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

Huvexxin 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: For subcutaneous use.
Pigs and sheep: For 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}
Shelf life after first opening the container: 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

Huvepharma NV

14. MARKETING AUTHORISATION NUMBERS

Vm 30282/3002

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

{Vial (20 ml / 50 ml / 100 ml / 250 ml)}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Huvexxin 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.

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}
Shelf life after first opening the container: 28 days.
Once broached use by

7. SPECIAL STORAGE PRECAUTIONS

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Huvepharma NV

9. BATCH NUMBER

Lot {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Huvexxin 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 solution, free from visible particles.

3. Target species

Cattle, pigs and sheep.

4. Indications for use

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

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

Pigs
Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica* susceptible to tulathromycin. The presence of the disease in the group must be established before the veterinary medicinal 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:
Cross resistance occurs with other macrolides. Do not administer simultaneously with antimicrobials with a similar mode of action such as other macrolides or lincosamides.
For 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 veterinary medicinal product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.
Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal product is used.
Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to tulathromycin and may decrease the effectiveness of treatment with other macrolides, lincosamides and group B streptogramins due to the potential for cross resistance.

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, vomitus) appropriate treatment should be administered. Seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy and lactation:
Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. 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.

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 5 to 6 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 pain[1] Injection site swelling[1] Injection site reactions (e.g. congestion, oedema (swelling), fibrosis (scarring) and haemorrhage)[2]

[1]transient and can persist for up to 30 days
[2]reversible and present for approximately 30 days after injection

Pigs:

Very common (>1 animal / 10 animals treated):	Injection site reactions (e.g. congestion, oedema (swelling), fibrosis (scarring) and haemorrhage)[3]

[3]reversible and present for approximately 30 days after injection

Sheep:

Very common (>1 animal / 10 animals treated):	Discomfort (e.g. head shake – behavioural disorder, injection site scratching, anxiety)[4]

[4]these signs are transient and resolve within a few minutes

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 or the local representative of the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system:

8. Dosage for each species, routes and method of administration

Cattle
Subcutaneous use.
2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml/40 kg bodyweight).

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

Pigs
Intramuscular use.
2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml/40 kg bodyweight).

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

Sheep
Intramuscular use.
2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml/40 kg bodyweight). 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, bodyweight should be determined as accurately as possible. The closure may be safely punctured 15 times. In order to prevent excessive broaching of the stopper, a suitable multiple dosing device should be used.

10. 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.

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.

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

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 system. These measures should help to protect the environment.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

20 ml, 50 ml, 100 ml, and 250 ml Type I colourless glass vials, sealed with chlorobutyl rubber stoppers and aluminium caps, supplied in cardboard boxes. One vial per box.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

December 2023

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:
Huvepharma NV
Uitbreidingstraat 80
2600 Antwerpen
Belgium
+32 3 288 18 49
pharmacovigilance@huvepharma.com

Manufacturer responsible for batch release:
Biovet JSC
39 Petar Rakov Str
4550 Peshtera
Bulgaria

Local representatives and contact details to report suspected adverse reactions

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, Mycoplasma bovis*, and *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumonia, 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 µg/ml susceptible and ≥64 µg/ml resistant. For *A. pleuropneumoniae* of swine respiratory origin the susceptible breakpoint is set at ≤64 µg/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 (MLSB resistance); by enzymatic inactivation; or by macrolide efflux. MLSB 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.

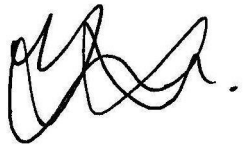
In addition to its antimicrobial properties, tulathromycin demonstrates immune-modulating and anti- inflammatory actions in experimental studies. In both bovine and porcine polymorphonuclear cells (PMNs; neutrophils), tulathromycin promotes apoptosis (programmed cell death) and the clearance of apoptotic 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 bodyweight, 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 µg/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 bodyweight, 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 µg/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 bodyweight, achieved a maximum plasma concentration (C_{max}) of 1.19 µg/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%.



Approved: 28 February 2024