Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

KEYTIL 300 mg/ml + 90 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:	
Tilmicosin	300 mg
Ketoprofen	90 mg
Excipients:	
Benzy alcohol (E1519)	0.04 ml
Butylhydroxytoluene (E-321)	0.05 mg
Propyl gallate (E-310)	0.05 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Brown yellow solution.

4 CLINICAL PARTICULARS

4.1 Target Species

Cattle (calves ≤ 330 kg)

4.2 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.

4.3 Contraindications

Do not administer intravenously.
Do not administer 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.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

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.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

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.

Additional operating safety warnings

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. To avoid self-injection do not use automatic injection equipment. 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 systemic arterial blood pressure and arterial pulse pressure.

DO NOT GIVE ADRENALIN OR BETA-ADRENERGIC ANTAGONISTS 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 an 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: 018379964

4.6 Adverse reactions (frequency and seriousness)

It is very common 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.

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)

4.7 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.

4.8 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.

4.9 Amounts to be administered and administration route

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.

4.10 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.

4.11 Withdrawal period(s)

Meat and offal: 93 days
Milk: Not authorised for use in animals producing milk for human consumption.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, combination of antibacterials and other substances
ATCvet code: QJ01FA99

5.1 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 ≤ 8 µg/ml susceptible, 16 µg/ml intermediate, and ≥ 32 µg/ml resistant.
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.

5.2 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_{max} 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 ($t_{1/2)}$ 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_{max} of 7199.7 µg/kg and a half-life ($t_{1/2)}$ 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_{max} 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 ($t_{1/2}$) of 16.85 hours was observed. Ketoprofen is strongly bound to proteins. The elimination occurred mainly via the urine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Major incompatibilities

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

6.3 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

6.4 Special precautions for storage

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

6.5 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.

6.6 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.

7 MARKETING AUTHORISATION HOLDER

Vetpharma Animal Health, S.L.
Les Corts, 23
08028 Barcelona
Spain

8 MARKETING AUTHORISATION NUMBER(S)

VPA10516/019/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th March 2019

10 DATE OF REVISION OF THE TEXT

May 2020