PARTICULARS TO APPEAR ON THE OUTER PACKAGE
Cardboard carton

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Tilmicosin 300 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml

5. TARGET SPECIES

Cattle and sheep.

6. INDICATION(S)

Read the fold out label or package leaflet before use.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

FOR SUBCUTANEOUS INJECTION ONLY
Read the fold out label or package leaflet before use.

Use 10 mg tilmicosin per kg body weight (corresponding to 1 ml Tilmodil per 30 kg body weight).
Do not treat lambs weighing less than 15 kg, since there is a risk of overdose toxicity.

8. WITHDRAWAL PERIOD

Cattle:
Meat and offal: 70 days
Milk: 36 days
Sheep:
Meat and offal: 42 days
Milk: 18 days

9. SPECIAL WARNING(S), IF NECESSARY

Read the fold out label or package leaflet before use.

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 Tilmodil 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 Tilmodil.
- In case of human injection SEEK IMMEDIATE MEDICAL ATTENTION and take the vial or the package insert with you. Apply a cold pack (not ice directly) to the injection site.

Additional operator safety warnings and NOTE TO THE PHYSICIAN:
Please see inside part of label or package leaflet for details.

10. EXPIRY DATE

EXP <*{month/year}*>
Once broached, use by 28 days.

11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. 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 products should be disposed of in accordance with *<national / 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

EMDOKA bvba, B-2321 Hoogstraten, Belgium.

16. MARKETING AUTHORISATION NUMBER

Vm 34534/4001

17. MANUFACTURER’S BATCH NUMBER

<Batch> <Lot> <BN> {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE
Fold out label for vials of 50 ml or 100 ml.

Text to appear on the visible side of the fold out label

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Tilmicosin 300 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml

5. TARGET SPECIES

Cattle and sheep

6. INDICATION(S)

Read the fold out label or package leaflet before use.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

FOR SUBCUTANEOUS INJECTION ONLY.

Read the fold-out label or package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal periods: See inside part of label or leaflet.

9. SPECIAL WARNING(S), IF NECESSARY

Injection of tilmicosin in humans can be fatal – Exercise extreme caution to avoid accidental self-injection and follow the administration instructions and the guidance on the inside of the label or the package leaflet precisely.

Operator safety warnings, NOTE TO THE PHYSICIAN: Please see inside part of label or package leaflet for details.

10. EXPIRY DATE

EXP <*{month/year}*>
Once broached, use by … … …

11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Protect from direct sunlight.

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

[Not to be mentioned on the immediate package– mentioned on carton/leaflet]

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

EMDOKA bvba, B-2321 Hoogstraten, Belgium

16. MARKETING AUTHORISATION NUMBER

Vm 34534/4001

17. MANUFACTURER'S BATCH NUMBER

<Batch> <Lot> <BN> {number}

Text to appear on the INSIDE of the fold out label

8. WITHDRAWAL PERIODS

Cattle:
Meat and offal: 70 days
Milk: 36 days
Sheep:
Meat and offal: 42 days
Milk: 18 days

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 Tilmodil 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 Tilmodil.
- In case of human injection SEEK IMMEDIATE MEDICAL ATTENTION and take the vial or the package insert with you. Apply a cold pack (not ice directly) to the injection site.

Additional operator safety warnings:

- Avoid contact with 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 adrenaline.

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: *[To be completed nationally]*

B. PACKAGE LEAFLET

TILMODIL 300 mg/ml
Solution for Injection for Cattle and Sheep

1. Name and address of the Marketing Authorisation Holder and the Manufacturing Authorisation Holder responsible for batch release:
Authorisation Holder: Emdoka bvba, John Lijsenstraat 16, B-2321 Hoogstraten, Belgium.
Manufacturer: Produlab Pharma bv, NL-4941 SJ Raamsdonksveer, The Netherlands.

2. Name of the veterinary medicinal product:
TILMODIL 300 mg/ml Solution for Injection for cattle and sheep
Tilmicosin

3. Statement of the active substance(s) and other ingredient(s):
TILMODIL is a clear, yellowish to brown-yellowish solution for injection containing 300 mg of tilmicosin per ml and propylene glycol.

4. Indications:
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. Contra-indications:
Do not administer intravenously.
Do not administer intramuscularly.
Do not administer to lambs weighing less than 15 kg.
Do not administer to primates, pigs, horses, donkeys and 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.

In very rare cases, dyspnoea leading to acute death has been observed following administration in cattle and sheep. Such cases may relate to relative overdosing and/or inadvertent intramuscular injection.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

If you notice any serious effect or any other effects not mentioned in this leaflet, 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 Tilmodil per 30 kg body weight).

To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid under-dosing.

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.
Wherever possible, the use of the product should be 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 macrolides and lincomycin due to the potential for cross-resistance.
To avoid self-injection do not use automatic injection equipment.
If no improvement is noted within 48 hours, the diagnosis should be confirmed.
Avoid introduction of contamination into vial during use. Do not use Tilmodil if you notice any foreign particulate matter and/or abnormal physical appearance.
Do not broach the vial more than 25 times.

10. Withdrawal periods:
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.
Do not store above 25 °C. 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 immediate packaging: 28 days.
Do not use Tilmodil if you notice any foreign particulate matter and/or abnormal physical appearance.

12. Special warnings:

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.

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 Tilmodil 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 Tilmodil.
- In case of human injection SEEK IMMEDIATE MEDICAL ATTENTION and take the vial or the package insert with you. Apply a cold pack (not ice directly) to the injection site.

Additional operator safety warnings:

- Avoid contact with 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 adrenaline.

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: *[To be completed nationally]*

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 have been observed in some species.

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 material, if any:
Medicines should not be disposed of via wastewater or household waste. Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with < national > or <local> requirements.

14. Date on which the package leaflet was last approved:

[To be completed nationally]

15. Other information:
Tilmodil is contained in 50 ml or 100 ml amber glass vials (Type II) sealed with a rubber stopper and aluminium overseal. Each vial is packed into a carton.

Not all pack sizes may be marketed.

[To be completed nationally]


08 June 2016