A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE AND THE IMMEDIATE PACKAGE

CARTON BOX of 50 ml, 100 ml and 250 ml AND LABELS OF 100 ml and 250 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

KEYTIL 300 mg/ml + 90 mg/ml solution for injection (AT, BE, CZ, DE, ES, IE, IT, NL, PT, SK)
TILDOKET 300 mg/ml + 90 mg/ml solution for injection (LT, LV, PL, RO)
Tilmicosin/Ketoprofen

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:

Active substances:
Tilmicosin .....300 mg
Ketoprofen.....90 mg

Excipients:
Benzyl alcohol (E1519).....0.04 ml
Butylhydroxytoluene **(E-321)** .....0.05 mg
Propyl gallate (E-310).....0.05 mg

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml
250 ml

5. TARGET SPECIES

Cattle (calves ≤ 330 kg)

6. INDICATIONS

7. METHOD AND ROUTES OF ADMINISTRATION

Single subcutaneous use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal period: 93 days
Milk: Not authorised for use in animals producing milk for human consumption.

9. SPECIAL WARNINGS, IF NECESSARY

Accidental injection is dangerous. Read the package leaflet before use.

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 (notice directly) to the injection site.

Note to the physician: Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once broached use by…
Shelf life after first opening the immediate packaging: 28 days

11. SPECIAL STORAGE CONDITIONS

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

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.
[To be completed in accordance with national requirements after conclusion of the DC/MR phase]

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

VETPHARMA ANIMAL HEALTH, S.L.
Les Corts, 23
08028 - Barcelona
Spain

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

<Batch><Lot> {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABELS OF 50 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

KEYTIL 300 mg/ml + 90 mg/ml solution for injection (AT, BE, CZ, DE, ES, IE, IT, NL, PT, SK)
TILDOKET 300 mg/ml + 90 mg/ml solution for injection (LT, LV, PL, RO)
Tilmicosin/ Ketoprofen

2. QUANTITY OF THE ACTIVE SUBSTANCES

Tilmicosin .....300 mg/ml
Ketoprofen.....90 mg/ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

50 ml

4. ROUTE OF ADMINISTRATION

Single subcutaneous use

5. WITHDRAWAL PERIODS

Withdrawal period: 93 days
Milk: Not authorised for use in animals producing milk for human consumption.

6. SPECIAL WARNINGS, IF NECESSARY

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 (notice directly) to the injection site.

Note to the physician: Read the package leaflet before use.

7. BATCH NUMBER

<Batch><Lot> {number}

8. EXPIRY DATE

EXP {month/year}
Once broached use by…
Shelf life after first opening the immediate packaging: 28 days

9. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

KEYTIL 300 mg/ml + 90 mg/ml solution for injection (AT, BE, CZ, DE, ES, IE, IT, NL, PT, SK)
TILDOKET 300 mg/ml + 90 mg/ml solution for injection (LT, LV, PL, RO)

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
VETPHARMA ANIMAL HEALTH, S.L.
Les Corts, 23
08028 - Barcelona
Spain

Manufacturer responsible for batch release:
LABORATORIOS MAYMÓ, S.A.
Ferro, 9 – Pol. Ind. Can Pelegrí
8755 Castellbisbal (Barcelona)
Spain

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

KEYTIL 300 mg/ml + 90 mg/ml solution for injection (AT, BE, CZ, DE, ES, IE, IT, NL, PT, SK)
TILDOKET 300 mg/ml + 90 mg/ml solution for injection (LT, LV, PL, RO)
Tilmicosin and Ketoprofen

3. STATEMENT OF THE ACTIVE SUBSTANCES AND OTHER INGREDIENTS

Each ml contains:

Active substances:
Tilmicosin .....300 mg
Ketoprofen.....90 mg

Excipients:
Benzyl alcohol (E1519).....0.04 ml
Butylhydroxytoluene (E-321) .....0.05 mg
Propyl gallate (E-310).....0.05 mg

Brown yellow solution.

4. INDICATIONS

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

5. 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.

6. ADVERSE REACTIONS

It is very common to observe local swellings of variable size at the site of injection. Subacute fibrinous to chronic 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)

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Cattle (calves ≤ 330 kg)

8. DOSAGE FOR EACH SPECIES, ROUTE AND METHOD OF 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.

9. ADVICE ON CORRECT ADMINISTRATION

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 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.

10. WITHDRAWAL PERIOD

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

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Keep the container in the outer carton in order to protect from light. Do not use this veterinary medicinal product after the expiry date which is stated on the label or carton after EXP. The expiry date refers to the last day of that month.
Shelf life after first opening the container: 28 days

12. SPECIAL WARNING(S)

Special warnings for each target species:
None.

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 package leaflet 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 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. In case of accidental injection, seek medical advice immediately and show the package leaflet or the label to a physician.
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: ... *relevant national*

number stated (to be completed nationally) [INCLUDE THE NAME OF THE COMPETENT AUTHORITY IN EACH COUNTRY AND THE TELEPHONE NUMBER]

Pregnancy and lactation:
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 interaction:
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):
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 size 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 kilogram) could cause an increase of CPK levels.

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
[IT]: Unused medicinal products or waste derived from medicinal products should not be disposed of via wastewater or household waste but must be given in the appropriate collection systems and disposal for unused or expired medicines.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

Carton box with one vial of 50 ml or 100 ml or 250ml.
Not all pack sizes may be marketed.

[To be completed in accordance with national requirements after conclusion of the DC/MR phase]
Administration only by a veterinary surgeon