ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Aivlosin 42.5 mg/g Premix for medicated feeding stuff for pigs.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Acetylisovaleryltylosin 42.5 mg/g
(as Acetylisovaleryltylosin tartrate)

Excipients:
Carrier: Magnesium trisilicate, wheat feed flour

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic properties

Pharmacotherapeutic group: Macrolide antibiotic, ATC vet code: QJ01FA92

Acetylisovaleryltylosin tartrate is a macrolide antibiotic that has antibacterial activity against Gram-positive and some Gram-negative organisms and against mycoplasma. It acts by inhibiting protein synthesis in the bacteria cell.

Macrolide antibiotics are the metabolites or semi-synthetic derivatives of metabolites of soil organisms obtained by fermentation. They fall into three classes depending on the size of the lactone ring. Those with a twelve membered ring have no clinical utility, whilst those with fourteen or sixteen membered rings are used in veterinary medicine. Acetylisovaleryltylosin has a sixteen membered ring. Due to the dimethylamino group, macrolides are basic.

The antibacterial spectrum is broadly similar for all macrolides irrespective of the size of the lactone ring. Macrolides interfere with protein synthesis by reversibly binding to the 50S ribosome subunit. They bind to the donor site and prevent the translocation necessary for keeping the peptide chain growing. Their effect is essentially confined to rapidly dividing organisms. Macrolides are generally considered bacteriostatic, but at high concentrations they may be bactericidal.

The MIC50 for acetylisovaleryltylosin is ≤0.015 µg/ml, the MIC90 for all isolates is 0.06 µg/ml and the range is 0.005-0.25 µg/ml. Based on clinical studies, strains of Mycoplasma hyopneumoniae with MIC ≤ 0.06 µg/ml for acetylisovaleryltylosin tartrate are regarded as sensitive for Aivlosin treatment.

Resistance mechanisms and development

It is considered that there are multiple mechanisms responsible for resistance development to macrolide compounds: namely alteration of the ribosomal target site, utilisation of active efflux mechanism and production of inactivating enzymes.

Resistance to acetylisovaleryltylosin by M. hyopneumoniae has not been reported or found in the field to date. Resistance does, however, have the potential to develop to antimicrobial products. Cross-resistance between Aivlosin and other macrolide antibiotics cannot be excluded.
4.2 Pharmacokinetic properties

Acetylisovaleryltylosin tartrate is rapidly absorbed after oral administration of Aivlosin. After administration of the recommended dose, the plasma concentrations are below the limit of quantification (12.5 ng/ml) at all time points measured; however, lung concentrations of 0.060 – 0.066 µg/ml were found. The parent compound and a metabolite 3-O-acetyltulosin are widely distributed in the tissues. Highest concentrations were found in the bile, spleen, lungs, kidney and liver. *In vitro* metabolism studies have confirmed that the parent compound is rapidly metabolised. In a trial with $^{14}$C aivlosin administered at 2.125 mg/kg to pigs for 7 days over 70% of the dose was excreted in the faeces, with urinary excretion accounting for 3 to 4% of the dose.

5. CLINICAL PARTICULARS

5.1 Target species

Pigs

5.2 Indications for use

Treatment and prevention 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.

5.3 Contraindications

None

5.4 Undesirable effects (frequency and seriousness)

None known.

5.5 Special precautions for use

It is sound clinical practice to base treatment on susceptibility testing.

5.6 Use during pregnancy and lactation

The safety of Aivlosin during pregnancy and lactation has not been established in pigs. Use only in accordance with risk/benefit assessment by the responsible veterinarian. Studies in laboratory animals have not produced any evidence of teratogenicity. Maternal toxicity in rodents has been observed at doses of 400 mg acetylisovaleryltylosin per kg bodyweight and above. In mice, a slight reduction in the foetal bodyweight was seen at doses causing maternal toxicity.

5.7 Interaction with other medicinal products and other forms of interaction

None known

5.8 Posology and method of administration

In-feed use.

The dosage is 2.125 mg acetylisovaleryltylosin per kg bodyweight per day in-feed for 7 consecutive days.

This is normally achieved by incorporating Aivlosin at a level of 1 kg/tonne feed to provide 42.5 mg acetylisovaleryltylosin per kg feed, assuming that a pig eats 5% of its bodyweight in feed.
The medicated feed should be fed as the sole ration for 7 days. In older pigs, or in pigs with reduced appetite, or on restricted feed intake, inclusion levels may need to be increased to achieve target dosage. Acute cases and severely diseased pigs with reduced food or water intake should be treated with a suitable injectable product.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

**Mixing Instructions:**

A horizontal ribbon mixer should be used to incorporate the product into the feeding stuff. It is recommended that Aivlosin is first mixed into 10 kg of the feeding stuff, followed by the rest of the feeding stuff and mixed well. Medicated feed may then be pelleted. Pelleting conditions involve pre-conditioning ingredients with steam for 5 minutes and pelleting at 70°C under normal conditions.

**5.9 Overdose**

No signs of intolerance have been observed in growing pigs at up to 10 times the recommended dosage.

**5.10 Special warnings for each target species**

Pigs with acute infections and severely reduced feed intake should be treated with a suitable injectable product first.

**5.11 Withdrawal period(s)**

Meat and offal: Two days

**5.12 Special precautions to be taken by the person administering the medicinal product to animals**

Because Aivlosin has been shown to cause hypersensitivity reactions in laboratory animals, people with known hypersensitivity to acetylisovaleryltylosin tartrate should avoid any contact with the product.

When mixing the veterinary medicinal product and handling the medicated feed, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment should be worn when mixing the veterinary medicinal product or handling the medicated feed: overalls, impervious gloves and either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator conforming to European Standard EN 140, with a filter to European Standard EN 143. Wash contaminated skin.

In case of accidental ingestion seek medical advice immediately and show the label to the physician.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 Major incompatibilities**

None known, but in the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

**6.2 Shelf life**

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf life after incorporation into meal or pelleted feed: 1 month
6.3. **Special precautions for storage**
Do not store above 25°C
Keep the container tightly closed.
Store in the original container.

6.4 **Nature and contents of container**
One polyethylene lined paper bag containing 20 kg.

6.5 **Special precautions for the disposal of unused medicinal product or waste materials, if any**
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. **NAME OR CORPORATE NAME AND ADDRESS OR REGISTERED PLACE OF BUSINESS OF THE MARKETING AUTHORISATION HOLDER**

ECO Animal Health Limited
78 Coombe Road
New Malden
Surrey
KT3 4QS
United Kingdom

**Prohibition of sale, supply and/or use**

Consideration should be given to official guidance on the incorporation of medicated premixes in final feed.

**Marketing Authorisation number**

EU/2/04/044/001

**Date of first authorisation**

<MAH to insert date of Commission Decision>

**Date of revision of the text**

<MAH to insert date of last Commission Decision>
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION INCLUDING RESTRICTIONS REGARDING SUPPLY AND USE

C. PROHIBITION OF SALE, SUPPLY AND/OR USE

D. STATEMENT OF THE MRLs
A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Gallows Green Services Limited
Cod Beck Blenders, Cod Beck Mill
Dalton, Thirsk, North Yorkshire
YO7 3HR
United Kingdom

B. CONDITIONS OF THE MARKETING AUTHORISATION INCLUDING RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

• OTHER CONDITIONS:

Consideration should be given to official guidance on the incorporation of medicated premixes in final feed.

C. PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable

D. STATEMENT OF THE MRLs

MRLs for acetylisovaleryltylosin have been included in Annex I of Council Regulation (EEC) No. 2377/90 as follows:

<table>
<thead>
<tr>
<th>Pharmacologically active substance(s)</th>
<th>Marker residue</th>
<th>Animal Species</th>
<th>MRLs</th>
<th>Target tissues</th>
<th>Other provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylisovaleryltylosin</td>
<td>Sum of acetyliso-valeryltylosin and 3-O-acetyltylosin</td>
<td>Porcine</td>
<td>50 µg/kg</td>
<td>Muscle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 µg/kg</td>
<td>Skin and fat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 µg/kg</td>
<td>Liver</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>50 µg/kg</td>
<td>Kidney</td>
<td></td>
</tr>
</tbody>
</table>

Magnesium trisilicate (= Sepiolite) is included in Annex II of Council Regulation (EEC) No. 2377/90 and an approved food additive with E-number (E553a) for all food producing species. Wheat feed flour is considered as not falling within the scope of Council Regulation (EEC) No 2377/90.
ANNEX III

LABELLING AND / PACKAGE INSERT*

*all text is included on the immediate label, since there is no package insert
A. LABELLING
1. **NAME OF THE VETERINARY MEDICINAL PRODUCT**

Aivlosin 42.5 mg/g premix for medicated feeding stuff for pigs.

2. **STATEMENT OF ACTIVE AND OTHER SUBSTANCES**

   **Active substance**
   Acetylisovaleryltylosin 42.5 mg/g
   (as Acetylisovaleryltylosin tartrate)

   **Carrier:**
   Magnesium trisilicate, wheat feed flour

3. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE IN THE EEA, IF DIFFERENT**

   **Marketing Authorisation Holder and Manufacturer:**
   ECO Animal Health Limited
   78 Coombe Road
   New Malden
   Surrey
   KT3 4QS
   United Kingdom

   **Manufacturer responsible for batch release:**
   Gallows Green Services Limited
   Cod Beck Blenders, Cod Beck Mill
   Dalton, Thirsk, North Yorkshire
   YO7 3HR
   United Kingdom

4. **PHARMACEUTICAL FORM:**

   Premix for medicated feeding stuff

5. **PACKAGE SIZE**

   20 kg

6. **TARGET SPECIES**

   Pigs
7. INDICATIONS

Treatment and prevention of Swine Enzootic Pneumonia caused by susceptible strains of *Mycoplasma hyopneumoniae*. At the recommended dose, lung lesions and weight loss are reduced but infection with *Mycoplasma hyopneumoniae* is not eliminated.

8. DOSAGE, METHOD AND ROUTE OF ADMINISTRATION

In-feed use.

The dosage is 2.125 mg acetylisovaleryltylosin per kg bodyweight per day.

This is normally achieved by incorporating Aivlosin at a level of 1 kg/tonne feed to provide 42.5 mg acetylisovaleryltylosin per kg feed, assuming that a pig eats 5% of its bodyweight in feed.

The medicated feed should be fed as the sole ration for 7 days. In older pigs, or in pigs with reduced appetite, or on restricted feed intake, inclusion levels may need to be increased to achieve target dosage. Acute cases and severely diseased pigs with reduced food or water intake should be treated with a suitable injectable product.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

9. ADVICE ON CORRECT ADMINISTRATION

Mixing Instructions

A horizontal ribbon mixer should be used to incorporate the product into feeding stuff. It is recommended that Aivlosin is first mixed with 10 kg of the feeding stuff, followed by the rest of the feeding stuff and mixed well. Medicated feed may then be pelleted. Pelleting conditions involve pre-conditioning ingredients with steam for 5 minutes and pelleting at 70°C under normal conditions.

No known incompatibilities, but in the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

10. CONTRAINDICATIONS

    None

11. UNDESIRABLE EFFECTS

None known
If you notice any side effects, please inform your veterinary surgeon.

12. WITHDRAWAL PERIOD

    Meat and offal: Two days
13. **SPECIAL STORAGE CONDITIONS**

Keep out of the reach and sight of children.
Do not store above 25°C.
Keep the container tightly closed.
Store in the original container.

Do not use after the expiry date stated on the label.

Shelf life after incorporation into meal or pelleted feed: 1 month

14. **EXPIRY DATE**

EXP **/****

15. **SPECIAL WARNING(S)**

When mixing the veterinary medicinal product and handling the medicated feed, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment should be worn when mixing the veterinary medicinal product or handling the medicated feed: overalls, impervious gloves and either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator conforming to European Standard EN 140, with a filter to European Standard EN 143. Wash contaminated skin.

In case of accidental ingestion seek medical advice immediately and show the label to the physician. Because Aivlosin has been shown to cause hypersensitivity reactions in laboratory animals, people with known hypersensitivity to acetylisovaleryltylosin tartrate should avoid any contact with the product.

The safety of Aivlosin during pregnancy and lactation has not been established in pigs. Use only in accordance with risk/benefit assessment by the responsible veterinarian. Studies in laboratory animals have not produced any evidence of teratogenicity. Maternal toxicity in rodents has been observed at doses of 400 mg acetylisovaleryltylosin per kg bodyweight and above. In mice, a slight reduction in the foetal bodyweight was seen at doses causing maternal toxicity.

16. **SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED VETERINARY MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH VETERINARY MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

17. **THE WORDS “FOR ANIMAL TREATMENT ONLY“**

For animal treatment only

18. **NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

EU/2/04/044/001
19. MANUFACTURER’S BATCH NUMBER

Batch No:

20. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription. Consideration should be given to official guidance on the incorporation of medicated premixes in final feed.

21. DATE ON WHICH THE TEXT WAS LAST REVISED

<to be included by MAH>