

ANNEX I
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

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 metaphylaxis 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 metaphylaxis is implemented.

4.3 Contraindications

Do not use in case 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

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 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 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 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).

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)

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) very commonly 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.

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

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 according 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

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 correct dose, 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)
<i>Actinobacillus pleuropneumoniae</i> (n=50)	2–16	2	4
<i>Bordetella bronchiseptica</i> (n=50)	0.5–8	2	2
<i>Pasteurella multocida</i> (n=50)	0.125–2	0.5	1
<i>Haemophilus parasuis</i> (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
<i>A. pleuropneumoniae</i>	60 µg	–	–	–	16	–	–
<i>P. multocida</i>		≥ 19	–	–	4	–	–
<i>B. bronchiseptica</i>		≥ 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 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 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 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

Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxmeer
The NETHERLANDS

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/11/124/001–004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 May 2011.
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu>).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

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)
<i>Mannheimia haemolytica</i> (n=50)	0.125->64	0.5	1
<i>Pasteurella multocida</i> (n=50)	0.125-2	0.5	0.5
<i>Histophilus somni</i> (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						
<i>M. haemolytica</i>		≥ 20	17-19	≤ 16	4	8	16
<i>P. multocida</i>		≥ 21	18-20	≤ 17	8	16	32
<i>H. somni</i>		≥ 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

Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxmeer
The NETHERLANDS

8. MARKETING AUTHORISATION NUMBERS

EU/2/11/124/005–008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 May 2011.
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu/>).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY OR USE**
- C. STATEMENT OF THE MRLs**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Intervet International GmbH
Feldstrasse 1 a
85716 Unterschleissheim
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY OR USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

The active substance in Zuprevo is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Tildipirosin	Tildipirosin	Porcine	1,200 µg/kg 800 µg/kg 5,000 µg/kg 10,000 µg/kg	Muscle Skin+fat Liver Kidney	NO ENTRY	Anti-infectious agents/ Antibiotics
Tildipirosin	Tildipirosin	Bovine	400 µg/kg 200 µg/kg 2000 µg/kg 3000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption.	

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this veterinary medicinal product.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Pigs
Carton Box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 40 mg/ml solution for injection for pigs
tildipirosin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

40 mg/ml of tildipirosin

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

20 ml
50 ml
100 ml
250 ml

5. TARGET SPECIES

Pigs

6. INDICATION

7. METHOD AND ROUTE OF ADMINISTRATION

Intramuscular injection
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period:
Meat and offal: 9 days

9. SPECIAL WARNINGS

Accidental injection is dangerous. Do not use in automatically powered syringes which have no additional protection system.

Read the package leaflet before use.

10. EXPIRY DATE

EXP:

Once opened, use within 28 days.

11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

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

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

Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxmeer
The Netherlands

16. MARKETING AUTHORISATION NUMBERS

EU/2/11/124/001
EU/2/11/124/002
EU/2/11/124/003
EU/2/11/124/004

17. MANUFACTURER'S BATCH NUMBER

Batch:

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cattle
Box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 180 mg/ml solution for injection for cattle
tildipirosin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

180 mg/ml of tildipirosin

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

20 ml
50 ml
100 ml
250 ml

5. TARGET SPECIES

Cattle

6. INDICATION(S)

7. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous injection
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period: 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.

9. SPECIAL WARNINGS

Accidental injection is dangerous. Do not use in automatically powered syringes which have no additional protection system.

Read the package leaflet before use.

10. EXPIRY DATE

EXP:

Once opened, use within 28 days.

11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

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

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

Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxmeer
The NETHERLANDS

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/11/124/005
EU/2/11/124/006
EU/2/11/124/007
EU/2/11/124/008

17. MANUFACTURER’S BATCH NUMBER

Batch:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pigs

Vial (20 ml, 50 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 40 mg/ml solution for injection for pigs
tildipirosin

2. QUANTITY OF THE ACTIVE SUBSTANCE

40 mg/ml of tildipirosin

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

20 ml
50 ml

4. ROUTE OF ADMINISTRATION

IM

5. WITHDRAWAL PERIOD

Withdrawal period:
Meat and offal: 9 days.

6. BATCH NUMBER

Batch:

7. EXPIRY DATE

EXP:
Once opened, use by:

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Pigs

Vial (100 ml, 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 40 mg/ml solution for injection for pigs
tildipirosin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

40 mg/ml of tildipirosin

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

100 ml
250 ml

5. TARGET SPECIES

Pigs

6. INDICATION

7. METHOD AND ROUTE OF ADMINISTRATION

Intramuscular injection
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period:
Meat and offal: 9 days.

9. SPECIAL WARNINGS

Read the package leaflet before use.
Accidental injection is dangerous.

10. EXPIRY DATE

EXP:

Once opened, use by:

11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

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

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

Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxtmeer
The NETHERLANDS

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/11/124/003
EU/2/11/124/004

17. MANUFACTURER’S BATCH NUMBER

Batch:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Cattle

Vial (20 ml, 50 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 180 mg/ml solution for injection for cattle
tildipirosin

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

180 mg/ml of tildipirosin

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

20 ml

50 ml

4. ROUTE OF ADMINISTRATION

SC

5. WITHDRAWAL PERIOD

Withdrawal period: Meat and offal: 47 days.
See package leaflet.

6. BATCH NUMBER

Batch:

7. EXPIRY DATE

EXP:

Once opened, use by:

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Cattle

Vial (100 ml, 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 180 mg/ml solution for injection for cattle
tildipirosin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

180 mg/ml of tildipirosin

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

100 ml
250 ml

5. TARGET SPECIES

Cattle

6. INDICATION(S)

7. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous injection
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period: 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.

9. SPECIAL WARNINGS

Read the package leaflet before use.

Accidental injection is dangerous.

10. EXPIRY DATE

EXP:

Once opened, use by:

11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

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

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

Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxmeer
The NETHERLANDS

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/11/124/007

EU/2/11/124/008

17. MANUFACTURER’S BATCH NUMBER

Batch:

B. PACKAGE LEAFLET

**PACKAGE LEAFLET FOR:
ZUPREVO 40 mg/ml solution for injection for 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:

Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxmeer
The NETHERLANDS

Manufacturer for the batch release:

Intervet International GmbH
Feldstrasse 1 a
85716 Unterschleissheim
GERMANY

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 40 mg/ml solution for injection for pigs
tildipirosin

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

The veterinary medicinal product is a clear yellowish solution for injection containing 40 mg/ml of tildipirosin

4. INDICATIONS

Treatment and metaphylaxis 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 metaphylaxis is implemented.

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to macrolide antibiotics, citric acid monohydrate or propylene glycol.

Do not administer intravenously.

Do not administer simultaneously with other macrolides or lincosamides (see section 12)

6. ADVERSE REACTIONS

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) very commonly 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. Following the maximum recommended injection site volume of 5 ml, injection site reactions resolved completely within 21 days.

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

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Pigs

8. DOSAGE FOR EACH SPECIES, ROUTE AND METHOD OF ADMINISTRATION

Intramuscular use.

Administer 4 mg tildipirosin/kg body weight (equivalent to 1 ml/10 kg body weight) once only.

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.

9. ADVICE ON CORRECT ADMINISTRATION

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.

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 injection volume should not exceed 5 ml per injection 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, body weight should be determined as accurately as possible to avoid underdosing.

10. WITHDRAWAL PERIOD

Meat and offal: 9 days.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Do not store above 25 °C.

Do not use after the expiry date stated on the vial after EXP.

Shelf life after first opening the container: 28 days.

12. 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 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).

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.

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.

Pregnancy and lactation:

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.

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.

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 bodyweight (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 bodyweight group and 2 piglets from the 20 mg/kg bodyweight 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 bodyweight group.

At 20 mg/kg bodyweight one 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 euthanised on welfare grounds. Mortality was observed at doses of 25 mg/kg body weight and higher.

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

Ask your veterinary surgeon/pharmacist how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu/>).

15. OTHER INFORMATION

Box containing 1 vial of 20 ml, 50 ml, 100 ml or 250 ml.
Not all pack sizes may be marketed.

**PACKAGE LEAFLET FOR:
ZUPREVO 180 mg/ml solution for injection for cattle**

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

Marketing authorisation holder:

Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxtmeer
The NETHERLANDS

Manufacturer for the batch release:

Intervet International GmbH
Feldstrasse 1 a
85716 Unterschleissheim
GERMANY

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 180 mg/ml solution for injection for cattle
tildipirosin

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

ZUPREVO is a clear yellowish solution for injection containing 180 mg/ml of tildipirosin

4. INDICATIONS

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.

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to macrolide antibiotics, citric acid monohydrate or propylene glycol.
Do not administer simultaneously with other macrolides or lincosamides (see section 12).

6. ADVERSE REACTIONS

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. Injection site reactions will largely resolve within 35 days.

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

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).

7. TARGET SPECIES

Cattle

8. DOSAGE FOR EACH SPECIES, ROUTE AND METHOD OF ADMINISTRATION

Subcutaneous use.

Administer 4 mg tildipirosin/kg body weight (equivalent to 1 ml/45 kg body weight) once only.

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.

9. ADVICE ON CORRECT ADMINISTRATION

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, body weight should be determined as accurately as possible to avoid underdosing.

10. WITHDRAWAL PERIOD

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.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Do not store above 25 °C.

Do not use after the expiry date which is stated on the vial after EXP.

Shelf life after first opening the container: 28 days.

12. SPECIAL WARNINGS

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.

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

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.

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.

Overdose (symptoms, emergency procedures, antidotes):

Overdoses of 10 times the recommended dose as well as repeated subcutaneous administration of the veterinary medicinal product only led to transient clinical signs attributed to injection site discomfort and injection site swellings associated with pain in calves.

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

Ask your veterinary surgeon/pharmacist how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu/>).

15. OTHER INFORMATION

Box containing 1 vial of 20 ml, 50 ml, 100 ml or 250 ml.

Not all pack sizes may be marketed.