ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin 100 mg/ml solution for injection for cattle, pigs and sheep

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains :

Active substance:

Tulathromycin 100 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Monothioglycerol	5 mg
Propylene glycol	
Citric acid	
Hydrochloric acid	
Sodium hydroxide	
Water for injections	

Clear colourless to slightly yellow solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle, pigs and sheep.

3.2 Indications for use for each target species

Cattle:
Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis*. The presence of the disease in the group must be established before the product is used.

Treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis*.

Pigs:
Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica*. The presence of the disease in the group must be established before the product is used. The veterinary medicinal product should only be used if pigs are expected to develop the disease within 2–3 days.

Sheep:
Treatment of the early stages of infectious pododermatitis (foot rot) associated with virulent *Dichelobacter nodosus* requiring systemic treatment.

3.3 Contraindications

Do not use in cases of hypersensitivity to macrolide antibiotics or to any of the excipients.

3.4 Special warnings

Cross-resistance has been shown between tulathromycin and other macrolides in the target pathogen(s). Use of the veterinary medicinal product should be carefully considered when susceptibility testing has shown resistance to tulathromycin because its effectiveness may be reduced. Do not administer simultaneously with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

Sheep:

The efficacy of antimicrobial treatment of foot rot might be reduced by other factors, such as wet environmental conditions, as well as inappropriate farm management. Treatment of foot rot should therefore be undertaken along with other flock management tools, for example providing dry environment.

Antibiotic treatment of benign foot rot is not considered appropriate. Tulathromycin showed limited efficacy in sheep with severe clinical signs or chronic foot rot and should therefore only be given at an early stage of foot rot.

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.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

If a hypersensitivity reaction occurs appropriate treatment should be administered without delay.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Tulathromycin is irritating to eyes. In case of accidental eye exposure, flush the eyes immediately with clean water.

Tulathromycin may cause sensitisation by skin contact resulting in e.g. reddening of the skin (erythema) and/or dermatitis. In case of accidental spillage onto skin, wash the skin immediately with soap and water.

Wash hands after use.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

If there is suspicion of a hypersensitivity reaction following accidental exposure (recognised by e.g. itching, difficulty in breathing, hives, swelling on the face, nausea, vomiting) appropriate treatment should be administered. Seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle:

Very common (>1 animal / 10 animals treated):	Injection site swelling[1], Injection site fibrosis[1], Injection site haemorrhage[1], Injection site oedema[1], Injection site reaction[2], Injection site pain[3]

[1] Can persist for approximately 30 days after injection.
[2] Reversible changes of congestion.
[3] Transient.

Pigs:

Very common (>1 animal / 10 animals treated):	Injection site reaction[1,2], Injection site fibrosis[1], Injection site haemorrhage[1], Injection site oedema[1]

[1] Can persist for approximately 30 days after injection.
[2] Reversible changes of congestion.

Sheep:

Very common (>1 animal / 10 animals treated):	Discomfort[1]

[1] Transient, resolving within a few minutes: head shaking, rubbing injection site, backing away.

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. Use only according to the benefit/risk assessment by the responsible veterinarian. Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

Cattle:

Subcutaneous use.

A single subcutaneous injection of 2.5 mg tulathromycin/kg body weight (equivalent to 1 ml of the veterinary medicinal product/40 kg body weight). For treatment of cattle over 300 kg body weight, divide the dose so that no more than 7.5 ml are injected at one site.

Pigs:

Intramuscular use.

A single intramuscular injection of 2.5 mg tulathromycin/kg body weight (equivalent to 1 ml of the veterinary medicinal product/40 kg body weight) in the neck.

For treatment of pigs over 80 kg body weight, divide the dose so that no more than 2 ml are injected at one site.

For any respiratory disease, 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.

Sheep:

Intramuscular use.

A single intramuscular injection of 2.5 mg tulathromycin/kg body weight (equivalent to 1 ml of the veterinary medicinal product/40 kg body weight) in the neck.

To ensure a correct dosage, body weight should be determined as accurately as possible. For multiple vial entry, an aspirating needle or multi-dose syringe is recommended to avoid excessive broaching of the stopper.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

In cattle at dosages of three, five or ten times the recommended dose, transient signs attributed to injection site discomfort were observed and included restlessness, head-shaking, pawing the ground, and brief decrease in feed intake. Mild myocardial degeneration has been observed in cattle receiving five to six times the recommended dose.

In young pigs weighing approximately 10 kg given three or five times the therapeutic dose transient signs attributed to injection site discomfort were observed and included excessive vocalisation and restlessness. Lameness was also observed when the hind leg was used as the injection site.

In lambs (approx. 6 weeks old), at dosages of three or five times the recommended dose, transient signs attributed to injection site discomfort were observed, and included walking backwards, head shaking, rubbing the injection site, lying down and getting up, bleating.

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

Cattle (meat and offal): 22 days.

Pigs (meat and offal): 13 days.

Sheep (meat and offal): 16 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: QJ01FA94

4.2 Pharmacodynamics

Tulathromycin is a semi-synthetic macrolide antimicrobial agent, which originates from a fermentation product. It differs from many other macrolides in that it has a long duration of action that is, in part, due to its three amine groups; therefore, it has been given the chemical subclass designation of triamilide.

Macrolides are bacteriostatic acting antibiotics and inhibit essential protein biosynthesis by virtue of their selective binding to bacterial ribosomal RNA. They act by stimulating the dissociation of peptidyl-tRNA from the ribosome during the translocation process.

Tulathromycin possesses *in vitro* activity against *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis*, and *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica*, the bacterial pathogens most commonly associated with bovine and swine respiratory disease, respectively. Increased minimum inhibitory concentration (MIC) values have been found in some isolates of *Histophilus somni* and *Actinobacillus pleuropneumoniae. In vitro* activity against *Dichelobacter nodosus (vir)*, the bacterial pathogen most commonly associated with infectious pododermatitis (foot rot) in sheep has been demonstrated.

Tulathromycin also possesses *in vitro* activity against *Moraxella bovis*, the bacterial pathogen most commonly associated with infectious bovine keratoconjunctivitis (IBK).

The Clinical and Laboratory Standards Institute CLSI has set the clinical breakpoints for tulathromycin against *M. haemolytica*, *P. multocida*, and *H. somni* of bovine respiratory origin and *P. multocida* and *B. bronchiseptica* of swine respiratory origin as ≤16 mcg/ml susceptible and ≥64 mcg/ml resistant. For *A. pleuropneumoniae* of swine respiratory origin the susceptible breakpoint is set at ≤64 mcg/ml. CLSI has also published clinical breakpoints for tulathromycin based on a disk diffusion method (CLSI document VET08, 4th ed, 2018). No clinical breakpoints are available for *H. parasuis*. Neither EUCAST nor CLSI have developed standard methods for testing antibacterial agents against veterinary *Mycoplasma* species and thus no interpretative criteria have been set.

Resistance to macrolides can develop by mutations in genes encoding ribosomal RNA (rRNA) or some ribosomal proteins; by enzymatic modification (methylation) of the 23S rRNA target site, generally giving rise to cross-resistance with lincosamides and group B streptogramins (MLS_B resistance); by enzymatic inactivation; or by macrolide efflux. MLS_B resistance may be constitutive or inducible. Resistance may be chromosomal or plasmid-encoded and may be transferable if associated with transposons, plasmids, integrative and conjugative elements. Additionally, the genomic plasticity of *Mycoplasma* is enhanced by the horizontal transfer of large chromosomal fragments.

In addition to its antimicrobial properties, tulathromycin demonstrates immune-modulating and anti-inflammatory actions in experimental studies. In both bovine and porcine polymorphonuclear cells (PMNs; neutrophils), tulathromycin promotes apoptosis (programmed cell death) and the clearance of apoptotic cells by macrophages. It lowers the production of the pro-inflammatory mediators leukotriene B4 and CXCL-8 and induces the production of anti-inflammatory and pro-resolving lipid lipoxin A4.

4.3 Pharmacokinetics

In cattle, the pharmacokinetic profile of tulathromycin when administered as a single subcutaneous dose of 2.5 mg/kg body weight, was characterised by rapid and extensive absorption followed by high distribution and slow elimination. The maximum concentration (C_{max}) in plasma was approximately 0.5 mcg/ml; this was achieved approximately 30 minutes post-dosing (T_{max}). Tulathromycin concentrations in lung homogenate were considerably higher than those in plasma. There is strong evidence of substantial accumulation of tulathromycin in neutrophils and alveolar macrophages. However, the *in vivo* concentration of tulathromycin at the infection site of the lung is not known. Peak concentrations were followed by a slow decline in systemic exposure with an apparent elimination half-life ($t_{1/2}$) of 90 hours in plasma. Plasma protein binding was low, approximately 40%. The volume of distribution at steady-state (V_{ss}) determined after intravenous administration was 11 l/kg. The bioavailability of tulathromycin after subcutaneous administration in cattle was approximately 90%.

In pigs, the pharmacokinetic profile of tulathromycin when administered as a single intramuscular dose of 2.5 mg/kg body weight, was also characterised by rapid and extensive absorption followed by high distribution and slow elimination. The maximum concentration (C_{max}) in plasma was approximately 0.6 mcg/ml; this was achieved approximately 30 minutes post-dosing (T_{max}). Tulathromycin concentrations in lung homogenate were considerably higher than those in plasma. There is strong evidence of substantial accumulation of tulathromycin in neutrophils and alveolar macrophages. However, the *in vivo* concentration of tulathromycin at the infection site of the lung is not known. Peak concentrations were followed by a slow decline in systemic exposure with an apparent elimination half-life ($t_{1/2}$) of approximately 91 hours in plasma. Plasma protein binding was low, approximately 40%. The volume of distribution at steady-state (V_{ss}) determined after intravenous administration was 13.2 l/kg. The bioavailability of tulathromycin after intramuscular administration in pigs was approximately 88%.

In sheep, the pharmacokinetic profile of tulathromycin, when administered as a single intramuscular dose of 2.5 mg/kg body weight, achieved a maximum plasma concentration (C_{max}) of 1.19 mcg/ml in approximately 15 minutes (T_{max}) post-dosing and had an elimination half-life ($t_{1/2}$) of 69.7 hours. Plasma protein binding was approximately 60-75%. Following intravenous dosing the volume of distribution at steady-state (V_{ss}) was 31.7 l/kg. The bioavailability of tulathromycin after intramuscular administration in sheep was 100%.

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: 3 years.
Shelf life after first opening the immediate packaging: 28 days.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

Type I glass with a fluoropolymer coated chlorobutyl stopper and an aluminium overseal.

Pack sizes:
Cardboard box containing one vial of 20 ml.
Cardboard box containing one vial of 50 ml.
Cardboard box containing one vial of 100 ml.
Cardboard box containing one vial of 250 ml.
Cardboard box containing one vial of 500 ml.

The 500 ml vials must not be used for pigs and sheep.

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

Zoetis Belgium

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/03/041/001 (20 ml)
EU/2/03/041/002 (50 ml)
EU/2/03/041/003 (100 ml)
EU/2/03/041/004 (250 ml)
EU/2/03/041/005 (500 ml)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 11/11/2003.

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{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

Draxxin 25 mg/ml solution for injection for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains :

Active substance:

Tulathromycin 25 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Monothioglycerol	5 mg
Propylene glycol	
Citric acid	
Hydrochloric acid	
Sodium hydroxide	
Water for injections	

Clear colourless to slightly yellow 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*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica*. The presence of the disease in the group must be established before the product is used. The veterinary medicinal product should only be used if pigs are expected to develop the disease within 2–3 days.

3.3 Contraindications

Do not use in cases of hypersensitivity to macrolide antibiotics or to any of the excipients.

3.4 Special warnings

Cross-resistance has been shown between tulathromycin and other macrolides in the target pathogen(s). Use of the veterinary medicinal product should be carefully considered when susceptibility testing has shown resistance to tulathromycin because its effectiveness may be reduced. Do not administer simultaneously with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

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.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach."

If a hypersensitivity reaction occurs appropriate treatment should be administered without delay.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Tulathromycin is irritating to eyes. In case of accidental eye exposure, flush the eyes immediately with clean water.

Tulathromycin may cause sensitisation by skin contact resulting in e.g. reddening of the skin (erythema) and/or dermatitis. In case of accidental spillage onto skin, wash the skin immediately with soap and water.

Wash hands after use.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

If there is suspicion of a hypersensitivity reaction following accidental exposure (recognised by e.g. itching, difficulty in breathing, hives, swelling on the face, nausea, vomiting) appropriate treatment should be administered. Seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Pigs:

Very common (>1 animal / 10 animals treated):	Injection site reaction[1,2], Injection site fibrosis[1], Injection site haemorrhage[1], Injection site oedema[1]

[1] Can persist for approximately 30 days after injection.
[2] Reversible changes of congestion.

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. Use only according to the benefit/risk assessment by the responsible veterinarian. Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

Intramuscular use.

A single intramuscular injection of 2.5 mg tulathromycin/kg body weight (equivalent to 1 ml of the veterinary medicinal product/10 kg body weight) in the neck.

For treatment of pigs over 40 kg body weight, divide the dose so that no more than 4 ml are injected at one site.

For any respiratory disease, 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.

To ensure correct dosage, body weight should be determined as accurately as possible. For multiple vial entry, an aspirating needle or multi-dose syringe is recommended to avoid excessive broaching of the stopper.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

In young pigs weighing approximately 10 kg given three or five times the therapeutic dose transient signs attributed to injection site discomfort were observed and included excessive vocalisation and restlessness. Lameness was also observed when the hind leg was used as the injection site.

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: 13 days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01FA94

4.2 Pharmacodynamics

Tulathromycin is a semi-synthetic macrolide antimicrobial agent, which originates from a fermentation product. It differs from many other macrolides in that it has a long duration of action that is, in part, due to its three amine groups; therefore it has been given the chemical subclass designation

of triamilide.

Macrolides are bacteriostatic acting antibiotics and inhibit essential protein biosynthesis by virtue of their selective binding to bacterial ribosomal RNA. They act by stimulating the dissociation of peptidyl-tRNA from the ribosome during the translocation process.

Tulathromycin possesses *in vitro* activity against *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica*, the bacterial pathogens most commonly associated with swine respiratory disease. Increased minimum inhibitory concentration (MIC) values have been found in some isolates of *Actinobacillus pleuropneumoniae*.

The Clinical and Laboratory Standards Institute CLSI has set the clinical breakpoints for tulathromycin against *P. multocida* and *B. bronchiseptica* of swine respiratory origin, as ≤16 mcg/ml susceptible and ≥64 mcg/ml resistant. For *A. pleuropneumoniae* of swine respiratory origin the susceptible breakpoint is set at ≤64 mcg/ml. CLSI has also published clinical breakpoints for tulathromycin based on a disk diffusion method (CLSI document VET08, 4th ed, 2018). No clinical breakpoints have been set for *H. parasuis*. Neither EUCAST nor CLSI have developed standard methods for testing antibacterial agents against veterinary Mycoplasma species and thus no interpretative criteria have been set.

Resistance to macrolides can develop by mutations in genes encoding ribosomal RNA (rRNA) or some ribosomal proteins; by enzymatic modification (methylation) of the 23S rRNA target site, generally giving rise to cross-resistance with lincosamides and group B streptogramins (MLS_B resistance); by enzymatic inactivation; or by macrolide efflux. MLS_B resistance may be constitutive or inducible. Resistance may be chromosomal or plasmid-encoded and may be transferable if associated with transposons, plasmids, integrative and conjugative elements. Additionally, the genomic plasticity of *Mycoplasma* is enhanced by the horizontal transfer of large chromosomal fragments.

In addition to its antimicrobial properties, tulathromycin demonstrates immune-modulating and anti-inflammatory actions in experimental studies. In porcine polymorphonuclear cells (PMNs; neutrophils), tulathromycin promotes apoptosis (programmed cell death) and the clearance of apoptotic cells by macrophages. It lowers the production of the pro-inflammatory mediators leukotriene B4 and CXCL-8 and induces the production of anti-inflammatory and pro-resolving lipid lipoxin A4.

4.3 Pharmacokinetics

In pigs, the pharmacokinetic profile of tulathromycin when administered as a single intramuscular dose of 2.5 mg/kg body weight, was also characterised by rapid and extensive absorption followed by high distribution and slow elimination. The maximum concentration (C_{max}) in plasma was approximately 0.6 mcg/ml; this was achieved approximately 30 minutes post-dosing (T_{max}). Tulathromycin concentrations in lung homogenate were considerably higher than those in plasma. There is strong evidence of substantial accumulation of tulathromycin in neutrophils and alveolar macrophages. However, the *in vivo* concentration of tulathromycin at the infection site of the lung is not known. Peak concentrations were followed by a slow decline in systemic exposure with an apparent elimination half-life ($t_{1/2}$) of approximately 91 hours in plasma. Plasma protein binding was low, approximately 40%. The volume of distribution at steady-state (V_{ss}) determined after intravenous administration was 13.2 L/kg. The bioavailability of tulathromycin after intramuscular administration in pigs was approximately 88%.

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: 3 years.
Shelf life after first opening the immediate packaging: 28 days.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

Type I glass with a fluoropolymer coated chlorobutyl stopper and an aluminium overseal.

Pack sizes:
Cardboard box containing one vial of 50 ml.
Cardboard box containing one vial of 100 ml.
Cardboard box containing one vial of 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

Zoetis Belgium

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/03/041/006 (50 ml)
EU/2/03/041/007 (100 ml)
EU/2/03/041/008 (250 ml)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 11/11/2003.

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{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

CARDBOARD BOX (20 ml / 50 ml / 100 ml / 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin 100 mg/ml Solution for injection.

2. STATEMENT OF ACTIVE SUBSTANCES

Tulathromycin 100 mg/ml

3. PACKAGE SIZE

20 ml
50 ml
100 ml
250 ml

4. TARGET SPECIES

Cattle, pigs and sheep.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Cattle: subcutaneous use.
Pigs and sheep: intramuscular use.

7. WITHDRAWAL PERIODS

Withdrawal periods:
Meat and offal:
Cattle: 22 days.
Pigs: 13 days.
Sheep: 16 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 broached use within 28 days.

9. SPECIAL STORAGE PRECAUTIONS

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

Read the package leaflet before use.

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

Zoetis Belgium

14. MARKETING AUTHORISATION NUMBERS

EU/2/03/041/001 (20 ml)
EU/2/03/041/002 (50 ml)
EU/2/03/041/003 (100 ml)
EU/2/03/041/004 (250 ml)

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARDBOARD BOX (500 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin 100 mg/ml Solution for injection.

2. STATEMENT OF ACTIVE SUBSTANCES

Tulathromycin 100 mg/ml

3. PACKAGE SIZE

500 ml

4. TARGET SPECIES

Cattle.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Subcutaneous use.

7. WITHDRAWAL PERIODS

Withdrawal period:
Meat and offal: 22 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 broached use within 28 days.

9. SPECIAL STORAGE PRECAUTIONS

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE”

Read the package leaflet before use.

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

Zoetis Belgium

14. MARKETING AUTHORISATION NUMBERS

EU/2/03/041/005 (500 ml)

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARDBOARD BOX (50 ml / 100 ml / 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin 25 mg/ml Solution for injection.

2. STATEMENT OF ACTIVE SUBSTANCES

Tulathromycin 25 mg/ml

3. PACKAGE SIZE

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: 13 days.

8. EXPIRY DATE

Exp. {mm/yyyy}
Once broached use within 28 days.

9. SPECIAL STORAGE PRECAUTIONS

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

Read the package leaflet before use.

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

Zoetis Belgium

14. MARKETING AUTHORISATION NUMBERS

EU/2/03/041/006 (50 ml)
EU/2/03/041/007 (100 ml)
EU/2/03/041/008 (250 ml)

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

VIAL (100 ml / 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin 100 mg/ml Solution for injection.

2. STATEMENT OF ACTIVE SUBSTANCES

Tulathromycin 100 mg/ml

3. TARGET SPECIES

Cattle, pigs and sheep.

4. ROUTES OF ADMINISTRATION

Cattle: SC.
Pigs and sheep: IM.

Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal periods:
Meat and offal:
Cattle: 22 days.
Pigs: 13 days.
Sheep: 16 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.

6. EXPIRY DATE

Exp. {mm/yyyy}

Once broached use within 28 days. Use by…

7. SPECIAL STORAGE PRECAUTIONS

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Zoetis Belgium

9. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

VIAL (500 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin 100 mg/ml Solution for injection.

2. STATEMENT OF ACTIVE SUBSTANCES

Tulathromycin 100 mg/ml

3. TARGET SPECIES

Cattle.

4. ROUTES OF ADMINISTRATION

Subcutaneous use.

Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal period:
Meat and offal: 22 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.

6. EXPIRY DATE

Exp. {mm/yyyy}

Once broached use within 28 days. Use by…

7. SPECIAL STORAGE PRECAUTIONS

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Zoetis Belgium

9. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

VIAL (100 ml / 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin 25 mg/ml Solution for injection.

2. STATEMENT OF ACTIVE SUBSTANCES

Tulathromycin 25 mg/ml

3. TARGET SPECIES

Pigs.

4. ROUTES OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal period:
Meat and offal: 13 days.

6. EXPIRY DATE

Exp. {mm/yyyy}

Once broached use within 28 days. Use by…

7. SPECIAL STORAGE PRECAUTIONS

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Zoetis Belgium

9. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL (20 ml / 50 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Tulathromycin 100 mg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

Once broached use within 28 days. Use by…

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL (50 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Tulathromycin 25 mg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}
Once broached use within 28 days. Use by…

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Draxxin 100 mg/ml solution for injection for cattle, pigs and sheep.

2. Composition

Each ml contains:

Active substance:
Tulathromycin 100 mg

Excipient:
Monothioglycerol 5 mg

Clear colourless to slightly yellow solution for injection.

3. Target species

Cattle, pigs and sheep.

4. Indications for use

Cattle
Treatment and metaphylaxis of bovine respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis*. The presence of the disease in the group must be established before the product is used.

Treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis.*

Pigs
Treatment and metaphylaxis of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica*. The presence of the disease in the group must be established before the product is used. The veterinary medicinal product should only be used if pigs are expected to develop the disease within 2–3 days.

Sheep
Treatment of the early stages of infectious pododermatitis (foot rot) associated with virulent *Dichelobacter nodosus* requiring systemic treatment.

5. Contraindications

Do not use in cases of hypersensitivity to macrolide antibiotics or to any of the excipients.

6. Special warnings

Special warnings for each target species:
Cross-resistance has been shown between tulathromycin and other macrolides in the target pathogen(s). Use of the veterinary medicinal product should be carefully considered when susceptibility testing has shown resistance to tulathromycin because its effectiveness may be reduced.

Do not administer simultaneously with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

Sheep:

The efficacy of antimicrobial treatment of foot rot might be reduced by other factors, such as wet environmental conditions, as well as inappropriate farm management. Treatment of foot rot should therefore be undertaken along with other flock management tools, for example providing dry environment.

Antibiotic treatment of benign foot rot is not considered appropriate. Tulathromycin showed limited efficacy in sheep with severe clinical signs or chronic foot rot, and should therefore only be given at an early stage of foot rot.

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. An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

If a hypersensitivity reaction occurs appropriate treatment should be administered without delay.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Tulathromycin is irritating to eyes. In case of accidental eye exposure, flush the eyes immediately with clean water.

Tulathromycin may cause sensitisation by skin contact resulting in e.g. reddening of the skin (erythema) and/or dermatitis. In case of accidental spillage onto skin, wash the skin immediately with soap and water.

Wash hands after use.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

If there is suspicion of a hypersensitivity reaction following accidental exposure (recognised by e.g. itching, difficulty in breathing, hives, swelling on the face, nausea, vomiting) appropriate treatment should be administered. Seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only according to the benefit/risk assessment by the responsible veterinarian. Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.

Interaction with other medicinal products and other forms of interaction:
None known.

Overdose:
In cattle at dosages of three, five or ten times the recommended dose, transient signs attributed to injection site discomfort were observed and included restlessness, head-shaking, pawing the ground, and brief decrease in feed intake. Mild myocardial degeneration has been observed in cattle receiving five to six times the recommended dose.

In young pigs weighing approximately 10 kg given three or five times the therapeutic dose transient signs attributed to injection site discomfort were observed and included excessive vocalisation and restlessness. Lameness was also observed when the hind leg was used as the injection site.

In lambs (approx. 6 weeks old), at dosages of three or five times the recommended dose, transient signs attributed to injection site discomfort were observed and included walking backwards, head shaking, rubbing the injection site, lying down and getting up, bleating.

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):
Injection site swelling[1], Injection site fibrosis[1], Injection site haemorrhage[1], Injection site oedema[1], Injection site reaction[2], Injection site pain[3]

[1] Can persist for approximately 30 days after injection.
[2] Reversible changes of congestion.
[3] Transient.

Pigs:

Very common (>1 animal / 10 animals treated):
Injection site reaction[1,2], Injection site fibrosis[1], Injection site haemorrhage[1], Injection site oedema[1]

[1] Can persist for approximately 30 days after injection.
[2] Reversible changes of congestion.

Sheep:

Very common (>1 animal / 10 animals treated):
Discomfort[1]

[1] Transient, resolving within a few minutes: head shaking, rubbing injection site, backing away.

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

Cattle:
2.5 mg tulathromycin/kg body weight (equivalent to 1 ml of the veterinary medicinal product/40 kg body weight).

A single subcutaneous injection. For treatment of cattle over 300 kg body weight, divide the dose so that no more than 7.5 ml are injected at one site.

Pigs:
2.5 mg tulathromycin/kg body weight (equivalent to 1 ml of the veterinary medicinal product/40 kg body weight).

A single intramuscular injection in the neck. For treatment of pigs over 80 kg body weight, divide the dose so that no more than 2 ml are injected at one site.

Sheep:
2.5 mg tulathromycin/kg body weight (equivalent to 1 ml of the veterinary medicinal product/40 kg body weight).

A single intramuscular injection in the neck.

9. Advice on correct administration

For any respiratory disease, 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.

To ensure a correct dosage, body weight should be determined as accurately as possible. For multiple vial entry, an aspirating needle or multi-dose syringe is recommended to avoid excessive broaching of the stopper.

10. Withdrawal periods

Cattle (meat and offal): 22 days.

Pigs (meat and offal): 13 days.

Sheep (meat and offal): 16 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.

11. Special storage precautions

Keep out of the sight and reach of children.

This veterinary medicinal product does not require any special storage conditions.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after Exp. The expiry date refers to the last day of that month.
Shelf life after first opening the immediate packaging: 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/2/03/041/001-005

Pack sizes:
Cardboard box containing one vial of 20 ml.
Cardboard box containing one vial of 50 ml.
Cardboard box containing one vial of 100 ml.
Cardboard box containing one vial of 250 ml.
Cardboard box containing one vial of 500 ml.

500 ml vials must not be used for pigs and sheep.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{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:
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Manufacturer responsible for batch release:
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Finca La Riba
Vall de Bianya
Gerona 17813
Spain

17. Other information

Tulathromycin is a semi-synthetic macrolide antimicrobial agent, which originates from a fermentation product. It differs from many other macrolides in that it has a long duration of action that

is, in part, due to its three amine groups; therefore, it has been given the chemical subclass designation of triamilide.

Macrolides are bacteriostatic acting antibiotics and inhibit essential protein biosynthesis by virtue of their selective binding to bacterial ribosomal RNA. They act by stimulating the dissociation of peptidyl-tRNA from the ribosome during the translocation process.

Tulathromycin possesses *in vitro* activity against *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis*, and *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica*, the bacterial pathogens most commonly associated with bovine and swine respiratory disease, respectively. Increased minimum inhibitory concentration (MIC) values have been found in some isolates of *Histophilus somni* and *Actinobacillus pleuropneumoniae*. *In vitro* activity against *Dichelobacter nodosus (vir),* the bacterial pathogen most commonly associated with infectious pododermatitis (foot rot) in sheep has been demonstrated.

Tulathromycin also possesses *in vitro* activity against *Moraxella bovis*, the bacterial pathogen most commonly associated with infectious bovine keratoconjunctivitis (IBK).

The Clinical and Laboratory Standards Institute CLSI has set the clinical breakpoints for tulathromycin against *M. haemolytica*, *P. multocida*, and *H. somni* of bovine respiratory origin and *P. multocida and B. bronchiseptica* of swine respiratory origin as ≤16 mcg/ml susceptible and ≥64 mcg/ml resistant. For *A. pleuropneumoniae* of swine respiratory origin the susceptible breakpoint is set at ≤64 mcg/ml. CLSI has also published clinical breakpoints for tulathromycin based on a disk diffusion method (CLSI document VET08, 4th ed, 2018). No clinical breakpoints are available for *H. parasuis*. Neither EUCAST nor CLSI have developed standard methods for testing antibacterial agents against veterinary *Mycoplasma* species and thus no interpretative criteria have been set.

Resistance to macrolides can develop by mutations in genes encoding ribosomal RNA (rRNA) or some ribosomal proteins; by enzymatic modification (methylation) of the 23S rRNA target site, generally giving rise to cross-resistance with lincosamides and group B streptogramins (MLS_B resistance); by enzymatic inactivation; or by macrolide efflux. MLS_B resistance may be constitutive or inducible. Resistance may be chromosomal or plasmid-encoded and may be transferable if associated with transposons, plasmids, integrative and conjugative elements. Additionally, the genomic plasticity of *Mycoplasma* is enhanced by the horizontal transfer of large chromosomal fragments.

In addition to its antimicrobial properties, tulathromycin demonstrates immune-modulating and anti-inflammatory actions in experimental studies. In both bovine and porcine polymorphonuclear cells (PMNs; neutrophils), tulathromycin promotes apoptosis (programmed cell death) and the clearance of apoptotic cells by macrophages. It lowers the production of the pro-inflammatory mediators leukotriene B4 and CXCL-8 and induces the production of anti-inflammatory and pro-resolving lipid lipoxin A4.

In cattle, the pharmacokinetic profile of tulathromycin when administered as a single subcutaneous dose of 2.5 mg/kg body weight, was characterised by rapid and extensive absorption followed by high distribution and slow elimination. The maximum concentration (C_{max}) in plasma was approximately 0.5 mcg/ml; this was achieved approximately 30 minutes post-dosing (T_{max}). Tulathromycin concentrations in lung homogenate were considerably higher than those in plasma. There is strong evidence of substantial accumulation of tulathromycin in neutrophils and alveolar macrophages. However, the *in vivo* concentration of tulathromycin at the infection site of the lung is not known. Peak concentrations were followed by a slow decline in systemic exposure with an apparent elimination half-life ($t_{1/2}$) of 90 hours in plasma. Plasma protein binding was low, approximately 40%. The volume of distribution at steady-state (V_{SS}) determined after intravenous administration was 11 l/kg. The bioavailability of tulathromycin after subcutaneous administration in cattle was approximately 90%.

In pigs, the pharmacokinetic profile of tulathromycin when administered as a single intramuscular

dose of 2.5 mg/kg body weight, was also characterised by rapid and extensive absorption followed by high distribution and slow elimination. The maximum concentration (C_{max}) in plasma was approximately 0.6 mcg/ml; this was achieved approximately 30 minutes post-dosing (T_{max}). Tulathromycin concentrations in lung homogenate were considerably higher than those in plasma. There is strong evidence of substantial accumulation of tulathromycin in neutrophils and alveolar macrophages. However, the *in vivo* concentration of tulathromycin at the infection site of the lung is not known. Peak concentrations were followed by a slow decline in systemic exposure with an apparent elimination half-life ($t_{1/2}$) of approximately 91 hours in plasma. Plasma protein binding was low, approximately 40%. The volume of distribution at steady-state (V_{SS}) determined after intravenous administration was 13.2 l/kg. The bioavailability of tulathromycin after intramuscular administration in pigs was approximately 88%.

In sheep, the pharmacokinetic profile of tulathromycin, when administered as a single intramuscular dose of 2.5 mg/kg body weight, achieved a maximum plasma concentration (C_{max}) of 1.19 mcg/ml in approximately 15 minutes (T_{max}) post-dosing and had an elimination half-life ($t_{1/2}$) of 69.7 hours. Plasma protein binding was approximately 60-75%. Following intravenous dosing the volume of distribution at steady-state (V_{ss}) was 31.7 l/kg. The bioavailability of tulathromycin after intramuscular administration in sheep was 100%.

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Draxxin 25 mg/ml solution for injection for pigs

2. Composition

Each ml contains:

Active substance:
Tulathromycin 25 mg

Excipient:
Monothioglycerol 5 mg

Clear colourless to slightly yellow solution for injection.

3. Target species

Pigs

4. Indications for use

Treatment and metaphylaxis of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis and Bordetella bronchiseptica*. The presence of the disease in the group must be established before the product is used. The veterinary medicinal product should only be used if pigs are expected to develop the disease within 2–3 days.

5. Contraindications

Do not use in cases of hypersensitivity to macrolide antibiotics or to any of the excipients.

6. Special warnings

Special warnings for each target species:
Cross-resistance has been shown between tulathromycin and other macrolides in the target pathogen(s). Use of the veterinary medicinal product should be carefully considered when susceptibility testing has shown resistance to tulathromycin because its effectiveness may be reduced. Do not administer simultaneously with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

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. An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

If a hypersensitivity reaction occurs appropriate treatment should be administered without delay.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Tulathromycin is irritating to eyes. In case of accidental eye exposure, flush the eyes immediately with clean water.

Tulathromycin may cause sensitisation by skin contact resulting in e.g. reddening of the skin (erythema) and/or dermatitis. In case of accidental spillage onto skin, wash the skin immediately with soap and water.

Wash hands after use.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

If there is suspicion of a hypersensitivity reaction following accidental exposure (recognised by e.g. itching, difficulty in breathing, hives, swelling on the face, nausea, vomiting) appropriate treatment should be administered. Seek medical advice immediately and show the package leaflet or the label to the physician

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only according to the benefit/risk assessment by the responsible veterinarian. Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.

Interaction with other medicinal products and other forms of interaction:
None known.

Overdose:
In young pigs weighing approximately 10 kg given three or five times the therapeutic dose transient signs attributed to injection site discomfort were observed and included excessive vocalisation and restlessness. Lameness was also observed when the hind leg was used as the injection site.

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):
Injection site reaction[1,2], Injection site fibrosis[1], Injection site haemorrhage[1], Injection site oedema[1]

[1] Can persist for approximately 30 days after injection.
[2] Reversible changes of congestion.

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

A single intramuscular injection of 2.5 mg tulathromycin/kg body weight (equivalent to 1 ml of the veterinary medicinal product/10 kg body weight) in the neck.

For treatment of pigs over 40 kg body weight, divide the dose so that no more than 4 ml are injected at one site.

9. Advice on correct administration

For any respiratory disease, 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.

To ensure a correct dosage body weight should be determined as accurately as possible. For multiple vial entry, an aspirating needle or multi-dose syringe is recommended to avoid excessive broaching of the stopper.

10. Withdrawal periods

Meat and offal: 13 days.

11. Special storage precautions

Keep out of the sight and reach of children.

This veterinary medicinal product does not require any special storage conditions.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after Exp. The expiry date refers to the last day of that month.

Shelf life after first opening the immediate packaging: 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/2/03/041/006-008

Pack sizes:
Cardboard box containing one vial of 50 ml.
Cardboard box containing one vial of 100 ml.
Cardboard box containing one vial of 250 ml.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{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:
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17. Other information

Tulathromycin is a semi-synthetic macrolide antimicrobial agent, which originates from a fermentation product. It differs from many other macrolides in that it has a long duration of action that is, in part, due to its three amine groups; therefore, it has been given the chemical subclass designation of triamilide.

Macrolides are bacteriostatic acting antibiotics and inhibit essential protein biosynthesis by virtue of their selective binding to bacterial ribosomal RNA. They act by stimulating the dissociation of peptidyl-tRNA from the ribosome during the translocation process.

Tulathromycin possesses *in vitro* activity against *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica*, the bacterial pathogens most commonly associated with swine respiratory disease. Increased minimum

inhibitory concentration (MIC) values have been found in some isolates of *Actinobacillus pleuropneumoniae*.

The Clinical and Laboratory Standards Institute CLSI has set the clinical breakpoints for tulathromycin against *P. multocida and B. bronchiseptica* of swine respiratory origin as ≤16 mcg/ml susceptible and ≥64 mcg/ml resistant. For *A. pleuropneumoniae* of swine respiratory origin the susceptible breakpoint is set at ≤64 mcg/ml. CLSI has also published clinical breakpoints for tulathromycin based on a disk diffusion method (CLSI document VET08, 4th ed, 2018). No clinical breakpoints are available for *H. parasuis*. Neither EUCAST nor CLSI have developed standard methods for testing antibacterial agents against veterinary *Mycoplasma* species and thus no interpretative criteria have been set.
Resistance to macrolides can develop by mutations in genes encoding ribosomal RNA (rRNA) or some ribosomal proteins; by enzymatic modification (methylation) of the 23S rRNA target site, generally giving rise to cross-resistance with lincosamides and group B streptogramins (MLS_B resistance); by enzymatic inactivation; or by macrolide efflux. MLS_B resistance may be constitutive or inducible. Resistance may be chromosomal or plasmid-encoded and may be transferable if associated with transposons, plasmids, integrative and conjugative elements. Additionally, the genomic plasticity of *Mycoplasma* is enhanced by the horizontal transfer of large chromosomal fragments.

In addition to its antimicrobial properties, tulathromycin demonstrates immune-modulating and anti-inflammatory actions in experimental studies. In porcine polymorphonuclear cells (PMNs; neutrophils), tulathromycin promotes apoptosis (programmed cell death) and the clearance of apoptotic cells by macrophages. It lowers the production of the pro-inflammatory mediators leukotriene B4 and CXCL-8 and induces the production of anti-inflammatory and pro-resolving lipid lipoxin A4.

In pigs, the pharmacokinetic profile of tulathromycin when administered as a single intramuscular dose of 2.5 mg/kg body weight, was also characterised by rapid and extensive absorption followed by high distribution and slow elimination. The maximum concentration (C_{max}) in plasma was approximately 0.6 mcg/ml; this was achieved approximately 30 minutes post-dosing (T_{max}). Tulathromycin concentrations in lung homogenate were considerably higher than those in plasma. There is strong evidence of substantial accumulation of tulathromycin in neutrophils and alveolar macrophages. However, the *in vivo* concentration of tulathromycin at the infection site of the lung is not known. Peak concentrations were followed by a slow decline in systemic exposure with an apparent elimination half-life ($t_{1/2}$) of approximately 91 hours in plasma. Plasma protein binding was low, approximately 40%. The volume of distribution at steady-state (V_{ss}) determined after intravenous administration was 13.2 L/kg. The bioavailability of tulathromycin after intramuscular administration in pigs was approximately 88%.