# ANNEX III

# LABELLING AND PACKAGE LEAFLET

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE AND THE IMMEDIATE PACKAGE**

**100 ml outer carton + immediate label**
**250 ml outer carton + immediate label**
**50 ml outer carton**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tyljet 200 mg/ml solution for injection for cattle and pigs
Tylosin

## 2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains 200 000 IU of tylosin (equivalent to approximately 200 mg).

## 3. PHARMACEUTICAL FORM

Solution for injection.

## 4. PACKAGE SIZE

100 ml
250 ml
50 ml

## 5. TARGET SPECIES

Cattle and pigs

## 6. INDICATION(S)

## 7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

*[Immediate label]*
Pigs: IM. Cattle: IM or IV
*[Outer carton]*
Pigs: intramuscular use.
Cattle: intramuscular use or slow intravenous use.

## 8. WITHDRAWAL PERIODS

**Withdrawal periods:**
Cattle: Meat and offal: 28 days. Milk: 108 hours
Pigs: Meat and offal: 16 days

## 9. SPECIAL WARNING(S), IF NECESSARY

## 10. EXPIRY DATE

EXP:
Once opened, use within 28 days by __/__/__

## 11. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.
Do not store above 25°C.
Do not freeze.

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

*Not required on the immediate label*
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 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

Ceva Animal Health Ltd
Explorer House
Mercury Park
Wycombe Lane
Wooburn Green
High Wycombe
Buckinghamshire
HP10 0HH
United Kingdom

## 16. MARKETING AUTHORISATION NUMBER(S)

Vm 15052/4157

## 17. MANUFACTURER'S BATCH NUMBER

Lot:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**50 ml**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tyljet 200 mg/ml solution for injection for cattle and pigs
Tylosin

## 2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

1 ml contains 200 000 IU of tylosin (equivalent to approximately 200 mg).

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

50 ml

## 4. ROUTE(S) OF ADMINISTRATION

Pigs: IM. Cattle: IM or IV

## 5. WITHDRAWAL PERIOD(S)

**Withdrawal periods:**
Cattle: Meat and offal: 28 days. Milk: 108 hours
Pigs: Meat and offal: 16 days

## 6. BATCH NUMBER

Lot

## 7. EXPIRY DATE

Once opened, use within 28 days by __/__/__
EXP

## 8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

# B. PACKAGE LEAFLET

# PACKAGE LEAFLET

## Tyljet 200 mg/ml solution for injection for cattle and pigs

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

Marketing authorisation holder:

Ceva Animal Health Ltd
Explorer House
Mercury Park
Wycombe Lane
Wooburn Green
High Wycombe
Buckinghamshire
HP10 0HH
United Kingdom

Manufacturer responsible for batch release:

Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne, France
Vetem S.p.A., Lungomare L. Pirandello 8, 92014 Porto Empedocle (AG), Italy

## 2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tyljet 200 mg/ml solution for injection for cattle and pigs
Tylosin

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

One ml contains:
Active substance: Tylosin: 200 000 IU (equivalent to approximately 200 mg)
Excipient: Benzyl alcohol (E1519): 0.04 ml
Yellow clear solution.

## 4. INDICATION(S)

For the treatment of specific infectious conditions (stated below) caused by microorganisms susceptible to tylosin.

Cattle (adult):
Respiratory infections, metritis caused by Gram-positive microorganisms, mastitis caused by *Streptococcus* spp*., Staphylococcus* spp. and interdigital necrobacillosis, *i.e.* panaritium or foot rot.

Calves:
Respiratory infections and necrobacillosis.

Pigs:
Enzootic pneumonia, haemorrhagic enteritis, erysipelas and metritis.
Arthritis caused by *Mycoplasma* spp. and *Staphylococcus* spp.
For information regarding swine dysentery see section "Special precautions for use in animals".

## 5. CONTRAINDICATIONS

Do not administer to horses or other equines.
Intramuscular injection can be fatal in chickens and turkeys.
Do not use in animals with known hypersensitivity to tylosin, other macrolides or to any of the excipients.

## 6. ADVERSE REACTIONS

Hypersensivity reactions may occur.
Blemishes may occur at the site of injection and can persist for up to 21 days following administration.

In very rare cases the following have been observed:
- Swelling/inflammation at the site of injection,
- Vulval swelling in cattle,
- Oedema of the rectal mucosa, partial anal protrusion (rosebudding), erythema and pruritus in pigs,
- Anaphylactic shock and death.

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, including isolated reports treated).

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 pigs

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

For intramuscular injection or, only in cattle, slow intravenous injection.

Cattle:
5-10 mg tylosin / kg bodyweight per day during 3 days (2.5 to 5 ml solution for injection per 100 kg bodyweight). Maximum injection volume per injection site should not exceed 15 ml.

Pigs:
5-10 mg tylosin / kg bodyweight per day during 3 days (2.5 to 5 ml solution for injection per 100 kg bodyweight).

In pigs do not administer more than 5 ml per injection site.

To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid underdosing.
The closures should not be broached more than 20 times. Otherwise, the use of a multiple-dose syringe is recommended.

## 9. ADVICE ON CORRECT ADMINISTRATION

## 10. WITHDRAWAL PERIODS

Cattle: Meat and offal: 28 days. Milk: 108 hours
Pigs: Meat and offal: 16 days

## 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 store above 25°C.
Do not freeze.
Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
Shelf life after first opening the immediate packaging: 28 days.

## 12. SPECIAL WARNING(S)

Special warnings for each target species
None.

Special precautions for use in animals
Due to likely variability (time, geographical) in susceptibility of bacteria to tylosin, bacteriological sampling and susceptibility testing are recommended.
Official, national and regional antimicrobial policies should be taken into account when the product is used.
Use of the product deviating from the instructions given in this package leaflet may increase the prevalence of bacteria resistant to tylosin and may decrease the effectiveness of treatment with other macrolide antibiotics due to the potential for cross-resistance.
The efficacy data do not support the use of tylosin for the treatment of bovine mastitis caused by *Mycoplasma* spp.
A high rate of *in vitro* resistance has been demonstrated in European strains of *Brachyspira hyodysenteriae* implying that the product will not be sufficiently efficacious against swine dysentery.
Where repeat injections are to be administered, use different sites for each injection.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Care should be taken to avoid accidental self-injection.
In case of accidental self- injection, seek medical advice immediately and show the package leaflet or the label to the physician.
Tylosin may induce irritation. In the event of accidental skin contact, wash thoroughly with soap and water. In case of accidental eye contact, flush the eyes with plenty of clean, running water.
Wash hands after use.
Macrolides, such as tylosin, may also cause hypersensitivity (allergy) following injection, inhalation, ingestion or contact with skin or eye. Hypersensitivity to tylosin may lead to cross reactions to other macrolides and vice versa. Allergic reactions to these substances may occasionally be serious and therefore direct contact should be avoided.
Do not handle the product if you are allergic to ingredients in the product.
If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Pregnancy and lactation
Studies in laboratory animals have neither produced any evidence of a teratogenic or foetotoxic effects nor consequences on animals' fertility.
The safety of the veterinary medicinal product has not been established during pregnancy and lactation
in the target species.
Use only according to the benefit/risk assessment by the responsible veterinarian.

Interaction
None known.

Overdose (symptoms, emergency procedures, antidotes)
In pigs and calves, an intramuscular injection of 30 mg/kg per day during 5 consecutive days produced no adverse effects.

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.

## 14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

October 2022

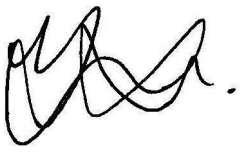
## 15. OTHER INFORMATION

Pack sizes:
Cardboard box containing 1 vial of 50 ml.
Cardboard box containing 1 vial of 100 ml.
Cardboard box containing 1 vial of 250 ml.
Not all pack sizes may be marketed.

**Pharmacodynamic properties**
Tylosin is a macrolide antibiotic with a pKa of 7.1. Tylosin is structurally similar to erythromycin. It is produced by *Streptomyces fradiae*. Tylosin has a low solubility in water.
Tylosin exerts its antibiotic activity by a similar mechanism to other macrolides, i.e. by binding the 50 S fraction of the ribosomes, resulting in an inhibition of the synthesis of proteins. Tylosin has mainly a bacteriostatic activity.
Tylosin has an antibiotic effect against Gram-positive cocci (Staphylococci, Streptococci), Gram-positive bacilli (*Trueperella* spp., *Clostridium* spp., *Erysipelothrix*, *Actinomyces*), some Gram-negative bacilli (*Haemophilus* spp., *Pasteurella* spp., *Mannheimia* spp.) and *Mycoplasma*.
Resistance to macrolides is usually plasmid-mediated but modification of ribosomes may occur through chromosomal mutation. Resistance can occur by i) decreased entry into bacteria (most common with the gram-negative bacteria), ii) synthesis of bacterial enzymes that hydrolyze the drug and, iii) modification of the target (the ribosome).
This latter resistance type may also lead to cross-resistance with other antibiotics that preferentially bind to bacterial ribosome. Gram-negative anaerobic bacteria are often resistant.

**Pharmacokinetic particulars**
Absorption:
Following intramuscular injection the tylosin concentration reaches its maximum at 3-4 hours.
Distribution, Biotransformation and Elimination:
The maximum concentration in milk of cattle and sows is 3-6 times higher than the blood concentration about 6 hours following injection. In bovine and porcine lungs maximum tylosin concentrations of 7-8 times higher than the maximum concentrations in serum were found at 6-24 hours following intramuscular injection.
In cattle (whether in heat or not) the Mean Residence Time (MRT) in uterus secretions of tylosin injected by intravenous route at a dose rate of 10 mg/kg was

about 6-7 times higher than the one measured in serum. This illustrates that in uterine secretions a single tylosin injection at a dose rate of 10 mg/kg during 24 hours can result in concentrations exceeding the MIC90 of tylosin for *Trueperella pyogenes*, one of the pathogens frequently isolated when metritis is diagnosed in cattle.
Tylosin is eliminated in unchanged form in bile and urine.
Environmental properties:
Tylosin is persistent in some soils.



Approved: 07 October 2022