SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cyclofin 300 mg/ml + 20 mg/ml solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Active substances:
Oxytetracycline 300 mg (equivalent to 323.5 mg of oxytetracycline dihydrate)
Flunixin 20 mg (equivalent to 33.2 mg of flunixin meglumine)

Excipient:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Glycerol formal	
Polyethylene glycol 200	
Magnesium oxide, light	
Sodium Formaldehyde Sulphoxylate	2.0 mg
Ethanolamine	
Water for injection	

Clear, orange to reddish-brown solution for injection, practically free from visible particles.

3. CLINICAL INFORMATION

3.1 Target species

Cattle

3.2 Indications for use for each target species

For the treatment of acute respiratory disease caused by *Mannheimia haemolytica* and *Pasteurella multocida* where an anti-inflammatory and anti-pyretic effect is required.

3.3 Contraindications

Do not use in animals suffering from cardiac, hepatic or renal disease, where there is a possibility of gastrointestinal ulceration or bleeding.
Do not use in dehydrated, hypovolaemic or hypotensive animals as there is a potential risk of increased renal toxicity.
Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
Do not use the veterinary medicinal product where there are signs of blood dyscrasias or haemostasis alteration.

3.4 Special warnings

Cross-resistance has been shown between oxytetracycline and other tetracyclines in *Mannheimia haemolytica* and *Pasteurella multocida.* Use of oxytetracycline should be carefully considered when susceptibility testing has shown resistance to tetracyclines because its effectiveness may be reduced.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Use in any animals less than 6 weeks of age or in aged animals may involve additional risk due to the anti-prostaglandin effects of flunixin on renal function. If such use cannot be avoided, animals may require careful clinical management.
Flunixin is toxic to avian scavengers. Do not administer to animals susceptible to enter wild fauna food chain. In case of death or sacrifice of treated animals, ensure that they are not made available to wild fauna.
Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogens. 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 veterinary medicinal 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:
This veterinary medicinal product may be harmful after accidental self-injection. In case of accidental self-injection seek medical advice immediately and show the package leaflet or the label to the physician.

This veterinary medicinal product may be irritating to the skin and/or eye. Avoid skin and/or eye contact. Latex or nitrile gloves should be worn during application. In case of accidental contact with skin or eyes, rinse with copious amounts of water. If irritation persists, seek medical advice.

This veterinary medicinal product may cause hypersensitivity reactions due to the presence of oxytetracycline, flunixin, polyethylene glycol or ethanolamine. People with known hypersensitivity to tetracyclines, non-steroidal anti-inflammatory drugs (NSAIDs) or one of the excipients should avoid contact with the veterinary medicinal product. If allergic symptoms develop, such as a skin rash, swelling of the face, lips or eyes or difficulty in breathing, you should seek medical attention immediately and show the package leaflet or label to the doctor.

Laboratory studies in rats with the excipient glycerol formal have shown evidence of teratogenic and foetotoxic effects. Pregnant women, and women of childbearing age should use the veterinary medicinal product with particular caution to avoid accidental self-injection.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Cattle:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Hypersensitivity reactions [a]
Undetermined frequency (cannot be estimated from the available data)	Injection site reaction [b], Mild increase in body temperature [c], Dental discoloration [d], Bone discoloration [d]

[a] Can be fatal.
[b] A usually mild reaction at the injection site may be observed following intramuscular administration and may persist for up to 30 days. Studies in cattle at the normal dose rate have shown transient and dose dependent reactions at the injection site.
[c] Any increase is transient and will be unlikely to occur in animals already suffering from pyrexia.
[d] The use of tetracyclines during the period of tooth and bone development may lead to discoloration.

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 its local representative 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

Pregnancy and lactation:
The use is not recommended during pregnancy and lactation.
The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Studies in laboratory animals have shown evidence of foetotoxicity after oral (rabbit and rat) and intramuscular (rat) administration of flunixin at maternotoxic doses and also a lengthening of the duration of gestation (rat).

3.8 Interactions with other medicinal products and other forms of interaction

Some NSAIDs may be highly bound to plasma proteins and compete with other highly bound drugs which can lead to toxic effects.
Do not administer other NSAIDs concurrently or within 24 hours of each other.
Avoid concurrent administration of potentially nephrotoxic veterinary medicinal products, particularly aminoglycosides. Flunixin may reduce the renal excretion of certain veterinary medicinal products and increase their toxicity, such as for aminoglycosides.
Concurrent use of corticosteroids should be avoided.
Flunixin may reduce the effect of some anti-hypertensive medicinal products, such as diuretics and beta blockers, by inhibition of prostaglandin synthesis.
Oxytetracycline may interfere with the action of bactericidal antimicrobials, such as penicillins and cephalosporins, and therefore they should not be used simultaneously.

3.9 Administration routes and dosage

The veterinary medicinal product is indicated for deep intramuscular administration to cattle. The recommended dosage is 2 mg/kg flunixin and 30 mg/kg oxytetracycline (equivalent to 1 ml per 10 kg bodyweight).
To ensure a correct dosage, body weight should be determined as accurately as possible
This veterinary medicinal product is recommended for single administration only. Maximum volume per injection site: 15 ml.

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

Following administration at twice the recommended treatment dose (4 mg/kg flunixin and 60 mg/kg oxytetracycline) the veterinary medicinal product is expected to be well tolerated. At this 2x dose level transient dysentery with or without apathy may occur; symptoms resolving without treatment within 48-72 hours.
Studies in cattle at twice the normal dose rate have shown transient and dose dependent reactions at the injection site.
At higher dose levels, above 3x the recommended treatment dose, there is an increased risk of renal toxicity. This may manifest as elevated plasma urea and creatinine levels and pathological changes to the kidneys (cortical tubular necrosis).
Management of overdose should be symptomatic, ensuring adequate hydration is maintained.

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

3.12 Withdrawal periods

Meat and offal: 28 days.
Not authorised for use in cattle producing milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01AA56

4.2 Pharmacodynamics

Oxytetracycline and flunixin in the combined formulation provide anti-bacterial and anti-inflammatory activities respectively following a single administration.

Oxytetracycline is the 5-OH derivative of tetracycline. The tetracyclines are a family of broad-spectrum bacteriostatic antibiotics which inhibit protein synthesis in susceptible microorganisms. Oxytetracycline is active against *Mannheimia haemolytica* and *Pasteurella multocida* associated with acute respiratory disease in cattle.

After oxytetracycline diffuses through the outer bacterial cell membrane, an active carrier mediated process transports the drugs through the inner cytoplasmic membrane.
Inside the cell, oxytetracycline binds irreversibly to receptors on the 30S sub-unit of the bacterial ribosome where it interferes with the binding of the aminoacyl-transfer RNA to the acceptor site on the messenger RNA ribosome complex. This effectively prevents the addition of amino acids to the elongating peptide chain, inhibiting protein synthesis.

Acquired resistance to oxytetracycline has been noted. Such resistance is usually plasmid mediated. Cross-resistance to other tetracyclines occurs. Continuous treatment with low doses of oxytetracycline can also result in increased resistance to other antibiotics.
Resistance to tetracyclines has been reported in bovine (calves) respiratory pathogens in some EU countries. Tetracycline CLSI veterinary-specific breakpoints for *Mannheimia haemolytica* and *Pasteurella multocida* isolates from cattle are: S $\leq$2 µg/ml, I=4 µg/ml, R $\geq$8 µg/ml (CLSI, 2023).

Flunixin meglumine is a relatively potent non-narcotic, non-steroidal analgesic with anti-inflammatory, anti-endotoxic and anti-pyretic properties.

Flunixin meglumine acts as a reversible inhibitor of cyclo-oxygenase, an important enzyme in the arachidonic acid cascade pathway which is responsible for converting arachidonic acid to cyclic endoperoxides. Consequently, synthesis of eicosanoids, important mediators of the inflammatory process involved in central pyrexia, pain perception and tissue inflammation, is inhibited. Through its effects on the arachidonic acid cascade, flunixin also inhibits the production of thromboxane, a potent platelet pro-aggregator and vasoconstrictor which is released during blood clotting. Flunixin exerts its antipyretic effect by inhibiting prostaglandin E 2 synthesis in the hypothalamus. By inhibiting the arachidonic acid cascade pathway, flunixin also produces an anti-endotoxic effect by suppressing eicosanoid formation and therefore preventing their involvement in endotoxin associated disease states.

4.3 Pharmacokinetics

Once absorbed, tetracyclines are well distributed throughout the body, with highest concentrations found in liver, spleen, kidney and lung. Tetracyclines are slowly excreted in urine, explaining their long persistence in blood.

Flunixin is characterised by a very high degree of plasma protein binding and hence volumes of distribution are generally low. The unbound fraction is distributed throughout the body fluid, including the CNS. It tends to accumulate in inflamed tissue. Renal excretion contributes extensively to the elimination of flunixin from the body.

After intramuscular administration of the recommended dose of the veterinary medicinal product to cattle (2 mg flunixin and 30 mg oxytetracycline per kg bodyweight) the following parameters were observed:

Oxytetracycline: C_{max} 11.11 µg/ml; AUC 376.5 µg/ml/hr; T_{max} 5.1 hrs, T½ elimination 36.54 hrs.
Flunixin: C_{max} 2.4 µg/ml; AUC 11.22 µg/ml/hr; T_{max} 1.0 hrs, T½ elimination 4.51 hrs.

Environmental properties
Flunixin is toxic to avian scavengers although foreseen low exposure leads to low risk.

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

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

5.4 Nature and composition of immediate packaging

Supplied in Type II, clear glass vials of 100 ml, with a 20 mm bromobutyl rubber stopper, and aluminium cap. One glass vial is packaged in a cardboard box.

5.5 Special precautions for the disposal of unused veterinary medicinal product 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

Dechra Regulatory BV

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: DD/MM/YYYY

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*).

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE
{CARDBOARD BOX / 100 ML}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cyclofin 300 mg/ml + 20 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
Oxytetracycline 300 mg (equivalent to 323.5 mg of oxytetracycline dihydrate)
Flunixin 20 mg (equivalent to 33.2 mg of flunixin meglumine

3. PACKAGE SIZE

100 ml

4. TARGET SPECIES

Cattle

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Intramuscular injection.

7. WITHDRAWAL PERIODS

Withdrawal period:
Meat and offal: 28 days.
Not authorised for use in cattle producing milk for human consumption.

8. EXPIRY DATE

Exp. {mm/yyyy}
Once opened use within 28 days, use by __/__

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

Dechra Regulatory BV

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

{LABEL / 100 ML)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cyclofin 300 mg/ml + 20 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
Oxytetracycline 300 mg (equivalent to 323.5 mg of oxytetracycline dihydrate)
Flunixin 20 mg (equivalent to 33.2 mg of flunixin meglumine)

3. TARGET SPECIES

Cattle

4. ROUTES OF ADMINISTRATION

Intramuscular injection. Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal period:
Meat and offal: 28 days.
Not authorised for use in cattle producing milk for human consumption.

6. EXPIRY DATE

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

7. SPECIAL STORAGE PRECAUTIONS

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Dechra Regulatory BV (logo)

9. BATCH NUMBER

Lot {number}

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Cyclofin 300 mg/ml + 20 mg/ml solution for injection for cattle

2. Composition

Each ml contains:

Active substances:
Oxytetracycline 300 mg (equivalent to 323.5 mg of oxytetracycline dihydrate)
Flunixin 20 mg (equivalent to 33.2 mg of flunixin meglumine)

Excipient:
Sodium Formaldehyde Sulphoxylate 2.0 mg

Clear, orange to reddish-brown solution for injection, practically free from visible particles.

3. Target species

Cattle

4. Indications for use

For the treatment of acute respiratory disease caused by *Mannheimia haemolytica* and *Pasteurella multocida* where an anti-inflammatory and anti-pyretic effect is required.

5. Contraindications

Do not use in animals suffering from cardiac, hepatic or renal disease, where there is a possibility of gastrointestinal ulceration or bleeding.
Do not use in dehydrated, hypovolaemic or hypotensive animals as there is a potential risk of increased renal toxicity.
Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
Do not use the veterinary medicinal product where there are signs of blood dyscrasias or haemostasis alteration.

6. Special warnings

Special warnings:
Cross-resistance has been shown between oxytetracycline and other tetracyclines in *Mannheimia haemolytica* and *Pasteurella multocida.* Use of oxytetracycline should be carefully considered when susceptibility testing has shown resistance to tetracyclines because its effectiveness may be reduced.

Special precautions for safe use in the target species:
Use in any animals less than 6 weeks of age or in aged animals may involve additional risk due to the anti-prostaglandin effects of flunixin on renal function. If such use cannot be avoided, animals may require careful clinical management.
Flunixin is toxic to avian scavengers. Do not administer to animals susceptible to enter wild fauna food chain. In case of death or sacrifice of treated animals, ensure that they are not made available to wild fauna.
Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogens. 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 veterinary medicinal 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:
This veterinary medicinal product may be harmful after accidental self-injection. In case of accidental self-injection seek medical advice immediately and show the package leaflet or the label to the physician.
This veterinary medicinal product may be irritating to the skin and/or eye. Avoid skin and/or eye contact. Latex or nitrile gloves should be worn during application. In case of accidental contact with skin or eyes, rinse with copious amounts of water. If irritation persists, seek medical advice.

This veterinary medicinal product may cause hypersensitivity reactions due to the presence of oxytetracycline, flunixin, polyethylene glycol or ethanolamine. People with known hypersensitivity to tetracyclines, non-steroidal anti-inflammatory drugs (NSAIDs) or one of the excipients should avoid contact with the veterinary medicinal product. If allergic symptoms develop, such as a skin rash, swelling of the face, lips or eyes or difficulty in breathing, you should seek medical attention immediately and show the package leaflet or label to the doctor.

Laboratory studies in rats with the excipient glycerol formal have shown evidence of teratogenic and foetotoxic effects. Pregnant women, and women of childbearing age should use the veterinary medicinal product with particular caution to avoid accidental self-injection.

Special precautions for the protection of the environment:
Not applicable.

Pregnancy and lactation:
The use is not recommended during pregnancy and lactation.
The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Studies in laboratory animals have shown evidence of foetotoxicity after oral (rabbit and rat) and intramuscular (rat) administration of flunixin at maternotoxic doses and also a lengthening of the duration of gestation (rat).

Interaction with other medicinal products and other forms of interaction:
Some NSAIDs may be highly bound to plasma proteins and compete with other highly bound drugs which can lead to toxic effects.
Do not administer other NSAIDs concurrently or within 24 hours of each other.
Avoid concurrent administration of potentially nephrotoxic veterinary medicinal products, particularly aminoglycosides. Flunixin may reduce the renal excretion of certain veterinary medicinal products and increase their toxicity, such as for aminoglycosides.
Concurrent use of corticosteroids should be avoided.
Flunixin may reduce the effect of some anti-hypertensive medicinal products, such as diuretics and beta blockers, by inhibition of prostaglandin synthesis.
Oxytetracycline may interfere with the action of bactericidal antimicrobials, such as penicillins and cephalosporins, and therefore they should not be used simultaneously.

Overdose:
Following administration at twice the recommended treatment dose (4 mg/kg flunixin and 60 mg/kg oxytetracycline) the veterinary medicinal product is expected to be well tolerated. At this 2x dose level transient dysentery with or without apathy may occur; symptoms resolving without treatment within 48-72 hours.
Studies in cattle at twice the normal dose rate have shown transient and dose dependent reactions at the injection site.
At higher dose levels, above 3x the recommended treatment dose, there is an increased risk of renal toxicity. This may manifest as elevated plasma urea and creatinine levels and pathological changes to the kidneys (cortical tubular necrosis).

Management of overdose should be symptomatic, ensuring adequate hydration is maintained.

Special restrictions for use and special conditions for use:

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 rare (<1 animal / 10,000 animals treated, including isolated reports):	Hypersensitivity reactions [a]
Undetermined frequency (cannot be estimated from the available data)	Injection site reaction [b], Mild increase in body temperature [c], Dental discoloration [d], Bone discoloration [d]

[a] Can be fatal.
[b] A usually mild reaction at the injection site may be observed following intramuscular administration and may persist for up to 30 days. Studies in cattle at the normal dose rate have shown transient and dose dependent reactions at the injection site.
[c] Any increase is transient and will be unlikely to occur in animals already suffering from pyrexia.
[d] The use of tetracyclines during the period of tooth and bone development may lead to discoloration.

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: {national system details}.

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

The veterinary medicinal product is indicated for deep intramuscular administration to cattle. The recommended dosage is 2 mg/kg flunixin and 30 mg/kg oxytetracycline (equivalent to 1 ml per 10 kg bodyweight).
To ensure a correct dosage, body weight should be determined as accurately as possible.
Dosing guide:

Body weight (kg)	Dosage in ml single intramuscular administration.:
50	5
70	7
90	9
100	10
110	11
130	13
150	15
200	20*
250	25*

* maximum volume per injection site: 15 ml, 2 injection sites per animal required

This veterinary medicinal product is recommended for single administration only.

9. Advice on correct administration

Not applicable

10. Withdrawal periods

Meat and offal: 28 days.
Not authorised for use in cattle producing milk for human consumption.

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

Supplied in Type II, clear glass vials of 100 ml, with a 20 mm bromobutyl rubber stopper, and aluminium cap. One glass vial is packaged in a cardboard box.

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:
Dechra Regulatory BV
Handelsweg 25
5531 AE Bladel
The Netherlands
+31 348 563434

Manufacturer responsible for batch release:
Eurovet Animal Health BV
Handelsweg 25
5531 AE Bladel

The Netherlands

Local representatives and contact details to report suspected adverse reactions:

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

17. Other information

Environmental properties
Flunixin is toxic to avian scavengers although foreseen low exposure leads to low risk.