This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved on May 2016

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Zuprevo 40 mg/ml Veterinary

Solution for injection for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains:
Active substance:
Tildipirosin 40 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

Pigs

4.2 Indications for use, specifying the target species

Treatment and prevention of swine respiratory disease (SRD) associated with Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica and Haemophilus parasuis 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 intravenously.

4.4 Special warnings

In line with responsible use principles, metaphylactic use of Zuprevo 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 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 Zuprevo 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 etaphylactic 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).

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 veterinary medicinal product is used.

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

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.

4.6 Adverse reactions (frequency and seriousness)

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 animals in 10,000 animals, including isolated reports).

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

In very rare cases, transient lethargy in piglets has been observed.

In target animal safety studies, administration of the maximum recommended injection volume (5 ml) occasionally caused slight swellings at the injection site that were not painful on palpation. Swellings persisted for up to 3 days. Pathomorphological injection site reactions resolved completely within 21 days.

During clinical trials, pain on injection and injection site swellings were seen very commonly in treated pigs. These swellings resolved within 1 to 6 days.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.7 Use during pregnancy and 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 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. Do not administer with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

4.9 Amounts to be administered and administration route

Intramuscular use.

Administer 4 mg tildipirosin/kg body weight (equivalent to 1ml/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 correct dosage, body weight should be determined as accurately as possible to avoid under-dosing.

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)

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 generalized 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 euthanized on welfare grounds. Mortality was observed at doses of 25 mg/kg body weight and higher.

4.11 Withdrawal period

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, Pasteurella multocida, Bordetella bronchiseptica and Haemophilus parasuis, which are the bacterial pathogens most commonly associated with swine respiratory disease (SRD).
In vitro, the effect of tildipirosin is bacteriostatic against Pasteurella multocida and B. bronchiseptica, and bactericidal for A. pleuropneumoniae and H. 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=100)	2–16	8	8
Bordetella bronchiseptica (n=87)	0.5–8	2	4
Pasteurella multocida (n=99)	0.125–2	0.5	1
Haemophilus parasuis (n=63)	0.032–4	0.5	1

The following proposed preliminary tildipirosin breakpoints have been determined for swine respiratory disease:

Species	Disk content	Zone diameter (mm)			MIC breakpoint (µg/ml)		
		S	I	R	S	I	R
A. pleuropleumoniae	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 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 streprogramins 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 (Tmax).
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 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

Store below 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 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 destroyed as toxic waste. Do not dispose into sewage.

7. NAME OF MANUFACTURER

Intervet International GmbH, Feldstrasse 1a, 85716 Unterschleissheim, Germany

8. NAME OF REGISTRATION HOLDER

Intervet Israel Ltd., Neve Neeman, 45240 Hod HaSharon, Isreal