TILMI PLUS 200 Premix

MAL no.:

Active Ingredient:
Each kg contains
Tilmicosin (as phosphate) ---------- 200.0g

Product Description:
Almost white to slightly yellow powder which is incorporated in animal feeding stuff

Dosage form:
Premix for medicated feeding stuff

Pharmacodynamics:
Tilmicosin is a semi-synthetic antibiotic of the macrolide group, and is believed to affect protein synthesis. It has bacteriostatic action but at high concentrations it may be bactericidal. This antibacterial activity is predominantly against Gram-positive microorganism with activity against certain gram-negative ones and Mycoplasma of a bovine, porcine, ovine and avian origin. In particular its activity has been demonstrated against the following micro-organism: Pigs- *Mycoplasma hyopneumoniae, Pasteurella multocida, Actinobacillus pleuropneumoniae.* Rabbits- *Pasteurella multocida, Staphylococcus aureus* and *Bordetella bronchoseptica*. Scientific evidence suggests that macrolides act synergistically with the host immune system. Macrolides appear to enhance phagocyte killing of bacteria. Tilmicosin has been shown to inhibit *in vitro* the replication of the Porcine Reproductive and Respiratory Syndrome virus in alveolar macrophages in a dose dependent fashion. Cross resistance between tilmicosin and other macrolides and lincomycin has been observed.

Pharmacokinetics:
Pigs:
Absorption: When administered to pigs via the oral route at a dose of 400 mg tilmicosin/kg feed (equivalent to approximately 21.3 mg tilmicosin/kg bodyweight/day), tilmicosin moves rapidly out of the serum into areas of low pH. The highest concentration in the serum (0.23 ± 0.08 μg/ml) was recorded on day 10 of medication, but concentrations above the limit of quantification (0.10 μg/ml) were not found in 3 out of 20 animals examined. Lung concentrations increased rapidly between days 2 and 4 but no significant changes were obtained following four days of dosing. The maximum concentration in lung tissue (2.59 ± 1.01 μg/ml) was recorded on day 10 of medication. When administered at a dose of 200 mg tilmicosin/kg feed (equivalent to approximately 11.0 mg/kg/day), plasma concentrations above the limit of quantification (0.10 μg/ml) were found in 3 out of 20 animals examined. Quantifiable levels of tilmicosin were found in lung tissue with the maximum concentration (1.43 ± 1.13 μg/ml) being recorded on day 10 of medication.
Distribution: Following oral administration, tilmicosin is distributed throughout the body with especially high levels found in the lung and in lung tissue macrophages. It is also distributed in the liver and kidney tissues.
Rabbits:
Absorption: When administered orally to rabbits at a dose of 12 mg tilmicosin/kg b.w. as a single dose there is a quick absorption.
Maximum concentrations were reached in 30 minutes, being the Cmax obtained of 0.35 μg/ml. Tilmicosin plasma concentrations decreased to 0.1 μg/ml within 2 hours and to 0.02 μg/ml after 8 hours. The elimination half-life was 22 hours.
Distribution: Following oral administration, tilmicosin is distributed throughout the body with especially high levels found in lungs. After 5 days of treatment with medicated feed at a dosage of 200 ppm of product, tilmicosin concentrations in lung tissues were of 192 ± 103 μg/g.
Applicable to both species:
Biotransformation: Several metabolites are formed, the predominant one being identified as T1. However the bulk of tilmicosin is excreted unchanged.
Elimination: Following oral administration, tilmicosin is excreted mainly via the bile into the faeces, but a small proportion is excreted via the urine.

Environmental properties:
The primary route of environmental exposure is from manure applied to agricultural land as fertilizer. Tilmicosin degrades/declines slowly in the soil. Therefore, to protect soil and ground water, pig manure should not be spread onto grass land and when spread onto arable land should be plough to a depth of 30 cm. Environmental assessments have demonstrated that the use of the product as indicated is not expected to have any impact on the environment.

Indication:
Pigs- Prevention and treatment of respiratory disease caused by *Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae, Pasteurella multocida* and other organisms sensitive to tilmicosin.
Rabbits- Prevention and treatment of respiratory disease caused by *Pasteurella multocida* and *Bordetella bronchiseptica*, susceptible to tilmicosin.

Mode of Administration:
Oral administration after incorporation in animal feed

Recommended Dosage:
In-feed use.
The intake of medicated feed depends on the clinical condition of the animals. In order to obtain a correct dosage, the concentration of tilmicosin may need to be adjusted accordingly.
Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

$$\text{Kg Product/ tonne feed} = \frac{(mg\ product/kg\ bw\ /day)\ x\ Average\ bw\ (kg) of animals\ to\ be\ treated}{Average\ daily\ feed\ intake\ (kg/animal)\ x\ product\ strength\ (g/kg)}$$

Pigs
Administer in the feed at a dose of 8 to 16 mg/kg body weight/day of tilmicosin (equivalent to 200 to 400 ppm in the feed) for a period of 15 to 21 days.

Indication	Dose rate	Duration of treatment	Inclusion rate in feed
Prevention and treatment of respiratory disease	8- 16mg/kg bodyweight/ day	15- 21 days	1-2 kg product/ tonne

Rabbits
Administer in the feed at 12.5 mg/kg body weight/day of tilmicosin (equivalent to 200 ppm in the feed) for 7 days.

Indication	Dose rate	Duration of treatment	Inclusion rate in feed
Prevention and treatment of respiratory disease	12.5 mg/kg bodyweight /day	7 days	1kg product/tonne

To ensure thorough dispersion of the product, it should first be mixed with a suitable quantity of feed ingredients (20-50 kg) before incorporation into the finished feed.
This product can be incorporated into pelleted feed, preconditioned for the minimum time-period at a temperature not exceeding 75° C.

Contraindications:
Horses or other Equidae, must not be allowed access to feeds containing tilmicosin. Horses fed with tilmicosin medicated feeds may present signs of toxicity with lethargy, anorexia, reduction of feed consumption, loose stools, colic, distension of the abdomen and death.
Do not use in case of hypersensitivity to tilmicosin or to any of the excipients.

Special Warnings for each Target Species:
Under practical conditions, the management of respiratory disease outbreaks recognises that acutely ill animals are inappetant and require parenteral therapy.
Inappropriate use of the product may increase the prevalence of bacteria resistant to tilmicosin and may decrease the effectiveness of treatment with tilmicosin related substances.
Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge susceptibility of the target pathogens at farm level, or at local/regional level.
Use of the product should be in accordance with official, national and regional antimicrobial policies.
An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

Special Precautions to be taken by the Person Administering the Veterinary Medicinal Product to Animals:
Tilmicosin may induce irritation. Macrolides, such as tilmicosin, may also cause hypersensitivity (allergy) following injection, inhalation, ingestion or contact with skin or eye. Hypersensitivity to tilmicosin may lead to cross reactions to other macrolides and vice versa. Allergic reactions to these substances may occasionally be serious and therefore direct contact should be avoided. Personal protective equipment consisting of overalls, safety glasses, impervious gloves and either a disposable half mask respirator or a non-disposable respirator with a filter should be worn when handling the product.
Do not eat, drink or smoke when handling this product. Wash hands after use. In case of accidental ingestion, wash out mouth immediately with water and seek medical advice immediately and show the label to the physician. In case of accidental spillage onto skin, wash thoroughly with soap and water and seek medical advice immediately and show the label to the physician. In case of accidental eye contact, flush the eyes with plenty of clean, running water and seek medical advice immediately and show the label to the physician. People with known hypersensitivity to tilmicosin should avoid contact with the product. If you develop symptoms following exposure, such as skin rash, seek medical advice and show the label to the physician. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Interactions with other Medicaments:
None known.

Usage during Pregnancy and Lactation:
Pigs:
The safety of the veterinary medicinal product has not been established during pregnancy. Do not use in breeding animals.

Adverse Effects:
Pigs and rabbits:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Reduced food intake[1]

[1]Transient
Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product.

Overdose and Treatment:
No symptoms of overdose have been seen in pigs fed a ration containing levels of tilmicosin up to 80 mg/kg bodyweight (equivalent to 2000 ppm in the feed or ten times the recommended dose) for 15 days.

Withdrawal Periods (Meat and Offal):
Pigs: 21 days
Rabbits: 4 days

Storage Condition:
Store in a cool and dry place (< 30°C). Protect from direct sunlight.

Shelf Life:
36 months

Shelf Life after Opening:
Discard any unused powder immediately after opening

Shelf Life after Incorporation into Feed:
24 hours

Packaging Available:
100g/packet, 100packets/carton, 10kg/carton;
500g/packet, 30 packets/carton, 15kg/carton;
1kg/packet, 20 packets/carton, 20kg/carton.

Manufacturer:
N.S. Laboratory Sdn. Bhd.
54, Jalan S2C2, Green Technology Park, Seremban 2, 70300 Seremban, Negeri Sembilan, Malaysia.

Registration Holder:
GNC Agritech Sdn. Bhd.
24, Jalan Industri Cherok Tokun 3, Taman Tokun Jaya 14000 Bukit Mertajam Pulau Pinang, Malaysia

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