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

Active substance:
One ml contains:
Tildipirosin 40 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

Pigs

3.2 Indications for use for each 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.

3.3 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 3.8).

3.4 Special warnings

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.

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.

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.

3.6 Adverse events

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.

3.7 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 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

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.

3.10 Symptoms of overdose (and where applicable, emergency procedures and 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 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.

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: 9 days

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:
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. 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 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 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).

4.3 Pharmacokinetics

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.

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 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.

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/2/11/124/001–004

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).

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).

ANNEX II

OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

None.

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

2. STATEMENT OF ACTIVE SUBSTANCES

40 mg/ml of tildipirosin

3. PACKAGE SIZE

20 ml
50 ml
100 ml
250 ml

4. TARGET SPECIES

Pigs.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Intramuscular use.

7. WITHDRAWAL PERIODS

Withdrawal period:
Meat and offal: 9 days

8. EXPIRY DATE

Exp. {mm/yyyy}

Once opened, use within 28 days.

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 25°C.

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

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

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

12. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Intervet International B. V.

14. MARKETING AUTHORISATION NUMBERS

EU/2/11/124/001 (20 ml)
EU/2/11/124/002 (50 ml)
EU/2/11/124/003 (100 ml)
EU/2/11/124/004 (250 ml)

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cattle
Carton box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZUPREVO 180 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

180 mg/ml of tildipirosin

3. PACKAGE SIZE

20 ml
50 ml
100 ml
250 ml

4. TARGET SPECIES

Cattle.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Subcutaneous use.

7. WITHDRAWAL PERIODS

Withdrawal period:
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.

8. EXPIRY DATE

Exp. {mm/yyyy}

Once opened, use within 28 days.

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C.

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

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

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

12. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Intervet International B. V.

14. MARKETING AUTHORISATION NUMBERS

EU/2/11/124/005 (20 ml)
EU/2/11/124/006 (50 ml)
EU/2/11/124/007 (100 ml)
EU/2/11/124/008 (250 ml)

15. BATCH NUMBER

Lot {number}

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

2. STATEMENT OF ACTIVE SUBSTANCES

40 mg/ml of tildipirosin

3. TARGET SPECIES

Pigs

4. ROUTES OF ADMINISTRATION

Intramuscular use.
Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal period:
Meat and offal: 9 days.

6. EXPIRY DATE

Exp. {mm/yyyy}
Once opened use by:

7. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C.

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Intervet International B. V.

9. BATCH NUMBER

Lot {number}

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

2. STATEMENT OF ACTIVE SUBSTANCES

180 mg/ml of tildipirosin

3. TARGET SPECIES

Cattle

4. ROUTES OF ADMINISTRATION

Subcutaneous use. Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal period:
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 excepted parturition.

6. EXPIRY DATE

Exp. {mm/yyyy}
Once opened use by:

7. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C.

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Intervet International B. V.

9. BATCH NUMBER

Lot {number}

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

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

40 mg/ml of tildipirosin

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}
Once opened use by:

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

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

180 mg/ml of tildipirosin

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}
Once opened use by:

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

ZUPREVO 40 mg/ml solution for injection for pigs

2. Composition

Active substance:
One ml contains:
Tildipirosin 40 mg.

Clear yellowish solution.

3. Target species

Pigs

4. Indications for use

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.

5. 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 "Special warnings").

6. Special warnings

Special warnings:

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 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.

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.

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.

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:

The product should not be administered with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

Overdose:

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 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.

Special restrictions for use and special conditions for use:

Not applicable.

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

7. Adverse events

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 product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system: {national system details}.

8. Dosage for each species, routes 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 a correct dosage, body weight should be determined as accurately as possible.

10. Withdrawal periods

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 this veterinary medicinal product after the expiry date which is stated on the carton and on the vial after Exp.
Shelf life after first opening the container: 28 days.

12. Special precautions for disposal

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 applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

EU/2/11/124/001–004

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

15. Date on which the package leaflet was last revised

{DD/MM/YYYY}

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

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:
Intervet International B.V., Wim de Körverstraat 35, 5831 AN Boxmeer, The Netherlands

België/Belgique/Belgien
Tél/Tel: + 32 (0)2 370 94 01

Република България
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Česká republika
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Manufacturer responsible for batch release:
Intervet International GmbH
Feldstrasse 1 a
85716 Unterschleissheim
GERMANY

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

ZUPREVO 180 mg/ml solution for injection for cattle

2. Composition

Active substance:
One ml contains:
Tildipirosin 180 mg.

Clear yellowish solution.

3. Target species

Cattle

4. Indications for use

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.

5. 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 "Special warnings).

6. Special warnings

Special warnings:

There is cross resistance with other macrolides.

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.

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:

The product should not be administered with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

Overdose:

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.

Special restrictions for use and special conditions for use:

Not applicable.

Major incompatibilities:

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

7. 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 product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the

medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system: {national system details}.

8. Dosage for each species, routes 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 a correct dosage, body weight should be determined as accurately as possible.

10. Withdrawal periods

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 this veterinary medicinal product after the expiry date which is stated on the carton and on the vial after Exp
Shelf life after first opening the container: 28 days.

12. Special precautions for disposal

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 applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

EU/2/11/124/005–008

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

15. Date on which the package leaflet was last revised

{DD/MM/YYYY}

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

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