ADVICE SUMMARY

APPLICATION FOR REGISTRATION OF A CHEMICAL PRODUCT

Product name: SEQUEL ABAMECTIN/LEVAMISOLE COMBI DRENCH FOR SHEEP
Applicant: ANCARE SCIENTIFIC LTD
Product number: 64460
Application number: 48413

Purpose of Application and Description of Use:
Registration of a 1 g/L Abamectin, 40 g/L Levamisole hydrochloride, 0.5 g/L Selenium and 2.2 g/L Cobalt oral drench product for the treatment and control of susceptible strains of adult and immature gastro-intestinal parasites in sheep.

Active Constituent(s):
- ABAMECTIN
- LEVAMISOLE (AS HYDROCHLORIDE)
- SELENIUM (AS SELENATE)
- COBALT (AS DISODIUM EDTA)

Regulatory Decision:
To grant the application subject to the following conditions:

Standard Conditions of Registration/Approval
1. Containers must meet AgVet Code Regulation 18
2. Product must not be supplied without meeting GMP Requirements
3. Label must contain an Expiry Date and Batch Number

For full conditions, refer to Standard Conditions for Applications on the APVMA website.
Non-Standard Conditions of Registration/Approval
NIL

ADVICE

Australian Government Department Of Health And Ageing, Office Of Chemical Safety (OCSEH)

The Office of Chemical Safety (OCSEH) conducted a health risk assessment for the new combination and concluded that there were no objections based on human health grounds to the registration of this product and that the APVMA should be satisfied that the registration and proposed use of the product/actives would not be an undue health hazard for humans.

Both anthelmintic actives are known and approved for use in food producing animals (including sheep) with ADIs already set for both active constituents. Cobalt and selenium have no ADI or ARfD and no new data was submitted for evaluation. No acute toxicological or occupational health and safety studies were submitted with this application.

The acute toxicity of the product was estimated based on calculations using the tolerable daily doses of abamectin and levamisole. The product was considered likely to have moderate acute oral and dermal toxicity, low inhalational toxicity, be a slight skin and eye irritant and not to be a skin sensitiser.

The following labelling recommendations were provided.

SCHEDULING:

OCSEH advised that, based on levels of levamisole and abamectin, the product was included in Schedule 5 of the MUSDP and that, based on selenium content, the product was included in Schedule 6 of the MUSDP

FIRST AID INSTRUCTIONS:

Adequately covered by existing instructions (a and f). These codes translate to: If poisoning occurs, contact a doctor or Poisons information Centre. Phone Australia 131126; New Zealand 0800 764 766. If skin contact occurs, remove contaminated clothing and wash skin thoroughly
SAFETY DIRECTIONS: New entry for this new combination of active constituents:

[Hazards] Harmful if inhaled. Poisonous if absorbed by skin contact or swallowed. May irritate eyes and skin.

[Precautions] Avoid contact with eyes and skin

[When mixing or using] When opening the container and using product, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length, chemical resistant gloves. If clothing becomes contaminated with product remove clothing immediately. If product in eyes, wash it out immediately with water. If product on skin, wash area immediately with soap and water.

[After use]: After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each day’s use wash gloves and contaminated clothing

RE-ENTRY and RE-HANDLING STATEMENTS: Not required

GENERAL STATEMENTS AND SAFETY PRECAUTIONS: Not required

MSDS. The product was determined to be hazardous requiring the following risk phrase; R20/21/22 Harmful by inhalation, in contact with skin and if swallowed.

APVMA Veterinary Residues Team

Data was submitted by Ancare Scientific Limited to support the application. That data included one Australian study to determine residues of abamectin and levamisole in edible issues of merino and crossbred sheep. The Veterinary Residues Team evaluated the available metabolism, residues trials, analytical methodology, fate in storage, processing data and residues in trade issues and concluded that this new product was not an undue hazard to the safety of consumers exposed to residues, and that there was no undue prejudice to Australia’s overseas trade in commodities from treated animals.

The Veterinary Residues Team supported registration of the product provided that the following statements appeared on the approved label:

Restraints:
DO NOT treat lambs less than 15 kg bodyweight.
DO NOT USE in sheep which are producing or may in future produce milk where the milk or milk products may be used for human consumption.

Re-treatment Interval:
DO NOT re-treat animals for 6 weeks after last treatment

Withholding Periods:
MEAT: DO NOT USE less than 14 days before slaughter for human consumption
MILK:: DO NOT USE in sheep which are producing or may in future produce milk where the milk or milk products may be used for human consumption.

Trade Advice:
Export Slaughter Interval (ESI): DO NOT USE less than 42 days before slaughter for export.

Data relied on to provide the advice

<table>
<thead>
<tr>
<th>Data No</th>
<th>Data Source*</th>
<th>Author(s)</th>
<th>Title</th>
<th>Date</th>
<th>Data Type</th>
<th>Data Sub-type</th>
<th>Authorising Party</th>
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<tr>
<td>43126</td>
<td>S</td>
<td>Agrisearch Analytical Pty Ltd</td>
<td>Determination of Levamisole Residues in Animal Tissues and Milk by LC/MS/MS, AATM-R-88, Revision 2</td>
<td>May 2007</td>
<td>Residues</td>
<td>Analytical Methods</td>
<td>Applicant</td>
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<td>43127</td>
<td>S</td>
<td>Agrisearch Analytical Pty Ltd</td>
<td>Determination of Macrocyclic Lactone Residues in Bovine and Ovine Tissues, AATM-R-53, Revision 7</td>
<td>August 2007</td>
<td>Residues</td>
<td>Analytical Methods</td>
<td>Applicant</td>
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<td>43156</td>
<td>S</td>
<td>Ridley, I</td>
<td>Tissue residues of Abamectin and Levamisole in edible tissues of sheep following oral drenching with Switch Hi-Mineral Oral Sheep Drench</td>
<td>September 2009</td>
<td>Residues</td>
<td>Animal Commodity Residues Direct Application</td>
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<td>43134</td>
<td>S</td>
<td>EMEA</td>
<td>EMEA Summary Report of the European Agency for the Evaluation of Medicinal Products - Levamisole (2)</td>
<td>Unknown</td>
<td>Residues</td>
<td>Other Information</td>
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External Efficacy and Safety Reviewer

Efficacy:

Efficacy was assessed by an external efficacy reviewer where it was concluded that the product, if used as proposed and approved, would be effective according to criteria determined by the APVMA.

Two confirmatory clinical studies were conducted in New South Wales in which the test product was assessed against artificial infections of susceptible strains of major GIT parasite infections. In these studies the test product was found to be highly effective (>99%) in reducing faecal egg output and
eliminating susceptible strains of adult and immature (L4) stages of *H. contortus*, *Teladorsagia circumcincta*, *Trichostrongylus colubriformis* and *Oesophagostomum spp.*

Two confirmatory field studies were also conducted in northern and southern NSW where the test product was assessed against naturally acquired infections of major GIT parasite species (*Haemonchus* spp, *Teladorsagia* spp, *Trichostrongylus* spp, *Cooperia* spp and *Oesophagostomum* spp. The test product was shown to be highly effective in eliminating established burdens of mixed GIT strongyle parasites including strains showing single resistance to either benzimidazole or levamisole.

Collectively the proposed label claims for the control of adult and immature GIT parasites (including those showing single resistance to benzimidazole and imidaothiazoles) in sheep were supported.

Claims for the effective supplementation of selenium and cobalt, where dietary intakes are known to be deficient, were supported.

**Target animal safety:**

Two target animal safety studies were assessed by an external efficacy reviewer where it was concluded that an adequate 3x margin of safety had been demonstrated and that the product, if used in accordance with its approved use, would not be likely to have an unintended effect that is harmful to the host animals.

One of these studies also used two developmental products containing either 3 or 4 active constituents where young lambs were treated at 1x and 3x dose rates and compared to untreated controls. Such an extrapolation was considered not appropriate for determining the margin of safety of the test product.

In a further study using the proposed product, at either 1x or 3x the nominal label dose rate of test product, was also evaluated. Each treatment group was compared to a third group of untreated control lambs. Individual clinical examinations as well as haematological and biochemical analyses were conducted. No significant effects were found between treated and control animals for the measured variables indicating that the product had no adverse effects at three times the approved label dose rate.

**Data relied on to provide the advice**

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<tr>
<td>43154</td>
<td>S</td>
<td>Neilsen, R</td>
<td>Therapeutic efficacy against <em>Haemonchus contortus</em>, <em>Teladorsagia circumcincta</em>, <em>Trichostrongylus colubriformis</em> and <em>Oesophagostomum spp.</em> of a mineralised combination abamectin and levamisole drench when administered orally to sheep, relative to negative controls. (Artificial Infection, Faecal Egg Count Reduction and Sacrifice Study).</td>
<td>November 2008</td>
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<td>43128</td>
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<td>Cooper, C</td>
<td>Determination of the anthelmintic efficacy (via Faecal Egg Count Reduction) of an oral mineralised combination abamectin and levamisole drench against a naturally acquired roundworm infection in sheep. Southern NSW.</td>
<td>September 2008</td>
<td>Efficacy and Safety</td>
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<td>43129</td>
<td>S</td>
<td>Cooper, C</td>
<td>Determination of the anthelmintic efficacy (via Faecal Egg Count Reduction) of an oral mineralised combination abamectin and levamisole drench against a naturally acquired roundworm infection in sheep. Northern NSW.</td>
<td>September 2008</td>
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<td>43155</td>
<td>S</td>
<td>Dever, M</td>
<td>Therapeutic efficacy against susceptible strains of immature Haemonchus contortus, Teladorsagia circumcincta and Trichostrongylus colubriformis of a mineralised combination abamectin and levamisole drench and a moxidectin and selenium oral drench when administered orally to sheep, relative to a negative control group. (Artificial Infection, Faecal Egg Count Reduction and Sacrifice)</td>
<td>July 2009</td>
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<td>Efficacy</td>
<td>Applicant</td>
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<td>43148</td>
<td>S</td>
<td>Loveridge, B</td>
<td>Safety of a combination abamectin/levamisole/oxfendazole oral drench and a combination abamectin/levamisole/oxfendazole/praziquantel oral drench when administered at 1X and 3X the standard dose rate to lambs</td>
<td>October 2003</td>
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<td>50735</td>
<td>S</td>
<td>Short, C</td>
<td>Target animal safety study to evaluate the safety profile in sheep of a combined abamectin and levamisole mineralised drench when administered at 1x and 3x the recommended dose rate 526-2-CS23-0211</td>
<td>March 2011</td>
<td>Efficacy and Safety</td>
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*S = Data submitted with the application