10 October 2013
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Aivlosin (EMEA/V/C/000083/X/0051)

International non-proprietary name: tylvalosin

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

Introduction

An application for an extension to the Community marketing authorisation for Aivlosin was submitted by ECO Animal Health Ltd. to the European Medicines Agency (the Agency) on 1 August 2012 in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 3 thereof.

Aivlosin contains tylvalosin (as tylvalosin tartrate), a macrolide antibiotic, and was first authorised for use in the Community on 9 September 2004. It is currently available in different pharmaceutical forms (premix for medicated feeding stuff, oral powder, granules for use in drinking water) for different target species (pigs, chickens, pheasants).

This extension application for Aivlosin is to add a new food-producing target species, turkeys to the already authorised granules for use in drinking water for the following (new) indication(s): Treatment of respiratory disease associated with *Ornithobacterium rhinotracheale*.

The authorised packs/containers that are applicable to this extension are the 40 g and 400 g sachets, at a strength of 625 mg/g. The route of administration is use in drinking water. The proposed withdrawal period is 2 days (meat and offal). The product is not authorised for use in laying birds producing eggs for human consumption, and should not be used within 14 days of onset of the laying.

In line with the "Policy for classification and incentives for veterinary medicinal products indicated for minor use or minor species (MUMS)/limited markets" (EMEA/429080/2009), the new target species turkeys was considered a minor species and data requirements as per CVMP guideline on target animal safety and efficacy requirements for veterinary medicinal products intended for MUMS (EMEA/CVMP/EWP/117899/2004) apply.

The CVMP adopted an opinion and CVMP assessment report on 10 October 2013.

On 4 December 2014, the European Commission adopted a Commission Decision for this application.

Scientific advice

The applicant obtained scientific advice (CVMP/SA/029/06) from the CVMP in November 2006 (EMEA/SAWP-V/085/2006) on questions in regard to residues, target animal safety and clinical studies. This advice related to use of the same formulation in turkeys, but for treatment of a different target pathogen, *Mycoplasma gallisepticum*.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant provided a detailed description of the pharmacovigilance system (dated 15 February 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

A declaration of compliance of the manufacture of the active substance (tylvalosin) with EU good manufacturing practice (GMP) requirements for starting materials has been provided by the qualified person of the batch release site.

Manufacturer of the finished product has a manufacturing authorisation issued by the Veterinary Medicines Directorate, UK. Batch release for the EU will be carried out by Gallows Green Services Limited, Thirsk, North Yorkshire, UK. A certificate of compliance with the principles of GMP for the manufacturer responsible for batch release is presented. This is based upon an inspection carried out in April 2010.

No GMP inspections were considered necessary.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system is considered to be in line with legal requirements. Manufacturing authorisations and GMP certificates were satisfactory.

Part 2 - Quality

The application is to add turkeys as a new target species to the marketing authorisation for Aivlosin 625 mg/g granules for use in drinking water. Currently this presentation is approved for use in pheasants and chickens. The product is identical in terms of its formulation, manufacture and control to the Aivlosin 625 mg/g granules for drinking water products currently authorised in pigs, chickens and pheasants. The formulation and manufacture of Aivlosin was well described and specifications set will ensure that a product of consistent quality will be produced. There is no change to the currently approved part 2. It should be noted that the currently authorised inclusion rates for pheasants and chickens also apply to turkeys and product solubility and in-use stability data previously submitted are still applicable.

The shelf life and storage conditions have been updated in accordance with the recently approved variation EMEA/V/C/083/IB/053. Therefore, for the 400 g presentation, the shelf life is now reduced from 36 months to 24 months and the maximum storage temperature reduced from 30 °C to 25 °C. For the smaller presentation these are unchanged.

Overall conclusions on quality

In connection with the shelf life and storage conditions, the shelf life and storage conditions have been updated in the product information during the procedure in accordance with the recently approved variation EMEA/V/C/083/IB/053. Therefore, for the 400 g presentation, the shelf life is now reduced from 36 months to 24 months and the maximum storage temperature reduced from 30 °C to 25 °C.

There have been no other changes to the currently approved part 2 of the dossier and the quality of the product remains satisfactory.

Part 3 – Safety

No data were provided in part 3 of the dossier, instead reference has been made to safety data provided for a previous application for the use of the same product in chickens (EU/2/04/044/007). All these data have been assessed by the CVMP during the evaluation of the presentation for use in chickens. The proposed posology for turkeys, 25 mg/kg bodyweight (bw) for five consecutive days, is slightly different from that authorised in chickens, which is 25 mg/kg bw for three consecutive days.

Development of resistance

Because of its lack of activity against *Escherichia coli* and *Salmonella* spp., the concern for the production of macrolide resistant bacteria in food borne pathogens is restricted to enterococci and *Campylobacter* spp. *Campylobacter* infection is a self-limiting disease in man and antibiotics are not advocated in the majority of cases. If antibiotics are prescribed, erythromycin, a macrolide, still remains one of the drugs of choice. Surveillance data from EFSA, MARAN and DANMAP show that levels of resistance to erythromycin in *Campylobacter* from chickens and humans have remained low and stable, and erythromycin still remains a drug of choice for treating this infection in humans. Levels of macrolide resistance in *Enterococcus* spp. isolated from poultry are high; however, macrolides are not used to treat *Enterococcus* infections in man. Since this application relates specifically to use in a minor species and considering that the duration of treatment is only two days longer in this target species, i.e. five consecutive days as opposed to three days in chicken while the dose remains the same, there will not be a substantial increase in exposure of foodborne bacteria.

The risk for antimicrobial resistance of public health concern resulting from the addition of a new target species change is deemed acceptable.

User safety

The product will present the same hazards, routes and extent of exposure, and overall risk whether it is chickens or turkeys being treated. It was considered that the user safety warnings already included for product remain appropriate when used in turkeys:

- Tylvalosin has been shown to cause hypersensitivity reactions in laboratory animals; therefore, people with known hypersensitivity to tylvalosin tartrate should avoid contact with the veterinary medicinal product.
- When mixing the veterinary medicinal product and handling the medicated water, direct contact, with eyes, skin and mucous membranes should be avoided. Personal protective equipment consisting of impervious gloves and a half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator conforming to European Standard EN 140, with a filter conforming to European Standard EN 143 should be worn when mixing the veterinary medicinal product. Wash contaminated skin.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Environmental risk assessment

No new environmental risk assessment (ERA) was provided, but reference was made to the ERA submitted in support of the product for use in chickens. It was concluded that the risk to the environment from the use of the product in chickens was acceptable when used as recommended. No risk mitigation measures were considered necessary.

The ERA submitted for the major species, chickens, was carried out using a dose rate of 30 mg/kg bw for 5 consecutive days resulting in a PECsoil of 1,122 µg/kg. The dose rate for turkeys of 25 mg/kg bw for 5 consecutive days gives a PECsoil of 553 µg/kg. Exposure of the environment from treatment of turkeys is lower than that resulting from the treatment of chickens and the conclusions of the ERA for chickens applies equally to turkeys.

Overall conclusions on the safety documentation

No data were provided in part 3 of the dossier, instead reference has been made to safety data provided for a previous application for the use of the same product in chickens (EU/2/04/044/007).

The product is not expected to pose a risk for the user or environment when used as recommended.

The risk for antimicrobial resistance of public health concern is deemed acceptable.

Residues documentation

MRLs

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

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Tylvalosin	Sum of tylvalosin and 3-O-acetyltylosin	Poultry	50 µg/kg 50 µg/kg	Skin and fat Liver	Not for use in animals from which eggs are produced for human consumption	Anti-infectious agents/ Antibiotics

The excipients contained in the product are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Withdrawal periods

MRLs for tylvalosin (skin and fat and liver) have been established for poultry, but not for eggs. Therefore, tylvalosin is not authorised for use in birds producing eggs for human consumption, and should not be used within 21 days of onset of laying based on extrapolation of the time taken for egg formation in the chicken.

No new residues studies have been provided for turkeys instead reference has been made to the residues depletion data provided for the major species, chickens.

The pivotal residue depletion study in chickens was conducted using a dose rate of 30 mg/kg bw for 5 consecutive days, a dose in excess of that proposed for the minor species, turkeys (25 mg/kg bw for 5 days). The same withdrawal period as agreed for chickens of 2 days for meat and offal has been proposed for turkeys. This proposal for extrapolation of the withdrawal period from the major to the minor species, without the addition of a safety span to cover species differences is in accordance with the CVMP guideline on safety and residue data requirement for veterinary products for minor use or minor species (EMEA/CVMP/SWP/66781/2005).

Overall conclusions on the residues documentation

No new residues studies have been provided for turkeys but reference was made to the previously assessed residue depletion study for chicken.

The proposed withdrawal period of 2 days for turkey meat will be sufficient to ensure the safety of consumers of products derived from animals treated with this product. The product is not authorised for use in birds producing eggs for human consumption, and should not be used within 21 days of the onset of lay.

In light of the extension of the indication to a new target species, it is recommended to re-start the PSUR cycle for Aivlosin to ensure more frequent pharmacovigilance monitoring. The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 31 March 2014.

Part 4 – Efficacy

Pharmacodynamics

Although the applicant is largely relying on data previously assessed to characterise the pharmacodynamics of the active substance, tylvalosin, the results of six studies demonstrating its activity against the target pathogen, *Ornithobacterium rhinotracheale* (ORT) have been reported. These provide the minimum inhibitory concentration (MIC) data for 172 EU isolates of ORT from turkeys spanning the period 1997 to 2011. The origin of the samples was not specified in all studies, but the majority of isolates were obtained from different flocks of turkeys known to be suffering from respiratory disease.

The results suggested a wide variation in the susceptibility of ORT to tylvalosin, with MIC values ranging from 0.016 to >32 µg/ml and MIC_{90} = 4 µg/ml based on the pooled data. Due to lack of standardisation of techniques, it was hard to make comparison between studies (which were not all conducted in accordance with GLP). The data presented indicated that MIC values obtained for the same isolates could vary from between zero and five dilutions when different methodologies were used and this limits their interpretation.

The applicant also demonstrated that while tylvalosin is known to be bacteriostatic, it can be bactericidal and results of the bacterial kill kinetics study indicate that its activity is concentration-dependent at lower concentrations (up to 4x MIC) and predominantly time-dependent at higher concentrations. No claims were made relating to a post antibiotic effect (PAE).

Development of resistance (target pathogens)

There are generally considered to be three mechanisms that are responsible for resistance to the macrolide class of compounds, this is often referred to as MLS resistance as it affects macrolides, lincosamides and streptogramins. The mechanisms involve (i) alteration of the ribosomal target site, (ii) utilization of active efflux mechanism and (iii) production of inactivating enzymes.

Similar macrolides have been used in other poultry species for treatment of ORT and there is evidence for resistance development to these antibiotics, for example tylosin and tilmicosin. It is envisaged that use of Aivlosin for treatment of ORT in turkeys will replace existing macrolide use and therefore will not increase selection pressure on ORT.

Pharmacokinetics

No new pharmacokinetic data were submitted which was acceptable given that turkeys are a minor species and extrapolation of data from chickens to pheasants was previously accepted, on the basis of similar absorption characteristics between pigs and chickens. It was noted that PK/PD integration is not straightforward for macrolides, and this is especially the case for this antibiotic/organism combination without reliable MICs and knowledge of drug concentration in cells of clinically relevant target tissues.

Target animal tolerance

No target animal safety study was conducted in turkeys, but on the basis of data previously assessed in chickens, showing good safety at 30 mg/kg bw for 15 days (i.e. three times the proposed treatment duration for turkeys), and the minor species status of the new target species, this was acceptable. Further evidence of the safety of Aivlosin when used in turkeys was provided by the dose determination and dose confirmation studies, where there were no adverse events relating to treatment at up to 30 mg/kg bw once daily for 5 days.

Dose determination/justification

Prior to dose determination/confirmation, the applicant conducted a virulence study at the University of Ghent in Belgium to verify the virulence of the ORT challenge strain DWC 13090. This study involved a challenge model where two groups of 17 turkeys were inoculated with avian metapneumovirus (APV) at 20 days of age, and one of these groups subsequently inoculated with the specified ORT strain three days later. Necropsy revealed a statistically significant increased incidence of lower respiratory lesions (air sacculitis) in the APV/ORT group compared with the APV-only group ($p = 0.0476$ at day 5 post bacterial infection (pbi) necropsy; $p = 0.0094$ at day 13 pbi necropsy). Clinical score was also higher in the APV/ORT group (AUC of score from 0 to 9 days pbi 22.5) than in the APV-only group (AUC of score from 0 to 9 days pbi 12.75) and this difference was statistically significant ($p = 0.0068$). On the basis of these differences and a calculated 43% of the clinical signs attributed to ORT, the applicant concluded that virulence had been demonstrated for the challenge strain DWC 13090 and it was taken forward for the dose determination and confirmation studies.

A GCP compliant dose determination study undertaken in Belgium under controlled conditions (randomised block design) was provided. This study used a challenge model whereby 85 female turkey poults were first challenged with APV at 20 days of age and subsequently with ORT 3 days later, before treatment was administered the following day (or withheld, in the case of the control group). The study animals were confirmed to be free from APV and ORT prior to inclusion and free from *E. coli* on culture of air sac swabs at necropsy. Although presence of other respiratory pathogens was not investigated, the good health status of the parent flock, high biosecurity housing of the birds and disease-free three week quarantine period provide reassurance that the clinical picture was not complicated by the presence of other respiratory pathogens.

In this study, 17 birds were allocated to each of five groups, being administered tylvalosin in differing dosing regimens: 15 mg/kg bw once daily for 5 days, 25 mg/kg bw once daily for either 3 or 5 days, 30 mg/kg bw once daily for 5 days or no treatment (negative control).

Statistical analysis of clinical and pathological observations made both prior to and after necropsy (up to 2 weeks pbi) revealed that for the primary efficacy variable (lung and air sac lesion scores) there were statistically significant differences between all groups treated for 5 days and the negative control, but there was no difference between the 25 mg/kg and 30 mg/kg groups.

The 25 mg/kg bw once daily for 5 days posology was therefore taken forward to the dose confirmation study. Notably 25 mg/kg bw given for 3 days was clearly insufficient.

There were no fatalities linked to the induction of respiratory disease, nor were there any signs of intolerance to the product detected.

Dose confirmation

A GCP compliant dose confirmation study was undertaken in Belgium at the University of Ghent under controlled conditions (randomised block design). The study was conducted to a very similar protocol to that of the dose determination study, involving a challenge model whereby 85 female turkey poults, which had been confirmed to be free of respiratory pathogens were first challenged with avian pneumovirus at 35 days old and (in most cases) subsequently to *Ornithobacterium rhinotracheale* 3 days later before treatment was administered the following day (or withheld in the case of the control groups).

In this study, 34 birds were allocated to each of the treatment (receiving 25 mg/kg bw tylvalosin once daily for 5 days) and negative control groups. A further 17 birds were allocated to an additional group which received no treatment and was challenged with APV only. The purpose of this group was to demonstrate the effect of secondary infection with ORT, and this was shown to be statistically significant for mean combined lung and air sac lesion score, and for clinical score parameters.

The primary efficacy endpoint was combined macroscopic lesion score for lungs and air sacs. This was selected as the primary efficacy variable as these lesions predispose to bacterial air sacculitis and pneumonia which commonly result from secondary infections in the field. The lesion score in the Aivlosin treated group was significantly lower compared to the control group ($p=0.0008$), although the score was not high for either group: 2.13 for treated birds and 4.75 for untreated controls out of a possible total score of 20. A statistically significant benefit was shown for the treated group for one of three secondary clinical variables, the mean clinical score AUC at days 5 to 13 post bacterial infection ($p=0.0413$). Based on previous studies the applicant justified that this was the most relevant time period for assessment of this parameter as APV was shown to account for a significant proportion of clinical scores in the period from 0 to 9 days, with ORT signs predominating later. For the other two clinical score variables there was a trend towards a significant benefit ($0.05 < p < 0.1$), but it is noted that the size of the treatment benefit was small: mean clinical score on days 0 to 9 was 2.37 for the Aivlosin group compared to 2.73 for the negative control group (possible score range 0 to 6). However, ORT lesions predominantly affect the lower respiratory tract and therefore detectable clinical signs (largely upper respiratory signs) reflect disease caused by this pathogen less accurately than the primary efficacy variable. As before, there were no fatalities linked to the induction of respiratory disease, nor were any signs of intolerance to the product detected.

At 0.016 µg/ml (determined using standardised agar dilution methodology), the MIC of the challenge strain used in all three studies (virulence; dose determination; dose confirmation) appeared to lie at the most sensitive extreme of the distribution of field isolates presented in the section 'Pharmacodynamics'. However, due to the lack of harmonised MIC methodology for ORT, the true sensitivity of the strain remained uncertain: the MIC for the same isolate was found to be five dilutions higher when evaluated using a broth microdilution method. Therefore, no conclusion could be drawn as to whether the ORT challenge strain is representative of the range of MICs of field isolates. Nevertheless, it was recognised that use of a single strain is part of the design of a challenge study and such studies are inherently limited in their representativeness of the field situation.

Overall the observed efficacy in this trial was considered modest. The small magnitude of the treatment benefit demonstrated in the dose confirmation challenge study raised the question of whether antibiotic use was justified under these circumstances. However, although ORT manifests as a mild clinical disease in the absence of complicating factors in the challenge studies, the CVMP concluded that the indication was clinically relevant on the basis that a clear reduction in airway lesions was demonstrated and in the field early treatment of infection is good veterinary practice, and is necessary to prevent development of chronic tenosynovitis, reduce lesions of air sacculitis that lead to

carcase condemnation and to reduce need for treatment of more serious secondary infections, notably *E. coli*. It was also recognised that airway lesions together with the reduced weight gain that was seen in control birds, was likely to reflect reduced welfare status of these birds.

Field studies

No field studies were performed. Taking into account that the new target species is a minor species, the CVMP had confirmed in a scientific advice prior to submission of the application that adequate and controlled dose confirmation studies might replace the need for a field study, consistent with the CVMP guideline on target animal safety and efficacy requirements for veterinary medicinal products intended for MUMS (EMEA/CVMP/EWP/117899/2004) which makes provision for waiving the requirement for a field study if justified. The applicant provided justification for the absence of a field study on the basis that the disease in the field is very variable in presentation and as it depends on many factors including husbandry conditions and infection pressure from other pathogens, it is necessary to instigate treatment at short notice but not possible to predict which farms/flocks will require treatment. Taking into consideration the scientific advice given, the recommendations in the CVMP guideline on target animal safety and efficacy requirements for veterinary medicinal products intended for MUMS (EMEA/CVMP/EWP/117899/2004) and the applicant's justification for not conducting a field study, the CVMP considered that the absence of such a study could be accepted for this application.

Overall conclusion on efficacy

Recent data from within the EU suggested that there is a wide variation in the susceptibility of ORT to tylvalosin, with MIC values ranging from 0.016 to more than 32 µg/ml. However, due to lack of standardisation of techniques, it was hard to make comparison between studies (which were not all conducted in accordance with GLP) or to draw any firm conclusions on the MIC distribution.

Although classical pharmacokinetics studies were not conducted in the turkey, this is a MUMS application and it was previously agreed (in relation to the application for pheasants) that such data could be waived.

The applicant investigated tylvalosin doses of 15, 25 and 30 mg/kg bw once daily for either 3 or 5 days in a challenge study using both APV and ORT inoculates. Statistical analysis revealed that for the primary efficacy variable (lung and air sac lesion scores) there were significant differences between all groups treated for 5 days and the negative control but there was no difference between the 25 mg/kg and 30 mg/kg bw groups. The 25 mg/kg bw once daily for 5 days posology was therefore taken forward to the dose confirmation study.

The dose confirmation study used an APV and ORT challenge model similar to that used for dose determination. Statistical analysis confirmed a significant difference between the treated and control groups for the primary efficacy variable (lung and air sac lesion scores), although the treatment benefit appeared to be small when compared to the range of possible scores. At some time points during both studies there were significant differences detected between treatment and control groups for some secondary efficacy parameters. The apparent small magnitude of the treatment benefit raised the question of whether antibiotic use could be justified under these circumstances. Although ORT manifests as a mild clinical disease in the absence of complicating factors in the challenge studies, the clinical relevance of the indication was accepted on the basis that a clear reduction in airway lesions was demonstrated and in the field early treatment of infection is good veterinary practice, and is necessary to prevent development of chronic tenosynovitis, reduce lesions of air sacculitis that lead to carcase condemnation and to reduce need for treatment of more serious secondary infections, notably *E. coli,* which are a common sequel. It was also recognised that airway lesions, together with the

reduced weight gain that was seen in control birds, was likely to reflect reduced welfare status of these birds.

The CVMP acknowledged that there are inherent limitations with the degree to which challenge studies can reflect the field situation. However, taking into consideration the scientific advice given, the recommendations in the CVMP guideline on target animal safety and efficacy requirements for veterinary medicinal products intended for MUMS (EMEA/CVMP/EWP/117899/2004) and the applicant's justification for not conducting a field study, the CVMP considered that the absence of such a study could be accepted for this application.

Part 5 – Benefit-risk assessment

Introduction

This is an extension application for Aivlosin 625 mg/g granules for drinking water, submitted according to Article 12(3) of Directive 2004/28/EC to add turkeys as a target food producing species. Reduced data requirements apply due to the agreed MUMS classification. The product contains tylvalosin as the active substance. The benefit-risk analysis is based on the fact that this is the first application to authorise tylvalosin for "treatment of respiratory disease associated with *Ornithobacterium rhinotracheale* (ORT) in turkeys".

Benefit assessment

Direct therapeutic benefit

The product is intended for use in commercial turkey farms following outbreaks of disease, which, often in conjunction with viral infection and secondary bacterial infections such as *E. coli*, can cause high morbidity and mortality.

A dose of 25 mg/kg bw for 5 days was sufficiently investigated.

The efficacy of the product in treatment of respiratory disease associated with *Ornithobacterium rhinotracheale* in turkeys was investigated in an APV and ORT challenge study and justified on the basis that in the field early treatment of infection (while still mild) is good veterinary practice, and is necessary to prevent development of chronic tenosynovitis, reduce lesions of air sacculitis that lead to carcase condemnation and to reduce need for treatment of more serious secondary infections, notably *E. coli,* which are a common sequel. It was also recognised that airway lesions, together with the reduced weight gain that was seen in control birds, was likely to reflect reduced welfare status of these birds.

Additional benefits

Aivlosin granules for oral solution is administered through the drinking water supply which provides a simple but effective means of medicating large numbers of animals to ensure that therapeutic levels are achieved without additional stress placed on birds from handling. Treatment of ORT may help to reduce the need for antimicrobials to treat secondary infections such as *E. coli*.

Risk assessment

The product is identical in terms of its formulation, manufacture and control to the Aivlosin 625 mg/g granules for drinking water products currently authorised in pigs, chickens and pheasants. The

formulation and manufacture of Aivlosin has been previously well described and specifications set will ensure that a product of consistent quality will be produced.

Therefore there will be no changes to the risks for the user and the user warnings currently in place remain valid. The risk for the environment was addressed by the assessment of the major species, chickens and no risk mitigation measures were required. The product is not expected to pose a risk for the user or the environment when used as recommended in the SPC.

No residue depletion study in turkeys has been provided, but the withdrawal period for chicken meat can be extrapolated to turkeys, in line with the CVMP guideline on target animal safety and efficacy requirements for veterinary medicinal products intended for MUMS (EMEA/CVMP/EWP/117899/2004) as turkeys are considered a minor species; the product is not expected to pose a risk to consumers when a meat withdrawal period of 2 days is observed. The product is not authorised for use in birds producing eggs for human consumption, and should not be used within 21 days of the onset of lay.

Based on the data presented previously, there are mechanisms for resistance to tylvalosin and since macrolides are used in man, there is a potential for the development of resistance in zoonotic foodborne bacteria (*Campylobacter*, enterococci). The risk level is assumed similar to that of oral macrolide use in chicken.

Although no target animal safety study has been conducted in turkeys, data that has been previously assessed in chickens demonstrated a good safety profile at 30 mg/kg bw for three times the proposed treatment duration for turkeys and no adverse events related to treatment were reported in either of the dose determination or confirmation studies.

The report of CVMP scientific advice given in 2006, stated that either an adequate controlled dose confirmation study or a field study would be necessary to support efficacy; the applicant provided satisfactory justification for the absence of a field study and this approach was therefore accepted in line with the recommendations in the CVMP guideline on target animal safety and efficacy requirements for veterinary medicinal products intended for MUMS (EMEA/CVMP/EWP/117899/2004).

In light of the extension to add a new target species, it is recommended to re-start the PSUR cycle for Aivlosin to ensure more frequent pharmacovigilance monitoring. The DLP for the first 6-monthly PSUR of the re-started cycle would be 31 March 2014.

Evaluation of the benefit-risk balance

The formulation and manufacture of Aivlosin is well described and specifications set ensure that product of consistent quality is produced.

Although no specific target animal safety study was conducted in turkeys, on the basis of data previously assessed in chickens it is expected that Aivlosin would be well tolerated by the target animals. The product presents a low risk for users and the environment and appropriate warnings have been included in the SPC. A sufficient withdrawal period has been set.

The selected dose has been sufficiently investigated. Based on the modest but reproducible improvement seen in lung lesion and air sac scores, and on recognition that in the field it is good practice to treat disease in the early (mild) stages in order to prevent secondary infections and chronic disease, the clinical relevance of the treatment effect demonstrated in the challenge studies was considered to have been adequately supported. The absence of a field study has been adequately justified in line with the CVMP guideline on target animal safety and efficacy requirements for veterinary medicinal products intended for MUMS (EMEA/CVMP/EWP/117899/2004).

As a result of the above the product has shown to have a positive benefit-risk balance overall and been shown to be efficacious for the indication treatment of respiratory disease associated with *Ornithobacterium rhinotracheale* in turkeys.

In light of the extension of the indication to a new target species, it is recommended to re-start the PSUR cycle for Aivlosin to ensure more frequent pharmacovigilance monitoring. The DLP for the first 6-monthly PSUR of the re-started cycle would be 31 March 2014.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the extension application to authorise Aivlosin 625 mg/g granules for drinking water for treatment of respiratory disease associated with *Ornithobacterium rhinotracheale* in turkeys is approvable.

Divergent position on the CVMP opinion for Aivlosin extension to turkeys (EMEA/V/C/0083/X/051)

Aivlosin is intended for the treatment of respiratory disease caused by *Ornithobacterium rhinotracheale* (ORT) in turkeys. The product is intended for use in commercial turkey farms following outbreaks of disease, which, often in conjunction with viral infection and secondary bacterial infections such as *E coli*, can cause high morbidity and mortality. Although considered a minor species within the EU, turkeys are an important food-producing species.

The pathogenicity of ORT strains vary considerably in the field, as well as the manifestation of disease is also influenced by other factors resulting in variable disease severity. In field cases, ORT is part of a respiratory complex of pathogens that includes *Avian* Pneumovirus and secondary pathogens (e.g. *E. coli*, *Pasteurella spp*.). Thus, the true role of ORT in the pathogenesis and pathology of this respiratory complex syndrome is uncertain and could not be elucidated from the data presented in the dossier. From the clinical trials, statistical significance was demonstrated for some parameters, but the clinical relevance of the shown effect has not been demonstrated. The data presented in support of efficacy of treatment is not regarded as sufficient due to the following reasons:

1. Only one strain of ORT has been used in clinical challenge trials. Due to the recognised lack of harmonised methods for MIC determination for ORT, then it is not possible to conclude whether this single challenge strain represents the field situation. Therefore, the relevance of results from the challenge trials for the actual situation in the field is not established. The lack of harmonised methods for MIC determination for ORT also has implications for veterinary product users in field situations of ORT involved outbreaks.
2. The magnitude of recorded treatment effect is low in the experimental model and it is not possible to conclude on whether the chosen dose utilises the full potential of the molecule or if the model detects low (and thus clinically irrelevant) effect levels. At best, the experimental challenge studies only provided data on early infections with ORT, before any chronic effects of infections (e.g. tenosynovitis or secondary infections). Without field data, then it remains unclear whether Aivlosin, at the dose suggested, has the capacity of reducing mortality and clinical signs of ORT infected turkeys to an extent that would be clinically meaningful. If sufficient efficacy is not obtained, this would compromise animal health as the turkeys would then be withheld more effective treatment or at least, effective treatment would be delayed.
3. Although ORT manifests as a mild disease, in the absence of complicating factors, during the challenge studies, it is advised that prompt treatment should be initiated to prevent development of chronic tenosynovitis, reduce lesions of airsacculitis that lead to carcase condemnation and reduce need for treatment of more serious secondary infections, notably *E coli*. However, in the absence of field data it is considered speculative to assume that secondary infections - with subsequent impact on animal health - will be reduced as a consequence of treatment with Aivlosin. Without sufficient knowledge about when treatment is to be initiated and what effect to anticipate, it is not possible to guide prescribers as how to use the product in a prudent and responsible way.

Having considered all the information presented, it is the opinion of the undersigned that the issues listed above preclude a conclusion on efficacy of Aivlosin in the treatment of ORT and it remains to be conclusively demonstrated that turkeys, under field conditions, will benefit clinically from the treatment with the product. Hence, a positive benefit-risk balance for this application can not be supported.

London, 10 October 2013

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