[Version 9, 07/2021]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

BIOTILINA 100 mg/g premix for medicated feed for pigs and rabbits

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Active substances:
Valnemulin .....100.0 mg
(as valnemulin hydrochloride ...…….106.5 mg)

Excipients: Qualitative composition of excipients and other constituents
Almond hulls
Silicon dioxide E 551
Paraffin, light liquid

Brown powder without lumps and homogeneous appearance.

3. CLINICAL INFORMATION

3.1 Target species

Pigs and rabbits.

3.2 Indications for use for each target species

Pigs:
- Treatment and metaphylaxis of swine dysentery associated with *Brachyspira hyodysenteria* susceptible to valnemulin.
- Treatment of clinical signs of porcine proliferative enteropathy (ileitis) associated with *Lawsonia intracellularis* susceptible to valnemulin.
- Treatment and metaphylaxis of swine enzootic pneumonia associated with *Mycoplasma hyopneumoniae* susceptible to valnemulin.

The presence of the disease in the group must be established before the product is used.

Rabbits: Reduction of mortality during an outbreak of epizootic rabbit enteropathy (ERE). Treatment should be started early in the outbreak, when the first rabbit has been diagnosed with the disease clinically.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

Do not administer the veterinary medicinal product to pigs or rabbits receiving ionophores. Do not overdose in rabbits – increased doses may disturb gastrointestinal flora leading to the development of enterotoxaemia.

3.4 Special warnings

Pigs: As an adjunct to treatment, good management and hygiene practices should be introduced in order to reduce the risk of infection and to control the potential build-up of resistance.

Especially in the case of swine dysentery, a targeted early eradication programme of the disease should be considered.

Rabbits: The product should be used as part of a programme including measures aimed at controlling the disease on farm such as biosecurity and husbandry controls. Clinical diagnosis should be confirmed by necropsy. Rabbits may still show clinical signs of Epizootic Rabbit Enteropathy (ERE) even when treated with the product. However, mortality in affected rabbits is reduced by administering the product. In a field trial, treated rabbits showed a lower frequency of impaction and diarrhoea than untreated rabbits (4% and 12% vs 9% and 13%, respectively). Impaction is more frequently seen in rabbits that die. Tympanism is more frequently reported in rabbits treated with the product than untreated rabbits (27% vs16%). A large proportion of tympanic rabbits will recover.

Animals with reduced ingestion should be treated parenterally.

Cross-resistance has been shown between pleuromutilins and oxazolidinones, phenicols, streptogramin A, lincosamides in porcines isolates of MRSA. Use of the valnemulin should be carefully considered when antimicrobial susceptibility testing has shown resistance to pleuromutilins, oxazolidinones, phenicols, streptogramin A and lincosamides because its effectiveness may be reduced.

Long term or repeated use should be avoided by improving management practice and thorough cleansing and disinfection.

At the recommended dosage of 10–12 mg/kg bodyweight, lung lesions and weight loss are reduced, but infection with *Mycoplasma hyopneumoniae* is not eliminated.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Adverse reactions have occurred in pigs following the use of the veterinary medicinal product. Their occurrence appears to be mainly associated with breed mixes that include Danish and/or Swedish Landrace. Extreme care should therefore be taken in the use of the veterinary medicinal product in pigs of the Danish and Swedish Landrace breeds, and their crossbreeds thereof, especially in younger pigs. When treating infections caused by *Brachyspira spp.*, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.

Only use in the case of confirmed epizootic rabbit enteropathy (ERE) outbreaks when diagnosis has been made clinically and confirmed by necropsy.
Due to the likely variability (time, geographical) in the occurrence of resistance of bacteria for pleuromutilins, the use of the product should be based on susceptibility testing and take into account official and local antimicrobial policies.
Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to valnemulin and may decrease the effectiveness of treatment with other pleuromutilins and other antimicrobials due to the potential for cross - resistance (refer to section3.4 and 4.2).
If there is no response to treatment within 3 days, the diagnosis should be re-established.
Special precautions to be taken by the person administering the veterinary medicinal product to animals
Valnemulin may cause allergic reactions. People with known hypersensitivity to valnemulin should administer the veterinary medicinal product with caution. When mixing the veterinary medicinal product, and handling the final feed containing the product, direct contact with the skin and mucous membranes should be avoided. Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:Valnemulin is toxic for terrestrial plants.
Valnemulin is classified as persistence substance.

3.6 Adverse events

Rabbits: See section3.4

Pigs: Adverse drug reactions following the use of the veterinary medicinal product are mainly associated with breeds and cross breeds of Danish and/or Swedish Landrace.

Very common (>1 animal / 10 animals treated):	Pyrexia[1] Anorexia[1] Ataxia[1] Recumbency[1]
Common (1 to 10 animals / 100 animals treated):	Mortality[2] Oedema Erythema (on the hindquarters) Palpebral oedema Reduced feed intake[3]

[1] *On affected farms, one third of the pigs treated were affected, with a mortality of 1%.*
[2] *In controlled trials in susceptible animals mortality was less than 1%."*
[3] *At concentrations above 200 mg valnemulin / kg feed, associated with unpalatability during the first few days of feeding.*

In the case of an adverse reaction, immediate withdrawal of medication is recommended. Severely affected pigs should be removed to clean dry pens and given appropriate treatment, including treatment for concurrent disease.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder, or its local representative or the national competent authority via the national reporting system. See also the last section of the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:

The safety of the veterinary medicinal product has not been established during pregnancy nor lactation.
Laboratory studies in rats and mice have not produced any evidence of a teratogenic effects.
Use only according to the benefit/risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

Valnemulin has been shown to interact with ionophores such as monensin, salinomycin and narasin and may result in signs indistinguishable from an ionophore toxicosis. Animals should not receive products containing monensin, salinomycin or narasin, during or at least 5 days before or after treatment with valnemulin. Severe growth depression, ataxia, paralysis or death may result.

3.9 Administration routes and dosage

In feed use
The intakeof medicated feed depends on the clinical condition of the animal. In order to obtain the correct dosage, the concentration of Valnemulin may need to be adjusted accordingly. Incorporation rate may also need to be increased in older pigs or pigs on restricted feed to achieve target dosage.

To ensure a correct dosage, body weight should be determined as accurately as possible.

The incorporation rate of premix per kg of feed should be calculated according to following formula:
mg of premix/kg feed = Dosage required (mg of valnemulin/kg bodyweight) x 10 x bodyweight (kg)/Daily feed intake (kg).

Pigs:

Treatment and metaphylaxis of swine dysentery
3–4 mg valnemulin/kg bodyweight/day for 7-10 days. For a feed intake of 50 g/kg of bodyweight, this dose corresponds to 0.6-0.8 kg/ton of premix in medicated feed (equivalent to 60 - 80 g of valnemulin per ton of medicated feed).

It is important to institute medication as early as possible in an outbreak of swine dysentery. If there is no response to treatment within 5 days, the diagnosis should be re-established. The presence of the disease in the group must be established before the product is used.

Treatment of clinical signs of porcine proliferative enteropathy (ileitis)
3–4 mg valnemulin/kg bodyweight/day for 2 weeks. For a feed intake of 50 g/kg of bodyweight, this dose corresponds to 0.6-0.8 kg/ton of premix in medicated feed (equivalent to 60 - 80 g of valnemulin per ton of medicated feed).

It is important to institute medication as early as possible in an outbreak of porcine proliferative enteropathy. If there is no response to treatment within 5 days, the diagnosis should be re-established.
For severely affected animals which fail to respond to treatment within 3–5 days, parenteral treatment should be considered.

Treatment and metaphylaxis of swine enzootic pneumonia
10-12 mg valnemulin/kg bodyweight/day up to 3 weeks. For a feed intake of 50 g/kg of bodyweight, this dose corresponds to 2-2.4 kg/ton of premix in medicated feed (equivalent to 200 - 240 g of valnemulin per ton of medicated feed).

Secondary infection by organisms such *as Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication. The presence of the disease in the group must be established before the product is used.

Rabbits:

Reduction of mortality caused by epizootic rabbit enteropathy
3 mg/kg bodyweight/day for 21 days. For a feed intake of 85 g/kg of bodyweight, this dose corresponds to 0.35 kg/ton of premix in medicated feed (equivalent to 35 g of valnemulin per ton of medicated feed).
The daily feed consumption should be recorded and the inclusion rate should be adjusted accordingly.

Repeated use of valnemulin should be avoided by improving management practice and thorough cleansing and disinfection. Consideration should be given to the eradication of infection from the farm.

Mixing instructions:

Aggressive pelleting conditions such as temperatures in excess of 80 °C (matrix temperature), and the use of abrasive substances for pre-mixture should be avoided.

To ensure adequate distribution of the product in the final feed it is recommended to premix the product at a ratio of 1:10-200 with a feed ingredient of similar physical nature (e.g. wheat middlings) before blending into the final feed.

To prepare the premixture, the amount of premix that will be incorporated to 50 kg of feed ingredient, for manufacturing 1000 kg feedstuff is detailed below:

35 ppm medicated feeding stuff: 350 g of premix in 50 kg of similar nature feed ingredient.
75 ppm medicated feeding stuff: 750 g of premix in 50 kg of similar nature feed ingredient.
200 ppm medicated feeding stuff: 2000 g of premix in 50 kg of similar nature feed ingredient.

After the preparation of the medicated premixture, it is incorporated into the remaining quantity of feeding stuff to reach 1000 kg and mixed.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Toxic signs have not been seen in pigs given 5 times the recommended dose. Do not overdose in rabbits – increased doses may disturb gastrointestinal flora leading to the development of enterotoxaemia (see section 3.3).

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

This veterinary medicinal product is intended to be used for the preparation of medicated feed.
Do not use for prophylaxis.

3.12 Withdrawal period

Pigs:
Meat and offal: 1 day.

Rabbits:
Meat and offal: Zero days.

4. PHARMACOLOGICAL INFORMATION

4.1. **ATCvet code:** QJ01XQ02

4.2 Pharmacodynamics

Valnemulin is an antibiotic belonging to the pleuromutilin group, which acts by the inhibition of the initiation of protein synthesis at the level of the bacterial ribosome. Valnemulin shows activity against *Mycoplasma spp*., *Lawsonia intracellularis,* and spirochaetes such as *Brachyspira hyodysenteriae.*

Valnemulin binds to the 50S subunit of the ribosome and strongly inhibits peptidyl transferase involved in bacterial protein synthesis. Resistance development primarily occurs by chromosomal mutations in the 23 rRNA and rplC genes associated with bacteria ribosoma. These mutations emerge relatively slowly and in a stepwise fashion and are not transferred horizontally. Furthermore, resistance genes like vga genes and cfr genes can be located in mobile genetic elements and hence transferable between bacteria and different bacterial species.

In some European regions, an increasing proportion of *Brachyspira hyodysenteriae* isolates from clinical cases demonstrate significantly reduced *in vitro* susceptibility to pleuromutilins. Cross-resistance has been shown between pleuromutilins and oxazolidinones, phenicols, streptogramin A, lincosamides in porcine isolates of MRSA. (refer to section 3.4).

4.3 Pharmacokinetics

In pigs, after a single oral dose of radiolabelled material >90% absorption was demonstrated. Maximum plasma concentrations (C_{max}) of radio-labelled or 'cold' material were obtained 1–4 hours after dosing (t_{max}) with a terminal half-life ($t_{½}$), estimated from non-radioactive data, between 1 and

4½ hours. A linear relationship between concentration and dose administered was established. After repeat dosing, slight accumulation occurred, but a steady state was achieved within 5 days.

Because of a marked 'first pass' effect, plasma concentrations are affected by the method of administration, but valnemulin is highly concentrated in tissues, particularly the lungs and liver, relative to plasma. Five days after the last of 15 doses of radiolabelled valnemulin administered to pigs, the concentration in liver was >6 times that in plasma. Two hours after withdrawal of premix given in feed twice daily for 4 weeks at a dose of 15 mg/kg bodyweight/day, liver concentration was 1.58 µg/g and lung concentration 0.23 µg/g whereas concentrations in plasma were below the limit of detection.

In pigs valnemulin is extensively metabolised and excretion of parent molecule and metabolites occurs mainly via bile. 73% – 95% of the daily dose of total radioactivity was recovered from the faeces. The plasma half-life was 1.3–2.7 hours, and the majority of the total radioactivity administered was excreted within 3 days of the last administration. In rabbits, valnemulin is extensively metabolised with the same metabolites being found as in pigs. In liver, traces of valnemulin were observed.

Environmental properties

Valnemulin is toxic for terrestrial plants. Valnemulin is classified as persistence substance.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 30 months
Shelf life after first opening the immediate packaging: 6 months
Shelf life after incorporation into meal pig feed: 1 month
Shelf life after incorporation into pelleted pig feed and protected from light and moisture: 3 weeks
Shelf life after incorporation into pelleted rabbit feed and protected from light and moisture: 4 weeks

5.3. Special precautions for storage

Keep the bag tightly closed in order to protect from light.

5.4. Nature and composition of immediate packaging

25 kg multi-layer bag made of low-density polyethylene/paper/paper/paper.

Package size:
Bag of 25 kg

Not all pack sizes may be marketed.

5.5. Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

VETPHARMA ANIMAL HEALTH, S.L.
Les Corts, 23
08028 - Barcelona
Spain

7. MARKETING AUTHORISATION NUMBERS

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}>

9 DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{MM/YYYY}

PROHIBITION OF SALE, SUPPLY AND/OR USE

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

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database. (https://medicines.health.europa.eu/veterinary)