Leaflet

For Veterinary Use Only

MAKROVİL

Solution For Injection

Veterinary Systemic Antibacterial

COMPOSITION

It is yellow to amber colored solution, containing tilmicosin phosphate equivalent to 300 mg tilmicosin per ml.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Tilmicosin is a semi-synthetic antibiotic belonging to the macrolide group. It is thought to exert its effect by interfering with protein synthesis. It has bacteriostatic effects but exhibits bactericidal activity at high concentrations. It is effective against certain Gram-negative bacteria and *Mycoplasma*, primarily Gram-positive bacteria. It is particularly effective against the following bacteria originating in cattle and sheep: *Mannheimia, Pasteurella, Actinomyces (Corynebacterium), Fusobacterium, Dichelobacter, Staphylococcus,* and *Mycoplasma*.

In Europe, the MIC values for field strains isolated from cattle with respiratory system diseases between 2009 and 2012 are as follows.

Bacteria	MIC (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
P. multocida	0.5- > 64	4	8
M. haemolytica	1 - 64	8	16

The Institute for Clinical and Laboratory Standards has determined the tilmicosin values for *M. haemolyica*, which causes bovine respiratory disease, as follows: ≤8µg/ml = susceptible, 16 µg/ml = moderately susceptible, and ≥ 32 µg/ml = resistant. Although there is no criterion for *P. multocida* of bovine origin, the tilmicosin values for these bacteria of porcine origin are as follows: ≤16 µg/ml = susceptible and ≥ 32 µg/ml = resistant.

Scientific studies have shown that macrolides have a synergistic effect with the host defense system. Macrolides enhance the ability of phagocytes to eliminate bacteria.

Following oral or parenteral administration, the target organ for toxicity is the heart. The primary cardiac effects are tachycardia and negative inotropic effects. Cardiovascular toxicity is due to the blockade of calcium channels.

In dogs, $CaCl_2$ treatment has shown a positive effect on the inotropic effect in the left ventricle after tilmicosin administration, following its effects on vascular blood pressure and pulse.

Dobutamine partially counteracts the negative inotropic effect of tilmicosin in dogs. Beta-adrenergic antagonists such as propranolol exacerbate the negative inotropic effect of tilmicosin in dogs.

In pigs, intramuscular administration at a dose of 10 mg/kg caused an increase in respiratory rate, agitation, and convulsions; administration at a dose of 20 mg/kg caused death in 3 of 4 pigs; and administration at a dose of 30 mg/kg caused death in all 4 animals tested. Intravenous administration of tilmicosin at a dose of 4.5–5.6 mg/kg following 2–6 intravenous injections of 1

ml of epinephrine (1/1000) resulted in the death of all 6 animals tested. No deaths were observed in animals that did not receive epinephrine. These results indicate that intravenous epinephrine administration is contraindicated.

Cross-resistance has been observed between tilmicosin and other macrolides and lincomycin.

Pharmacokinetics Properties

The kinetic parameters for recommended dose and way of administration are as below;

	Dose	T_{max}	C_{max}
Cattle:			
Neonatal calve	10 mg/kg	1 hour	1.55 µg/ml
Beef cattle	10 mg/kg	1 hour	0.97 µg/ml
Sheep:			
40 kg	10 mg/kg	8 hours	0.44 µg/ml
28-50 kg	10 mg/kg	8 hours	1.18 µg/ml

After subcutaneous administration, tilmicosin is distributed throughout the body but reaches high concentrations in the lungs. It is converted into numerous metabolites, primarily N-demethyl tilmicosin. However, it is mainly excreted unchanged. It is mainly excreted via the bile duct and therefore in the feces, and to a lesser extent in the urine. The half-life in cattle is 2-3 days.

AREA OF USE/INDICATIONS

Cattle: Used for the treatment of respiratory system infections caused by *Mannheimia haemolytica* and *Pasteurella multocida* and Interdigital necrobacillosis.

Sheep: Used for the treatment of respiratory system infections caused by *Mannheimia haemolytica* and *Pasteurella multocida,* Foot rot caused by *Dichelobacter nodosus* and *Fusobacterium necrophorum, acute mastitis caused by Staphylococcus aureus* and *Mycoplasma agalactia.*

USAGE AND DOSAGE

It is administered ony subcutaneously.

10 mg tilmicosin/kg body weight (1 ml for 30 kg body weight)

Cattle: Method: Draw the required amount of product from the vial by using the syringe, leaving the needle in the vial and removing the syringe from the needle. If animals are to be treated in groups, leave the needle in the vial so that subsequent doses can be drawn into the syringe. Completely restrain the animal to be treated and insert another needle subcutaneously into the injection site (preferably in a skin fold behind the shoulder and above the rib cage). Attach the syringe to the needle and inject the product. Do not apply more than 20 ml of product to any one area.

Sheep: It is extremely important to measure the weight of lambs accurately to avoid overdosing. A 2 ml or smaller syringe can be used to ensure correct dosing.

Draw the required amount of product from the vial into the syringe, leaving the needle in the vial, and remove the syringe from the needle. Hold the animal firmly and insert another needle

subcutaneously into the injection site (preferably in a skin fold behind the shoulder and above the rib cage). Attach the syringe to the needle and inject the product. Do not apply more than 2 ml of product to one area.
If improvement is not seen within 48 hours, the diagnosis should be reviewed.
Take necessary precautions to prevent contamination of the bottle during use. The bottle should be visually inspected for any particles or abnormal physical appearance; if any are found, the product should not be used.

SPECIAL CLINICAL INFORMATION AND SPECIAL WARNINGS FOR TARGET SPECIES

Sheep

Clinical studies have not proven the bacteriological treatment of acute mastitis caused by Staphylococcus aureus and Mycoplasma agalactiae in sheep with tilmicosin.
It should not be administered to lambs weighing less than 15 kg due to the risk of overdose toxicity. To avoid overdose in lambs, accurate measurement of the animals' weight is very important. Using a syringe with a volume of 2 ml or less can facilitate accurate dosing.
Official, regional, and national antimicrobial policies should be considered when using this product. The use of this product should be based on susceptibility test results whenever possible.
Use during pregnancy: The safe use of this product during pregnancy has not been established. It should only be administered based on the veterinarian's benefit/risk assessment.

ADVERSE EFFECTS

Rarely, swelling may occur at the injection site, which disappears within 5-8 days. Very rarely, supine position, incoordination, and convulsions have been observed. In cattle, administration of 5 mg/kg intravenously followed by subcutaneous administration every 72 hours resulted in death. In pigs, administration of 20 mg/kg intramuscularly, and in sheep, a single dose of 7.5 mg/kg intravenously resulted in death.

DRUG INTERACTIONS

Makrovil Solution for Injection should not be mixed with other parenteral solutions. It should not be administered concomitantly with phenicols, lincosamides, and other macrolide antibacterials due to antagonism.
There is an interaction between macrolides and ionophores. It should not be mixed with other products.

SYMPTOMS OF OVERDOSE, PRECAUTIONS AND ANTIDOTE

No deaths were observed in cattle at doses of 10, 30, and 50 mg/kg administered subcutaneously three times at 72-hour intervals. Edema formed at the injection sites. Necrosis was observed in the myocardium of one animal in the group receiving 50 mg/kg.
Administration at a dose of 150 mg/kg subcutaneously at 72-hour intervals resulted in death. In this administration, edema at the injection site and mild necrosis in the myocardium were

observed. Other observed side effects included difficulty in movement, decreased appetite, and tachycardia.
In sheep, a single dose of 30 mg/kg caused a slight increase in respiration. Administration at a dose of 150 mg/kg led to ataxia, lethargy, and inability to lift the head.
In cattle, a single intravenous dose of 5 mg/kg, and in sheep, a single intravenous dose of 7.5 mg/kg resulted in death.

WITHDRAWAL PERIODS
Meat: 70 days for cattle, 42 days for sheep.
Milk: 36 days for cows, 18 days for sheep. If the product is used during the dry period or during pregnancy, 36 days for cows and 18 days for sheep.

CONTRAINDICATIONS
Do not administer intramuscularly or intravenously.
Do not administer to lamb less than 15 kg.
Do not administer to primate, pig, horse, donkey and goat.
Do not administer to animals known to be sensitive to any ingredient in the composition.

GENERAL WARNINGS
Consult a veterinarian before use and if any unexpected effects are observed. Keep out of reach of children and away from foodstuffs.

PRECAUTIONS TO BE TAKEN BY THE ADMINISTRATOR AND WARNINGS FOR VETERINARY SURGEON

INJECTION OF TILMICOSIN INTO HUMANS CAN CAUSE DEATH. TO AVOID ACCIDENTAL INJECTION TO YOURSELF OR ANOTHER PERSON, EXERCISE THE ULTIMATE CAUTION AND FOLLOW THE APPLICATION INSTRUCTIONS BELOW.

• This product should only be administered by a veterinarian.
• Never carry a syringe containing this product with the needle attached. The needle should only be attached to the syringe when drawing up the medication or during injection. Keep the syringe and needle separate at all other times.
• Do not use an automatic syringe.
• Ensure that the animals to be treated are restrained in a manner that does not compromise their safety, and take necessary precautions to prevent other animals from interfering with the administration.
• Do not administer this product alone.
• **IF YOU (OR SOMEONE ELSE) ACCIDENTALLY INJECT YOURSELF WITH THIS PRODUCT, THAT PERSON MUST SEEK MEDICAL ATTENTION IMMEDIATELY.** Take the product with you to show to the relevant healthcare professional, along with the package insert and label. Apply a cold compress to the injection site (do not apply ice directly).

Additional safety warnings:

The product should not come into contact with skin or eyes. If this happens, immediately wash the affected areas with plenty of water.

May cause skin sensitivity. Wash your hands after use.

WARNING FOR HUMAN DOCTORS
INJECTING THIS DRUG INTO HUMANS CAN CAUSE DEATH.

Injection causes toxicity in the cardiovascular system. This toxicity is probably related to the blocking of calcium channels. Intravenous administration of calcium chloride should only be performed if it is certain that the person has been injected with tilmicosin.

In studies conducted on dogs, tilmicosin injection resulted in a negative inotropic effect leading to tachycardia and a decrease in systemic arterial and pulse pressure.

DO NOT ADMINISTER ADRENALINE OR PROPRANOLOL-LIKE BETA-ADRENERGIC ANTAGONISTS TO THE PATIENT.

In pigs, tilmicosin-related deaths increase when adrenaline is used.

In dogs, intravenous calcium chloride administration has had a positive effect on the inotropic state of the left ventricle and has provided some improvement in vascular blood pressure and tachycardia.

Preclinical data and a clinical report indicate that calcium chloride infusion in humans may be effective in reversing changes in blood pressure and heart rate associated with tilmicosin.

Even if it is not effective on tachycardia, the use of dobutamine should also be considered due to its positive inotropic effects.

Since tilmicosin remains in tissues for days, the cardiovascular system should be closely monitored and supportive treatment should be administered.

Physicians treating individuals exposed to this drug are advised to contact the National Poison Center. ***(National Poison Center tel no.: 114; Cemal Gürsel Cad. No: 18 Sıhhiye/ANKARA; zehir@saglik.gov.tr).***

STORAGE CONDITIONS AND SHELF LIFE

Before and after opening it should be stored in the original packages, protected from light, and stored below 25°C without placed in the refrigerator or freezer. The shelf life is 3 years.

DISPOSAL AFTER USE AND WARNINGS FOR NON-TARGET SPECIES

Used or leftover product should be disposed of according to the relevant regulations. The product should not be disposed of in wastewater, water sources, or drainage systems or their vicinity.

COMMERCIAL PRESENTATION FORM

20 ml, 50 ml, 100 ml and 250 ml amber-colored Type II glass vials with stoppers and flip-off in boxes.

PLACE AND CONDITIONS OF SALE

It is sold in pharmacies and veterinary clinics with a veterinarian's prescription. (VHP)

APPROVAL DATE OF LEAFET: 31.08.2023

MARKETING AUTHORIZATION DATE AND NO: 09.03.2005 – 014/0048

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER
VİLSAN Veteriner İlaçları Tic. ve San. A.Ş.
Balıkhisar Mah. Balıkhisar Köy İçi Küme Evleri No765A Akyurt/Ankara – Türkiye

MANUFACTURER COMPANY
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Made in Turkiye

Box

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Sheep: Used for the treatment of respiratory system infections, Foot rot and acute mastitis.

USAGE AND DOSAGE
It is administered ony subcutaneously to cattle and sheep
10 mg tilmicosin/kg body weight (1 ml for 30 kg body weight)
Read the leaflet for detailed information.

WITHDRAWAL PERIODS
Meat: 70 days for cattle, 42 days for sheep.
Milk: 36 days for cows, 18 days for sheep.

GENERAL WARNINGS
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Label

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