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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Zeleris (EMEA/V/C/004099/0000)

International non-proprietary name: florfenicol / meloxicam

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

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Introduction

The applicant CEVA Santé Animale submitted on 30 November 2015 an application for a marketing authorisation to the European Medicines Agency (the Agency) for Zeleris solution for injection for cattle, through the centralised procedure falling within Article 3(2)(a) of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 9 October 2014 as Zeleris contains a new fixed combination of active substances which is not yet authorised as a veterinary medicinal product in the Community. The fixed combination contains two known active substances, florfenicol (400 mg/ml), an antimicrobial substance, and meloxicam (5 mg/ml), a non-steroidal anti-inflammatory substance; which are both used in EU-authorised single-substance veterinary medicinal products, but not hitherto in a fixed combination for therapeutic purposes.

The CVMP appointed Wilhelm Schlumbohm as rapporteur and Ljiljana Markus Cizelj as co-rapporteur for the assessment of this application.

Zeleris is a solution for subcutaneous injection in cattle, containing as active substances a fixed combination of 400 mg/ml florfenicol and 5 mg/ml meloxicam. Zeleris is available in three pack sizes, 50 ml, 100 ml and 250 ml. The withdrawal period is 56 days (meat and offal); Zeleris is not authorised for use in lactating animals producing milk for human consumption. The recommended indication is: "For therapeutic treatment and reduction of clinical signs of bovine respiratory disease (BRD) in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* susceptible to florfenicol".

The dossier has been submitted in line with the requirements for submissions under Article 13(b) of Directive 2001/82/EC - fixed combination application.

On 16 March 2017 the CVMP adopted an opinion and CVMP assessment report.

On 15 May 2017 the European Commission adopted a Commission Decision granting the marketing authorisation for Zeleris.

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 (dated September 2015), 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 events occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The complete manufacture, batch control/testing arrangements take place in the EEA. Batch release of Zeleris solution for injection is performed by Ceva Santé Animale, France. The site has a manufacturing authorisation issued on 3 January 1985 by the Agence Nationale du Médicament Vétérinaire, France. The latest inspection of this site was conducted by the competent authority (France) confirmed that it complies with good manufacturing practice (GMP) requirements.

According to the Qualified Person (QP) declaration from the QP at the EU batch release site, the manufacture of meloxicam is in accordance with the detailed guideline on GMP for active substances used as starting materials. The last on-site audit was performed by a third party.

For the active substance florfenicol an on-site audit has been performed and a QP declaration has been provided, indicating that the manufacture of florfenicol is in accordance with the detailed guideline on GMP for active substances used as starting materials.

The primary containers and closures (plastic vials and rubber stoppers) are sterilised and a GMP certificate for this site has been provided.

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

Zeleris is presented as a solution for injection containing 400 mg/ml florfenicol and 5 mg/ml meloxicam as active substances.

The finished product is a clear, yellow coloured, non-aqueous solution which includes the solvents dimethyl sulfoxide and glycerol formal (stabilised), as described in section 6.1 of the SPC. The product has been demonstrated to be self-preserving and so no preservative is included.

Container

Zeleris is packed in multi-layered plastic vials, consisting of translucent polypropylene/adhesive/ethylene vinyl alcohol/adhesive/polypropylene, which are closed with red chlorobutyl rubber stoppers sealed with aluminium closures (with plastic flip caps). The proposed pack sizes are 50 ml, 100 ml and 250 ml. Secondary packaging is a cardboard box (containing 1 vial). The pack sizes are consistent with the dosage regimen and duration of use.

The plastic vials are sterilised. The sterilisation process has been validated. The rubber stoppers are sterilised according to European Pharmacopoeia (Ph. Eur.), therefore, no additional validation is deemed necessary. Data on fragmentation and self-sealing of the stoppers have been generated under worst case conditions, and the numbers of fragments for each test complies with the Ph. Eur requirements.

Development pharmaceutics

The aim of the development pharmaceutics was a solution for injection containing a combination of the two active substances, florfenicol and meloxicam, both of which are effectively insoluble in water.

The choice of the composition was based on existing EU-authorised products containing the single active substances, and the formulation was then optimised with regard to solubility and syringeability. The result was a simple non-aqueous solution for injection of the two active substances dissolved in dimethyl sulfoxide and glycerol formal (stabilised). Both solvents have been used in similar injectable products for the same target species.

There was no need to include an antimicrobial preservative in the formulation, as it was demonstrated that the proposed formulation complies with Ph. Eur. general text 5.1.3 requirements (efficacy of antimicrobial preservation).

The choice of the manufacturing process (aseptic manufacture) has been justified taking into account the Annex to the note for guidance on development pharmaceutics for veterinary medicinal products: decision trees for the selection of sterilisation methods (EMEA/CVMP/065/99).

The compatibility of the packaging material with the proposed formulation has been confirmed. Potential additives were extracted from the plastic sample according to the methodology described in the Ph. Eur. general chapter 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) and were analysed by HPLC. Furthermore, migration and sorption studies were performed as part of the stability studies of the finished product. Results after storage for 6 months at 40 °C/75% RH show however that the additives are below the limits of determination. In addition, the stability studies do not show any significant degradation of either of the active substances.

Method of manufacture

A range is accepted for commercial batch size.

The manufacturing process is a simple one consisting of dissolution of both the active substances in the two solvents, pre-filtration and sterilisation by filtration (through a 0.2 µm filter). The process is considered to be a non-standard manufacturing process. The choice of the manufacturing process has been justified taking into account the Annex to the note for guidance on development pharmaceutics for veterinary medicinal products: decision trees for the selection of sterilisation methods (EMEA/CVMP/065/99).

The multi-layered plastic vials and rubber stoppers are pre-sterilised The vials are then aseptically filled, stoppered and crimped. In-process controls for each step are described and are considered adequate.

The manufacturing process has been validated for two commercial scale batches of the smallest size proposed From the data provided in the dossier it can be concluded that the manufacturing process is well controlled and results in a veterinary medicinal product of adequate and consistent quality. The applicant has provided confirmation that the validation of the manufacturing process will be completed with a third batch of the biggest commercial batch size proposed, therefore at present no additional validation data are deemed necessary. The validation protocol for this batch size has been provided and comprises adequate controls for the different stages of the manufacturing process.

Control of starting materials

Active substances

Meloxicam

The information on this active substance is provided according to the ASMF procedure.

Meloxicam is described in the Ph. Eur. and complies with the requirements of the current monograph and an additional test for residual solvents.

Meloxicam is a pale yellow powder, which is practically insoluble in water and soluble in dimethylformamide. The synthesis and purification of meloxicam has been described in sufficient detail. Meloxicam can exist in five polymorphic forms. It has been demonstrated that the supplier routinely produces the same polymorph. Evidence of structure has been confirmed. The impurity profile has been justified in comparison with the impurities listed in the Ph. Eur. monograph.

Detailed information on the manufacture of the active substance has been provided in the restricted part of the ASMF and was considered satisfactory.

An adequate specification for the control of the active substance has been presented. The analytical methods have been described and validated according to the relevant VICH guidelines. The studies performed confirm that the analytical methods used are stability indicating.

Batch analysis data have been presented for three batches of meloxicam.

Stability studies have been performed in compliance with the relevant VICH guidelines. Data are presented for numerous batches of meloxicam from the proposed manufacturer resembling the proposed commercial packaging.

Stability data have been performed according to VICH guidelines and were provided for the following batches 28 batches for up to 60 months under long term conditions at 25 ºC/60% RH; four batches stored at 30 °C/65% RH; 9 batches stored for up to 6 months under accelerated conditions at 40 ºC/75% RH.

All tested parameters were within specification. The stability results justify the proposed retest period of 5 years without any special storage recommendation.

Florfenicol

The information on this active substance is provided according to the ASMF procedure.

Florfenicol is not described in the Ph. Eur. or in any pharmacopoeia of an EU member state, but is the subject of a monograph in the Chinese Pharmacopoeia. An in-house specification has therefore been provided which covers all relevant quality attributes.

Florfenicol is a white crystalline powder, which is insoluble in water and very soluble in dimethylformamide. The synthesis and purification of florfenicol have been described in sufficient detail. Evidence of structure has been confirmed. Absolute stereochemistry has been confirmed. Additional physicochemical characterisation has been performed.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

An adequate specification for the control of the active substance has been presented. The specification of related substances has been established on basis of the manufacturing process and batch analysis

data. The analytical methods have been described and validated according to the relevant VICH guidelines. The studies performed confirm that the analytical methods used are stability indicating.

Batch analysis data have been presented for three consecutive batches These batches were also used for stability studies.

Stability studies have been performed in compliance with the relevant VICH guidelines. Data are presented for three batches of florfenicol from the proposed manufacturer(s) stored in double polyethylene bags contained in cardboard drums and stored under long term and accelerated storage conditions. All tested parameters were within specification. The stability results justify the proposed retest period of 2 years when stored below 30 °C.

Excipients

Dimethyl sulfoxide (DMSO) is controlled according to the current Ph. Eur. monograph.

For the glycerol formal (stabilised), the specification complies with that of the current Ph. Eur. monograph "glycerol formal" except for relative density. A certificate of analysis confirms compliance with the proposed specification. Three stabilisers are included in this excipient.

The stabilising agents are included to prevent degradation of the glycerol formal.

The total quantity of stabilisers which could be included in the finished product is extremely low and does not impact on the finished product's quality.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the starting materials used for the active pharmaceutical ingredients, meloxicam and florfenicol, 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.

TSE declarations for the components of Zeleris have been provided accordingly.

Control tests on the finished product

The specifications proposed for use at release and at the end of shelf-life are appropriate to control the quality of the finished product. The following parameters are included: appearance, relative density, filling volume, clarity and colour of the solution, water content, identity and assay of the active substances, and sterility.

The analytical methods are well described and validated in accordance with the relevant VICH guidelines.

Batch analysis data of two production scale batches of the finished product are presented and these comply with the required specification and demonstrate consistency and uniformity of the product.

Stability

The shelf-life specification of the finished product is identical to the release specification, including with regard to the assay limits for both the florfenicol and the meloxicam. No significant amounts of

degradation products of florfenicol or meloxicam have been found during the stability studies.

The stability studies were conducted in line with the relevant stability guidelines. Stability studies were performed on two commercial scale batches of the smallest size proposed both filled into the proposed commercial vials of 50 ml, 100 ml and 250 ml. The samples were stored in the upright and inverted positions at 25 °C/60% RH (long term conditions) and at 40 °C/75% RH (accelerated conditions). Long term storage is scheduled for 36 months, and accelerated storage for 6 months. The test methods described for finished product testing were used; it had been demonstrated that these methods are stability indicating.

At present, stability data after storage up to 24 months at 25 °C/60% RH and 6 months at 40 °C/75% RH are available; the study is ongoing. All test results comply with the specified limits and show no or only minor changes. No plastic additives could be detected in the solution. After 24 months under long term conditions and 6 months under accelerated conditions, the test results did not show any significant differences between storage in the upright and inverted positions.

Photostability studies have been performed according to VICH guideline (GL) 5 (Photostability testing of New Veterinary Drug Substances and Medicinal Products) on two batches of the finished product in 100 ml CLAS vials with an overall illumination of 1.2 million lux hours and an integrated near ultraviolet energy of 200 Wh/m². Results obtained after light exposure of the product in the immediate packaging and in the secondary packaging (cardboard box) were compared to those obtained on the product stored in a colourless glass flask and protected from light (wrapped in aluminium foil). An additional sample not submitted to photo degradation was also analysed. All testing results complied with the specifications, thus confirming that the finished product is not prone to photo degradation. The proposed packaging provides adequate protection for the finished product and no special light storage recommendations are therefore required.

For a freeze-thaw cycling study on two batches in the commercial 250 ml vials, all product characteristics and the appearance of the packaging remained unchanged, thus confirming that the quality of the finished product is not impacted by several freeze-thaw cycles.

By extrapolating from the long term and accelerated stability data provided, a shelf-life of 36 months without any specific storage conditions was claimed. This is acceptable and reflected accordingly in the SPC (section 6.3).

The in-use stability of the product was investigated in accordance with the CVMP Note for guidance on in-use stability testing of veterinary medicinal products (EMEA/CVMP/424/01). The data demonstrate that the proposed in-use shelf life of 28 days is considered acceptable.

Overall conclusions on quality

The development pharmaceutics of the formulation has been suitably explained. The manufacturing process and in-process controls have been described in sufficient detail.

The information on both active substances is provided in Active Substance Master Files (ASMFs), and is deemed satisfactory.

The information on the excipients and packaging materials is acceptable.

The finished product specification includes all relevant quality attributes and is sufficient to assure consistent quality. The control methods are described and appropriately validated.

Stability studies on the finished product are performed under VICH conditions. The proposed shelf life of 36 months without any specific storage conditions is considered acceptable. In-use stability has

been accepted.

Based on the review of the data on quality, the manufacture and control of Zeleris are considered acceptable and conform to current EU quality guidelines.

In addition, the applicant is recommended, and has committed to, provide information on process validation and in-use stability post-authorisation.

Part 3 – Safety

Safety documentation

Data relating to pharmacodynamics, pharmacokinetics and toxicity of florfenicol and meloxicam have been previously reviewed by the CVMP as part of the applications for maximum residue limits. Based on those data, florfenicol and meloxicam are included as allowed substances in table 1 of the Annex to Commission Regulation (EU) No 37/2010 indicating that the active substances are approved for use in food-producing species.

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicological studies

The applicant cross-referred to the public assessment reports for florfenicol (Florfenicol Summary Report (1), 1996) and meloxicam (EMEA/CVMP/152255/2006-FINAL), in addition, new toxicity studies were provided with the fixed combination product. This is considered acceptable.

Single dose toxicity

Florfenicol has low acute toxic potential, with an oral LD_{50} greater than 2000 mg/kg bw and an intraperitoneal LD_{50} of close to 2000 mg/kg bw in rats.

Meloxicam has moderate acute toxic potential, with reported oral LD_{50} values between 83.5 mg/kg bw and 200 mg/kg bw in rats (depending on strain and sex).

Repeat dose toxicity

In repeat dose toxicity studies, a NOEL value of 1 mg florfenicol/kg bw/day from a 52-week study in the dog was determined based on an in increase in liver weight. This value was used by CVMP to establish an ADI.

For meloxicam, the lowest repeat dose toxicity NOEL was 0.2 mg/kg bw in rats based on gastrointestinal and renal toxicity in a 52-week study.

Tolerance in the target species of animal

See part 4.

Reproductive toxicity, including developmental toxicity

In toxicity studies conducted in rats and rabbits investigating potential reproductive and/or developmental toxicity, florfenicol produced adverse effects on the male reproductive system whereas meloxicam led to reduced implantation, an increase in resorption rate, prolonged pregnancy and decreased pup viability.

There is no evidence that florfenicol or meloxicam are teratogenic.

The LOEL value of 0.125 mg meloxicam/kg bw/day was associated with prolonged pregnancy in a segment-III study in Sprague Dawley rats and was used to establish a toxicological ADI of 1.25 µg/kg bw.

Genotoxicity / Carcinogenicity

In vitro studies and studies with laboratory animals did not reveal evidence of mutagenic activity or carcinogenic potential of florfenicol and meloxicam.

Studies of other effects

Skin/eye irritation, hypersensitivity

Two studies were conducted with the finished product to assess the irritation potential of the product to the skin and the eye of New Zealand rabbits. The results demonstrate that under the experimental conditions of these GLP studies the product was non-irritant to the skin but slightly irritant to the eye.

The data from a local lymph node assay (LLNA) demonstrate that the formulation does not induce delayed contact hypersensitivity.

Resistance development in food-borne bacteria

See part 4 (resistance).

User safety

A user safety assessment of the finished product has been conducted in accordance with the Guideline for User Safety for Pharmaceutical Veterinary Medicinal Products (EMEA/CVMP/543/03-Rev1) including a hazard identification, exposure assessment, risk characterization and formulation of corresponding warning phrases. The product will be administered by professionals, i.e. veterinarians.

Parenteral, dermal and ocular are possible routes of exposure. Since the product is slightly irritant to the eye, a precautionary statement is included in the SPC.

The worst case route of exposure will be parenteral by accidental self-injection. It can be considered that 1.5 ml (10% of the maximum administration volume) represents a reasonable worst case estimate of the volume that might be accidentally injected into a person (60 kg bw).

Accidental self-injection of 1.5 ml of the product would correspond to a florfenicol dose of 10 mg/kg bw. The only available toxicological reference value to compare with is the intraperitoneal LD_{50} of 2000 mg florfenicol/kg in rats. Although comparison with an LD_{50} is not ideal, in the absence of a more suitable comparator it can be accepted in this case. Using the LD_{50} provides a margin of safety of 200, which is considered acceptable.

Meloxicam is considered to be maternotoxic and embryotoxic. Accidental self-injection of 1.5 ml of the product would correspond to a meloxicam dose of 0.125 mg/kg bw. Comparing this dose with the lowest LOEL value of 0.125 mg meloxicam/kg bw/day derived from a segment-III study in rats no margin of safety can be calculated which is considered unacceptable. Therefore, pregnant women should not handle the product, and this is reflected in the product literature. Warnings and precaution phrases included in the SPC are adequate to mitigate the risk to the user in particular to pregnant women.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the relevant VICH guideline. The predicted environmental concentrations for the active substances florfenicol and meloxicam were calculated in accordance with VICH GL6 (Guideline on environmental impact assessment (EIAS) for veterinary medicinal products – Phase I) and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines 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 summed initial predicted environmental concentrations of florfenicol and meloxicam in soil are less than 100 µg/kg ($PEC_{soil, initial}$ = 88, 50, 78 and 90 µg/kg for intensively reared calf, dairy cow, cattle 0-1 years and cattle <2 years, respectively; 44 and 65 µg/kg for dairy cow and beef cattle on pasture, respectively).

Based on the data provided, the ERA can stop at Phase I. Zeleris is not expected to pose a risk to the environment when used according to the SPC.

Overall conclusions on the safety documentation

Data relating to pharmacodynamics, pharmacokinetics and toxicity of florfenicol and meloxicam have been previously reviewed by the CVMP as part of the applications for maximum residue limits. (Florfenicol Summary Report (1), 1996; EMEA/CVMP/152255/2006-FINAL).

Data from studies with the fixed combination product demonstrate that the formulation is not irritant to the skin but slightly irritant to the eye of rabbit and does not induce delayed contact hypersensitivity. A user safety assessment identified a risk for pregnant women after accidental self-injection and, therefore, pregnant women should not handle this product. Adequate warnings and precautionary phrases are included in the SPC to mitigate the risk for the user, in particular pregnant women.

Based on the data provided the ERA can stop at Phase I. Zeleris is not expected to pose a risk to the environment when used according to the SPC.

Residues documentation

Pharmacokinetics

Data from a three-armed GLP pharmacokinetic study were used to demonstrate plasma kinetics of Zeleris following a single subcutaneous injection to cattle at a dose of 40 mg/kg bw of florfenicol and 0.5 mg/kg bw of meloxicam, which is the intended dose.

Mean maximal florfenicol plasma concentration was around 4600 µg/l and mean terminal half-life was about 61 h. At 168 h after dosing, for all animals, plasma concentrations of florfenicol were measured above the lower limit of quantification (>50 µg/l). The mean plasma concentration of florfenicol at 168 h was approximately 290 µg/l. The mean maximal plasma concentration of meloxicam was 2011 µg/l. Meloxicam plasma concentrations declined slowly, with a mean terminal half-life of about 23 h.

For distribution, metabolism and excretion literature data were provided.

Depletion of residues

For the purpose of calculating withdrawal periods the depletion of the marker residue concentrations were investigated in a marker residue study in the bovine tissues liver, kidney, skeletal muscle, and injection site muscle. In these GLP compliant residue studies, twenty beef cattle received a single subcutaneous injection of Zeleris in the neck, at the recommended dose of 40 mg florfenicol and 0.5 mg meloxicam per kg bodyweight. Tissue residues were determined at 42, 49, 56 and 63 days post application. Validated analytical methods (LC-MS/MS) were available for the determination of florfenicol amine and meloxicam in bovine tissues.

The design and conduct of the studies were appropriate and all current requirements were taken into account.

Meloxicam concentrations were below the respective LOQs in all tissues at all slaughter days.

Florfenicol amine concentrations above the MRL were measured in kidney tissues at day 42 only. In the core injection site, concentrations above the LOQ (but below the MRL) were found in five animals at day 42, and in four out of five animals at day 49.

MRLs

The active substances used in Zeleris solution for injection for cattle are included in Table 1 of Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances as follows:

Substance	Marker residue	Animal species	MRL	Target tissues	Other provisions
Florfenicol	Sum of florfenicol and its metabolites measured as florfenicol-amine	Bovine	200 µg/kg 3000 µg/kg 300 µg/kg	Muscle Liver Kidney	Not for animals from which milk is produced for human consumption
Meloxicam	Meloxicam	Bovine	20 µg/kg 65 µg/kg 65 µg/kg 15 µg/kg	Muscle Liver Kidney Milk	No entry

The excipients listed in section 6.1 of the SPC (dimethyl sulphoxide, glycerol formal) are allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required.

Analytical method

As products containing the same active substance are already approved for use in the same species, no further consideration of the analytical methods is required in relation to this application.

Withdrawal periods

For withdrawal period calculations the marker residue levels in tissues were assessed against the respective MRLs. The longest withdrawal period was derived from kidney tissue concentrations of florfenicol amine using the alternative approach according to the CVMP guideline "Approach Towards Harmonization of Withdrawal Periods" (EMEA/CVMP/036/95), resulting in an overall withdrawal period of 56 days for meat and offal for cattle treated at the intended dose.

In the absence of an MRL for florfenicol in milk, Zeleris is not allowed to be used in animals producing milk for human consumption.

The following sentence is included the product literature 'Not authorised for use in lactating animals producing milk for human consumption. Do not use in pregnant cows, which are intended to produce milk for human consumption, within 2 months of expected parturition.' The limit of 2 months before parturition proposed by the applicant was considered acceptable, taking in to consideration the half-life of the substance, the time to reach virtual clearance in plasma, the time interval for residues to deplete from edible tissues, and the addition of a safety span.

Overall conclusions on the residues documentation

An overall withdrawal period of 56 days for meat and offal from cattle treated at the intended dose is considered acceptable based on residue depletion data, with florfenicol amine in kidney being the withdrawal period determining residue and tissue.

Part 4 – Efficacy

Pharmacodynamics

The applicant provided published literature to document the pharmacodynamic properties of the active substances florfenicol and meloxicam. Florfenicol and meloxicam are well-established substances in veterinary medicine and authorised in veterinary medicinal products containing the single active substance ("mono-preparation").

Meloxicam

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. It acts as inhibitor of prostaglandin synthesis, thereby exerting anti-inflammatory, anti-exudative, analgesic and antipyretic effects. Meloxicam is not COX-2 specific but inhibits preferentially COX-2. It reduces leukocyte infiltration into the inflamed tissue and may inhibit collagen-induced thrombocyte aggregation. Meloxicam has anti-endotoxic properties.

Florfenicol

Florfenicol is a synthetic broad-spectrum antibiotic belonging to the group of amphenicols. The main action is bacteriostatic. Its activity is time-dependent. However, studies have also shown concentration-dependent bactericidal activity against the target pathogens *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.* Florfenicol blocks the 50S ribosomal subunit of bacteria

to disrupt protein synthesis. Clinical breakpoints have been established by the Clinical and Laboratory Standards Institute (CLSI), VET01-S2. The applicant provided MIC data derived from surveillance studies (Vetpath programs II and III) and the EU field trial.

Surveillance studies

In order to demonstrate the antimicrobial activity of florfenicol against the bovine target pathogens, *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni*, the applicant submitted MIC data derived from a European Animal Health Study Centre (CEESA) monitoring programme (Vetpath programs II and III), covering the time periods 2004-2006, 2009-2010, and 2011-2012. The isolates were collected from a total of 9 European countries from cattle aged 3 weeks to 11 months, suffering from respiratory disease. Samples were collected via deep nasopharyngeal swabs or lung samples taken from euthanised animals. MICs were determined by agar and broth microdilution standard method according to CLSI. The data were considered representative regarding the number of clinical isolates which were likely to be epidemiologically unrelated, and EU regions. MIC_{50} and MIC_{90} values were reported, and the underlying MIC distribution profile was unimodal for all target pathogens. Clinical breakpoints established by CLSI for florfenicol against bacterial pathogens in bovine respiratory disease were used for interpretation of the MIC data.

All 205 target pathogens isolated during 2011-2012 (Vetpath program III; 90 strains of *M. haemolytica*, 80 strains of *P. multocida* and 36 strains of *H. somni*) showed good susceptibility against florfenicol with MIC ranges between 0.125 and 2 µg/ml (except for one *M. haemolytica* isolate being out of range: MIC of 4 µg/ml). The MIC_{90} values of *M. haemolytica, P. multocida and H. somni* were 1 µg/ml, 0.5 µg/ml and 0.2 µg/ml, respectively. In the Vetpath II monitoring program MIC values were determined for two previous periods between 2004 and 2010. Taking into account all three periods, susceptibility rate for a total of 571 strains tested was close to 100% (*Mannheimia haemolytica;* MIC_{90} 0.9 µg/ml*, Pasteurella multocida;* MIC_{90} 0.5 µg/ml, *Histophilus somni;* MIC_{90} 0.3 µg/ml).

These European surveillance studies indicate that the susceptibility of target pathogens causing BRD against florfenicol remained good and has not changed over the years. The results reflect the resistance situation reported from other monitoring programs in the EU including the German GE*RM* Vet monitoring program and data reported from literature.

EU Field study

Within the clinical field study a total of 281 clinical isolates from 195 animals suffering from BRD was collected for MIC determinations from three study sites (DE, HU, PT). The 281 isolates included 222 samples from nasopharyngeal swabs (NPS) and 24 samples from trans-tracheal aspiration (TTA) taken prior to treatment as well as 35 samples taken post-treatment. MIC determinations were conducted according to CLSI standard procedures.

According to CLSI breakpoints, all investigated field isolates proved to be susceptible to florfenicol. The MIC values of target pathogens ranged between 0.125 and 2 µg/ml and MICs were comparable at all study sites.

Development of resistance

Resistance to florfenicol is mainly mediated by an efflux system due to specific (Flo-R) or multidrug transporter (AcrAB-TolC). The genes coding for these mechanisms are located on mobile genetic elements such as plasmids, transposon or genes cassettes.

Target pathogens

The resistance mechanism against florfenicol, and the low prevalence of transferable resistance determinants among bovine respiratory pathogens contribute to the continuous low level of resistance in bovine respiratory isolates despite a long period of florfenicol use. The absence of florfenicol resistance was confirmed by data obtained from surveillance studies provided by the applicant (see above). Taking into account all data reported and in the absence of further findings on florfenicol resistance, the potential for development of resistance in bovine target pathogens appears to be low.

Food-borne pathogens and commensal organisms

The applicant provided a report on the potential impact of the intended product to select for antimicrobial-resistant zoonotic and non-zoonotic bacteria of human health concern, and their transfer to humans from animals according to the VICH GL 27 (CVMP/VICH/644/01-FINAL, 14 January 2004).

The current resistance situation of food-borne pathogens and commensals is considered favourable, despite the use of florfenicol over many years in the EU in various products for cattle suffering from BRD.

Overall, the impact of florfenicol to select for antimicrobial-resistant food-borne pathogens or commensal organisms is so far low, and, consequently, the contribution to human exposure of antimicrobial resistant microorganisms is likewise considered low.

Pharmacokinetics

The applicant presented a GLP compliant three-way cross-over pharmacokinetic study to determine the pharmacokinetic profiles of florfenicol (40 mg/kg bw) and meloxicam (0.5 mg/kg bw) after single subcutaneous injection to young healthy cattle (24 animals), at the age of 10 $\pm$ 3 months, weighing 221$\pm$ 39 kg (149-306 kg).

Animals were randomly allocated to one out of 6 treatment groups (n=4) and received three treatments at three different periods, with either the fixed combination, florfenicol alone or meloxicam alone (see table below). The wash-out period was at least 20 days between treatments, equivalent to at least 10 times the terminal half-life of the active ingredients.

Sequence group	No. of animals	Period 1	Period 2	Period 3
1	4	Combination	Florfenicol	Meloxicam
2	4	Combination	Meloxicam	Florfenicol
3	4	Florfenicol	Combination	Meloxicam
4	4	Florfenicol	Meloxicam	Combination
5	4	Meloxicam	Florfenicol	Combination
6	4	Meloxicam	Combination	Florfenicol

The study was well-designed, performed and documented and followed current guidelines, i.e. CVMP Guideline on the conduct of pharmacokinetic studies in target animal species (CVMP/133/1999) and the CHMP Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2). Comparison of pharmacokinetic parameters and statistical analysis followed the principles outlined in CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal (CVMP/016/2000

Rev. 2). A validated HPLC and Mass Spectrometry detection method was used for the determination of florfenicol and meloxicam concentrations in bovine plasma.

Florfenicol

After single subcutaneous injection of 40 mg/kg bw of florfenicol, the mean exposure to florfenicol, expressed by AUC, was comparable when florfenicol was administered as mono-preparation or as fixed combination with meloxicam. Mean florfenicol C_{max} was significantly increased by about 30% after administration of the fixed combination product compared to the mono-preparation. The t_{max} values were largely comparable (about 10 h).

Since florfenicol exerts time-dependant antimicrobial activity, time over MIC_{90} of the target pathogens was compared. As regards all three target pathogens, *P. multocida*, *H. somni*, and *M. haemolytica,* there was no statistically significant difference in time above the MIC_{90} between the treatments. While for *P. multocida* and *H. somni* the confidence intervals for the time above the MIC_{90} ratios were within the usual acceptance range of 0.80-1.25 for equivalence, for *M. haemolytica* at least the lower confidence bound was above 0.80.

Meloxicam

After single subcutaneous injection of 0.5 mg/kg bw of meloxicam the mean C_{max} as well as t_{max} were comparable between meloxicam administered as mono-preparation or in fixed combination with florfenicol. The exposure in the first 24 hours appears comparable, even though the lower limit of the predefined acceptance range of 0.80-1.25 was not met (90% CI 0.79-0.93).

However, the overall exposure (AUC_{0-t}) was clearly lower with the fixed combination product compared to the overall exposure after administration of meloxicam as mono-preparation, resulting in a relative bioavailability of meloxicam of 73 $\pm$ 25% in the fixed combination. The applicant pointed out that anti-inflammatory activity of meloxicam is more important in the first 24 hours of treatment; therefore, emphasis is put on comparison of AUC_{0-24h} rather than AUC_{0-t}. In principle, this is agreed for acute respiratory infections with pronounced clinical signs.

Overall, it can be concluded from this study that after a single subcutaneous dose of 40 mg/kg bw florfenicol and 0.5 mg/kg bw meloxicam as fixed combination, the pharmacokinetic profiles of meloxicam and florfenicol are similar to those after administration of the respective mono-preparations; however, bioequivalence according to the criteria of the EMA/CVMP bioequivalence guideline (CVMP/016/2000 Rev. 2) could not be demonstrated.

No firm conclusions on possible interactions between the active substances, florfenicol and meloxicam, can be drawn, since the excipients in the fixed combination solution for injection differ from those contained in the mono-preparations, and an impact of different excipients on each substance bioavailability cannot be excluded.

Justification of the fixed combination

The fixed combination of florfenicol and meloxicam is in principle justified because both active substances contribute to a well-defined clinical indication by complementary/synergistic modes of action in the treatment of bovine respiratory infections.

Florfenicol acts as a broad-spectrum antibiotic against the target pathogens responsible for bovine respiratory disease (BRD), whilst meloxicam is expected to reduce the clinical signs including pyrexia associated with the respiratory disease.

In the GLP compliant three-way cross-over pharmacokinetic study, the bioavailability of meloxicam in the fixed combination proved to be significantly lower compared to the use of the meloxicam mono-product alone, but no data are available comparing the pharmacokinetics of the fixed combination with the concurrent use of the mono-products. Moreover, equivalence of the combination product to the concurrent use of florfenicol and meloxicam as mono-products has not been demonstrated in any clinical study. Insofar, the fixed combination has not been justified fully in line with the provisions of the CVMP Guideline on pharmaceutical fixed combinations (EMEA/CVMP/83804/2005). However, exposure in the first 24 hours appears comparable, and superiority of the fixed combination was demonstrated in the pivotal field study in regard to pyrexia (see below). This is appropriately reflected in the indications. The CVMP took note of the (restricted) indications, and accepted the justification for this fixed combination.

Dose determination/justification

No dose determination studies were provided, but reference was made by the applicant to the already approved doses of 40 mg florfenicol and 0.5 mg meloxicam/kg bw in authorised mono-preparations for the treatment of BRD. The applicant justified the proposed dose in the fixed combination based on similar pharmacokinetic profiles of florfenicol and meloxicam alone or in fixed combination (see above, pk section).

A dose confirmation study (mono-centric, parallel, randomised, blinded) was provided to demonstrate the efficacy of the 0.5 mg/kg bw meloxicam dose in the fixed combination with florfenicol (40 mg/kg bw) after single subcutaneous injection in the reduction of pyrexia and other clinical signs associated with an experimentally induced respiratory tract infection caused by *M. haemolytica* in calves. The study was intended to show superiority of the proposed fixed combination compared to a negative control based on percentage of calves with rectal temperature below 39.5 °C at 6 h post treatment as primary efficacy parameter (success rate), and the percentage of animals being cured on Day 4, and using other clinical signs and lung lesion scores at necropsy as secondary parameters. In addition, comparison was made to a positive control.

Experimental infection of 86 non-ruminating calves (age: 42 ± 4.5 days) with a *Mannheimia haemolytica* field isolate (serotype A1, MIC against florfenicol: 0.5 µg/ml) induced clinical signs of BRD. Treatment was initiated when the calves showed moderate to severe signs of respiratory disease (clinical sum score ≥3, rectal temperature > 39.5 °C), mostly within 4 to 8 hours after challenge. Twenty-six calves were treated with NaCl 0.9% (negative control) at a dose of 1 ml/10 kg bw, 26 calves were treated with the proposed fixed combination product (0.5 mg meloxicam/kg bw and 40 mg florfenicol/kg bw) subcutaneous, and 27 calves were treated with the same dose of both active substances administered concurrently as mono-preparations (positive control).

Study results demonstrate the overall efficacy and safety of the combination administered either as fixed combination or as mono-preparation in the treatment of experimentally induced respiratory tract infection caused by *Mannheimia haemolytica* associated with pyrexia, when compared to the negative control. The fixed combination product was superior in reduction of pyrexia (6 h post appl.) and other clinical signs (demeanour, respiration, nasal discharge and coughing) up to the last study day (D4) when compared to the negative control.

When compared to the positive control, no statistical difference was seen with the fixed combination product for the efficacy parameters analysed. The mean reduction of rectal temperature was likewise similar 6h after treatment: -0.7°C in both groups. However, the success rate for the primary efficacy parameter, i.e. the number of calves with rectal temperature below 39.5 °C at 6 hours post treatment was numerically lower for the fixed combination product (54%, 14/26) when compared to the

administration of both substances as single products (positive control, 67%, 18/27). Non-inferiority of the fixed combination product with the positive control could not be confirmed statistically because this was not the aim of the chosen study design.

The CVMP also noted that the study design (controls and primary efficacy parameter) was not appropriately chosen to meet the study objective. A positive control using florfenicol alone would have been necessary to clearly demonstrate effects of meloxicam, when given in fixed combination with florfenicol. In addition, in relation to the anti-inflammatory properties of meloxicam it would have been useful to include other primary clinical endpoints than pyrexia, e.g. respiratory signs.

Thus, the dose of meloxicam in the fixed combination could not be evaluated under these study conditions.

Target animal tolerance

Target animal safety was investigated in two target animal safety studies, and supported by date from preclinical studies.

Initial TAS study

A well-designed GLP compliant target animal safety study in pre-ruminating calves was submitted in line with VICH guideline 43 on Target Animal Safety. Thirty two calves aged approximately 5 to 12 weeks (8 animals/group) received either 0 (saline), 1X, 3X and 5X the recommended treatment dose (RTD), administered via subcutaneous route, 3 times at 7-day intervals. The maximum injection volume was 15 ml/injection site.

No mortality was observed in group 1 (saline control) compared to 1/8 animals in group 2(1X RTD), 1/8 animals in group 3 (3X RTD) and 7/8 animals in group 4 (5X RTD). No clinical abnormalities were recorded in group 1 (control) and 2 (1X) except for 2 cases of transient diarrhoea in group 1. One animal of group 2 (1X) was euthanised on Day 13 for ethical reasons. This animal showed already signs of illness and worsening of clinical conditions from Day -5 onwards. Necropsy revealed pneumonia with necrotic and purulent area in the lung. In group 3 (3X RTD) some diarrhoea was recorded in 3 animals from the second dose (Day 7) onwards with worsening of the clinical conditions in one animal and euthanasia of this animal on Day 17. In group 4 (5X RTD) diarrhoea was noted from Day 0 onwards in increasing number of animals, and severe deterioration of health conditions in all animals from Day 12 with diarrhoea , lethargy, prostration, cachexia, dehydration, recumbency; 7 animals in this group died or were euthanized in moribund conditions. The only one surviving animal showed lethargy, prostration and was very thin on Day 19-21. The observed hypothermia in the animals of this group is related to the poor conditions of these animals. Over the course of treatment, animals of groups 1 and 2 (control, 1X RTD) gained weight as expected for this breed and age. However, in animals of groups 3 (3X RTD) and 4 (5X RTD) lost weight from Day 7 (after the second dose) onwards. While milk consumption remained stable in groups 1 and 2, milk intake decreased in group 3 and 4 after the second dose with drastic reduction up to stop of milk intake in group 4. The observed changes in haematology, blood chemistry and urine reflect the poor clinical conditions of the calves in group 3 and 4. While histological data revealed no remarkable difference between group control and group 1X, the occurrence and severity of lesions increased with the dose for group 3X and group 5X animals.

Local reactions at the injection site (pain on injection, swelling and mild to moderate induration at the injection site) was recorded in all animals treated with the fixed combination independent from dose, but not in the control animals. Induration persisted until study termination (Day 21) or death of the animal. Macroscopic examination of the injection site at necropsy revealed thickening of the subcutaneous connective tissue. Histological analysis of the injection sites revealed necrosis of adipose

and muscular tissue and subsequent inflammatory and fibroplastic changes typical for traumatic lesions induced by injection.

Overall, the study results indicate that the proposed fixed combination product appears to cause local reactions, but is in general systemically well-tolerated in pre-ruminating calves at the intended treatment dose, repeated twice in weekly intervals. However, repeated injections of overdoses (3X and 5X dose at 7-day intervals) were harmful to calves. The observed impact on animal health which was fatal in the 5X group was due to dysbiosis/malfunction of the gut flora induced by repeated administration of high doses of florfenicol accompanied with the typical adverse effects of meloxicam on the gastrointestinal mucosa (haemorrhagia, ulceration in the rennet). Both led to decrease in milk consumption which promoted the deterioration of the health conditions of the animals even further. However, it was also noted that the calves were not in good health at treatment begin, since they required metaphylactic/therapeutic treatments (*inter alia* dietary supplement for rehydration, diarrhoea and antimicrobials (tulathromycin, doxycycline, tylosine) during the acclimatisation phase and during the study period.

The data indicated that this product might not be safe for use in young pre-ruminating calves since severe adverse reactions which may be fatal cannot be excluded. In addition, the representativeness of these young animals for the target species was questioned. Overall, the CVMP considered that the study was insufficient to reach conclusions on the tolerance of the fixed combination. Therefore, the applicant conducted the second TAS study below.

Second TAS study

The applicant conducted a second GLP compliant target animal safety study in pre-ruminating calves aged 4 weeks on average following single SC dose of 0 (saline), or 1X (1 ml/10 kg bw), 2X (2 ml/10 kg bw) or 3X (3 ml/10 kg bw) the recommended treatment dose (RTD) of the fixed combination product.

Parameters included daily clinical observations, clinical pathology on day 0 and day 7, and urine analyses on day 7 before necropsy. The data indicate that the proposed fixed combination was overall well tolerated after single injection up to 3 times the recommended dose. However, mild signs of respiratory and gastrointestinal disease conditions that may be common in calves of this age were detected in animals of all groups before treatment or after treatment. SC injection of the proposed product induced moderate pain resulting in movement of the head and/or neck upon injection which was independent from dose volume, and swelling which turned into induration from day 2 to day 7 after treatment. Induration was more severe in the 3X dose group compared to the 1X dose group. These adverse reactions are adequately reflected in the product literature. In addition, a dose-related increased incidence and/or severity of decreased lymphocytes in the Peyer's patches was noticed in the saline, 1X, 2X, and 3X RTD group, respectively. Thus, a relationship to meloxicam in the combination product cannot be excluded. However, since no associated clinical signs occurred, respective information in the product literature is not deemed necessary. No other adverse events were observed that could be related to treatment.

Since the safety of the product has not been investigated in calves of less than 4 weeks of age, a corresponding warning has been added in section 4.5 of the SPC. A maximum dose volume of 15 ml per injection site is proposed, which corresponds to the volume used in the residue studies.

Other studies:

In preclinical (PK) studies, administration of the fixed combination products to young healthy cattle (24 animals) resulted in local reactions (pain, swelling, induration) at the injection site. In most animals swelling and induration were observed 24-48 hours after injection and disappeared within 21 days, but

in some animals these reactions persisted up to 49 days. Mild pain at the injection site was observed in 3 animals at day 2 or 3 after administration of the fixed combination, and lasted in 2 of these animals for 4-5 days.

Similarly, in the experimental dose confirmation study, the fixed combination was generally well tolerated, but local reactions were frequently noted (discomfort and pain immediately after injection in 7 out of 26 animals, and 2 out of the 26 animals presented local reactions over the entire study period of 4 days).

In the clinical field study injection site reactions were observed in 44 animals (26.8%) treated with Zeleris and mostly consisted of swellings, induration, heat, pain, which resolved within 5 to 15 days without any treatment.

Field trials

A clinical field study (multi-centre, blinded, controlled, randomized) was provided to evaluate the efficacy and safety of one subcutaneous injection of Zeleris in the treatment of acute respiratory tract infections in bovines due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* and in reduction of clinical signs associated in comparison with one subcutaneous injection of florfenicol, given as mono-preparation.

329 calves (age: 2 to 87 weeks, weight: 66 to 359 kg) of study sites in Germany (3 farms), Hungary (one farm), and Portugal (one farm) showing clinical signs of BRD (rectal temperature ≥40 °C + sum of behavioural (range 0-3) and respiratory scores (range 0-3) ≥ 3 with each score ≥1) were included. Animals were treated subcutaneously either with the proposed fixed combination product (0.5 mg meloxicam/kg bw and 40 mg florfenicol/kg bw) or with florfenicol alone (40 mg/kg bw).

Target pathogens were determined at inclusion in 222 samples from nasopharyngeal swabs (NPS) and in 24 samples from trans-tracheal aspiration (TTA). The significance of bacteriological results derived from NPS and TTA samples with regard to clinical etiology is debatable. *M. haemolytica* was isolated from 78/304 animals (25.7%) and *P. multocida* from 127/304 animals (41.8%) in the different countries with varying percentages at the respective study sites at inclusion. *H. somni* was isolated in 37/304 animals (12.2%), and only found in acceptable numbers at the study site in Portugal (35/92). It was not isolated at the study site in Hungary and only in single cases at two of three study sites in Germany (one isolate from NPS per study site). Thus, the database presented for *H. somni* in this multicentre field study is somewhat weak. However, given the good susceptibility of this pathogen to florfenicol, and the pharmacokinetic profiles of florfenicol revealed no significant differences in the time over MIC_{90} for *H. somni* following administration of the fixed combination vs. individual administration of florfenicol, this is considered acceptable.

With regard to the primary endpoint (clinical cure on D7: behavioural and respiratory score ≤ 1 + a temperature < 40.0 °C) non-inferiority of the fixed combination compared to florfenicol alone was demonstrated (CI 95% [-1.15%; 10.90%]) with success rates of 93.9% (154/164) for the combination and 89.0% (146/164) for florfenicol with homogenous results at all study sites. However, these success rates were determined on efficacy parameters with low discriminating power. To derive a more meaningful conclusion a more stringent criterion, i.e. cure defined by rectal temperature <39.5 and a clinical sum score ≤1 on Day 7, was used for recalculation of success rates. Recalculated cure rates were 67.1% for the combination and 64.8% for florfenicol, respectively. Non-inferiority of the treatment groups was demonstrated also by means of the new analysis (CI 95% [-8.01; 12.46]).

With regard to the co-primary endpoint (alleviation of clinical signs (rectal temperature) associated with acute respiratory infections at 6±1 hours post treatment), superiority of the fixed combination to

florfenicol alone (p<0.0001) was shown (CI 95% of [0.37; 0.57]; p< 0.0001) and for animals showing no pyrexia up to day 2. These results confirm the antipyretic effect of meloxicam in the fixed combination over a period of 48 hours.

The effect of meloxicam on respiratory and behaviour scores was less pronounced and was observed during shorter periods, only. Statistically significantly better results for Zeleris as compared to florfenicol alone were found in regard to moderate or severe respiratory distress (6 hours post treatment) and behavioural score (6 hours post treatment and at D1).

With regard to the secondary endpoints ("relapse rates between D8 to D14, and between D15 to D30"), non-inferiority of the fixed combination to florfenicol alone was also shown. Relapse rates were considerably high: between D8 to D14 for the combination 9.7% (15/154) and for florfenicol 8.9% (13/146), and between D15 to D30 for the combination 16.9% and for florfenicol 15.1%. Since the post treatment observation period is rather long, it can be assumed that the "relapses" observed between study Day 15 and Day 30 are new or re-infections rather than relapses.

In conclusion, non-inferiority of the fixed combination product in comparison with florfenicol alone was demonstrated in the treatment of bovine respiratory disease due to *M. haemolytica*, *P. multocida* and *H. somni*. Superiority of the fixed combination product to florfenicol alone was shown for the reduction of rectal temperature 6 hours after treatment and the number of animals without pyrexia up to day 2, confirming the antipyretic effect of meloxicam in this fixed combination. However, the effect of meloxicam in the fixed combination on respiratory and behavioural scores was less pronounced, was observed during shorter time periods, and was not discriminating enough to justify the claim "reduction of clinical signs".

For all safety criteria no statistically significant difference was observed between the fixed combination and the control group based on the data provided. For animals treated with the combination two severe adverse events (BRD related deaths) were reported as well as three other adverse events (diarrhoea and coccidiosis) that were unlikely related to treatment. Injection site reactions were observed in 44 animals (26.8%) treated with Zeleris and in 57 animals (34.5%) treated with florfenicol alone. Injections site reactions mostly consisted of swellings, induration, heat, pain and resolved within 5 to 15 days without any treatment.

Overall conclusion on efficacy

Pharmacodynamics

Both florfenicol and meloxicam are well-established substances in veterinary medicine. Their modes of action (antibacterial and anti-inflammatory) are well described based on publically available scientific literature. The antimicrobial activity of florfenicol against the target pathogens (*M. haemolytica, P. multocida, H. somni*) was well demonstrated and showed good susceptibility to florfenicol during all time periods.

Resistance development

Based on the data available the resistance situation for bovine respiratory pathogens to florfenicol is considered favourable. The resistance situation of food-borne pathogens and commensals is favourable, although florfenicol is used since many years in the EU in various products in cattle suffering from BRD. The impact of florfenicol to select for antimicrobial-resistant food-borne pathogens or commensal organisms is so far low and consequently the contribution to human exposure of antimicrobial resistant microorganisms is likewise considered low.

Pharmacokinetics

A GLP compliant three-way cross-over pharmacokinetic study comparing the pharmacokinetics of meloxicam alone, florfenicol alone and florfenicol & meloxicam in fixed combination showed comparable PK parameter for florfenicol alone or in fixed combination. However, the overall availability of meloxicam when administered in the fixed combination was significantly lower (reduced by approximately 30%) when compared to the administration of meloxicam as mono-substance.

Justification of the fixed combination

The combination of florfenicol and meloxicam is in principle justified because of their complementary modes of action in the treatment of bovine respiratory infections. The bioavailability of meloxicam in the fixed combination proved to be significantly lower compared to the meloxicam mono-product, and equivalence of the combination product to the concurrent use of florfenicol and meloxicam as mono-products has not been demonstrated in any study. Thus, the fixed combination is not justified fully in line with the provisions of the CVMP Guideline on pharmaceutical fixed combinations (EMEA/CVMP/83804/2005). However, the clinical benefit resulting from this combination was confirmed in a pivotal field study (see below), and, based on this data, the contribution of meloxicam to the overall therapeutic effect of the fixed combination is sufficiently justified.

Dose determination/confirmation

The applicant justified the proposed dose of 40 mg/kg bw florfenicol and 0.5 mg meloxicam/kg bw in the fixed combination with the same dose being already authorised as mono-substances in the treatment of BRD. However, the pharmacokinetic study did not fully support this rationale since the availability of meloxicam in the fixed combination was reduced by approximately 30% when compared to the administration as mono-substance.

No conclusions on the contribution of meloxicam to the overall therapeutic effect of the fixed combination can be drawn from the dose confirmation study (experimental challenge of calves with *M. haemolytica)* due to inappropriate control groups. Consequently the dose of meloxicam in the fixed combination could not be evaluated under these study conditions. Irrespectively, the overall efficacy of the fixed combination proved to be superior over the negative control group. When compared to the positive control, no statistical difference was seen with the fixed combination product for the efficacy parameters. With regard to the primary efficacy parameter, i.e. the number of calves with rectal temperature below 39.5 °C, the success rate of the fixed combination product was numerically lower when compared to the administration of both substances as single products. Non-inferiority of the fixed combination product with the positive control could not be evaluated due to the study design.

Target animal safety

Two studies on target animal safety in young pre-ruminating calves were provided. In the first study, performed in pre-ruminating calves after repeated dose administrations corresponding to 0, 1X, 3X and 5X the recommended therapeutic dose (RTD), the proposed fixed combination product appeared to be systemically well- tolerated at the intended treatment dose, repeated twice in weekly intervals. However, repeated injections of overdoses (3X and 5X RTD at 7-day intervals) were harmful to calves and no margin of safety could be derived from this study. Therefore a second TAS study was performed in pre-ruminating calves after single administration of 0, 1X, 2X and 3X RTD and the data indicate that the proposed fixed combination was overall well tolerated up to 3 x RTD. Subcutaneous injection of the product induced moderate pain upon injection and local swelling at the injection site in all treated animals. The data do not indicate a relation between dose volume and severity of pain. Swelling at the injection site turned into induration which was more severe in the highest dose group compared to the lowest dose group. In addition, a dose-related increased incidence and/or severity of decreased lymphocytes in the Peyer's patches was noticed. Since this finding was dose dependent, a relation to

treatment (meloxicam in the combination) cannot be excluded. However, since no associated clinical signs occurred, respective information in the product literature is not considered necessary. No other adverse events were observed in this second TAS study that could be related to treatment according to the final study report. All adverse reactions including injection site reactions and adverse events following overdoses recorded in the TAS studies are properly reflected in the product literature. Furthermore, advice has been added in section 4.5 of the SPC that, in the absence of safety data, it is not recommended to treat calves under 4 weeks of age with this product.

Field study

In a clinical field study non-inferiority of the fixed combination product in comparison with florfenicol alone was demonstrated in the treatment of bovine respiratory disease due to *M. haemolytica*, *P. multocida* and *H. somni*. In addition, superiority of the fixed combination product to florfenicol alone was shown for the reduction of rectal temperature 6 hours after treatment and the proportion of animals without pyrexia up to day 2, confirming the antipyretic effect of meloxicam in this combination product. However, the effect of meloxicam on respiratory and behavioural scores was less pronounced, and observed during shorter time periods only, and thus, was not discriminating enough to justify the claim "reduction of clinical signs".

Overall conclusions

Bioequivalence of the fixed combination product to the concurrent use of florfenicol and meloxicam as mono-products has not been demonstrated. The bioavailability of meloxicam in the fixed combination proved to be significantly lower compared to the mono-product. However, the clinical benefit resulting from this combination was confirmed in a pivotal field study, where a clinically relevant antipyretic effect over 48 hours after administration of the combination product was demonstrated, which was superior to the administration of florfenicol alone. The effect of meloxicam in the fixed combination on respiratory and behaviour signs associated with BRD was less pronounced and was observed during shorter periods, only. Consequently, the clinical indication was amended to adequately reflect the outcome of the field study: "For therapeutic treatment of bovine respiratory disease (BRD) associated with pyrexia due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* susceptible to florfenicol".

In addition, the following information is included in the SPC section 5.1 and in section 15 of the package leaflet: "The bioavailability of meloxicam in this combination product is lower compared to the use of meloxicam when administered on its own. The impact of this difference on anti-inflammatory effects has not been investigated in field trials. However, a clear antipyretic effect has been demonstrated in the first 48 hours after administration".

Part 5 – Benefit-risk assessment

Introduction

Zeleris is a non-aqueous solution for subcutaneous injection in cattle, containing as active substances a fixed combination of florfenicol (400 mg/ml) and meloxicam (5 mg/ml). Both active substances are well known in EU-authorised single-substance veterinary medicinal products. The combination is considered a new fixed combination of known active substances previously authorised within EU and is therefore considered a new active substance.

The product is intended for the following indication: "For therapeutic treatment and reduction of clinical signs of bovine respiratory disease (BRD) in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* susceptible to florfenicol".

The proposed withdrawal period is 56 days (meat and offal); Zeleris is not authorised for use in lactating animals producing milk for human consumption. The product must not be used in pregnant animals which are intended to produce milk for human consumption within 2 months of expected parturition.

The dossier has been submitted in line with the requirements for submissions under Article 13(b) of Directive 2001/82/EC - fixed combination application.

Benefit assessment

Direct therapeutic benefit

Both active substances in the proposed fixed combination product, meloxicam and florfenicol, are well-established substances in single-product veterinary medicines with well-described modes of action. The pharmacodynamic properties of meloxicam are well-described (NSAID), and for florfenicol recent MIC data showed good susceptibility of the relevant bovine target pathogens (*M. haemolytica, P. multocida, H. somni*) to florfenicol during all time periods. Data indicate that the risk for development of florfenicol resistance towards the target pathogens appears to be low.

The clinical benefit of this combination product as demonstrated in a pivotal field trial is a clinically relevant antipyretic effect over 48 hours after administration which proved to be superior to the administration of florfenicol alone. The effect of meloxicam in the fixed combination on respiratory and behaviour signs of BRD was less pronounced and was observed during shorter periods only. In the absence of appropriate studies, conclusions on the clinical equivalence of the fixed combination to concurrent use of florfenicol and meloxicam when administered as mono-products cannot be drawn.

The wording of the clinical indication adequately reflects the outcome of the pivotal field study and an appropriate statement is included in the product literature to inform the user that while there is a clear antipyretic effect in the first 48 hours after administration, the bioavailability of meloxicam in this combination product is lower compared to the use of meloxicam when administered on its own, and that the impact of this difference on anti-inflammatory effects has not been investigated in field trials.

Additional benefits

Zeleris facilitates increased administration compliance as it requires only one single injection for therapy of BRD combining antimicrobial and anti-inflammatory/antipyretic treatment. The use of a fixed combination product facilitates animal handling by reducing the total number of injections to be given.

Risk assessment

Main potential risks have been identified as follows:

Quality:

Information on development, manufacture and control of both of the active substances and also 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.

Safety:

Risks for the target animal

Adverse reactions including injection site reactions (pain, swelling, induration) and adverse events following overdoses recorded in the TAS studies are properly reflected in the product literature.

Advice has been added in section 4.5 of the SPC that, in the absence of safety data, it is not recommended to treat calves of less than 4 weeks of age with this product.

Risk for the user

The product is proved to be slightly irritant to eyes. Meloxicam is considered to be maternotoxic/embryotoxic. Appropriate warnings and precaution phrases are included in the SPC to mitigate the risk for the user in particular for pregnant women.

Risk for the environment

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

Risk for the consumer

A withdrawal period of 56 days for meat and offal is considered appropriate to manage risks for the consumer. In the absence of an MRL for florfenicol in milk, Zeleris is not authorised for use in lactating animals producing milk for human consumption. Also, this product must not be used in pregnant animals which are intended to produce milk for human consumption within 2 months of expected parturition.

Emergence of antimicrobial resistance

Based on current knowledge, the risk of antimicrobial resistance to public health is considered low when the product is used according to the SPC.

Risk management or mitigation measures

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

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for therapeutic treatment of bovine respiratory disease (BRD) associated with pyrexia due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* susceptible to florfenicol.

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 Medicinal Products for Veterinary Use (CVMP) concluded that the application for Zeleris 400 mg/ml

+ 5 mg/ml solution for injection for cattle 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.