ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard carton

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Micotil 300 mg/ml Solution for Injection
Tilmicosin

2. STATEMENT OF ACTIVE SUBSTANCES

Tilmicosin 300 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

25 ml
50 ml
100 ml
250 ml

5. TARGET SPECIES

Cattle and sheep

6. 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*.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

FOR SUBCUTANEOUS INJECTION ONLY.

Read the fold out label or package leaflet before use.

Official, national and regional antimicrobial policies should be taken into account when the product is used.
To avoid self-injection do not use automatic injection equipment.
The use of the product should be based on susceptibility tests.
Avoid introduction of contamination into the vial during use. The vial should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vial.
Use 10 mg tilmicosin per kg body weight (corresponding to 1 ml Micotil per 30 kg body weight).
Do not treat lamb weighing less than 15 kg, since there is a risk of overdosage toxicity.
Accurate weighing of lambs is important to avoid overdosing. The use of a 2 ml syringe or smaller improves accurate dosing.
If no improvement is noted within 48 hours, the diagnosis should be confirmed.

8. WITHDRAWAL PERIOD(S)

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

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

9. SPECIAL WARNING(S), IF NECESSARY

Do not administer intravenously. Intravenous injection in cattle and sheep has been fatal.
Do not administer intramuscularly.
Do not administer to lambs weighing less than 15 kg.
Do not administer to horses, donkeys, pigs, goats or primates. Injection of the product in goats and pigs has been fatal.
Do not use in case of hypersensitivity to the active substance or to any of the excipients.

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 Micotil 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 Micotil.
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 PHYSICIAN: please see inside of label or package leaflet for details.

Additional operator safety warnings:
• Avoid contact with skin and eyes. Rinse any splashes from skin or eyes immediately with water.
• May cause sensitisation by skin contact. Wash hands after use.

10. EXPIRY DATE

EXP

Once broached use within 28 days.

11. SPECIAL STORAGE CONDITIONS

Protect from direct sunlight.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS 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.

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

For animal treatment only.

To be supplied only on veterinary prescription.

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

Elanco Europe Ltd.
Form 2, Bartley Way
Bartley Wood Business Park
Hook
RG27 9XA
United Kingdom

16. MARKETING AUTHORISATION NUMBER(S)

Vm 00879/4203

17. MANUFACTURER'S BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Glass vial – base label (fold out label details are the same as the package leaflet)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Micotil 300 mg/ml Solution for Injection
Tilmicosin

2. STATEMENT OF ACTIVE SUBSTANCES

Tilmicosin 300 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

25 ml
50 ml
100 ml
250 ml

5. TARGET SPECIES

Cattle and sheep

6. 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*.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

FOR SUBCUTANEOUS INJECTION ONLY.

Read the fold out label or package leaflet before use.

8. WITHDRAWAL PERIOD(S)

See fold out label or package leaflet for details.

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 Micotil 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 Micotil.
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 PHYSICIAN: please see inside of label or package leaflet for details.

10. EXPIRY DATE

EXP

Once broached use within 28 days.
Discard date.....

11. SPECIAL STORAGE CONDITIONS

Protect from direct sunlight.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS 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.

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

For animal treatment only.
To be supplied only on veterinary prescription.

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

Elanco Europe Ltd.
Form 2, Bartley Way
Bartley Wood Business Park
Hook
RG27 9XA
United Kingdom

16. MARKETING AUTHORISATION NUMBER(S)

Vm 00879/4203

17. MANUFACTURER'S BATCH NUMBER

Lot

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

Micotil 300 mg/ml Solution for Injection

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

Marketing authorisation holder:
Elanco Europe Ltd.
Form 2, Bartley Way
Bartley Wood Business Park
Hook
RG27 9XA
United Kingdom

Manufacturers responsible for batch release:
Elanco UK AH Limited
Elanco Speke Operations
Fleming Road, Speke, Liverpool L24 9LN, UK

Elanco France S.A.S
26 Rue de la Chapelle
68330 Huningue
France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Micotil 300 mg/ml Solution for Injection
Tilmicosin

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

Tilmicosin 300 mg/ml

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 cases of hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

A soft diffuse swelling may occur at the injection site very rarely but this disappears within five to eight days. Recumbency, incoordination and convulsions have been observed in rare cases.

Hypersensitivity reactions may occur in very rare cases. Such reactions may include anaphylaxis, which may be life-threatening. If such reactions occur appropriate treatment is recommended. Death may occur in very rare cases.

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 and sheep.

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

FOR SUBCUTANEOUS INJECTION ONLY.
Use 10 mg tilmicosin per kg body weight (corresponding to 1 ml Micotil per 30 kg body weight).

Cattle:

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 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

Official, national and regional antimicrobial policies should be taken into account when the product is used.
To avoid self-injection do not use automatic injection equipment.
The use of the product should be based on susceptibility tests.
If no improvement is noted within 48 hours, the diagnosis should be confirmed.
Avoid introduction of contamination into vial during use. Do not use Micotil if you notice any foreign particulate matter and/or abnormal physical appearance.

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.
Protect from direct sunlight.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP.

Shelf-life after first opening the container: 28 days
Do not use Micotil 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 *Staphyloccocus 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. The use of a 2 ml or smaller syringe will facilitate accurate dosing.

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 Micotil 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 Micotil.
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 or 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: UK:0844 8920111 IE: 01809 2166

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.

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

Medicines should not be disposed of via wastewater or household waste.
Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

February 2021

15. OTHER INFORMATION

Micotil is contained in 25 ml, 50 ml, 100 ml or 250 ml amber glass vials (Type I or Type II) sealed with a rubber stopper and aluminium overseal. Each vial is packed into a carton. Not all pack sizes may be marketed.

Approved: 18/02/21