ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE AND THE IMMEDIATE PACKAGE

250 ml glass vial with rubber stopper
100 ml glass vial with rubber stopper
50 ml glass vial with rubber stopper
25 ml glass vial with rubber stopper

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tilmovet 300 mg/ml solution for injection for cattle and sheep
Tilmicosin

2. STATEMENT OF ACTIVE SUBSTANCES

Tilmicosin 300 mg/ ml

3. PHARMACEUTICAL FORM

Solution for Injection

4. PACKAGE SIZE

250 ml
100 ml.
50 ml
25 ml

5. TARGET SPECIES

Cattle and sheep

6. INDICATION(S)

***** Only for those Member States where space permits *****

Cattle
Treatment of bovine respiratory disease associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Treatment of interdigital necrobacillosis.

Sheep
Treatment of respiratory tract infections caused by *Mannheimia haemolytica* and *Pasteurella multocida*.

Treatment of foot rot in sheep caused by *Dichelobacter nodosus* and *Fusobacterium necrophorum.*
Treatment of acute ovine mastitis caused by *Staphylococcus aureus* and *Mycoplasma agalactiae*.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

FOR SUBCUTANEOUS USE ONLY.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal period

Cattle:
Meat and offal: 70 days
Milk: 36 days

If the product is administered to cows during the dry period or to pregnant dairy heifers, milk should not be used for human consumption until 36 days after calving.

Sheep:
Meat and offal: 42 days
Milk: 18 days

If the product is administered to ewes during the dry period or to pregnant ewes, milk should not be used for human consumption until 18 days after lambing.

9. SPECIAL WARNING(S), 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 product should only be administered by a veterinary surgeon.
- Never carry a syringe loaded with Tilmovet 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 Tilmovet.
- 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.

NOTE TO THE PHYSICIAN: please see inside of label or package leaflet for details

10. EXPIRY DATE

EXP: {mm/yy}
Shelf-life after first broaching the immediate packaging: 28 days
Once broached, use by

11. SPECIAL STORAGE CONDITIONS

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

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

Veterinary medicinal product must not be disposed of via waste water or the drainage systems.

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

For animal treatment only. **<***Delivery as per the national requirements.* **>**

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

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerp
Belgium

16. MARKETING AUTHORISATION NUMBER(S)

Vm 30282/4041

17. MANUFACTURER'S BATCH NUMBER

<Batch><Lot> {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Tilmovet 300 mg/ml Solution for Injection for cattle and sheep

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

Marketing authorisation holder

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerp
Belgium

Manufacturer responsible for batch release:

Biovet JSC, 39 Petar Rakov Str, 4550 Peshtera - Bulgaria

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tilmovet 300 mg/ml Solution for Injection for cattle and sheep
Tilmicosin

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each ml of clear, amber yellow solution contains:

Active substance
Tilmicosin 300 mg

4. INDICATION(S)

Cattle
Treatment of bovine respiratory disease associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Treatment of interdigital necrobacillosis.

Sheep
Treatment of respiratory tract infections caused by *Mannheimia haemolytica* and *Pasteurella multocida*.

Treatment of foot rot in sheep caused by *Dichelobacter nodosus* and *Fusobacterium necrophorum.*

Treatment of acute ovine mastitis caused by *Staphylococcus aureus* and *Mycoplasma agalactiae*

5. CONTRAINDICATIONS

Do not administer intravenously.
Do not administer intramuscularly
Do not administer to lambs weighing less than 15 kg.

Do not administer to primates.
Do not administer to pigs.
Do not administer to horses and donkeys.
Do not administer to goats.
Do not use in case of hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

Occasionally, a soft diffuse swelling may occur at the injection site but this disappears within five to eight days. In rare cases recumbency, incoordination and convulsions have been observed.

Deaths of cattle have been observed following a single intravenous dose of 5 mg/kg body weight, and following the subcutaneous injection of doses of 150 mg/kg body weight at 72 hour intervals. In pigs, intramuscular injection at 20 mg/kg body weight has caused deaths. Sheep have died following a single intravenous injection of 7.5 mg/kg body weight.

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 and sheep.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

FOR SUBCUTANEOUS USE ONLY

Use a single treatment of 10 mg tilmicosin per kg body weight (corresponding to 1 ml Tilmovet per 30 kg body weight).

Cattle:
Method of administration:
To ensure the correct dosage, the body weight must be determined as accurately as possible in order to avoid underdosing.

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 20 ml per injection site.

Sheep:
Method of administration:
Accurate weighing of lambs is important to avoid overdosing. The use of a 2 ml syringe or smaller improves accurate dosing.

Withdraw the required dose from the vial and remove the syringe from the needle, leaving the needle in the vial. Restrain the sheep whilst leaning over the animal and

insert a separate needle subcutaneously into the injection site, which should be in a skinfold over the rib cage behind the shoulder. Attach the syringe to the needle and inject into the base of the skin fold. Do not inject more than 2 ml per injection site.

9. ADVICE ON CORRECT ADMINISTRATION

If no improvement is noted within 48 hours, the diagnosis should be confirmed.
Avoid introduction of contamination into vial during use. Do not use Tilmovet if you notice any foreign particulate matter and/or abnormal physical appearance.
The closure should not be broached more than 15 times. In order to prevent excessive broaching of the stopper, a suitable multiple dosing device should be used.

10. WITHDRAWAL PERIOD(S)

Cattle:
Meat and offal: 70 days
Milk: 36 days

If the product is administered to cows during the dry period or to pregnant dairy heifers, milk should not be used for human consumption until 36 days after calving.

Sheep:
Meat and offal: 42 days
Milk: 18 days

If the product is administered to ewes during the dry period or to pregnant ewes, milk should not be used for human consumption until 18 days after lambing.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Keep the vial 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 vial and carton after “EXP”. The expiry date refers to the last day of that month.
|
Shelf-life after first broaching the immediate packaging: 28 days.

Do not use Tilmovet if you notice any foreign particulate matter and/or abnormal physical appearance.

12. SPECIAL WARNING(S)

Special warnings for each target species:

Sheep
The clinical trials did not demonstrate a bacteriological cure in sheep with acute mastitis caused by *Staphylococcus aureus* and *Mycoplasma agalactiae.*
Do not administer to lambs weighing less than 15 kg since there is a risk of overdose toxicity. Accurate weighing of lambs is important to avoid overdose.

Special precautions for use in animals

Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.

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 macrolides, lincosamides and streptogramin B due to the potential for cross-resistance.

The feeding of waste milk containing residues of tilmicosin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

Do not administer to lambs weighing less than 15 kg since there is a risk of overdose toxicity.

Official, national and regional antimicrobial policies should be taken into account when the product is used

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 product should only be administered by a veterinary surgeon.
- Never carry a syringe loaded with Tilmovet 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 Tilmovet.
- 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 operator safety warnings:

- Avoid contact with skin and eyes. Rinse any splashes from skin and eyes immediately with water.
- May cause sensitisation by skin contact. 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: XXXXXXX(National)

Pregnancy:

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

Interaction with other medicinal products and other forms of interaction:

Interactions between macrolides and ionophores could be observed in some species.
Tilmicosin may lessen the antibacterial activity of beta-lactam antibiotics.
Do not use simultaneously with bacteriostatic antimicrobial agents

Overdose (symptoms, emergency procedures, antidotes):

In cattle subcutaneous injections of 10, 30 and 50 mg/kg body weight, repeated three times with a 72 hours interval, did not cause death. As expected, oedema developed at the site of injection. The only lesion observed at autopsy was a necrosis of the myocardium in the group treated with 50 mg/kg body weight.

Doses of 150 mg/kg body weight, administered subcutaneously with an interval of 72 hours caused death. Oedema at the site of injection was observed and at autopsy a light necrosis of the myocardium was the only lesion determined. Other symptoms observed were: difficulty in moving, reduced appetite and tachycardia.

In sheep single injections (approximately 30 mg/kg body weight) may cause a slight increase of the rate of respiration. Higher doses (150 mg/kg body weight) caused ataxia, lethargy and the inability to raise the head.
Deaths occurred after one single intravenous injection of 5 mg/kg body weight in cattle and 7.5 mg/kg in sheep body weight.

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.

Veterinary medicinal product must not be disposed of via waste water or the drainage systems

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

May 2022

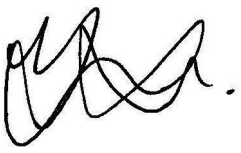
15. OTHER INFORMATION

250 ml, 100 ml, 50 ml and 25 ml vials.

25 ml Type I amber glass vials, 50 ml, 100 ml, and 250 ml Type II amber glass vials sealed with Type I bromobutyl stoppers and aluminium caps, supplied in cardboard boxes. One vial per box.

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.



Approved: 11 October 2023