SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 180 mg/ml solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains:

Active substance:
Tildipirosin 180 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear yellowish solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle

4.2 Indications for use, specifying the target species

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

The presence of the disease in the herd should be confirmed before preventive treatment.

4.3 Contraindications

Do not use in case of hypersensitivity to macrolide antibiotics or to any of the excipients. Do not administer simultaneously with other macrolides or lincosamides (see section 4.8)

4.4 Special warnings

None.

4.5 Special precautions for use

Special precautions for use in animals
Whenever possible, the veterinary medicinal product should only be used based on susceptibility testing.
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
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.

4.6 Adverse reactions (frequency and seriousness)

In very rare cases, anaphylactic reactions, with a potentially fatal outcome, might occur.

Pain on injection and injection site swellings are very common in treated animals. Following the maximum recommended injection site volume of 10 ml, injection site swellings may be associated with pain on palpation for about one day in individual animals. The swellings are transient and will usually resolve within 7 to 16 days; in individual animals swellings may persist for 21 days.
Pathomorphological injection site reactions will largely resolve within 35 days.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions 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).

4.7 Use during pregnancy and lactation

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.

4.8 Interaction with other medicinal products and other forms of interaction

There is cross resistance with other macrolides. Therefore, the product should not be administered with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

4.9 Amounts to be administered and administration route

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 correct dosage, bodyweight should be determined as accurately as possible to avoid underdosing.

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.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

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.

4.11 Withdrawal period

Cattle (meat and offal): 47 days.

Not authorised for use in lactating 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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use, macrolides.
ATCvet code: QJ01FA96.

5.1 Pharmacodynamic properties

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:
Mannheimia haemolytica, *Pasteurella multocida* and *Histophilus somni*, the bacterial pathogens most commonly associated with bovine respiratory disease (BRD). *In vitro*, the effect of tildipirosin is bactericidal against *M. haemolytica* and *H. somni*, 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 MLS_B 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).

5.2 Pharmacokinetic particulars

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Propylene glycol
Water for injections

6.2 Incompatibilities

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

6.3 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.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 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.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MSD Animal Health UK Limited
Walton Manor, Walton
Milton Keynes
Buckinghamshire
MK7 7AJ

8. MARKETING AUTHORISATION NUMBER

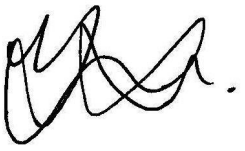
Vm 01708/5060

9. DATE OF FIRST AUTHORISATION

06 May 2011

10. DATE OF REVISION OF THE TEXT

March 2022



Approved: 09 March 2022