1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 180 mg/ml solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
One ml contains:
Tildipirosin 180 mg.

Excipients:

Qualitative composition of excipients and other constituents
Citric acid monohydrate
Propylene glycol
Water for injections

Clear yellowish solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle

3.2 Indications for use for each target species

For the treatment and prevention of bovine respiratory disease (BRD) associated with *Histophilus somni*, *Mannheimia haemolytica* and *Pasteurella multocida*.

The presence of the disease in the group must be established before the product is used.

3.3 Contraindications

Do not use in cases of hypersensitivity to macrolide antibiotics or to any of the excipients.
Do not administer simultaneously with other macrolides or lincosamides (see section 3.8).

3.4 Special warnings

There is cross resistance with other macrolides.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

Use of the product should be in accordance with official, national and regional antimicrobial policies.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

People with known hypersensitivity to tildipirosin should avoid contact with the veterinary medicinal product.

Tildipirosin may cause sensitisation by skin contact. If accidental skin exposure occurs, wash the skin immediately with soap and water. If accidental eye exposure occurs, flush eyes immediately with clean water.

Wash hands after use.

Special caution should be taken to avoid accidental self-injection, as toxicology studies in laboratory animals showed cardiovascular effects after intramuscular administration of tildipirosin. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Do not use in automatically powered syringes which have no additional protection system.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle

Very common (>1 animal / 10 animals treated):	Immediate pain upon injection, Injection site swelling[1], Injection site pain[2], Injection site reaction[3]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Anaphylaxis[4]

[1] may be present up to 21 days post treatment
[2] may be present up to 1 day post treatment
[3] pathomorphological, will largely resolve within 35 days
[4] may be fatal

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation. However, there was no evidence for any selective developmental or reproductive effects in any of the laboratory studies. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

The product should not be administered with antimicrobials with a similar mode of action such as other macrolides or lincosamides. Please also refer to sections 3.3 and 3.4.

3.9 Administration routes and dosage

Subcutaneous use.

Administer 4 mg tildipirosin/kg body weight (equivalent to 1 ml/45 kg body weight) once only. For treatment of cattle over 450 kg body weight, divide the dose so that no more than 10 ml are injected at one site.

The rubber stopper of the vial may be safely punctured up to 20 times. Otherwise, the use of a multiple-dose syringe is recommended.

To ensure a correct dosage, bodyweight should be determined as accurately as possible.

It is recommended to treat animals in the early stages of the disease and to evaluate the response to treatment within 2 to 3 days after injection. If clinical signs of respiratory disease persist or increase, treatment should be changed using another antibiotic, and continued until clinical signs have resolved.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

In calves, a single subcutaneous injection of 10 times the recommended dose (40 mg/kg body weight) and repeated subcutaneous administration of tildipirosin (on three occasions in intervals of 7 days) at 4, 12 and 20 mg/kg (1, 3 and 5 times the recommended clinical dose) were well tolerated, apart from transient clinical signs attributed to injection site discomfort and injection site swellings associated with pain in some animals.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Meat and offal: 47 days.
Not authorised for use in animals producing milk for human consumption.
Do not use in pregnant animals, which are intended to produce milk for human consumption, within 2 months of expected parturition.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01FA96.

4.2 Pharmacodynamics

Tildipirosin is a 16-membered semi-synthetic macrolide antimicrobial agent. Three amine substituents at the macrocyclic lactone ring result in a tri-basic character of the molecule. The product has a long duration of action; however, the exact clinical effect duration after a single injection is unknown.

Macrolides in general are bacteriostatic antibiotics but for certain pathogens can be bactericidal. They inhibit essential protein biosynthesis by virtue of their selective binding to bacterial ribosomal RNA and act by blocking the prolongation of the peptide chain. The effect is generally time-dependent. The antimicrobial activity spectrum of tildipirosin includes:
Histophilus somni, Mannheimia haemolytica and *Pasteurella multocida*,the bacterial pathogens most commonly associated with bovine respiratory disease (BRD). *In vitro*, the effect of tildipirosin is bactericidal against *H. somni* and *M. haemolytica* and bacteriostatic against *P. multocida*. Minimum inhibitory concentration (MIC) data for the target pathogens (wild type distribution) are presented in the table below.

Species	Range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Mannheimia haemolytica (n=50)	0.125–>64	0.5	1
Pasteurella multocida (n=50)	0.125–2	0.5	0.5
Histophilus somni (n=50)	0.5–4	2	4

The following tildipirosin breakpoints have been established for bovine respiratory disease (according to CLSI Guideline VET02 A3):

Disease Species	Disk content	Zone diameter (mm)			MIC breakpoint (µg/ml)		
		S	I	R	S	I	R
Bovine respiratory disease	60 µg						
M. haemolytica		≥ 20	17–19	≤ 16	4	8	16
P. multocida		≥ 21	18–20	≤ 17	8	16	32
H. somni		≥ 17	14–16	≤ 13	8	16	32

S: susceptible; I: intermediate; R: resistant

Resistance to macrolides generally results from three mechanisms: (1) the alteration of the ribosomal target site (methylation), often referred to as MLSB resistance as it affects macrolides, lincosamides and group B streptogramins; (2) the utilisation of active efflux mechanism; (3) the production of inactivating enzymes. Generally, cross-resistance between tildipirosin and other macrolides, lincosamides or streptogramins is to be expected.
Data were collected on zoonotic bacteria and commensals. MIC values for *Salmonella* were reported to be in the range of 4-16 µg/ml, and all strains were wild type. For *E. coli*, *Campylobacter* and *Enterococci*, both wild type and non-wild type phenotypes were observed (MIC range 1–> 64 µg/ml).

4.3 Pharmacokinetics

Tildipirosin administered subcutaneously to cattle at a single dose of 4 mg/kg body weight resulted in rapid absorption with average peak plasma concentration of 0.7 µg/ml within 23 minutes (T_{max}) and high absolute bioavailability (78.9%).
Macrolides are characterised by their extensive partitioning into tissues.
Accumulation at the site of respiratory tract infection is demonstrated by high and sustained tildipirosin concentrations in lung and bronchial fluid, which far exceed those in blood plasma. The mean terminal half-life is approximately 9 days.
In vitro binding of tildipirosin to bovine plasma and bronchial fluid proteins is limited with approximately 30%.
In cattle, it is postulated that metabolism of tildipirosin proceeds by cleavage of the mycaminose sugar moiety, by reduction and sulphate conjugation with subsequent hydration (or ring opening), by demethylation, by mono- or dihydroxylation with subsequent dehydration and by S-cysteine and S-glutathione conjugation.
The mean total excretion of the total dose administered within 14 days was about 24% in urine and 40% in faeces.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 28 days.

5.3 Special precautions for storage

Do not store above 25 °C.

5.4 Nature and composition of immediate packaging

Type I amber glass vial with chlorobutyl rubber stopper and an aluminium cap.
Box containing 1 vial of 20 ml, 50 ml, 100 ml or 250 ml.

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Intervet International B. V.

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/11/124/005–008

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 06/05/2011

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{DD/MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).