Issued: January 2024
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 40 mg/ml solution for injection for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
One ml contains:
Tildipirosin 40 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear yellowish solution.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs

4.2 Indications for use, specifying the target species

Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Bordetella bronchiseptica*, *Glaesserella parasuis* and *Pasteurella multocida*.

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

4.3 Contraindications

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

4.4 Special warnings for each target species

In line with responsible use principles, metaphylactic use of the veterinary medicinal product is only indicated in severe outbreaks of SRD caused by the indicated pathogens. Metaphylaxis implies that clinically healthy animals in close contact with diseased animals are administered the veterinary medicinal product at the same time as the treatment of the clinically diseased animals, to reduce the risk for development of clinical signs.

The efficacy of metaphylactic use of the veterinary medicinal product was demonstrated in a placebo controlled multi-centre field study, when outbreak of clinical disease was confirmed (i.e. animals in at least 30% of the pens sharing the same airspace showed clinical signs of SRD, including at least 10% animals per pen within 1 day; or 20% within 2 days or 30% within 3 days). Following metaphylactic use, approximately 86% of the healthy animals remained free of clinical signs of disease (as compared to approximately 65% of animals in the untreated control group).

There is cross resistance with other macrolides.

4.5 Special precautions for use

Special precautions for use in animals
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.

Administer strictly intramuscularly. Special attention should be paid to using the appropriate injection site and to use the appropriate needle size and length (adjusted to the size and weight of animal) according to good veterinary practice.

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.

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.

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 precautions for the protection of the environment:
Not applicable.

Other precautions
Not applicable.

4.6 Adverse reactions (frequency and seriousness)

Pigs:

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

[1] may be present up to 6 days post treatment
[2] pathomorphological, resolved completely within 21 days
[3] may be fatal
[4] has been observed in piglets and is transient

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.

4.7 Use during pregnancy, lactation or lay

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

4.8 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 4.3 and 4.4.

4.9 Amount(s) to be administered and administration route

Intramuscular use.

Administer 4 mg tildipirosin/kg body weight (equivalent to 1 ml/10 kg body weight) once only.
The injection volume should not exceed 5 ml per injection site.

The recommended injection site is the location just behind the ear at the highest point of the base of the ear, at the transition from bald to hairy skin.
Injection should be given in a horizontal direction and a 90° angle to the body axis.

Recommended needle size and diameter per production stage

	Needle length (cm)	Needle diameter (mm)
Piglet, newborn	1.0	1.2
Piglet, 3 – 4 weeks	1.5 – 2.0	1.4
Growing	2.0 – 2.5	1.5
Growing-finishing	3.5	1.6
Finishing/sows/boars	4.0	2.0

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, body weight 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 48 hours after injection. If clinical signs of respiratory disease persist or increase, or if relapse occurs, treatment should be changed using another antibiotic, and continued until clinical signs have resolved.

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

In piglets, intramuscular administration of tildipirosin (on three occasions in intervals of 4 days) at 8, 12 and 20 mg/kg body weight (BW) (2, 3 and 5 times the recommended clinical dose), resulted in transient slightly subdued behaviour in one piglet each from the 8 and 12 mg/kg BW group and 2 piglets from the 20 mg/kg BW group following the first or second injection.
Muscle tremors to the hind legs were observed following the first treatment in one pig each from the 12 and 20 mg/kg BW group. At 20 mg/kg body weight one out of eight animals showed transient generalised body tremors with inability to stand after the first administration and the animal showed transient unsteadiness on its feet after the third administration. Another animal developed treatment related shock after the first administration and was euthanised on welfare grounds. Mortality was observed at doses of 25 mg/kg body weight and higher.

4.11 Withdrawal period(s)

Meat and offal: 9 days.

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:
Actinobacillus pleuropneumoniae, *Bordetella bronchiseptica, Glaesserella parasuis* and *Pasteurella multocida,* which are the bacterial pathogens most commonly associated with swine respiratory disease (SRD).
In vitro, the effect of tildipirosin is bacteriostatic against *B. bronchiseptica* and *Pasteurella multocida* and bactericidal for *A. pleuropneumoniae* and *G. parasuis*. 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)**
Actinobacillus pleuropneumoniae (n=50)	2 – 16	2	4
Bordetella bronchiseptica (n=50)	0.5 – 8	2	2
Pasteurella multocida (n=50)	0.125 – 2	0.5	1
Glaesserella parasuis (n=50)	0.032 – 4	1	2

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

Species	**Disk content**	**Zone diameter (mm)**			**MIC breakpoint (µg/ml)**		
		S	**I**	**R**	**S**	**I**	**R**
A. pleuropneumoniae	60 µg	–	–	–	16	–	–
P. multocida		≥ 19	–	–	4	–	–
B. bronchiseptica		≥ 18	–	–	8	–	–

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).

5.2 Pharmacokinetic particulars

Tildipirosin administered intramuscularly to pigs at a single dose of 4 mg/kg body weight was rapidly absorbed reaching average peak plasma concentration of 0.9 µg/ml within 23 minutes (T_{max}). 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 (collected post mortem), which far exceed those in blood plasma. The mean terminal half-life is 4.4 days.

In vitro binding of tildipirosin to porcine plasma proteins is limited with approximately 30%.
In pigs, it is postulated that the metabolism of tildipirosin proceeds by reduction and sulphate conjugation with subsequent hydration (or ring opening), by demethylation, by dihydroxylation and by S-cysteine and S-glutathione conjugation.
The mean total excretion of the total dose administered within 14 days was about 17% in urine and 57% in faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Propylene glycol
Water for injections

6.2 Major 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 a 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 products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater.
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 01708/5061

9. DATE OF FIRST AUTHORISATION

06 May 2011

10. DATE OF REVISION OF THE TEXT

November 2023

11. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCT

Veterinary medicinal product subject to prescription.

Find more product information by searching for the 'Product Information Database' or 'PID' on www.gov.uk.

Approved 08 January 2024