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Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use (CVMP)

# CVMP assessment report for type II variation for Aivlosin (EMEA/V/C/000083/II/0064)

International non-proprietary name: Tylvalosin

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

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# 1. Background information on the variation

## *1.1. Submission of the variation application*

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Eco Animal Health Ltd (the applicant), submitted to the European Medicines Agency (the Agency) an application for a type II variation for Aivlosin.

### 1.1.1. Scope of the variation

| **Variation requested** | | **Type** |
|---|---|---|
| C.II.3 | Changes to the withdrawal period for a veterinary medicinal product | II |

The variation is to add a withdrawal period for eggs, to allow the use of Aivlosin 625 mg/g granules for use in drinking water in laying hens.

| **Current** | **Proposed by the applicant** |
|---|---|
| **4.11 Withdrawal period(s)**<br><br>Meat and offal: 2 days.<br>Not authorised for use in birds producing eggs for human consumption.<br>Chickens: do not use within 14 days of onset of lay. | **4.11 Withdrawal period(s)**<br><br>Meat and offal: 2 days.<br><u>Eggs: Zero days</u><br><br>Not authorised for use in ~~birds~~ turkeys producing eggs for human consumption.<br>~~Chickens: do not use within 14 days of onset of lay.~~ |
| **LABELLING-40 g Sachet**<br>**5. Withdrawal Period**<br>As in SPC (see above) | **LABELLING-40 g Sachet**<br>**5. Withdrawal Period**<br>As in SPC (see above) |
| **PACKAGE LEAFLET**<br>**10. WITHDRAWAL PERIOD**<br>As in SPC (see above) | **PACKAGE LEAFLET**<br>**10. WITHDRAWAL PERIOD**<br>As in SPC (see above) |
| | |

# 2. Quality assessment

The application does not affect the quality part of the dossier, as no changes to the pharmaceutical form and strengths are made.

# 3. Safety assessment

The proposed product formulation and dosage regimen (route/dose/frequency/duration) is identical to that already authorised for chickens, therefore no additional data in support of user safety have been submitted. Cross-reference is made to safety and residue data previously submitted and assessed. New data submitted with this variation are outlined below.

The ADI for tylvalosin was calculated to be 2.07 µg/kg bodyweight which corresponds to 124.2 µg per person per day (EU/05/149/ECO).

## *3.1. User Safety*

Cross-reference is made to user safety data previously submitted and assessed. With regard to the risk of resistance in food-borne bacteria, see part 4 (resistance).

The use of the product in laying hens is not considered to influence the way the product is handled by the user. Therefore, the existing risk mitigation measures remain acceptable. The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC

## *3.2. Environmental Safety*

Cross-reference is made to a Phase I and Phase II environmental risk assessment (ERA) according to VICH guidelines 6 and 38, and in line with CVMP Guideline EMEA/CVMP/ERA/418282/2005-Rev.1, which was already submitted and assessed with the previous application adding chickens as a target species (EMEA/V/C/083/X/026). In this ERA, the scenarios presented were for both broiler chickens and laying hens, assuming a dosage regimen of 30 mg tylvalosin (TVN)/kg bodyweight for 5 consecutive days. This was considered an overestimate and therefore was reflective of a worst case scenario. The use of the product in laying hens is not considered to alter the outcome of the Phase II ERA that was submitted and assessed previously. Based on the data provided, Aivlosin is not expected to pose a risk for the environment when used according to the SPC.

# 4. Residues assessment

The applicant has conducted a new residue depletion study in eggs of chickens receiving Aivlosin 625 mg/g Granules for use in drinking water for chickens and turkeys (referred to as Aivlosin Water Soluble Granules (WSG)).

## *4.1. Pharmacokinetics*

The pharmacokinetics of tylvalosin has been appropriately addressed in the original submission for Aivlosin 625 mg/g Granules for use in drinking water for chickens (EMEA/V/C/083/X/26) and in the extension of MRLs for tylvalosin to poultry eggs application (EMEA/V/MRL/003044/EXTN/005). No new data are submitted for this application.

## 4.2. Depletion of residues

A new GLP-compliant study was performed in accordance with VICH guideline 48, to investigate the tylvalosin (TVN) residues in eggs from laying hens following the standard dosing regimen of the medicated drinking water. The maximum dosing regimen of 25 mg TVN/kg bw per day for three consecutive 24 hour periods was used in the study, which is the authorised regimen in the SPC for the treatment and prevention of respiratory disease associated with *Mycoplasma gallisepticum* in chickens. Fresh medicated water was prepared daily to deliver a target dose of 25 mg/kg bw and offered *ad libitum* to each bird daily from an individual drinker. The study comprised of 15 laying hens, from which eggs were collected twice daily and the combined yolk and albumen was analysed.

The study used an acceptable number of birds. Twenty birds were originally included in the study; however, five were excluded prior to treatment due to highly variable water consumption. The inclusion of these birds may have been more representative of the natural variation that could occur; however, due to the low levels of residues found in the egg homogenates, this is not thought to have had an impact on the study.

Water intake, body weight gain and laying frequency remained consistent in the remaining birds throughout the pre-study and medicated phases. An acceptable number of eggs (greater than 10) were collected to ensure the study was in compliance with VICH GL48. Where multiple eggs were laid on one day, the samples were combined. This was not thought to influence the results given the residue values were so low, therefore this approach was acceptable.

Product exposure was within acceptable limits to indicate that the maximum recommended dose was achieved. The general conduct and reporting of the study was acceptable. It was noted that the humidity was generally higher during the study period when compared with the pre-study period; however, this was not thought to compromise the study.

## 4.3. MRLs

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

| **Pharmaco-logically active substance** | **Marker residue** | **Animal species** | **MRLs (µg/kg)** | **Target tissues** | **Other provisions** | **Therapeutic Classification** |
|---|---|---|---|---|---|---|
| Tylvalosin | Sum of Tylvalosin and 3-O-acetyl-tylosin | Porcine | 50 µg/kg<br>50 µg/kg<br>50 µg/kg<br>50 µg/kg | Muscle<br>Skin and fat<br>Liver<br>Kidney | No entry | Anti-infectious agents/Antibiotics |
| | | Poultry | 50 µg/kg<br>50 µg/kg | Skin/Fat<br>Liver | No entry | |
| Tylvalosin | Tylvalosin | Poultry | 200 µg/kg | Eggs | No entry | |

Lactose monohydrate, the only excipient, is a naturally occurring carbohydrate and as such is considered as not falling within the scope of Council Regulation (EC) No. 470/2009.

An MRL was established for chicken eggs in a previous application (EMEA/V/MRL/003044/EXTN/005), where tylvalosin was assigned as the marker residue. Lactose monohydrate is designated as 'out of scope', therefore does not require an MRL (EMA/CVMP/519714/2009–Rev.30, Carbohydrates naturally occurring).

### *4.4. Withdrawal periods*

A GLP compliant, pivotal residue study was performed in layer chickens in accordance with VICH GL48. Chickens were treated with the recommended dose (25 mg/kg bw over 3 days) and the concentration of TVN was measured in individual samples of egg homogenate collected until day 17. The highest detectable concentrations of TVN in eggs were observed in all birds between Study Days 4 and 7, after which the TVN concentration in eggs from all birds declined with time. However, at no timepoint were the TVN residues in any egg homogenate found to be over the MRL. From Study Day 10 onwards, all eggs collected contained TVN concentrations below the limit of detection. The limit of quantification of the method was 100 µg/kg.

A zero day withdrawal period is proposed for eggs following administration of the product in chickens for the treatment and prevention of respiratory disease associated with *Mycoplasma gallisepticum* at a dose of 25 mg TVN/kg bodyweight for 3 consecutive days. This is supported.

The use in turkeys laying eggs for human consumption remains contraindicated, and Aivlosin should not be used in turkeys within 21 days of the onset of lay.

### *4.5. Analytical method*

No discussion of the analytical method has been provided as part of this application. Instead reference is made to the MRL extension application, where the analytical method was established and validated. This confirms that the stability of the analyte was demonstrated for 29 days. QC data have not been provided again, however the applicant indicates that all samples were analysed within this timeframe, which has been confirmed by study dates.

However, data have been provided in the appendix, which indicate that all validation criteria have been met for this batch of samples, therefore calibration and sample data are valid.

## 5. Efficacy assessment

Aivlosin 625 mg/g granules for use in drinking water for chickens, was authorised in the EU in June 2008 for the treatment and prevention of respiratory disease associated with *Mycoplasma gallisepticum*. The approved dosage regimen is 25 mg tylvalosin per kg bodyweight per day in drinking water for three consecutive days.

Cross-reference is therefore made to data previously submitted and assessed. New data submitted with this variation, to support the use of this product in chickens laying eggs for human consumption, are outlined below.

### *5.1. Pharmacodynamics*

Cross-reference was made to data previously submitted and assessed. This was considered acceptable since the pharmacodynamics of tylvalosin relevant for this application in regard to its activity against mycoplasma were adequately characterised during the previous procedure, EMEA/V/C/083/X/026.

## 5.2. Development of resistance

The applicant submitted an updated Expert Report on the microbiological safety of Aivlosin 625 mg/g granules for use in drinking water.

*Target pathogen*

With regard to tylvalosin resistance in the target pathogen, MIC distributions from studies reported in 2005/2007 and a more recent study using isolates collected between 2008 and 2012 were presented in the expert report for microbiological safety. In the former, the MIC distribution appeared to be bimodal (0.001 - 0.008 mg/l and 0.06 - 0.25 mg/l), whereas it was unimodal in the latter (0.015 - 0.25 mg/l).

Owing to the absence of the putative wild type population in the more recent study, the data suggest that there may be an increased proportion of the target pathogen population with reduced susceptibility to tylvalosin. However, the number of isolates studied is small and therefore definitive conclusions cannot be reached. Furthermore, since there is a lack of internationally standardised susceptibility tests for veterinary mycoplasmas and clinical breakpoints have not been established, it is not possible to ascertain definitive resistance levels.

The CVMP therefore concluded that based on the data presented, there is no definitive evidence that use of the product has resulted in reduced susceptibility of *M. gallisepticum* to tylvalosin.

Foodborne pathogens

Regarding foodborne bacteria, tylvalosin is not active against either *Escherichia coli* or *Salmonella* spp., and therefore the greatest concern for public health would be the risk of accelerated macrolide resistance development in *Campylobacter jejuni,* particularly as erythromycin is a drug of choice for the treatment of severe cases of campylobacteriosis in humans.

Authorisation of Aivlosin for laying hens is anticipated to increase the extent of use of the product. However, a definitive relationship between macrolide use and resistance in *C. jejuni* has not been established. In addition, studies from the scientific literature have shown that vertical transmission of *C. jejuni* through the egg is likely to be a rare event, this further suggests that the risk of transmission of macrolide-resistant *C. jejuni* to humans via eggs is low. Laying hens, which are no longer productive and enter the food chain as meat, could pose a potential risk to public health via this route; however, the amount of such meat is small compared to that produced by the broiler industry.

Taking into account that current macrolide resistance levels in *C. jejuni* isolates from chickens across Europe appear to be low and stable, the CVMP concluded that the risk of resistance development with regard to the additional use of this product in laying hens is currently expected to be low.

In addition, appropriate warnings regarding prudent use of antimicrobials are already included in the SPC.

## 5.3. Pharmacokinetics

Cross-reference was made to data previously submitted and assessed for pharmacokinetics in chickens. In addition, since these studies were conducted in broilers as opposed to older laying hens, the applicant provided a brief literature review on age-related pharmacokinetics in chickens.

There was no scientific literature citing age-related pharmacokinetic differences for tylvalosin or other macrolides in chickens, and only very limited information in regard to other antimicrobials used in chicken.

The CVMP acknowledged that age-related changes in the pharmacokinetics of tylvalosin in chickens cannot be ruled out. Such changes could in principle have a detrimental impact on the efficacy,

development of antimicrobial resistance and/or safety. However, there is some evidence that intestinal P-glycoprotein expression decreases with age and also that macrolides are substrates transported by this protein. Therefore, if anything, a higher bioavailability would be expected in older birds, and efficacy would be maintained. In addition, the applicant had provided a new target animal safety study in hens (see below) confirming that the product is well tolerated in this age group.

The absence of new pharmacokinetic studies in laying hens was therefore accepted by the CVMP.

## *5.4. Tolerance in the target animal species*

### 5.4.1. Laying hens

Cross-reference is made to the target animal safety (TAS) study in chicken which was already submitted and assessed with the previous application adding chickens as a target species. The product is known to have a wide margin of safety in broilers. In addition, the applicant conducted a new study (see below) to investigate the effect of the recommended dose (1xRTD) of Aivlosin on egg quality in layers, in which no abnormal health observations were made.

The new GLP-compliant study was performed in the UK (2014) in laying hens. It compared egg quality following the oral administration of either non-medicated drinking water or drinking water containing the product at the recommended therapeutic dosage (1xRTD) of 25 mg tylvalosin/kg bodyweight for three consecutive days.

The study was undertaken in four groups of 12 laying hens each (approx. 45 weeks old, 1.4 - 2.1 kg bw, and housed individually), which produced at least five eggs per week, and husbandry was consistent with normal commercial practices. After the end of the dosing period, birds and their eggs were monitored for a sufficient period of time (14 days).

General health, bodyweight, and water consumption of the hens as well as egg production were not compromised. To assess the effect of the product on the function of the reproductive system, the applicant recorded egg production (number of eggs laid per hen), egg shape, egg weight, egg shell thickness, egg strength and Haugh unit (measure of the quality of albumen). Upon statistical analysis, the only parameter found to be significantly different between groups was egg shell thickness. However, the difference was marginal and no significant inter-group difference for the related parameter, egg strength, was detected. With regard to the other parameters, any absolute differences between groups were also noted to be present prior to dosing.

Overall, the product elicited no systemic adverse reactions in laying hens, approx. 48-weeks old at the time of treatment, and the study did not provide any evidence of reduction in egg production during or after the period of treatment. The CVMP therefore accepted that administration of the product at the recommended dosage regimen (1xRTD) does not appear to interfere with egg formation or the laying process.

### 5.4.2. Reproductive safety

In accordance with VICH GL 43 (Target Animal Safety) classical reproductive safety studies would require administration of the test product at 3x RTD, and egg fertility, hatchability and chick viability should also be investigated. As the applicant has not provided these data, the above new study (TAS.UK.140375) was not considered suitable to conclude on the safety in breeding birds producing eggs for broiler stock or as replacement layers, or to conclude on the effects of overdoses on egg formation and the egg laying process. To reflect this, additional warnings have been added to the SPC:

*Egg formation*

- Section 4.7 of the SPC (pregnancy and lay):
  Add: *"The safety of the veterinary medicinal product has not been established during lay in turkeys. The product can be used in chickens laying eggs for human consumption as it has been shown to have no adverse effects on egg formation or the laying process at the recommended treatment dose."*
- For section 4.10 of the SPC (overdose):
  Add: "The effects of overdose on egg formation and the egg laying process have not been established in chickens."

In view of the lack of data demonstrating the effect of overdose in laying hens it is proposed to restart the periodic safety update report (PSUR) cycle for Aivlosin.

*Breeding birds*

The applicant considered that the warning used for the pig presentation(s), which was based on extrapolation of developmental toxicity data from laboratory studies in mammals, could also be applied to chickens, which in turn would allow the use of the product in breeding birds in accordance with benefit-risk assessment by the responsible veterinarian. However, no justification for the extrapolation of mammalian developmental toxicity data to birds could be provided by the applicant. The following warning was therefore added to the SPC

- Section 4.7 of the SPC (pregnancy and lay):
  Add: *"As the effect of the product on egg fertility, hatchability and chick viability has not been investigated, use in breeding birds producing eggs for broiler stock or as replacement layers is not recommended."*

## *5.5. Clinical studies*

Aivlosin currently has two indications in chickens, as follows:

- Treatment and prevention of respiratory disease associated with *Mycoplasma gallisepticum* in chickens.
- As an aid in the prevention strategy to reduce the clinical signs and mortality from respiratory disease in flocks, where infection in ovum with *M. gallisepticum* is likely because the disease is known to exist in the parent generation. The prevention strategy should include efforts to eliminate the infection from the parent generation.

No new clinical studies in layers were submitted, but cross-reference was made to field studies conducted in chicken, which were already submitted and assessed with the previous application adding chickens as a target species (EMEA/V/C/083/X/026). The CVMP considered that the clinical efficacy of a dose of 25 mg tylvalosin/kg bw over 3 days against *M. gallisepticum* could be extrapolated from broilers to older laying hens, and therefore accepted the absence of new field studies.

However, whilst the benefit-risk assessment for the current indications is still considered to be favourable, it is proposed to change the wording of section 4.2 of the SPC (indications). In field studies to support the claim '*Treatment and prevention of respiratory disease associated with* Mycoplasma gallisepticum *in chickens*,' all birds were treated once clinical signs were evident in 2 - 5% of the flock. This is considered to be a "treatment and metaphylaxis" approach, as outlined in the revised CVMP Guideline on the demonstration of efficacy for veterinary medicinal products containing antimicrobial

substances (EMA/CVMP/627/2001 Rev. 1). Therefore the first indication has been reworded to reflect this, as follows:

- 'Treatment and ~~prevention~~ metaphylaxis of respiratory ~~disease~~ infections ~~associated with~~ caused by *Mycoplasma gallisepticum* in chickens. The presence of the disease in the flock should be established before metaphylactic treatment.'

In field studies to support the second indication ('*As an aid in the prevention strategy…*), a proportion of chicks was serologically positive for *M. gallisepticum* prior to product administration during the first 3 days of life. In strict accordance with the definitions given in the revised CVMP guideline (EMA/CVMP/627/2001 Rev. 1), medication was not consistent with 'metaphylaxis' as there were no birds with clinical signs in the group. Also, the definition of 'prevention' does not fully apply as a proportion of the birds were assumed to be infected prior to drug administration due to *in ovum* transmission of the pathogen. For these reasons, the CVMP has proposed a re-wording of the current 'prevention' indication:

- 'As an aid in reducing the development of ~~in the prevention strategy to reduce the~~ clinical signs and mortality from respiratory disease in flocks, where infection in ovum with *M. gallisepticum* is likely because the disease is known to exist in the parent generation. ~~The prevention~~ This strategy should include efforts to eliminate the infection from the parent generation.

Furthermore, the CVMP considered that it is important to provide the end-user with precise information on the extent of benefits that can be expected from metaphylactic treatment in a flock. Therefore, based on clinical score data obtained from the field studies, the following text has been added to section 4.4 of the SPC (Special warnings for each target species):

- In field studies investigating the effect of treatment and metaphylaxis on mycoplasmosis, all birds (approximately 3 weeks old) received the product when clinical signs were evident in 2 - 5% of the flock. At 14 days after initiation of treatment, 16.7 - 25.0% morbidity and 0.3 - 3.9% mortality were observed in the treated group in comparison to 50.0 - 53.3% morbidity and 0.3 - 4.5% mortality in the untreated group.

  In further field studies, chicks from parent stock with evidence of *Mycoplasma gallisepticum* infection were administered Aivlosin for the first three days of life followed by a second course at 16 - 19 days of age (a period of management stress). By 34 days after the initiation of treatment, 17.5 - 20.0% morbidity and 1.5 - 2.3% mortality were observed in the treated groups in comparison to 50.0 - 53.3% morbidity and 2.5 - 4.8% mortality in the untreated groups."

## *5.6. Other changes to the SPC*

In line with the definitions given in the revised CVMP guideline (EMA/CVMP/627/2001 Rev. 1), CVMP also agreed that the term "prevention" should be replaced by "metaphylaxis" for the current indications for the pig presentations (premix for medicated feeding stuff, EU/2/04/44/001, 002), granules for use in drinking water (EU/2/04/44/009, 010, 012) and oral powder (EU/2/04/44/013):

Section 4.2 has been amended accordingly:

***Premix/ oral powder (pigs)***

- Treatment and ~~prevention~~ metaphylaxis of swine enzootic pneumonia caused by susceptible strains of *Mycoplasma hyopneumoniae* in pigs. At the recommended dose, lung lesions and weight loss are reduced but infection with *Mycoplasma hyopneumoniae* is not eliminated.
- Treatment of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis* in herds where there is a diagnosis based on clinical history, post-mortem findings and clinical pathology results.

- Treatment and metaphylaxis of ~~clinical outbreaks~~ of swine dysentery, caused by *Brachyspira hyodysenteriae* in herds where the disease has been diagnosed~~ and prevention of further clinical cases.~~

**Oral granules (pigs)**

Treatment and metaphylaxis ~~prevention~~ of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis*. The presence of the disease in the herd should be established before metaphylaxis ~~preventive treatment~~.

# 6. Benefit-risk assessment

Aivlosin 625 mg/g granules for use in drinking water is currently authorised in chickens (and turkeys) for respiratory diseases; however, it is currently not authorised for use in birds producing eggs for human consumption, and should not be used in chickens within 14 days of onset of lay and turkeys within 21 days of lay. This extension proposes a change in the withdrawal period for chicken eggs (zero-days), which would consequently allow the use of Aivlosin 625 mg/g granules for use in drinking water in laying hens. The restrictions in regard to its use in turkeys remain unchanged.

## *6.1. Benefit assessment*

Recent MIC data provided by the applicant indicated no clear evidence that use of Aivlosin has resulted in reduced susceptibility of *M. gallisepticum* to tylvalosin.

No new clinical studies in layers were submitted, but cross-reference was made to field studies conducted in broiler chickens, which were already submitted and assessed with the previous application adding chickens as a target species. The CVMP considered that the clinical efficacy of a dose of 25 mg tylvalosin/kg bw over 3 days against infections with *M. gallisepticum* could be extrapolated from broilers to older laying hens, and therefore accepted the absence of new field studies

However, changes to the wording of the indications have been made and further information included in the SPC regarding the expected benefits from metaphylactic treatment.

***Additional benefits***

There are few products authorised for use in chickens laying eggs for human consumption. As such, the addition of laying hens to the target species will increase the availability of medicines for this specific group of chickens.

## *6.2. Risk assessment*

Quality

The application does not affect the quality part of the dossier, as no changes to the pharmaceutical form and strengths are made.

For the user and the environment

The addition of laying hens to the target species is not expected to pose a risk to the user or the environment, when the product is used as recommended in the SPC.

For the consumer

An ADI of 124.2 µg per person per day for tylvalosin was previously established, from which an MRL of 200 µg/kg has been determined for eggs. A residue study in eggs has been conducted for this variation in accordance with GLP and VICH guidance. All samples were below the MRL at all timepoints and all validation criteria were met. Therefore a proposed zero-day withdrawal period following a dosing regimen of 25 mg TVN/kg bodyweight for 3 days is supported.

The use in turkeys laying eggs for human consumption remains contraindicated, and Aivlosin should not be used in turkeys within 21 days of the onset of lay.

For the target animal

The product elicited no systemic adverse reactions in laying hens, approximately 48-weeks old at the time of treatment. In addition, administration of the product at 1x the recommended dosage regimen did not appear to interfere with egg formation or the laying process. However, the effect of overdose at 3x RTD on the latter has not been investigated and a warning has therefore been added to section 4.10 of the SPC.

Furthermore, the applicant did not provide data on egg fertility, hatchability and chick viability. To reflect this, an additional warning for section 4.7 of the SPC has been included, stating that the product is not recommended for use in breeding birds producing eggs for broiler stock or replacement layers.

In view of the lack of data demonstrating the effect of overdose in laying hens it is proposed to restart the periodic safety update report (PSUR) cycle for Aivlosin. PSURs covering all authorised presentations of the product would be required at 6 monthly intervals for the next two years, followed by yearly for the subsequent two years and thereafter at 3 yearly intervals. The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 31 March 2016.

Resistance

With respect to antimicrobial resistance, there is no definitive evidence that use of the product has resulted in reduced susceptibility of the target pathogen, *M. gallisepticum,* to tylvalosin.

Regarding foodborne bacteria, tylvalosin is not active against either *Escherichia coli* or *Salmonella* spp., and therefore the greatest concern for public health is the risk of accelerated macrolide resistance development in *Campylobacter jejuni*. However, current macrolide resistance levels in *C. jejuni* isolates from chickens appear to be low and stable. Authorisation of Aivlosin for layers is anticipated to increase the extent of use of the product, though the additional risk of transmission of any macrolide-resistant *C. jejuni* from layers/eggs to humans is considered to be low. Appropriate warnings regarding prudent use of antimicrobials are already included in the SPC.

## *6.3. Evaluation of the benefit-risk balance*

The benefits of the product have previously been demonstrated during the extension procedure, EMEA/V/C/083/X/026. However, in line with current guidance, changes have been made to the wording of the indications and additional information regarding the expected benefits of metaphylactic use of the product are to be included in the SPC.

The product is well tolerated by layer chickens at the recommended dosage regimen. However, the effect of overdose on egg formation and the laying process has not been established. In addition, the effect of treatment on egg fertility, hatchability and chick viability have not been investigated. Relevant warnings are included in the SPC.

A sufficient withdrawal period has been proposed.

No change to the impact on the environment is envisaged.

The benefit-risk balance remains unchanged.

It was also recommended to restart the periodic safety update report (PSUR) cycle for Aivlosin.

The CVMP considers that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

## *6.4. Changes to the community marketing authorisation*

Changes are required in the Annexes to the Community marketing authorisation.

I, II, IIIA and IIIB, Annex A