

# KEYTIL

Tilmicosin 300 mg/ml and Ketoprofen 90 mg/ml solution for injection

## DATA SHEET



### INDICATIONS

For therapeutic treatment of bovine respiratory disease (BRD) associated with pyrexia due to *Mannheimia haemolytica* susceptible to tilmicosin.

### VET ADMINISTRATION ONLY.

### BENEFITS

- Combination of tilmicosin antibiotic and ketoprofen NSAID
- Licensed for cattle under 330 kg live weight
- Licensed for the treatment of BRD associated with pyrexia due to *Mannheimia haemolytica*
- Subcutaneous administration
- Dose at 1ml per 30 kg live weight



LIST No	UNIT PACKAGE
1KEY002	100 ml

See reverse for Administration & Dosage



# KEYTIL



## Tilmicosin 300 mg/ml and Ketoprofen 90 mg/ml solution for injection

### PRESENTATION

Each ml contains: Tilmicosin 300 mg and Ketoprofen 90 mg  
Brown yellow solution for injection.

### TARGET SPECIES

Cattle (calves  $\leq$  330 kg)

### INDICATIONS FOR USE, SPECIFYING THE TARGET SPECIES

For therapeutic treatment of bovine respiratory disease (BRD) associated with pyrexia due to *Mannheimia haemolytica* susceptible to tilmicosin.

### DOSAGE AND ADMINISTRATION

For subcutaneous use only.

Use 10 mg tilmicosin and 3 mg ketoprofen per kg body weight (corresponding to 1 ml of the veterinary medicinal product per 30 kg body weight) on a single occasion only. To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

### METHOD OF ADMINISTRATION

Withdraw the required dose from the vial and remove the syringe from the needle, leaving the needle in the vial. When a group of animals has to be treated, leave the needle in the vial to remove the subsequent doses. Restrain the animal and insert a separate needle subcutaneously at the injection site, preferably in a skinfold over the rib cage behind the shoulder. Attach the syringe to the needle and inject into the base of the skinfold.

Do not inject more than 11 ml per injection site.

### CONTRAINDICATIONS

Do not administer intravenously or intramuscularly. Do not administer to primates, pigs, goats and horses. Do not use in animals suffering from gastro-intestinal lesions, haemorrhagic diathesis, blood dyscrasia, impaired hepatic, cardiac or renal function.

Do not use other non-steroidal anti-inflammatory drugs (NSAIDs) concurrently or within 24 hours.

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

### SPECIAL PRECAUTIONS FOR USE

Official, national and regional antimicrobial policies should be taken into account when this veterinary medicinal product is used. Wherever possible, the use of this veterinary medicinal product should only be used based on susceptibility testing.

Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to Tilmicosin and may decrease the effectiveness of treatment with other macrolide antimicrobials, due to the potential for cross-resistance.

Do not exceed the stated dose or duration of treatment.

Use with caution in dehydrated, hypovolemic or hypotensive animals as there is a potential risk of increased renal toxicity.

### OPERATOR SAFETY WARNINGS

Injection of Tilmicosin in humans can be fatal- exercise extreme caution to avoid accidental self-injection and follow the administration instructions and the guidance below, precisely. **This veterinary medicinal product should only be administered by a veterinary surgeon.** Never carry a syringe loaded with this veterinary medicinal product with the needle attached. The needle should be connected to the syringe only when filling the syringe or administering the injection. Keep the syringe and needle separate at all other times. Do not use automatic injection equipment. Ensure that animals are properly restrained, including those in the vicinity. Do not work alone when using this veterinary medicinal product. In case of

self-injection seek immediate medical attention. And take the vial or the package leaflet with you. Apply a cold pack (not ice directly) to the injection site.

People with known hypersensitivity to tilmicosin or ketoprofen, to non-steroidal anti-inflammatory drugs (NSAIDs) or to benzyl alcohol should avoid contact with the veterinary medicinal product.

Tilmicosin can induce serious effects on the heart, associated with fatalities. Ketoprofen can induce drowsiness and dizziness.

Take care to avoid accidental self-injection and dermal exposure. Personal protective equipment consisting of impervious gloves and protective glasses should be worn when handling the veterinary medicinal product.

Ketoprofen may cause congenital malformations. The veterinary medicinal product should not be administered by pregnant women.

The product is slightly irritant to the skin and eye. Avoid splashes on the skin and eyes. In the event of accidental contact with the skin or eyes, rinse thoroughly with clean water. If irritation persists, seek medical advice. Wash hands after use.

### NOTE TO THE PHYSICIAN

Injection of tilmicosin in humans has been associated with fatalities. The cardiovascular system is the target of toxicity, and this toxicity may be due to calcium channel blockade. Administration of intravenous calcium chloride should only be considered if there is positive confirmation of exposure to tilmicosin. In dog studies, tilmicosin induced a negative inotropic effect with consequent tachycardia, and a reduction in systematic arterial blood pressure and arterial pulse pressure.

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Do not give adrenalin or beta-adrenergic agonists such as propranolol. In pigs, tilmicosin-induced lethality is potentiated by adrenalin. In dogs, treatment with intravenous calcium chloride showed a positive effect on the left ventricular inotropic state and some improvements in vascular blood pressure and tachycardia. Pre-clinical data and isolated clinical report suggest that calcium chloride infusion may help to reverse tilmicosin induced changes in blood pressure and heart rate in humans. Administration of dobutamine should also be considered due to its positive inotropic effects although it does not influence tachycardia. As tilmicosin persists in tissues for several days, the cardiovascular system should be closely monitored and supportive treatment provided. Physicians treating patients exposed to this compound are advised to discuss clinical management with the National Poison Information Service on: 0183 79964.

### ADVERSE REACTIONS (FREQUENCY AND SERIOUSNESS)

It is very common (more than 1 in 10 animals treated displaying adverse reaction(s)) to observe local swellings of variable size at the site of injection. Subacute fibrinous to chronic fibrous necrotic panniculitis with mineralised areas, vacuoles and oedema and associated granulomatous reactions were observed microscopically. These lesions resolve over a period of 45 to 57 days.

In common with all NSAIDs, due to their action of inhibition of prostaglandin synthesis, there can be the possibility in certain individuals of gastric or renal intolerance.

Bovine deaths have been observed after a single intravenous dose of 5 mg tilmicosin/kg body weight, and after subcutaneous

injection of 150 mg tilmicosin/kg body weight at 72-hour intervals.

### USE DURING PREGNANCY, LACTATION OR LAY

The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only according to the benefit/risk assessment by the responsible veterinarian.

### INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

The veterinary medicinal product must not be administered in association/or combination with, or within 24 hours of administration of other NSAIDs and glucocorticoids. Concurrent administration of diuretics, nephrotoxic drugs and anticoagulative drugs should be avoided.

Ketoprofen is highly bound to plasma proteins, and may displace or be displaced by other highly protein bound medicines, such as anticoagulants. Due to the fact that ketoprofen may inhibit platelet aggregation and cause gastrointestinal ulceration, it should not be used with other medicines that have the same profile of adverse drug reactions.

Interactions between macrolides and ionophores could be observed in some species.

### OVERDOSE (SYMPTOMS, EMERGENCY PROCEDURES, ANTIDOTES), IF NECESSARY

Subcutaneous injection of the veterinary medicinal product at a single dose of 30 mg of tilmicosin and 9 mg of ketoprofen/kg body weight cause local swellings and injuries of variable sizes at the site of injection which evolve into necrosis. These lesions resolve over a period of 45 to 57 days.

The administration at 3 times the recommended dose of the veterinary medicinal product (30 mg of tilmicosin and 9 mg of ketoprofen per kg body weight) could cause an increase of CPK levels.

### WITHDRAWAL PERIOD(S)

Meat and offal: 93 days

Milk: Not authorised for use in animals producing milk for human consumption.

### PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties:

Tilmicosin is mainly a bactericidal semi-synthetic antibiotic of the macrolide group. Their antibacterial action is produced by an inhibition of protein synthesis by reversibly binding to 50S subunits of the ribosome. It has bacteriostatic action but at high concentrations it may be bactericidal. Tilmicosin is active against *Mannheimia haemolytica* which is involved in respiratory diseases in cattle.

Scientific evidence suggests that macrolides act synergistically with the host immune system. Macrolides appear to enhance phagocyte killing of bacteria. Bacteria can develop resistance to macrolides through three basic mechanisms:

1) Natural resistance, 2) Acquired resistance or 3) Horizontally transferable resistance. Cross resistance between tilmicosin and other macrolides and lincomycin has been observed.

The Clinical and Laboratory Standards Institute CLSI has set the interpretative criteria for tilmicosin against *M. haemolytica* of bovine origin and specifically for bovine respiratory disease, as  $\leq 8$  µg/ml susceptible, 16 µg/ml intermediate, and  $\geq 32$  µg/ml resistant.

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Ketoprofen is a substance belonging to the group non-steroidal anti-inflammatory drugs (NSAIDs). Ketoprofen has anti-inflammatory, analgesic and antipyretic properties. Not all aspects of its mechanism of action are known. Effects are obtained partially by the inhibition of prostaglandin and leukotriene synthesis by ketoprofen, acting on cyclooxygenase and lipoxygenase respectively. The formation of bradykinin is also inhibited. Ketoprofen inhibits thrombocyte aggregation.

### Pharmacokinetic particulars:

After single subcutaneous administration the maximum peak plasma concentrations of tilmicosin were achieved between 40 min and 6 hours after administration. Mean C<sub>max</sub> value of 455.97 ng/mL was obtained. A second peak in plasma tilmicosin was observed in some animals after administration probably due to an enterohepatic recirculation which has been described for macrolides. A mean elimination half-life (t<sub>1/2</sub>) of 41.62 hours was obtained. A lung pharmacokinetics study confirms that tilmicosin is rapidly and widely distributed in the animal body and bound to lung tissue and that causes a long-lasting concentration in the tissue, obtaining a C<sub>max</sub> of 7199.7 µg/kg and a half-life (t<sub>1/2</sub>) of 2.46 days. Approximately 70% of the administered dose is excreted via faeces and ± 20 % via urine.

The maximum peak concentrations of Ketoprofen were achieved at approximately 2.5 h after the subcutaneous administration. Mean C<sub>max</sub> value of 1.03 µg/mL was obtained. A second peak in plasma ketoprofen was also obtained (between 3 and 6 hours after

administration). A mean elimination half-life (t<sub>1/2</sub>) of 16.85 hours was observed. Ketoprofen is strongly bound to proteins.

The elimination occurred mainly via the urine.

### PHARMACEUTICAL PARTICULARS

#### Excipients:

Benzyl alcohol (E1519)  
Phosphoric acid, concentrated  
Butylhydroxytoluene (E-321)  
Propyl gallate (E-310)  
Propylene glycol  
Water for injections

### MAJOR INCOMPATIBILITIES

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

### SHELF-LIFE

Shelf life of the veterinary medicinal product as packaged for sale: 2 years  
Shelf life after first opening the immediate packaging: 28 days.

### SPECIAL PRECAUTIONS FOR STORAGE

Keep the container in the outer carton in order to protect from light.

### NATURE AND COMPOSITION OF IMMEDIATE PACKAGING

Polypropylene vials of 50 ml, 100 ml and 250 ml, closed with bromobutyl rubber stoppers and sealed with aluminium caps. Carton box with one vial of 50 ml or 100 ml or 250ml.

Not all pack sizes may be marketed.

Special precautions for the disposal of unused veterinary medicinal products 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.

### MARKETING AUTHORISATION HOLDER

**Vetpharma Animal Health, S.L.**

Les Corts, 23  
08028 Barcelona  
Spain

### MARKETED IN IRELAND BY

**Bimeda Animal Health Limited**

2, 3 & 4 Airton Close, Airton Road  
Tallaght, Dublin 24, Ireland  
Tel: +353 (0) 1 466 7900

### MARKETING AUTHORISATION NUMBER VPA 10516/019/001

### CLASSIFICATION

**VPO-1**

Veterinary Practitioner Only as defined in relevant national legislation

**Use medicines responsibly**

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