Veterinary Physician's Prescribing Information

ZACTRAN VETERINARY

1. TRADE NAME OF MEDICINAL PRODUCT: ZACTRAN VETERINARY

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Active substance: Gamithromycin 150 mg/ml
Excipient(s): Monothioglycerol 1 mg/ml
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM: Solution for injection. Colourless to pale yellow solution.

4. CLINICAL PARTICULARS:
4.1 Target species: Cattle, sheep and pigs (swine).

4.2 Indications for use, specifying the target species:
Cattle:
Therapeutic and preventive treatment (metaphylaxis) of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. The presence of the disease in the herd should be established before metaphylactic use.

Pigs (Swine):
Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Haemophilus parasuis*.

Sheep:
Treatment of infectious pododermatitis (foot rot) associated with virulent *Dichelobacter nodosus* and *Fusobacterium necrophorum* requiring systemic treatment.

4.3 Contraindications: Do not use in cases of hypersensitivity to macrolide antibiotics or to any of the excipients.
Do not use this veterinary medicinal product simultaneously with other macrolides or lincosamides (see section 4.8).

4.4 Special warnings for each target species:
Cattle and pigs (swine): None.
Sheep: The efficacy of antimicrobial treatment of foot rot might be reduced by other factors, such as wet environmental conditions, as well as inappropriate farm management. Treatment of foot rot should therefore be undertaken along with other flock management tools, for example providing dry environment. Antibiotic treatment of benign foot rot is not considered appropriate.

4.5 Special precautions for use:
Special precautions for use in animals: Use of the veterinary medicinal product should be based on susceptibility testing and take into account official and local policies on the use of antimicrobials in farm animals.

Special precautions to be taken by the person administering the veterinary medicinal product to animals: People with known hypersensitivity to the macrolide class should avoid contact

with the veterinary medicinal product. Gamithromycin may cause irritation to eyes and/or skin.
Avoid contact with skin or eyes. If eye exposure occurs, flush eyes immediately with clean water. If skin exposure occurs, wash the affected area immediately with clean water.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
Wash hands after use.

4.6 Adverse reactions (frequency and seriousness): During clinical trials transient injection site swellings were observed.

- Visible injection site swellings associated with occasional slight pain may develop very commonly in cattle for one day. The swellings typically resolve within 3 to 14 days but may persist in some animals for up to 35 days after treatment.
- Mild to moderate injection site swelling has been reported commonly in sheep and pigs in clinical trials, with occasional slight pain evident for one day in sheep. These local reactions are transient, and typically resolve within 2 (pigs) to 4 (sheep) days.

The frequency of adverse reactions is defined using the following convention:

- Very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- Common (more than 1 but less than 10 animals in 100 animals treated)
- Uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- Rare (more than 1 but less than 10 animals in 10,000 animals treated)
- Very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il /

4.7 Use during pregnancy, lactation or lay: Based on laboratory animal data, gamithromycin has not produced any evidence of specific developmental or reproductive effects. The safety of gamithromycin during pregnancy and lactation has not been evaluated in cattle, sheep and pigs. Use only according to the risk/benefit assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction: Cross resistance may occur with other macrolides.
Avoid simultaneous administration of antimicrobials with a similar mode of action such as other macrolides or lincosamides.

4.9 Amounts to be administered and administration route:
A single dose of 6 mg gamithromycin/kg body weight (equivalent to 1 ml/25 kg body weight) into the neck (cattle and pigs) or anterior to the shoulder (sheep). To ensure correct dose, body weight should be determined as accurately as possible to avoid underdosing.

Cattle and Sheep: Subcutaneous injection. For treatment of cattle over 250 kg and sheep over 125 kg body weight, divide the dose so that no more than 10 ml (cattle) or 5 ml (sheep) are injected at a single site.

Pigs (Swine): Intramuscular injection. The injection volume should not exceed 5 ml per injection site.

The cap may be safely punctured up to 50 times with a 16G needle and up to 80 times with a 18G needle. For multiple vial entry, an automatic dosing device is recommended to avoid excessive broaching of the stopper.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary: Clinical studies have demonstrated the wide margin of safety for gamithromycin injection in the target species. In young adult cattle, sheep and pig studies, gamithromycin was administered by injection at 6, 18, and 30 mg/kg (1, 3, and 5 times the recommended dose) and repeated three times at 0, 5 and 10 days (three times the recommended duration of use). Injection site reactions were noted in a dose related manner.

4.11 Withdrawal period(s):
Meat and offal: Cattle – 64 days ; Sheep – 29 days ; Pigs – 16 days.
Not authorised for use in lactating animals (cow and sheep) producing milk for human consumption.
Do not use in pregnant animals which are intended to produce milk for human consumption within 2 months (cows, heifers) or 1 month (ewes) of expected parturition.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides.
ATC vet code: QJ01FA95.

5.1 Pharmacodynamic properties: Gamithromycin is an azalide, 15-membered semisynthetic macrolide class antibiotic with uniquely positioned alkylated nitrogen at 7a-position of the lactone ring. This special chemistry facilitates rapid absorption at physiological pH and a long duration of action at the target tissues, the lung and the skin. Macrolides in general have both bacteriostatic and bactericidal action mediated through disruption of bacterial protein synthesis. Macrolides inhibit bacterial protein biosynthesis by binding to the 50S ribosomal subunit and by preventing peptide chain elongation. The *in vitro* data show that gamithromycin acts in a bactericidal manner. The broad spectrum antimicrobial activity of gamithromycin includes *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, *Actinobacillus pleuropneumoniae* and *Haemophilus parasuis,* the bacterial pathogens most commonly associated with BRD and SRD, and also *Fusobacterium necrophorum* and *Dichelobacter nodosus*. The MIC and MBC data (cattle and pig) are reported from a representative sample of isolates from field materials within different EU geographic areas.

Cattle	MIC_{90s}	MBC_{90s}
	µg/ml	
Mannheimia haemolytica	0.5	1
Pasteurella multocida	1	2
Histophilus somni	1	2
Pigs (Swine)	MIC_{90s}	MBC_{90s}
	µg/ml	
Actinobacillus pleuropneumoniae	4	4
Pasteurella multocida	1	2
Haemophilus parasuis	0.5	0.5

Sheep	MIC
	µg/ml
Fusobacterium necrophorum	MIC_{90}: 32
Dichelobacter nodosus	0.008 - 0.016

Three mechanisms are generally considered responsible for resistance to the macrolide class of compounds. This is often referred to as MLS_B resistance as it affects macrolides, lincosamides and streptogramins. The mechanisms involve the alteration of the ribosomal target site, the utilization of active efflux mechanism and the production of inactivating enzymes.

5.2 Pharmacokinetic particulars:
Cattle: Gamithromycin administered subcutaneously into the neck of cattle at a single dose of 6 mg/kg body weight, resulted in rapid absorption with peak plasma concentrations observed after 30 to 60 min with a long plasma half-life (> 2 days). The bioavailability of the compound was > 98% with no gender differences. The volume of distribution at steady-state was 25 l/kg. Gamithromycin levels in lung reached a maximum in less than 24 hr, with lung-to-plasma ratio of > 264 indicating that gamithromycin was absorbed rapidly into the target tissue for BRD.
In vitro plasma protein binding studies determined that the mean concentration of the free active substance was 74%. Biliary excretion of the unchanged drug substance was the major route of elimination.

Pigs (Swine): Gamithromycin administered intramuscularly in pigs at single dose of 6 mg/kg body weight, resulted in rapid absorption with peak plasma concentrations observed after 5 to 15 min, with a long plasma half-life (about 4 days). The bioavailability of gamithromycin was > 92%. The compound is absorbed rapidly into the target tissue for SRD. Accumulation of gamithromycin in the lung has been demonstrated by high and sustained concentrations in the lung and bronchial fluid which far exceed those in blood plasma. The volume of distribution at steady-state was approximately 39 l/kg. *In vitro* plasma protein binding studies determined that the mean concentration of the free active drug was 77%. Biliary excretion of the unchanged drug was the major route of elimination.

Sheep: Gamithromycin administered subcutaneously into the neck of sheep at a single dose of 6 mg/kg body weight is rapidly absorbed, and maximum plasma concentrations were observed between 15 minutes and 6 hours after dosing (2.30 hours on average) with high absolute bioavailability of 89%. Gamithromycin skin concentrations were much higher than the plasma concentrations resulting in skin/plasma concentration ratios of approximately 21, 58, and 138 at two, five and ten days post-dosing, respectively, demonstrating extensive distribution and accumulation in skin tissue.

6. PHARMACEUTICAL PARTICULARS:
6.1 List of excipients: Monothioglycerol, Succinic Acid, Glycerol Formal.

6.2 Incompatibilities: In the absence of compatibility studies, this veterinary medicinal product should not be mixed with other veterinary medicinal products.

6.3 Shelf life: The expiry date of the product is indicated on the label and packaging. Do not use after the expiry date.
Shelf life after first opening the immediate packaging: 28 days.

6.4 Special precautions for storage: Store below 30°C.

6.5 Nature and composition of immediate packaging: Type 1 glass vial of 50, 100 or 250 ml with a chlorobutyl rubber stopper, a polypropylene cap and an aluminium crimp seal.
Polypropylene vial of 100 or 250 ml with a chlorobutyl rubber stopper, a polypropylene cap and an aluminium crimp seal.
Cardboard box containing 1 vial of 50, 100 or 250 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products: Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. Israeli Drug Registration Number: 153-34-33711-00

8. Manufacturer: Boehringer Ingelheim Vetmedica GmbH, Ingelheim am Rhein, Germany (by Boehringer Ingelheim Animal Health France, Toulouse, France).

9. Israeli Marketing Authorization Holder: Beit Erez Havat Milatin Ltd., P.O.B. 209, Mishmar Hashiva 5029700, Israel.

10) REVISED ON: 10/2022 according to MOH's guidelines.
[Internal code: ZCTRN-VET-DCTR-10/22 dated 03/10/2022]