8 September 2016
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP final assessment report for DRAXXIN to add sheep as target species for the 100 mg/ml strength (not for the 500 ml vial) (EMEA/V/C/000077/X/0029)

International non-proprietary name: tulathromycin

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

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Product profile

Invented name:	DRAXXIN
Active Substances:	Tulathromycin
Target Species:	Cattle pigs and sheep
Pharmaceutical Form:	Solution for injection
Strength:	100 mg/ml
Therapeutic Indication:	Cattle: Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* sensitive to tulathromycin. The presence of the disease in the herd should be established before preventative treatment. Treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis* sensitive to tulathromycin. Pigs: Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica* sensitive to tulathromycin. The presence of the disease in the herd should be established before preventative treatment. DRAXXIN should only be used if pigs are expected to develop the disease within 2-3 days. Sheep: Treatment of the early stages of infectious pododermatitis (foot rot) associated with virulent *Dichelobacter nodosus* requiring systemic treatment.
ATCvet code	QJ01FA94
Pharmacotherapeutic group	Anti-infectives for systemic use
Applicant	Zoetis Belgium SA

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Introduction

On 25 July 2014, Zoetis Belgium SA submitted an application for an extension to the marketing authorisation for DRAXXIN to the European Medicines Agency (the Agency), in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 3 thereof. The rapporteur appointed to assess the application was C. Ibrahim, and the co-rapporteur C. Muñoz.

DRAXXIN (active substance: tulathromycin) was first authorised in the Community on 11 November 2003, and is available as a solution for injection for use in cattle (subcutaneous use) and pigs (intramuscular use) for the treatment and prevention of various infectious diseases.

This extension application is to add a new food-producing target species (sheep).

The indication proposed by the applicant is: "Treatment of infectious pododermatitis (foot rot) associated with *Dichelobacter nodosus* and *Fusobacterium necrophorum* sensitive to tulathromycin." The route of administration for sheep is intramuscular for a single dose of 2.5 mg/kg bw. The proposed withdrawal period for sheep meat and offal is 16 days.

On 8 September 2016, the CVMP adopted an opinion and CVMP assessment report.

On 9 November 2016, the European Commission adopted a Commission Decision granting the marketing authorisation for DRAXXIN.

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 18 July 2013) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The active substance tulathromycin is manufactured outside the EEA. The finished product is manufactured outside or inside the EEA. EU batch release is performed by Pfizer PGM, Pocé-sur-Cisse, France, or Zoetis Belgium SA, Louvain-la-Neuve, Belgium.

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

For all manufacturing sites, GMP compliance has been adequately confirmed and no additional GMP inspections are needed.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites were considered in line with legal requirements.

Part 2 - Quality

This is an application for an extension to the existing DRAXXIN marketing authorisation to add a new target species (sheep).

The application does not affect the quality part of the dossier, as no changes to the pharmaceutical form (solution for injection), strengths and presentations are made. No new data have been submitted, and cross-reference has been made to data that have already been submitted and assessed for previous application(s). This is considered acceptable.

Part 3 – Safety

This application is for addition of a new target species, sheep, for DRAXXIN 100 mg/ml solution for injection, which is already authorised for use in cattle and pigs. No data in addition to those already reviewed for the cattle and pig products have been provided as regards to the toxicology including reproductive toxicity, mutagenicity/carcinogenicity and on other effects. Given the nature of this application, this is considered acceptable.

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 3B and 4.

Tolerance in the target species of animal

See part 4.

User safety

The product is intended to be used in sheep at the same dosage regimen and route of administration as already authorised for cattle and/or pigs. The user safety assessment for DRAXXIN 100 mg/ml is considered applicable to the new target animal species, sheep, as no additional user risks arising from the

additional exposure due to the use in sheep are to be expected. A separate user safety evaluation specific for the intended use in sheep is therefore not necessary.

Consequently, the existing user safety precautions in the Summary of Product Characteristics (SPC) already agreed in relation to the use of the product in cattle and pigs, are equally applicable to the use in sheep; the precautionary measures proposed by the applicant are therefore sufficient to ensure that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

The CVMP concluded that the extension to add a new target species, sheep, does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

A new phase I environmental risk assessment (ERA) was provided for this extension according to the VICH guidelines. The Predicted environmental concentration for soil was calculated in accordance with VICH GL6 (Guideline on environmental impact assessment (EIAS) for veterinary medicinal products – phase I (CVMP/VICH/592/98-FINAL)) and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1). The predicted environmental concentration in soil (PEC_{soil}, initial = 4µg/kg) was less than 100 µg/kg. Consequently, no phase II assessment was requested.

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

Residues documentation

Pharmacokinetics

One well-described GLP study (Study No. 1545N-03-12-233) was provided to demonstrate plasma kinetics and excretion balance following a single intramuscular injection to three sheep at a dose of 2.5 mg [^{14}C]-tulathromycin/kg body weight, which is the intended dose. Raw data and representative LC/MS/MS chromatograms were presented. The reliability of the analytical methods used was demonstrated by in-test validation data.

Although three sheep showed slightly different plasma concentration profiles, the peak plasma radioactivity level occurred at 8 hours after administration and a continuous decline in total radioactivity was measured in all animals thereafter. Plasma radioactivity measurements were near background at day 49 post dose. The excretion pattern of total radioactive residue results was similar in the three sheep and nearly complete excretion of total radioactivity from sheep was shown.

The marker residue was demonstrated to account for 78% up to 95% of all residues in tissues, and consequently it can be accepted that no metabolic profiling in sheep has been conducted.

Depletion of residues

For the purpose of calculating withdrawal periods the depletion of the marker residue concentration was investigated in a marker residue study (Study 1541N-60-12-232) in ovine tissues (muscle, liver, kidney, fat and muscle at the injection site). Sheep (n=36) were treated with the recommended single intramuscular injection of 2.5 mg tulathromycin/kg bw and tissue residues were determined up to

49 days post application. A validated analytical method (LC-MS/MS) was available for the determination of the marker residue in sheep tissues (LOQ: 50 µg/kg in muscle and fat, 200 µg/kg in kidney, 300 µg/kg in liver). The design and conduct of the study was appropriate (GLP compliant) and all current requirements were taken into account.

Marker residues were highest at the injection site. At two days post-injection, mean tulathromycin residues were 5890 µg/kg and depleted to 3350 µg/kg after four days. Residues continued to deplete to 1330 µg/kg, 826 µg/kg, 361 µg/kg and 153 µg/kg after 7, 28, 35, and 42 days withdrawal. Residues remained approximately the same at 49 days withdrawal (170 µg/kg), which was the last time of tissue collection.

In liver, highest residue values were measured at 4 days after slaughter (up to 3800 µg/kg) and declined to concentrations below the LOQ at day 42. In kidney highest concentrations were measured at 2 days after slaughter (up to 2950 µg/kg) and declined to values below the LOQ in all animals at day 28. In fat residue concentrations declined from 413 µg/kg at 2 days after slaughter to concentrations below the LOQ in all animals at day 21.

MRLs

The MRL status of tulathromycin, the active constituent of DRAXXIN, in relation to sheep, is as follows:

Pharmacologically active substance	Marker residue	Animal species	MRL (µg/kg)	Target tissues	Other provisions	Therapeutic classification
Tulathromycin	(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-(dim ethylamino)- ß-D-xylohexopyranosyl]o xy]-1-oxa-6-azacyclopen tadecan-15-one expressed as tulathromycin equivalents	Ovine	450 250 5400 1800	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption.	Anti-infectious agents/ Antibiotics

In addition, the CVMP established an injection site residue reference value (ISRRV) of 6300 µg/kg for use in the derivation of withdrawal periods, as described in the draft CVMP draft Reflection paper on injection site residues: considerations for risk assessment and residue surveillance (EMA/CVMP/520190/2007-Rev.1).

The excipients of the intended product as listed in section 6.1 of the SPC (i.e. monothioglycerol, propylene glycol, citric acid (E330), hydrochloric acid, sodium hydroxide, water for injections) are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Analytical method

The analytical method for monitoring of residues of tulathromycin in sheep tissues was evaluated during the MRL evaluation and reviewed by the relevant European Union reference laboratory. The method was considered validated and adequate for monitoring of residues.

Withdrawal periods

For the withdrawal period calculations the marker residue levels in tissues were assessed against the respective MRLs and the total residues (corrected for ratios of marker/total residues) in a food basket including muscle from the injection site were compared against the ADI. In addition, the withdrawal period for the injection site alone was calculated against the ISRRV (injection site residue reference value).

For these calculations, which were based on the statistical approach according to the CVMP guideline "Approach Towards Harmonization of Withdrawal Periods" (EMEA/CVMP/036/95), the applicant used a SAS programme as in some tissues data from more than seven time points were available, which cannot be analysed using the standard WT1.4 programme. SAS codes used to calculate withdrawal periods have been provided and are considered acceptable.

Injection site tissue was the determining tissue for setting the withdrawal period, resulting in an overall withdrawal period of 16 days for meat and offal derived from sheep treated with DRAXXIN 100 mg/ml at a dosage of 2.5 mg/kg bw.

DRAXXIN is not authorised for use in animals producing milk for human consumption, and should not be used in pregnant animals which are intended to produce milk for human consumption, within 2 months of expected parturition.

Overall conclusions on the safety documentation

As this is an application for an extension to DRAXXIN already authorised for use in cattle and pigs, cross-reference has been made to the toxicology including reproductive toxicity, mutagenicity, carcinogenicity and on other effects, which have already been submitted and assessed. This is acceptable.

The user risk assessment report for DRAXXIN 100 mg/ml solution for injection for cattle and pigs is considered to be applicable to the new target species. The product does not pose an unacceptable risk to the user when used in accordance with the SPC. Appropriate warnings for the user are included in the product literature.

A new phase I environmental risk assessment was provided, and the extension to sheep is not expected to pose a risk for the environment when used according to the SPC.

A total residues study in sheep has demonstrated that the marker residue established for cattle and pigs is also appropriate for use in sheep. A residue depletion study in sheep has been provided. While a non-standard programme was used for withdrawal period calculation, the applicant has demonstrated the appropriateness of the method for the calculation of the withdrawal period.

A withdrawal period for sheep meat and offal of 16 days was established.

DRAXXIN is not authorised for use in animals producing milk for human consumption, and should not be used in pregnant animals which are intended to produce milk for human consumption, within 2 months of expected parturition.

Part 4 – Efficacy

This is an application for an extension to the existing DRAXXIN marketing authorisation to add a new target species (sheep). The initially proposed indication was: "Treatment of infectious pododermatitis foot rot associated with *Dichelobacter (D.) nodosus* and *Fusobacterium (F.) necrophorum* sensitive to tulathromycin." The proposed route of administration is intramuscular for a single dose of 2.5 mg/kg bw.

Pharmacodynamics

Tulathromycin is a semi-synthetic, 15-membered ring macrolide triamilide. Like other macrolides, tulathromycin inhibits essential protein biosynthesis by binding to bacterial 50S ribosomal subunits. It acts by stimulating the dissociation of the peptidyl-tRNA from the ribosome during the translocation process. The blocking of the protein synthesis confers a bacteriostatic, time-dependent effect on susceptible pathogens.

The *in vitro* antimicrobial spectrum of activity of tulathromycin includes gram-positive and gram-negative bacterial pathogens as well as *Mycoplasma spp*.

However, there are no MIC data of tulathromycin in regard to ovine foot rot target pathogens reported in the published literature submitted, and only limited MIC data are available for other macrolides. These data indicate good susceptibility of *D. nodosus* to erythromycin, spiramycin and tylosin; but considerably higher MIC values were reported for *F. necrophorum*.

In one proprietary MIC study, the *in vitro* activity of tulathromycin was determined in such low numbers of target pathogens that comprehensive MIC distribution profiles could not be established. A further MIC study was provided for the target pathogen *D. nodosus*. Based on the total number of strains tested, the applicant derived a bi-modal distribution profile of *D. nodosus* with MIC_{90} of 0.25 µg/ml for the wild-type population. However, the CVMP considered the total number of isolates tested (n=45) insufficient to establish a reliable MIC distribution profile of *D. nodosus* towards tulathromycin, and to determine valid MIC_{90}.

Due to the limited MIC data and poor recovery rate of *F. necrophorum* in the pivotal field study, the applicant removed this pathogen from the proposed indication.

Development of resistance

Regarding the risk to public health, an extensive Microbiology Safety Expert Report for DRAXXIN 100 mg/ml following the requirements of VICH Guideline 27 was provided. From the report it can be concluded that the line extension application in sheep is unlikely to give considerable rise to public (human) health concerns.

With regard to animal health, there are no data available which would indicate a shift in susceptibility of already granted target pathogens to tulathromycin since the first authorisation of DRAXXIN in 2003. However, no conclusion can be drawn in regard to the new target species, sheep, as only limited data are available for the *in vitro* activity of tulathromycin in the target pathogen *D. nodosus*. The risk of resistance development with regard to the proposed new target animal species (sheep) can therefore not be adequately assessed.

Pharmacokinetics

The pharmacokinetics of tulathromycin in sheep is well described with regard to absorption, volume of distribution, metabolism, excretion and bioavailability in a GLP compliant study in sheep (1542N-60-12-231).

Tulathromycin is rapidly absorbed following the recommended dose of 2.5 mg/kg intramuscular with plasma peak at 15 min. A mean peak concentration of 1.19 µg/ml was observed and the terminal elimination half-life was 69.7 h. Total body clearance was estimated to be 0.542 l/(h•kg) and the apparent steady state volume of distribution was 31.7 l/kg. Bioavailability of tulathromycin was found to be greater than 100% indicating complete absorption after intramuscular injection. Protein binding of tulathromycin in sheep was determined in the range of 60-75%. As in other animal species, tulathromycin is not extensively metabolised in sheep and is principally eliminated unchanged in urine and faeces.

Dose determination/justification

No placebo-controlled dose finding or dose confirmation studies were provided. The applicant justified the proposed dose by a comparison of pharmacokinetics in cattle and sheep, comparison to another macrolide antimicrobial authorised for sheep, and by PK-PD considerations based on MIC data for *D. nodosus* and a study on the determination of tulathromycin marker residue concentrations in interdigital tissue of treated sheep (A443R-US-15-046). In addition, a field study (see below) was conducted investigating the efficacy of a single intramuscular dose of either 1.25 mg/kg or 2.5 mg/kg bodyweight of tulathromycin (as compared to a positive control). Based on the data from the field study, the applicant selected the higher tulathromycin dose as the recommended treatment dose.

However, the justification and data are not conclusive.

Extrapolation of the tulathromycin pharmacokinetic profile from cattle to sheep is limited, as only some but not all pharmacokinetic parameters are comparable. Further on, comparable pharmacokinetics of antimicrobials of the same class do not provide evidence that clinical efficacy can be achieved when products are used in similar dose ratios, particularly as dose proportionality could not be demonstrated for tulathromycin in sheep.

The pharmacokinetic/pharmacodynamic (PK/PD) analysis is not considered scientifically sound to justify the recommended treatment dose.

The MIC data presented for the target pathogen *D. nodosus* were determined from a limited number of strains (45) and, hence, do not allow reliable conclusion on the modality of the *in vitro* MIC distribution profile and to establish valid MIC_{90} value.

Tulathromycin marker residue concentrations in interdigital tissues from sheep injected intramuscularly with DRAXXIN were determined following a single i.m. dose of 1.25 mg/kg and 2.5 mg/kg bw, respectively. Tulathromycin marker residue interdigital tissue concentrations determined on day 2, 7 and 14 after administration in 8 animals showed a clear dose response and depleted gradually from D2 to D14. In interdigital tissue samples from treated animals the mean tulathromycin marker residue concentrations at day 2, 7 and 14 were 116 µg/kg, 73 µg/kg; and 33 µg/kg (1.25 mg/kg bw) and 227 µg/kg, 110 µg/kg and 47 µg/kg (2.5 mg/kg), respectively. After conversion to µg/ml (= µg/kg/1000) concentration means were compared with the MIC_{90} determined for *D. nodosus* . It remains unclear if and to what extent tulathromycin marker residue concentrations are representative for the presence of the active parent compound in the target tissue. After the recommended treatment dose mean tulathromycin equivalent residue tissue concentrations of 0.227 µg/ml (D2), 0.11 µg/ml (D2), and 0.047 µg/ml (D14)

were determined, i.e. concentrations below the MIC_{90} value of 0.25 µg/ml, which was used by the applicant in the PK/PD considerations. No data were available for time points before D2.

Sub-inhibitory tulathromycin concentrations may prevail and thus, could lead to an increased risk of resistance. Considering also the bacteriostatic and time dependent activity of macrolides, the concentration-time profiles in the interdigital target tissue are not convincing to justify the proposed dose of 2.5 mg/kg bw for treatment of ovine foot rot.

In addition, irrespective of major shortcomings of the pivotal clinical field study, the results from this study testing doses of 1.25 and 2.5 mg/kg bw did not show significant differences in regard to efficacy or tolerance. Hence, the recommended treatment dose of 2.5 mg/kg bw is also not justified from a clinical perspective.

Target animal tolerance

The local tolerance of DRAXXIN 100 mg/ml solution for injection was investigated in one GLP compliant study on sheep (16 females and 16 males) aged approximately 7 months after intramuscular injection of the recommended dose of 2.5 mg tulathromycin/kg bw into the neck, corresponding to 0.025 ml/kg bw. The actual dose range of the test material was 0.9–1.4 ml per animal. Injection sites and surrounding areas were clinically assessed once daily up to day 28 post application and no abnormal findings were recorded. Macroscopic and microscopic examination of the injection sites were performed on days 3, 7, 14 and 28 post application and revealed only minimal transient irritant effects at the injection site in individual animals that were related to the procedural effect of injection rather than to a toxicological or pharmacological effect of the test item.

The pivotal target animal safety study was conducted in compliance with GLP and following the recommendations of VICH GL 43 (Guideline on target animal safety for veterinary pharmaceutical products). DRAXXIN 100 mg/ml solution for injection was intramuscularly administered to lambs (16 females, 16 males) aged 6 weeks or more at doses corresponding to 0, 1, 3 or 5 times the recommended label dose of 2.5 mg/kg bw, at three occasions, one week apart. The injection of DRAXXIN into the neck induced in almost all animals immediate clinical reactions related to discomfort or pain. All signs were mild and transient and resolved within less than a minute. No systemic adverse effects were observed for body weight, food consumption and clinical pathology that could be related to treatment with DRAXXIN. Macroscopic and microscopic post mortem examinations revealed no abnormal findings.

The CVMP concluded that the intramuscular injection is generally well-tolerated in sheep; appropriate information on immediate signs of discomfort observed in lambs following intramuscular injection of the recommended treatment dose is included in the SPC, section 4.6.

Field trials

One GCP compliant multi-centre European clinical field study (5143C-85-12-186) was conducted in 2013 in commercial sheep farms in France, Spain and the United Kingdom. The study population consisted of 477 sheep of different breeds, mainly females, which were kept in-house or on pasture. Groups of sheep with clinical signs of active foot rot (characteristic foul smell, exudate (not obligatory), inflammatory lesions of the interdigital space in at least one foot, and lameness) were included in the study and treated with DRAXXIN 100 mg/ml at a single intramuscular dose of either 1.25 mg/kg or 2.5 mg/kg bodyweight, or an injectable solution containing tilmicosin for positive control at the recommended dose. The efficacy of DRAXXIN was determined based upon non-inferiority to tilmicosin in terms of treatment success rates

on day 14 after treatment (primary endpoint); a non-inferiority margin of 15% and a 0.025 (on-sided) level of significance was used. Secondary clinical endpoints included clinical success rates at different time points up to day 28 after treatment, and relapse rates on day 21 and 28. Prior to treatment two swabs (one for bacteriological culture and one for PCR) were randomly taken from half of the study animals.

Non-inferiority to the reference product containing tilmicosin (primary endpoint) could not be demonstrated using the initially planned statistical method, but only *a posteriori* with a re-analysis using another statistical approach, which was not specified in the study protocol. In principle, this is not in line with the relevant CVMP guideline on Statistical principles for veterinary clinical trials (CVMP/EWP/81976/2010). However, there was a strong correlation between estimators of proportions when calculating the variance of the difference in proportions. This led to an overestimation of the variance in the original analysis that was accounted for in the revised analysis. Therefore, this re-analysis was accepted.

The overall treatment success rates, determined on day 14 after treatment, for DRAXXIN at a dose of 1.25 mg/kg or 2.5 mg/kg were 77.3% (1.25 mg/kg) and 84.4% (2.5 mg/kg), respectively, compared to 82.2% for the tilmicosin group. Following the revised analysis, this led to 95% confidence intervals [-24.1%; 14.1%] (DRAXXIN 1.25 mg/kg versus tilmicosin) and [-14.0%; 18.2%] (DRAXXIN 2.5 mg/kg versus tilmicosin) for the differences of success rates, thus non-inferiority of DRAXXIN at the higher dose could be demonstrated mathematically. However, since the assessment of the primary endpoint at least in part was subjective, and since study sites were included where the reference product showed almost no or only moderate efficacy, the differences between treatment groups were biased towards smaller differences. Therefore, the internal validity of the study was not given and, hence, the non-inferiority of DRAXXIN with regard to success rates was considered not valid.

Non-inferiority of DRAXXIN at either dose to tilmicosin could be demonstrated for relapse rates on day 21 and 28 (secondary endpoints): on day 21, relapse rates were 2.4% and 2.7% for DRAXXIN 1.25 mg/kg bw and 2.5 mg/kg bw, respectively, compared to 5.8% for the tilmicosin group. On day 28, relapse rates were 8.1% and 3.6% for DRAXXIN 1.25 mg/kg bw and 2.5 mg/kg bw, respectively, compared to 10.4% for the tilmicosin group.

Success rates were highly variable across study sites: the ranges were 0–100% in both DRAXXIN groups and 20.8%–100% in the tilmicosin group. The applicant listed several possible causes for this variability, the most important one possibly the presence of differences between environmental conditions (wet pastures, rainfall). However, this high variability makes it questionable if the study results could be generalized for the overall target population.

Sheep were enrolled into the study based on typical clinical criteria for foot rot (lesions of the claws, presence of smell and exudate, lameness). The proposed indication "naturally occurring foot rot" was revised to "infectious pododermatitis (foot rot)", taking into account that clinical foot rot and virulent strains of the *D. nodosus* were determined (clinical/ molecular biological diagnoses determined in the field study).

The presence of the target pathogens, *D. nodosus* and *F. necrophorum* was confirmed by species specific PCR at all study sites. Results from bacteriological cultivation were poor, only 7 strains of *D. nodosus* and 14 strains of *F. necrophorum* strains could be determined from a total of 229 swabs prior to treatment, but none of the *D. nodosus* strains and only 5 of the *F. necrophorum* strains could be re-confirmed. An additional PCR (*aprV2/B2* PCR) and subsequent DNA sequencing confirmed that all *D. nodosus* positive probes (174/232=75%) contained virulent strains. Although PCR results *per se* do not confirm a viable infection, the presence of virulent *D. nodosus* strains at all study sites in combination with typical clinical

signs demonstrated that animals enrolled in the study were affected with foot rot associated with *D. nodosus*.

Based on the poor recovery rate of *F. necrophorum* in the field study and the limited MIC data, the applicant withdrew the claim for this target pathogen in this application.

Based on the data presented the applicant selected the higher DRAXXIN dose as recommended treatment dose, justified by the numerically higher success rates on day 14 and lower relapse rates on day 28 compared to the lower dose. However, the differences between doses are indeed very small and not statistically significant probably because of the variability of success rates between the study sites. In the absence of dose determination/ confirmation studies and the non-conclusive PK-PD analysis this is considered a weak justification.

DRAXXIN at both doses was well tolerated in sheep as no adverse events related to treatment were recorded in any of the animals.

Overall conclusion on efficacy

Pharmacodynamics:

Based on the very limited MIC-data and poor recovery of *F. necrophorum* from the pivotal field study, the applicant deleted this target pathogen from the claimed indication. *In vitro* susceptibility of *D. nodosus* was assessed based on a total number of 45 epidemiologically unrelated strains collected from sheep suffering from foot rot. The number of strains tested is insufficient to conclude on the modality of the MIC distribution profile and to establish valid MIC_{90} value for this target pathogen.

Resistance development:

It is unlikely that the extension application for sheep will give considerable rise to public human health concerns. However, with regard to animal health, no clear conclusion can be drawn, as sparse data are available for the *in vitro* activity of tulathromycin in target pathogens.

Pharmacokinetics:

The pharmacokinetics of tulathromycin in sheep was sufficiently described with regard to absorption, volume of distribution, metabolism, excretion and bioavailability.

Dose finding/justification:

Dose justification was mainly based on a PK/PD analysis, using MIC_{90} data for *D. nodosus* and pharmacokinetic findings from a study on the determination of tulathromycin marker residue concentrations in healthy sheep after single intramuscular dose of 2.5mg/kg bw. However, in view of shortcomings in the PK/PD calculations as well as the inconclusive results of the clinical field study, the dose justification is considered not to be scientifically sound.

Target animal safety:

DRAXXIN proved to be well tolerated in sheep in a target animal safety study at dosages up to 5 times the recommended therapeutic dose. After intramuscular injection at the neck with the recommended dose of 2.5 mg/kg bw, transient clinical signs of discomfort or pain at the injection site were observed. Respective information is included in the SPC and other product literature.

Clinical studies:

The efficacy of DRAXXIN in the treatment of pododermatitis (foot rot) associated with *D. nodosus* at a single intramuscular dose of either 1.25 mg/kg or 2.5 mg/kg bodyweight was investigated in a European GCP-compliant multicentre controlled clinical field study.

Non-inferiority of DRAXXIN at the recommended treatment dose compared to the positive comparator product (tilmicosin) as regards to the primary endpoint "success rate" was demonstrated only after a revised statistical analysis *a posteriori*. Although the revised statistical analysis was accepted from a mathematical point of view, the non-inferiority of DRAXXIN with regard to success rates was considered not conclusive due to lack of internal validity of the clinical field study. In addition, the high variability of the success rates at the different study sites (0-100%) put the representativeness of the study outcome into question.

Part 5 – Benefit-risk assessment of the initial application

Introduction

This extension application for DRAXXIN (tulathromycin) concerns the addition of a new target species, sheep. DRAXXIN is already authorised for use in cattle and pigs as a solution for injection (intramuscular or subcutaneous use, respectively) for the treatment and prevention of various infectious diseases.

The proposed indication for sheep is "Treatment of pododermatitis (foot rot) associated with *Dichelobacter nodosus*". The proposed route of administration is intramuscular for a single dose of 2.5 mg/kg bw. The proposed withdrawal period for sheep meat and offal is 16 days.

Benefit assessment

Direct therapeutic benefit

The benefit of DRAXXIN would be its efficacy in the treatment of ovine pododermatitis (foot rot) associated with *D. nodosus*, which was investigated in one GCP-compliant multicentre controlled clinical field study.

However, due to major shortcomings of this pivotal field study efficacy of DRAXXIN was not sufficiently demonstrated. In addition, the preclinical data set was not sufficient to characterise the susceptibility of the target pathogen *D. nodosus* against tulathromycin and to justify the recommended treatment dose

Additional benefits

DRAXXIN would increase the range of available treatment possibilities in sheep.

Risk assessment

Quality:

The strength and pharmaceutical form remain as authorised, and cross-reference is made to data that have already been submitted and assessed as satisfactory for the product.

For the target animal:

DRAXXIN is well tolerated in sheep. Local signs of discomfort were observed following intramuscular injection, which were mild and transient in nature.

For the environment and the user:

The product is not expected to pose a risk for the user or the environment when used as proposed in the SPC and other product literature.

For the consumer:

A withdrawal period of 16 days for sheep meat and offal has been established and is considered adequate to ensure consumer safety. DRAXXIN is not authorised for use in animals producing milk for human consumption.

Resistance:

No conclusions can be drawn on the risk of development of resistance in the target pathogen, as too limited data are available.

Risk management or mitigation measures

Appropriate warnings had been proposed in the SPC and other product literature. The re-start of the PSUR cycle would be appropriate to ensure more frequent pharmacovigilance monitoring if a new target species is added.

Evaluation of the benefit-risk balance

The benefit of DRAXXIN for the intended use in sheep is considered inconclusive, as the product has not been shown to be efficacious in the treatment of ovine pododermatitis (foot rot) associated with *D. nodosus.* Based on the data presented, the overall benefit-risk is deemed negative.

Conclusion of the initial application

Based on the CVMP consideration and review of the data on quality, safety and efficacy, the CVMP considers that the application for this extension application (sheep) for DRAXXIN is not approvable since major concerns on the efficacy remain, i.e. it is not possible to conclude on the MIC distribution profile, the risk of development of resistance in the target pathogen, the therapeutic dose and the clinical efficacy. Therefore, the data do not satisfy the requirements for an authorisation set out in the legislation (Commission Regulation (EC) No 1234/2008 in conjunction with Directive 2001/82/EC.

The CVMP therefore considers by majority that the overall benefit-risk balance is negative and, therefore, recommends the refusal of the extension to the terms of the marketing authorisation for the above mentioned medicinal product.

Final assessment after re-examination

Following the negative CVMP opinion on 19 May 2016 for the extension application for DRAXXIN solution for injection for a new target species (sheep), Zoetis Belgium SA requested the re-examination of the CVMP opinion under Article 34(2) of Regulation (EC) 726/2004. On request of the applicant, an ad-hoc expert group (AHEG) meeting was held on 1 September 2016, which was also attended by the applicant.

Grounds for refusal 1 (MIC data)

The applicant considered that a total number of 45 isolates originating from six different countries (Norway, Germany, UK, Spain, Ireland and Slovenia) and 43 different farms (i.e. 43 different outbreaks) was representative of the EU area, scientifically justified and resulting in a meaningful MIC distribution; also, all isolates originated from sheep clinically affected by foot rot, and recovered within 5 years from initial submission. The applicant therefore considered that all the requirements outlined in the CVMP guideline on the Demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001) were therefore fulfilled. MIC determinations were performed by one of the few laboratories with sound experience in this particular target pathogen (*Dichelobacter (D.) nodosus*) and by the CLSI preferred method for anaerobes, i.e. agar microdilution.

In the published literature, only limited MIC data are available for macrolides (erythromycin, spiramycin, tylosin) indicating in general good susceptibility of *D. nodosus*; but considerably higher MIC values for *Fusobacterium (F.) necrophorum*. Data include also a study (A641Z-GB-14-023) on the MIC determination of tulathromycin against *F. necrophorum* (final number of isolates: 7) and *D. nodosus* (final number of isolates: 8). Due to the limited MIC data and poor recovery rate of *F. necrophorum* in the pivotal field study, the applicant withdrew this pathogen from the proposed indication.

For *D. nodosus,* a study (A641Z-GB-15-056) including 45 *D. nodosus* isolates was included in the dossier. Based on the results for this study, the applicant proposed a bi-modal distribution profile of *D. nodosus* with a MIC_{90} of 0.25 µg/ml for the wild-type population (see table 1).

Tulathromycin MIC values (µg/ml):	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**
Spain (n=4)		1		2		1							
Germany (n=8)		7						1					
UK (n=18)		9		6				3					
Norway (n=15)		9		6									
TOTAL (n=45)		26		14		1		4					

During the initial assessment, the CVMP considered the total number of isolates tested (n=45) as insufficient to establish a reliable MIC distribution profile of *D. nodosus* towards tulathromycin, and to determine valid MIC_{90}.

The Ad Hoc Expert Group (AHEG) was asked if with the withdrawal of *F. necrophorum* as a target pathogen, *D. nodosus* would be considered acceptable as a representative pathogen for foot rot in sheep, and if the MIC data for the target pathogen were considered sufficient taking account of the requirements of the guideline on the demonstration of efficacy for veterinary medicinal products containing antimicrobial substance (EMEA/CVMP/627/01-FINAL).

The AHEG considered that the virulent strain of *Dichelobacter nodosus (vir)*, defined by the gelatinase gel (GG) test or the aprV2-gene, is the main pathogen inducing severe (virulent) foot rot in sheep, while the

benign strain of *D. nodosus (bgn)* may only cause moderate symptoms (benign foot rot) in sheep. Bacteriological data and clinical signs confirmed the presence of *D nodosus (vir)* in the field studies. However, there is little information on whether the 45 isolates tested *in vitro* were of the virulent or benign strains to allow clear conclusions on the MIC_{90}. It is recommended that appropriate information should be put in the product literature that DRAXXIN should only be used for the treatment of virulent/severe foot rot caused by *D. nodosus* in the early stages of disease, in combination with appropriate management strategies. Antibiotic treatment of chronic foot rot is not considered appropriate. It is likely to be extremely difficult to obtain a collection of more than 100 epidemiologically unrelated *D. nodosus* isolates, hence the current number of isolates is deemed sufficient as long as MIC data are interpreted with caution.

The AHEG pointed out that the use of macrolides in veterinary medicines should in general be carefully considered, and avoided in cases where the disease in question would self-cure without antimicrobials. Therefore, use of DRAXXIN should only be considered as a treatment option of the severe (virulent) form of foot rot in sheep.

The CVMP agreed that *Dichelobacter nodosus (vir),* defined by the gelatinase gel (GG) test or the aprV2-gene, should be considered as the target pathogen for foot rot in sheep. Two forms exist, a virulent strain and a benign strain, and severe foot rot requiring treatment is usually associated with the presence of the virulent strain of *D. nodosus*. *Fusobacterium necrophorum* is regarded to be ubiquitous.

The AHEG had considered that a MIC_{90} could not be established as it was not clear if the strains tested belonged to the virulent or benign type, and if MIC values were equally distributed between these types in the bi-modular distribution model of the applicant, and also, it was not clear if strains are epidemiologically unrelated, as recommended by the CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1). However, the applicant provided the CVMP with an analysis of the virulence status of the bacterial strains used in the pre-clinical data setting the MIC values, which confirmed that 34 isolates belonged to the virulent type and they possess MICs over the whole range of values 0.06 to 4 µg/ml. The MIC of the benign isolates show MIC´s at the lower end (0.06-0.25 µg/ml). The strains used were not epidemiologically related.

The CVMP took the recommendation from the AHEG into account and agreed that treatment success of severe foot rot associated with *D. nodosum (vir),* defined by the gelatinase gel (GG) test or the aprV2-gene, is closely related to the time in the disease; any treatment should therefore be initiated at an early stage of the disease.

Conclusions on grounds for refusal 1:

The CVMP took note of the recommendations by the AHEG, and considered an additional analysis of data previously provided by the applicant in regard to the virulence status of the *D. nodosus* strains used to calculate the MIC_{90} data. The CVMP concluded that the data provided by the applicant were sufficient to describe the susceptibility for *Dichelobacter nodosus (vir),* defined by the gelatinase gel (GG) test or the aprV2-gene. Forty out of 45 strains possess MIC´s in the range 0.06 to 0.25 µg/ml.

Grounds for refusal 2 (resistance development)

The applicant argued that it was not likely that this extension would increase development of resistance causing a risk for public health.

The AHEG considered that the risk of development of resistance in *D. nodosus* to tulathromycin has not been sufficiently addressed.

The CVMP agreed that there is currently no indication that DRAXXIN used in sheep might cause a public health problem when used in line with SPC recommendations. In the absence of clearly established MIC data for the virulent strain of *D. nodosus*, no clinical breakpoint has currently been established, and consequently no final conclusions on resistance towards the target pathogen could be made. However, the Committee considered that the clinical efficacy in the field study indicated adequate susceptibility of the virulent strain of *D. nodosus*.

However, the applicant indicated that cross-resistance to tilmicosin might be possible, and adequate reference to this is made in the product information.

Grounds for refusal 3 (dose)

The applicant considered that a single treatment dose of 2.5 mg tulathromycin/kg b w was robust, and derived in a scientifically justified manner. The proposed dose was justified by a comparison of pharmacokinetics in cattle and sheep, comparison to another macrolide antimicrobial authorised for sheep, and by PK-PD considerations based on tulathromycin concentrations in interdigital tissues *(A443R-US-15-046).* In addition, a field study (5143C-85-12-186) was conducted investigating the efficacy of a single intramuscular dose of either 1.25 mg/kg or 2.5 mg/kg bodyweight of tulathromycin (as compared to a positive control).

In the PK-PD study (*A443R-US-15-046)*, tulathromyin concentrations in interdigital tissues were determined following a single intramuscular dose of 1.25 mg/kg or 2.5 mg/kg bw, respectively. Tulathromycin showed a clear dose response and depleted gradually from D2 to D14. Sampling and analysis was not performed before Day 2 (that is, tissue concentrations between treatment and Day 2 are not documented). In interdigital tissue samples from treated animals the mean tulathromycin concentrations at day 2, 7 and 14 were 116 µg/kg, 73 µg/kg, and 33 µg/kg (1.25 mg/kg bw), and 227 µg/kg, 110 µg/kg and 47 µg/kg (2.5 mg/kg bw), respectively. Even at the highest dose tulathromycin concentrations in interdigital tissues were below the proposed MIC_{90} value of 0.25 µg/ml.

The CVMP reassessed the data, and considered that it remains unclear if and to what extent tulathromycin marker residue concentrations in the skin would reflect the concentration at the infection site, as skin concentration is a composite of extra- as well as intracellular drug concentrations in a variety of cell types.

As stated in the CVMP Guideline on the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001), a PK-PD relationship should be confirmed by dose confirmation and clinical field studies. The guideline suggests using experimentally induced infections for dose determination, and preferably controlled studies using naturally infected animals for dose confirmation studies. However, in the absence of a robust infection model, the applicant only submitted a single dose confirmation study, using a positive-controlled European GCP-compliant multicentre clinical field study involving 477 animals (5143C-85-12-186), in which two different doses of tulathromycin (2.5 mg/kg and 1.25 mg/kg bodyweight) were tested in naturally infected sheep that displayed lesions and lameness (scores of 2-4 on a scale of 0 (normal) to 4 (severe interdigital dermatitis lesions) or 6 (will not stand or walk), respectively). Although no statistical difference could be demonstrated between a dose of 1.25 mg/kg bw and 2.5 mg/kg bw, the applicant selected the higher tulathromycin dose as the recommended treatment dose.

The AHEG was asked if it would be possible to set clinical break points for tulathromycin for the pathogen *D. nodosus* based on the MIC data and the provided pharmacokinetics of tulathromycin in sheep; and the AHEG considered that there is not sufficient current knowledge available to conclude on this question. The AHEG was also asked if the available PK/PD data were considered adequate to underpin the efficacy of the proposed dose of 2.5 mg tulathromycin/kg for the treatment of foot rot in sheep associated with *D. nodosus*. The AHEG considered the data not adequate since there is no clear link between the clinical efficacy and the pharmacokinetic data.

The CVMP considered that efficacy of a veterinary medicinal product is usually demonstrated by a number of different assessments, including PK/PD determination, determination of dose (including use of a negative control group), confirmation of dose and clinical field trials.

It is accepted that the interdigital skin concentrations of tulathromycin indicate that the drug accumulates in this organ but the total skin tissue concentration are insufficient to be used to establish the PK/PD relationship. It was confirmed by the applicant at the AHEG meeting that PK/PD in isolation does not provide pivotal data for dose justification in this application (which relies instead on an EU pivotal field study).

Conclusions on grounds for refusal 3:

Taking into consideration the detailed grounds for the request for re-examination by the applicant, and the recommendations by the AHEG, the reassessment of the data showed that parts of the concerns previously raised by the CVMP remained. The CVMP confirmed its previous position that the data provided could not be used for PK/PD calculations establishing the proposed therapeutic dose.

However, using PK/PD calculations for the finding of a dose for the treatment of ovine foot rot is known to be problematic and not indicative of efficacy.

The CVMP therefore considered that based on the result of the field study, the proposed single intramuscular dose of 2.5 mg tulathromycin/kg bw could be considered appropriate for treatment of foot rot in sheep (see below).

Grounds for refusal 4 (efficacy)

The pivotal EU field study was well designed, and non-inferiority of DRAXXIN to the positive control, tilmicosin, was adequately shown, even in suboptimal field conditions (rain, no provision of dry environment or other additional measures). The applicant also considered that the field study did not suffer from "lack of internal validity", and thus the differentiation between "mathematical non-inferiority" and "clinical non-inferiority" was not supported. The applicant considered that all the requirements outlined in relevant CVMP guidelines were fulfilled (demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001), statistical principles for veterinary clinical trials (CVMP/EWP/81976/2010)).

The efficacy of DRAXXIN was determined in a clinical field trial based upon non-inferiority to tilmicosin in terms of treatment success rates based on the scores for "lesions and lameness on day 14 after treatment" (primary endpoint); a non-inferiority margin of 15% and a 0.025 (one-sided) level of significance was used. A sheep was considered recovered from foot rot (clinical cure/treatment success) when all lesions present at the time of inclusion were no longer active on Day 14: no foul smell or exudate was present (although the tissue might not have completely returned to normal). In addition, animals should no longer be lame (lameness score = 0). Secondary clinical endpoints included clinical success

rates at different time points up to day 28 after treatment, and relapse rates on day 21 and 28. Prior to treatment two swabs (one for bacteriological culture and one for PCR) were randomly taken from half of the study animals.

Non-inferiority to the reference product (primary endpoint) could initially not be demonstrated using the planned statistical method, but only *a posteriori* with a re-analysis using another statistical approach. The revised method of the statistical analysis was in principle acceptable, from a mathematical point of view; and showed overall treatment success rates, determined on day 14 after treatment, for DRAXXIN at a dose of 1.25 mg/kg or 2.5 mg/kg bw were 77.3% (1.25 mg/kg) and 84.4% (2.5 mg/kg), compared to 82.2% for the tilmicosin group.

However, the CVMP questioned the internal validity of the study, as the assessment of the primary endpoint was subjective (at least in part), and success rates at the different study sites showed a high variability (see table below) putting the representativeness of the study outcome into question. Some study sites were included where the reference product showed almost no or only moderate efficacy and the differences between treatment groups were biased towards smaller differences. Therefore, CVMP concluded initially that the internal validity of the study was not given and, hence, the non-inferiority of DRAXXIN with regard to success rates was considered not valid.

	Success rates D 14			**Lower confidence limits**	
	T_{01} Micotil 10 mg/kg	T_{02} DRAXXIN 1.25 mg/kg	T_{03} DRAXXIN 2.5 mg/kg	T_{02} vs T_{01}	T_{03} vs T_{01}
FR01	89% (8/9)	100% (9/9)	100% (10/10)	-9.4%	-9.4%
FR02	100% (11/11)	100% (12/12)	100% (12/12)	0%	0%
FR03	100% (11/11)	100% (10/10)	100% (11/11)	0%	0%
SP01	83% (24/29)	97% (29/30)	97% (29/30)	-1.3%	-1.3%
SP02	95% (38/40)	72% (28/39)	90% (36/40)	-38.9%	-16.5%
SP03	53% (8/15)	44% (7/16)	75% (12/16)	-44.6%	-11.3%
UK01	21% (5/24)	24% (6/25)	23% (6/26)	-20.2%	-20.7%
UK02	67% (4/6)	50% (3/6)	0% (0/6)	-71.7%	-104.4%
UK03	33% (2/6)	0% (0/7)	33% (2/6)	-71.1%	-53.3%
France	97%	100%	100%	-9.8%	-3.0%
Spain	83%	75%	90%	-20.2%	-4.1%
UK	31%	24%	21%	-44%	-29.4%
Total	74%	68%	75%	-16.2%	-8.1%

The AHEG was asked if they would consider the clinical efficacy study (5143C-85-12-186) as sufficiently scientifically robust to demonstrate that DRAXXIN when administered to sheep at a dose of 2.5 mg tulathromycin/kg is effective in the treatment of foot rot associated with *D. nodosus.* In particular, it should be considered if the study design was appropriate, if the test population and the conditions under which the study was conducted was representative of the target population, if the sample size was appropriate, if the approach to efficacy assessment, including the choice of primary efficacy endpoints was appropriate, and if the final statistical analysis was considered appropriate.

The AHEG agreed that in general, the study design is acceptable, as this was a multicentric controlled study performed in three countries with different environmental conditions, in which the sites are

considered as random effects in the analyses, meaning that this study includes a sample of sites (countries) representative of the management systems, climates, ecology of bacteria of all the countries where the product is intended to be used. Inclusion criteria were the clinical signs of severe foot rot, lameness and lesion scores, and bacteriological data (presence of *D. nodosus,* by PCR) on the majority of animals, which gives sufficient reliability that the diagnosis of foot rot is correct, and the number of animals (n=477 sheep) was large enough to carry out this study. The primary clinical endpoints (healing of lesions and lameness) and methodology (difference in treatment success rates between treatment groups at day 14) were appropriate.

Regarding the concerns raised about the absence of a post-treatment bacteriological examination, the AHEG considered that elimination of the primary pathogen from the feet could not be expected, as the treatment was not performed as part of an elimination program. If the affected animals were not moved to clean housing or pasture after treatment, reinfection from the surroundings is likely, and bacteriological examinations to show reduction in bacterial load would therefore not be very informative; absence of a bacteriological examination at the end of the field trial was therefore considered acceptable.

The variability in treatment efficacy between study sites was considered acceptable for a multi-site study with differences in management, climate etc. across farms and countries. However, data from the UK studies had some shortcomings, including a higher amount of loss of data, and also had more serious cases (higher clinical scores) of foot root at the beginning of the trials, and lower efficacy rates than in Spain and France. The AHEG also considered that the risk of development of resistance in *D. nodosus* to tulathromycin was not sufficiently considered by the applicant, in relation to the limited efficacy results in the UK trials. However, the results were equally seen in the comparator group.

As other factors, such as climate, housing, management, or breed may affect the efficacy of antimicrobial treatment of ovine foot rot, and treatment also appears to be less efficient in animals with severe symptoms; reference to this should be made in the SPC.

The assessment of non-inferiority on treatment day (Day 14) was considered acceptable, and the statistical analysis appropriate. The AHEG considered that the field study showed that DRAXXIN at a dose of 2.5 mg tulathromycin/kg bw is non-inferior to tilmicosin in the treatment of severe (virulent) foot rot in sheep at Day 14 with a 15% margin of non-inferiority. However, at a margin of 10% non-inferiority could not be demonstrated. The AHEG considered that the margin of non-inferiority of 15% was not well justified, and expressed some doubts about the selected limit because it implies room for a lower treatment success.

The CVMP agreed with the AHEG that the design of the clinical field study is acceptable in general, and that the three countries selected for the study are considered representative of various climates in EU, which appear to be a major factor in treatment success.

The CVMP agreed that the margin of non-inferiority of 15% was not well-justified; however, no specific value has been set in relevant CVMP guidelines previously identified, and it also appears that the value may depend on the study conditions, i.e. selected endpoints. The CVMP also considered that the non-inferiority margin took into account the self-cure rate for foot rot and the treatment success rate for the control product. Currently, there is no explanation for the poor treatment success in UK, but weather conditions and the late stage of disease may have had some influence, which would need to be reflected in the product literature.

Although the efficacy results varied between countries, the CVMP considered that overall, the applicant demonstrated that tulathromycin in a dose of 2.5 mg/kg bw is effective the in treatment of foot rot. However, treatment should be accompanied by appropriate herd management options, such as

moving/keeping treated animals in a dry environment (housing or pasture). As the study only showed limited success in sheep with more severe clinical signs (indicating treatment at a later stages of disease), treatment with DRAXXIN of sheep with chronic foot rot is not indicated. Also, weather conditions (wet) and breed seem to influence treatment success.

Conclusions on grounds for refusal 4:

Taking into consideration the detailed grounds for the request for re-examination by the applicant, and the recommendations by the AHEG, reassessment of the data showed that some of the concerns previously raised by the CVMP remain, as success rates showed high variability at the different study sites (0–100%). However, although the efficacy results varied between countries, the CVMP considered that overall, the applicant demonstrated that tulathromycin in a dose of 2.5 mg/kg bw is effective in treatment of foot rot in sheep at an early stage of the disease.

Additional considerations

In addition, the applicant considered that DRAXXIN would provide an alternative treatment option with a lower user safety risk than other currently authorised products.

The CVMP noted, taking into account the views presented by the AHEG, that the comparator (tilmicosin) has known user safety risks and that based on the data from the field study, DRAXXIN also appeared to be better tolerated in the target species, in particular in younger animals than tilmicosin.

Overall assessment and conclusions on grounds for re-examination

The CVMP assessed the detailed grounds for re-examination and additional argumentations presented by the applicant and considered the advice provided by the AHEG.

The Committee concluded on the following:

- MIC data

The CVMP concluded that the data provided by the applicant were sufficient to describe the susceptibility of the virulent strains of *Dichelobacter nodosus (vir),* defined by the gelatinase gel (GG) test or the aprV2-gene, to tulathromycin.

- Resistance

There is currently no indication that DRAXXIN used in sheep might cause a public health problem when used in line with SPC recommendations. In the absence of clearly established MIC data for the virulent strain of *D. nodosus*, no clinical breakpoint has currently been established, and consequently no final conclusions on resistance towards the target pathogen could be made. However, clinical efficacy in the field study indicated adequate susceptibility of the virulent strain of *D. nodosus* (vir).

However, cross-resistance to tilmicosin might be possible, and adequate reference to this has been made in the product information.

- Dose

The CVMP reconfirmed its previous opinion that the data provided could not be used for PK/PD calculations establishing the proposed therapeutic dose. However, using PK-PD calculations for the finding of a dose for the treatment of ovine foot rot is known to be problematic and not necessarily indicative of clinical efficacy. The CVMP therefore considered that based on the result of the field study,

the proposed single intramuscular dose of 2.5 mg tulathomycin/kg bw could be considered appropriate for treatment of foot rot in sheep (see below).

- Efficacy

Success rates showed high variability at the different study sites (0–100%). However, although the efficacy results varied between countries, the CVMP considered that overall, the applicant demonstrated that tulathromycin in a dose of 2.5 mg/kg bw is effective in treatment of foot rot in sheep at an early stage of the disease. Testing tulathromycin at 2.5 mg/kg bw against tilmicosin (10 mg/kg bw) at a 15% margin of non-inferiority shows that the efficacy may be considered similar. For a margin of 10%, non-inferiority could not be demonstrated. It has been emphasized that weather conditions and the time of treatment may have a large impact on the treatment outcome. Based on these facts CVMP accepted the 15% margin and concluded that the tulathromycin is efficacious in the treatment of foot root in sheep.

Overall, the CVMP considered that although the preclinical data showed some deficiencies, the overall efficacy of DRAXXIN could be accepted.

Final benefit-risk assessment

Direct therapeutic benefit

The benefit of DRAXXIN in sheep is its efficacy in the treatment early stages of ovine pododermatitis (foot rot) associated with the virulent strain of *D. nodosus*, which was investigated in one GCP-compliant multicentre controlled clinical field study. This disease is of serious animal welfare concern.

The benefit of DRAXXIN at a single dose of 2.5 mg/kg bw for the treatment of treatment of ovine pododermatitis (foot rot) associated with the virulent strain of *D. nodosus (vir)* has been demonstrated in a clinical study. Efficacy of a single intramuscular injection of 2.5 mg/kg bw was demonstrated in a multicentre European field study, where non-inferiority to an authorised macrolide (tilmicosin) was shown.

Additional benefits

DRAXXIN would increase the range of available treatment possibilities in sheep.

Despite deficiencies in the preclinical data, the CVMP considered that the virulent form of foot rot is a welfare concern in sheep, and DRAXXIN would provide an additional treatment option.

Risk assessment

Quality:

The strength and pharmaceutical form remain as authorised, and reference is made to data that have already been submitted and assessed as satisfactory for the product in previous applications.

For the target animal:

DRAXXIN is well tolerated in sheep, including young animals (6 weeks old - 19 kg and above). Local signs of discomfort were observed following intramuscular injection, which were mild and very transient in nature.

For the environment and the user:

The product is not expected to pose a risk for the user or the environment when used as proposed in the SPC and other product literature.

For the consumer:

A withdrawal period of 16 days for sheep meat and offal has been established and is considered adequate to ensure consumer safety. DRAXXIN is not authorised for use in animals producing milk for human consumption.

Resistance:

The product is not expected to pose a public or animal health risk in regard to resistance development, when used as proposed in the SPC and other product literature.

Risk management or mitigation measures

Since the efficacy was not shown in sheep with chronic clinical signs, the use of DRAXXIN should be restricted to sheep in early stages of severe ovine foot rot. Benign foot rot should not be treated with antimicrobials. In addition, DRAXXIN should only be used together with other flock management measures, e.g. keeping/moving treated animals to dry housing/pasture.

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

The withdrawal period is set at 16 days for meat and offal for sheep.

The re-start of the PSUR cycle is considered appropriate to ensure more frequent pharmacovigilance monitoring since a new target species is added. The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 31/05/2017.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for the treatment of early stages of severe ovine pododermatitis (foot rot) associated with the virulent strain of *Dichelobacter nodosus* requiring systemic treatment.

Information on development, manufacture and control of the active substance and finished product has been assessed in previous applications concluding that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the new target species (sheep) 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.

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary data submitted in the application for the extension to the marketing authorisation to add a new food-producing target species (sheep), and the applicant's detailed grounds for the re-examination, the applicant's responses to the CVMP list of questions to the applicant, the report to the CVMP from the Ad Hoc Expert Group meeting, and the oral explanations provided by the applicant the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of DRAXXIN are considered to be in accordance with the requirements of Directive 2001/82/EC.

Based on the CVMP review of the data, the CVMP at the end of the re-examination concluded that the overall benefit-risk balance is positive and, therefore, recommends the granting of the extension to the marketing authorisation for DRAXXIN to add a new target species (sheep).

8 September 2016
EMA/CVMP/601159/2016

Divergent position on a CVMP opinion on the granting of an extension to the marketing authorisation of DRAXXIN (EMEA/V/C/077/X/029), following the re-examination

The undersigned wish to express a divergent position to the CVMP Opinion on this application for a marketing authorisation for a new target species (sheep).

In the opinion of the undersigned, the approval of the indication for virulent infectious pododermatitis in sheep is not justified. Infectious pododermatitis is a disease complex, resulting in an infection of the interdigital tissues and claws. The more common type of this infection is due to *Dichelobacter nodosus* as a secondary invader and working in conjunction with *Fusobacterium necrophorum*. Other bacteria can also be the cause. The pivitol clinical trials involved and inferiority study comparing Draxxin to a comparator product with the approved indication of the treatment of infectious pododermatitis in sheep. However, the comparator product has the approved indication for both *Dichelobacter nodosus* and *Fusobacterium necrophorum*, but the approval for Draxxin is only for *Dichelobacter nodosus*.

It is unclear as to the definition of virulent infectious pododermatitis in sheep for the indication and if it is appropriate for all European conditions. It appears to be a combination of clinical expression in the field and the characteristics of *Dichelobacter nodosus* with virulence genes. There are differences in the definition of virulent *Dichelobacter nodosus* based on clinical signs. For example, the Australian literature separates clinical sheep footrot into three categories, benign, intermediate or virulent, depending on the strain of *D. nodosus* present. However, in the USA benign and virulent footrot are considered to be the same (due to the difficulty of differentiating the two) and are treated accordingly. To base the decision of virulent based on clinical signs has further problems. For example, with the Australian claw scoring system, population definitions of virulent footrot is defined by >10% of the cohort (flock) with a lesion score=4. In the field trials, Draxxin was found to be far less effective in sheep with high claw lesion scores.

For the field trials, clinical cure/ treatment success was based primarily on no foul smell or exudate (although the tissue might not have completely returned to normal) and lameness score 0. Claw lesion scores were not an integral part of the cure definition. Claw lesions are an essential part of the cure definition, since *D. nodosus* does not survive long in the environment, but can survive virtually indefinitely in lesions. Also, the presence of exudate was not an obligatory inclusion criteria, and thus it is unclear as to how exudate is part of the clinical cure definition. It is also difficult to understand as to how smell can be part of cure definition, given the very subjective nature of this clinical sign.

Also, it is stated in the exclusion criteria that animals with contagious ovine digital dermatitis (CODD) were excluded. However, it is unclear concerning the diagnosis of CODD for exclusion. CODD is the more accepted term for the condition, and taking over from the older term (severe virulent ovine footrot - SVOFR). CODD has been described in Europe since 1997, and can be clinically indistinguishable from 'classical' footrot. Classical footrot is characterized clinically by lesions involving the heel and the interdigital area, CODD is characterized by ulcerative lesions of the coronary band which progress and

result in disruption of the abaxial wall lining the hoof and loss of the horn case in untreated cases. However, these lesions are not present in all cases of CODD, especially acute stages, and can be indistinguishable from classical footrot. Typically, CODD fails to respond to accepted treatment practices for 'classical' footrot, and thus it is important to establish the correct diagnosis. The exact cause of CODD has not been agreed upon. Suggestions have been made that there is a likely role for treponemes in the pathogenesis of CODD, as well as other bacteria. The role of *D. nodosus* in CODD is controversial but unlikely the main part of the pathogenesis. For example, Collighan *et al* (1998) primarily isolated treponemes from CODD lesions, and found mostly related to *Treponema vincentii* (Collighan RJ, Naylor RD, Martin PK, Cooley BA, Buller N, Woodward MJ A spirochete isolated from a case of severe virulent ovine foot disease is closely related to a Treponeme isolated from human periodontitis and bovine digital dermatitis. Vet Microbiol. 2000 Jun 1;74(3):249-57.). This has also been found by Demirkan *et al*. (2001), and Sayer *et al*. (2009), as well as finding other Treponema species (Demirkan I, Carter SD, Winstanley C, Bruce KD, McNair NM, Woodside M, Hart CA Isolation and characterisation of a novel spirochaete from severe virulent ovine foot rot. J Med Microbiol. 2001 50(12):1061-8.; Sayers *et al*. Identification of Spirochetes Associated with Contagious Ovine Digital Dermatitis J Clin Microbiol. Apr 2009; 47(4): 1199–1201.). However, Moore *et al*. (2005) did find *D. nodosus* were present in a high percentage (74%) of CODD lesions, as well as treponemes (Moore LJ, Woodward MJ, Grogono-Thomas R The occurrence of treponemes in contagious ovine digital dermatitis and the characterisation of associated *Dichelobacter nodosus*. Vet Microbiol. 2005 111(3-4):199-209.). The implication of this is that detecting the presence of *D. nodosus* does not differentiate between classical footrot and CODD.

There are also problems with defining virulent *D. nodosus* based on the presence of virulent genes. *D. nodosus* has several well described virulence factors such as its fimbriae, proteases and outer-membrane proteins. Most agree that the *fimA* gene as the essential virulence factor for *D. nodosus*. The *fimA* gene encodes for the type IV fimbrial subunit. The fimbriae of *D. nodosus* are required for binding to epithelial cells, providing twitching motility; are involved in the uptake of extra-cellular DNA and are part of a secretion system able to export extra-cellular proteases out of the cytoplasm (Myers *et al*., 2007). *D. nodosus* isolates that do not have an intact *fimA* gene cannot show virulence (Ruth *et al*., 2001). Thus, Ruth *et al*. (2001) was the first to show that the *fimA* gene is essential for virulence and later chosen for the foundation of a classification system because of its importance. The secretion of extra-cellular proteases by *D. nodosus* is particularly important in its biology and this was highlighted by Myers *et al*. (2007), whom showed that *D. nodosus* cannot synthesise any amino acids. Rather, *D. nodosus* derives its amino acids by importing them from digested extracellular protein in its environment.

The applicant did not screen clinical *D. nodosus* isolates fort he *fimA* gene, but for *aprV* genes. In strains that cause virulent footrot, special proteases are present called acidic protease isoenzymes 2 and 5 from virulent strains (*AprV2* and *AprV5*) and basic protease from virulent strains (*BprV*). However, it is not as straight forward as just possessing the *aprV2* gene for all field cases, where other virulent proteases can also contribute to disease.

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identification of candidate vaccine antigens from the animal pathogen Dichelobacter nodosus. Nat. Biotechnol. 25, 569–575.

Ruth M, Kennan OM, Dhungyel P, Whittington RJ, Egerton JR, Rood JI (2001) The Type IV Fimbrial Subunit Gene (fimA) of Dichelobacter nodosus Is

Essential for Virulence, Protease Secretion, and Natural Competence. JOURNAL OF BACTERIOLOGY, 183(15): 4451–4458.

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