1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tolfine 80 mg/ml (Austria, Belgium, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain) solution for injection for cattle

Tolfacton 80 mg/ml solution for injection for cattle (Denmark, Finland)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Tolfenamic acid 80 mg

Excipients:

Qualitative composition of excipients and other constituents
Diethylene glycol monoethyl ether
Ethanolamine
Water for injections

Clear colourless to slightly yellow-brown solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle.

3.2 Indications for use for each target species

The veterinary medicinal product is indicated as:
- Adjunct treatment for the reduction of acute inflammation associated with respiratory diseases.
- Adjunct treatment of acute mastitis.

3.3 Contraindications

Do not use in cases of cardiac disease.

Do not use in cases of impaired hepatic function or acute renal insufficiency.

Do not use in cases of ulceration or digestive bleeding or in cases of blood dyscrasia.

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

Do not administer other steroidal or non-steroidal anti-inflammatory drugs concurrently or within 24 hours of each other.

Do not use in dehydrated, hypovolaemia or hypotensive animals, due to its potential risk of renal toxicity.

3.4 Special warnings

Non-steroidal anti-inflammatory drugs (NSAIDs) can cause inhibition of phagocytosis and hence in the treatment of inflammatory conditions associated with bacterial infections appropriate concurrent antimicrobial therapy should be instigated.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Do not exceed the stated dosage and duration of treatment. Use aseptic precautions when administering the product.

Concurrent administration of potential nephrotoxic drugs should be avoided.

Young and aged animals are more sensitive to the digestive and renal side-effects of NSAIDs. Such a use should be done with careful clinical management.

In case of undesirable effects (digestive or renal side-effects) occurring during the treatment, your veterinarian should be contacted for advice and the possibility of stopping treatment should be considered.

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

The veterinary medicinal product is irritant to eyes.

In case of accidental eye exposure, flush the eyes immediately with clean water and seek medical advice immediately.

The veterinary medicinal product is irritant to skin. In case of accidental spillage onto skin, wash the skin immediately with soap and water.

Seek medical attention if irritation persists.

Wash hands after use.

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

People with known hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) should avoid contact with the veterinary medicinal product.

In view of the risk of accidental self-injection and the known adverse class-effects of NSAIDs on pregnancy and/or embryofoetal development, pregnant women or women attempting to conceive should administer this veterinary medicinal product with care.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle:

Common	Injection site inflammation[1,3], Injection site swelling[1,3]

(1 to 10 animals / 100 animals treated):	
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Collapse[2,3] Diarrhoea[3], Haemorrhagic diarrhoea[3] Hypersensitivity reaction[3], Anaphylaxis[3,4]

[1] Transient, lasting up to 38 days.
[2] After rapid intravenous injection.
[3] If relevant, the benefit-risk assessment should be re-assessed for the second administration.
[4] Sometimes fatal.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder <or 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:
Use only according to the benefit-risk assessment by the responsible veterinarian. NSAIDs might delay parturition through a tocolytic effect by inhibiting prostaglandins that are important in signalling the initiation of parturition.

Lactation:
Can be used during lactation.

3.8 Interaction with other medicinal products and other forms of interaction

Do not administer other steroidal or non-steroidal anti-inflammatory drugs concurrently or within 24 hours of each other.

Other NSAIDs, diuretics, anticoagulants and substances with high affinity to plasma proteins may compete for binding and produce toxic effects.

Do not administer in conjunction with anticoagulants.

Avoid simultaneous administration of potentially nephrotoxic drugs.

Do not administer in conjunction with glucocorticoids.

3.9 Administration routes and dosage

Intramuscular and intravenous use.

As an adjunct in the treatment of acute inflammation associated with respiratory disease in cattle, the recommended dosage is 2 mg tolfenamic acid per kg bodyweight (corresponding to 1 ml of the product/40 kg bodyweight) by intramuscular injection into the neck area. Treatment may be repeated once after 48 hours.

The maximum injected volume is 18 ml per intramuscular injection site.

As an adjunct in the treatment of acute mastitis, the recommended dosage is 4 mg tolfenamic acid per kg bodyweight (corresponding to 1 ml of the product/20 kg bodyweight) as a single intravenous injection.

When administered intravenously, the product should be injected slowly. At the first signs of

intolerance, the injection should be interrupted.

As the vial should not be broached more than 15 times, the user should select the most appropriate vial size according to the size and number of cattle to be treated.

When treating groups of animals in one run, use a draw-off needle that has been placed in the vial stopper to avoid excess broaching of the stopper. The draw-off needle should be removed after treatment.

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

At high dosages, neurological disorders have been observed.

Symptoms of overdose include: excitation, salivation, tremors, vibration of the eyelids and ataxia. These symptoms are short-term in nature. Reversible kidney damage resulting in elevated plasma urea and creatinine levels is also possible. An antidote is not known. In case of overdose, stop tolfenamic acid administration and administer symptomatic treatment.

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

Intramuscular injection:
Meat and offal: 20 days.
Milk: 0 hours.

Intravenous injection:
Meat and offal: 4 days.
Milk: 12 hours.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QM01AG02.

4.2 Pharmacodynamics

Tolfenamic acid (N-(2-methyl-3-chlorophenyl) anthranilic acid) is a non-steroidal anti-inflammatory drug (NSAID) belonging to the fenamate group. Tolfenamic acid exerts anti-inflammatory, analgesic and antipyretic activities.

The anti-inflammatory activity of tolfenamic acid is mainly due to an inhibition of cyclo-oxygenase and thus to a reduction of the synthesis of prostaglandins and thromboxanes, which are important inflammatory mediators.

4.3 Pharmacokinetics

In cattle, tolfenamic acid injected by I.M. route at a dose of 2 mg/kg is rapidly absorbed from the injection site with mean maximum plasma concentrations of 1.77 ± 0.45 µg/ml obtained at 2.4 hours (0.25-8 hours).

The volume of distribution is approximately 1.3 l/kg.

The absolute bioavailability is high.

Tolfenamic acid is extensively bound to plasma albumin (>97 %).

Tolfenamic acid is distributed in all the organs with a high concentration in the plasma, digestive tract, liver, lungs and kidneys. However, the concentration in the brain is low. Tolfenamic acid and its metabolites do not cross the placenta to any great extent.

Tolfenamic acid distribution involves extracellular fluids where concentrations similar to plasma are achieved both in healthy and inflamed peripheral tissues. It also appears in milk in the active form, mainly associated with the curds.

Tolfenamic acid undergoes extensive enterohepatic recirculation and, as a result prolonged concentrations are found in plasma.

The elimination half-life varies from 8 to 15 hours.

Tolfenamic acid is eliminated mainly unchanged in faeces (~30 %) and urine (~70 %).

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

Amber type I glass vials closed with chlorobutyl rubber stoppers and oversealed with an aluminium seal with a polypropylene flip-off cap.

Each vial is packaged in a cardboard box.

Package sizes:
Cardboard box with 1 vial of 50 ml.
Cardboard box with 1 vial of 100 ml.
Cardboard box with 1 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

To be completed nationally

7. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

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).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton Box for 50 ml (or 100 ml or 250 ml) vial

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tolfine 80 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

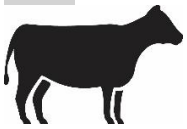
Tolfenamic acid 80 mg/ml

3. PACKAGE SIZE

50 ml.
100 ml
250 ml

4. TARGET SPECIES

Cattle.



5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Intramuscular and intravenous use.

7. WITHDRAWAL PERIODS

Withdrawal periods:

	i.m.	**i.v.**
Meat and offal:	20 days	4 days
Milk:	0 hours	12 hours

8. EXPIRY DATE

Exp. {mm/yyyy}

Once broached use by…..
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

To be completed according to application form for each Member State

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14. MARKETING AUTHORISATION NUMBERS

To be completed nationally

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

LABEL (100 – 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

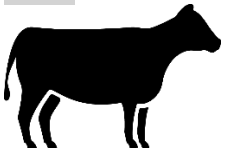
Tolfine 80 mg/ml solution for injection
100ml
250ml

2. STATEMENT OF ACTIVE SUBSTANCES

Tolfenamic acid 80 mg/ml

3. TARGET SPECIES

Cattle.



4. ROUTES OF ADMINISTRATION

i.m./i.v.

Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal periods:

	i.m.	**i.v.**
Meat and offal:	20 days	4 days
Milk:	0 hours	12 hours

6. EXPIRY DATE

Exp. {mm/yyyy}

Once broached, use by…
Once broached, use within 28 days.

7. SPECIAL STORAGE PRECAUTIONS

8. NAME OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

9. BATCH NUMBER

Lot {number}

Vetoquinol logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (50 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tolfine 80 mg/ml solution for injection
50ml

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Tolfenamic acid 80 mg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

Once broached, use by…
Once broached use within 28 days

Vetoquinol logo

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Tolfine 80 mg/ml solution for injection for cattle

2. Composition

Each ml contains:

Active substance:

Tolfenamic acid 80 mg

Clear, colourless to slightly yellow-brown solution.

3. Target species

Cattle.

4. Indications for use

The veterinary medicinal product is indicated as:
- Adjunct treatment for the reduction of acute inflammation associated with respiratory diseases.
- Adjunct treatment of acute mastitis.

5. Contraindications

Do not use in cases of cardiac disease.

Do not use in cases of impaired hepatic function or acute renal insufficiency.

Do not use in cases of ulceration or digestive bleeding or in cases of blood dyscrasia.

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

Do not administer other steroidal or non-steroidal anti-inflammatory drugs concurrently or within 24 hours of each other.

Do not use in dehydrated, hypovolaemia or hypotensive animals, due to its potential risk of renal toxicity.

6. Special warnings

Special warnings:

Non-steroidal anti-inflammatory drugs (NSAIDs) can cause inhibition of phagocytosis and hence in the treatment of inflammatory conditions associated with bacterial infections appropriate concurrent antimicrobial therapy should be instigated.

Special precautions for safe use in the target species:

Do not exceed the stated dosage and duration of treatment. Use aseptic precautions when administering the product.

Concurrent administration of potential nephrotoxic drugs should be avoided.

Young and aged animals are more sensitive to the digestive and renal side-effects of NSAIDs. Such a use should be done with careful clinical management.

In case of undesirable effects (digestive or renal side-effects) occurring during the treatment, your veterinarian should be contacted for advice and the possibility of stopping treatment should be considered.

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

The veterinary medicinal product is irritant to eyes.

In case of accidental eye exposure, flush the eyes immediately with clean water and seek medical advice immediately.

The veterinary medicinal product is irritant to skin. In case of accidental spillage onto skin, wash the skin immediately with soap and water.

Seek medical attention if irritation persists.
Wash hands after use.

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

People with known hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) should avoid contact with the veterinary medicinal product.

In view of the risk of accidental self-injection and the known adverse class-effects of NSAIDs on pregnancy and/or embryofoetal development, pregnant women or women attempting to conceive should administer this veterinary medicinal product with care.

Pregnancy:

Use only according to the benefit-risk assessment by the responsible veterinarian. NSAIDs might delay parturition through a tocolytic effect by inhibiting prostaglandins that are important in signalling the initiation of parturition.

Lactation:

Can be used during lactation.

Interaction with other medicinal products and other forms of interaction:

Do not administer other steroidal or non-steroidal anti-inflammatory drugs concurrently or within 24 hours of each other.

Other NSAIDs, diuretics, anticoagulants and substances with high affinity to plasma proteins may

compete for binding and produce toxic effects.

Do not administer in conjunction with anticoagulants.

Avoid simultaneous administration of potentially nephrotoxic drugs.

Do not administer in conjunction with glucocorticoids.

Overdose:

At high dosages, neurological disorders have been observed.

Symptoms of overdose include: excitation, salivation, tremors, vibration of the eyelids and ataxia. These symptoms are short-term in nature. Reversible kidney damage resulting in elevated plasma urea and creatinine levels is also possible. An antidote is not known. In case of overdose, stop tolfenamic acid administration and administer symptomatic treatment.

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:

Common (1 to 10 animals / 100 animals treated):
Injection site inflammation[1,3], Injection site swelling[1,3]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):
Collapse[2,3] Diarrhoea[3], Haemorrhagic diarrhoea[3] Hypersensitivity reaction[3], Anaphylaxis (severe allergic reaction)[3,4]

[1] Transient, lasting up to 38 days.
[2] After rapid intravenous injection.
[3] If relevant, the benefit-risk assessment should be re-assessed for the second administration.
[4] Sometimes fatal.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder <or its local representative> using the contact details at the end of this leaflet, or via your national reporting system:
To be completed nationally

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

Intramuscular (**i.m.**) and intravenous (**i.v.**) use.

As an adjunct in the treatment of acute inflammation associated with respiratory disease in cattle, the recommended dosage is 2 mg tolfenamic acid per kg bodyweight (corresponding to 1 ml of the

product/40 kg bodyweight) by intramuscular injection into the neck area. Treatment may be repeated once after 48 hours.

The maximum injected volume is 18 ml per intramuscular injection site.

As an adjunct in the treatment of acute mastitis, the recommended dosage is 4 mg tolfenamic acid per kg bodyweight (corresponding to 1 ml of the product/20 kg bodyweight) as a single intravenous injection.

9. Advice on correct administration

Avoid the introduction of contamination during use. Should any apparent growth or discoloration occur, the product should be discarded.

When administered intravenously, the product should be injected slowly. At the first signs of intolerance, the injection should be interrupted.

As the vial should not be broached more than 15 times the user should select the most appropriate vial size according to the size and number of cattle to be treated.

When treating groups of animals in one run, use a draw-off needle that has been placed in the vial stopper to avoid excess broaching of the stopper. The draw-off needle should be removed after treatment.

10. Withdrawal periods

Intramuscular (**i.m.**) injection:
Meat and offal: 20 days.
Milk: 0 hours.

Intravenous (**i.v.**) injection:
Meat and offal: 4 days.
Milk: 12 hours.

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 and on the carton and on the vial 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 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

To be completed nationally

Cardboard box with 1 vial of 50 ml.
Cardboard box with 1 vial of 100 ml.
Cardboard box with 1 vial of 250 ml.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{DD/MM/YYYY}

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

16. Contact details

Marketing authorisation holder <and manufacturer responsible for batch release> <and contact details to report suspected adverse reactions>:

To be completed nationally

<Local representatives <and contact details to report suspected adverse reactions>:>

To be completed nationally

Manufacturer responsible for batch release:

Vetoquinol S.A.
Magny-Vernois
70200 Lure
France
Tél: +33 3 84 62 55 55

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

17. Other information

Pharmacological information:

In cattle, tolfenamic acid injected by the I.M. route at a dose of 2 mg/kg is rapidly absorbed from the injection site with mean maximum plasma concentrations of 1.77 ± 0.45 µg/ml obtained at 2.4 hours (0.25-8 hours).

The volume of distribution is approximately 1.3 l/kg.
The absolute bioavailability is high.

Tolfenamic acid is extensively bound to plasma albumin (>97%).

Tolfenamic acid is distributed in all the organs with a high concentration in the plasma, digestive tract, liver, lungs and kidneys. However, the concentration in the brain is low. Tolfenamic acid and its metabolites do not cross the placental barrier to any great extent.

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