Veterinary Physician's Prescribing Information

ZACTRAN VETERINARY

Gamithromycin 150 mg/ml Solution for Injection for Cattle

The format and contents of this leaflet were determined, checked and approved by the Israeli Ministry of Health (on 09/2017)

1. TRADE NAME OF MEDICINAL PRODUCT

ZACTRAN VETERINARY

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Gamithromycin 150 mg/ml

Excipient: 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 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 preventive treatment.

Pigs (Swine)

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

4.3 Contraindications

Do not use in case 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: none.

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 or/and 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 pigs in clinical trials. These local reactions are transient, and typically resolve within 2 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 suspected adverse reactions after authorization 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

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.7 Use during pregnancy, lactation or lay

Based on laboratory animal data, gamithromycin has not produced any evidence of selective developmental or reproductive effects. The safety of gamithromycin during pregnancy and lactation has not been evaluated in cattle 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).

To ensure correct dose, body weight should be determined as accurately as possible to avoid underdosing.

Cattle

Subcutaneous injection. For treatment of cattle over 250 kg body weight, divide the dose so that no more than 10 ml 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 60 times. 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 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

Meat and offal: Cattle – 64 days; Pigs – 16 days.

Not authorised for use in lactating animals 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) of expected parturition.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides. ATCvet 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 tissue, 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. The MIC and MBC data (cattle and pig) are reported from a representative sample of isolates from field materials within different European Union (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

Three mechanisms are generally considered responsible for resistance to the macrolide class of compounds. This is often referred to as MLSB 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 single dosage 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 the 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

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.

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 vial label and box. 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 and an aluminum cap.

Polypropylene vial of 100 or 250 ml with a chlorobutyl rubber stopper and an aluminum cap.

Box containing 1 vial of 50, 100 or 250 ml solution.

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

Merial, Lyon, France (by Merial, Toulouse, France).

9. ISRAELI MARKETING AUTHORIZATION HOLDER

Beit Erez Havat Milatin, VAT no. 511088106, P.O.B. 209, Mishmar Hashiva 50297, Israel.

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