination product compared to the monotherapy products (12 *versus* 8 hours).

The ketoprofen dose selection was further supported by a PK/PD model that was used to simulate the effects of different ketoprofen doses when administered by the combination product. In general, the results of the simulations suggested that whilst a dose lower than 3 mg/kg would not be adequate to control the pyrexia, increasing the dose further would have no added benefit.

Field Trials

A pivotal field trial was conducted in the European Union, to evaluate the field efficacy and safety of a tulathromycin-ketoprofen fixed combination compared to tulathromycin, each formulation administered as a single subcutaneous dose, for the treatment of naturally occurring bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* .280 cattle, including 60 females and 220 males, with 39 to 320 kg of body weight were enrolled.

Two treatment groups were administered:
- Group 01, animals were treated with a single dose by subcutaneous route with the investigational product (2.5 mg/kg of the antimicrobial + 3 mg/kg of the NSAID).
- Group 02, animals were treated with a single dose by subcutaneous route with 2.5 mg/kg of the antimicrobial.

The primary efficacy variable, that is, Treatment Success for Pyrexia Reduction, has been demonstrated. In order to demonstrate this statement, the applicant described pyrexia reduction within the first 24 hours after administration between the fixed combination of tulathromycin and ketoprofen compared to tulathromycin as the primary efficacy parameter of the multi-centre EU field study, statistically significant (2-sided, 0.05 level of significance).

Regarding BRD treatment success on day 14, non-inferiority has been demonstrated taking into account clinical criteria.

A supportive field trial was conducted in the United States of America.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the veterinary Heads of Agencies website (www.hma.eu).