1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Histodine 10 mg/ml solution for injection for cattle (BE, CY, CZ, EE, ES, HU, IE, IS, IT, LT, LU, LV, NL, PL, PT, RO, SK, UK)
Histodine solution for injection for cattle (FR)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

Active substance:
Chlorphenamine maleate 10 mg
(equivalent to 7.03 mg chlorphenamine)

Excipients:
Methyl parahydroxybenzoate (E218) 1.0 mg
Propyl parahydroxybenzoate 0.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle

4.2 Indications for use, specifying the target species

For the symptomatic treatment of conditions associated with histamine release.

4.3 Contraindications

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

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Do not administer via subcutaneous route.

Although intravenous administration has an immediate therapeutic effect, it can have excitatory effects on the CNS. Consequently, administer slowly and interrupt administration for a few minutes if necessary, when using this route.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Chlorphenamine can cause sedation. Wash splashes from skin and eyes immediately. Precautions should be taken to avoid accidental self-injection with this drug. Preferably use a guarded needle until the moment of injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician. DO NOT DRIVE.

4.6 Adverse reactions (frequency and seriousness)

Chlorphenamine has a weak sedative effect.

4.7 Use during pregnancy and lactation

The safety of the product has not been established during pregnancy and lactation. Use only according to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interactions

Concomitant use of other antihistamines or barbiturates may boost the sedative effect of chlorphenamine. The use of antihistamines may conceal early signs of ototoxicity caused by some antibiotics (i.e. aminoglycosides and macrolides) and may shorten the effect of oral anticoagulants.

4.9 Amounts to be administered and administration route

Intramuscular or intravenous use.
Intravenous injection should be slow and, if necessary, discontinued for a few minutes (see 4.5).

Adult animals:
0.5 mg Chlorphenamine maleate /kg bodyweight (equivalent to 5 ml/100 kg bodyweight), once a day for three consecutive days.

Calves:
1 mg Chlorphenamine maleate /kg bodyweight (equivalent to 10 ml/100 kg bodyweight), once a day for three consecutive days.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Doses up to four times the therapeutic dose have been well tolerated. In very rare cases, local reactions were observed at the injection site. All the reactions were transient and resolved spontaneously.

4.11 Withdrawal periods

Meat and offal: 1 day
Milk: 12 hours

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antihistamines for systemic use.
ATC vet code: QR06AB04

5.1 Pharmacodynamic properties

Chlorphenamine maleate is a racemic compound classified as an alkyl amine group antihistamine that, due to its chemical characteristics, is able to bind to the H1 receptor present on the cell membrane and therefore compete with the natural endogenous ligand for the same site. Receptor occupation by chlorphenamine maleate does not, in itself, induce pharmacological responses, but significantly inhibits those induced by histamine. On the basis of these observations, chlorphenamine maleate behaves as a direct or reversible competitive receptor antagonist. Chlorphenamine maleate is not able to inhibit the synthesis or release of histamine.

5.2 Pharmacokinetic particulars

After intravenous administration the medicinal product's plasma concentration drops from 36 ng/mL to the method's limit of detection (1 ng/mL) 24 hours after administration. The calculated elimination half-life ($T_{1/2ß}$) is 2.11 hours, the mean residence time (MRT) is 2.35 hours, total clearance (Cl_B) 1.315 L/kg/h and the volume of distribution (Vd) just over 3 L/kg. Following intramuscular administration, peak concentration (C_{max} = 142 ng/mL) is reached in 28 minutes (T_{max}). Plasma concentrations then drop rapidly to reach values of 60 and 12 µg/kg after 2 and 8 hours before dropping below the limit of quantification (1 µg/kg) 24 hours after treatment. MRT and bioavailability were 3.58 hours and 100%, respectively.
The compound and its metabolites are excreted primarily via the kidneys in urine, with a small amount in unmodified form and the majority as a breakdown product, almost completely, within 24 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate
Disodium phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Water for injection

6.2 Major incompatibilities

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

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after opening of the immediate packaging: 56 days.

6.4 Special precautions for storage

This veterinary medicinal product does not require any special temperature storage precautions.
Store in the original package in order to protect from light.

6.5 Nature and composition of the immediate packaging

Clear Type II glass vials and polypropylene vials containing 100 ml or 250 ml, closed with a coated

bromobutyl rubber stopper and aluminium cap in a carton box.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

xxxxxxxxxxxxxxxxxx

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

xxxxxxxxxxxxxxxxxxx

PROHIBITION OF SALE, SUPPLY AND / OR USE

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Outer carton

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Histodine 10 mg/ml solution for injection for cattle
chlorphenamine maleate

2. STATEMENT OF ACTIVE SUBSTANCES

Chlorphenamine maleate 10 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

100 ml
250 ml

5. TARGET SPECIES

Cattle

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular or intravenous use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal period(s)
Meat and offal: 1 day
Milk: 12 hours

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Shelf life after opening of the immediate packaging: 56 days.
Once broached use by…

11. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

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

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING UNITS

100 ml and 250 ml glass vial or polypropylene vial

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Histodine 10 mg/ml solution for injection for cattle
chlorphenamine maleate

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Chlorphenamine maleate 10 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

100 ml
250 ml

5. TARGET SPECIES

Cattle

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

IM or IV
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal period(s)
Meat and offal: 1 day
Milk: 12 hours

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

Once broached use by…

11. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

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

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

Histodine 10 mg/ml solution for injection for cattle

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

Manufacturer responsible for batch release:
Produlab Pharma B.V.
Forellenweg 16
4941 SJ Raamsdonksveer
The Netherlands

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Histodine 10 mg/ml solution for injection for cattle
chlorphenamine maleate

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

1 ml contains:

Active substance:
Chlorphenamine maleate 10 mg
(equivalent to 7.03 mg chlorphenamine)

Excipients:
Methyl parahydroxybenzoate (E218) 1.0 mg
Propyl parahydroxybenzoate 0.2 mg

Clear, colourless solution.

4. INDICATION

For the symptomatic treatment of conditions associated with histamine release.

5. CONTRAINDICATIONS

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

6. ADVERSE REACTIONS

Chlorphenamine has a weak sedative effect. 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 inform your veterinary surgeon.
Alternatively you can report via your national reporting system {national system details}

7. TARGET SPECIES

Cattle.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Intramuscular or intravenous use.
Intravenous injection should be slow and, if necessary, discontinued for a few minutes (see section 12).

Adult animals:
0.5 mg Chlorphenamine maleate /kg bodyweight (equivalent to 5 ml/100 kg bodyweight), once a day for three consecutive days.

Calves:
1 mg Chlorphenamine maleate /kg bodyweight (equivalent to 10 ml/100 kg bodyweight), once a day for three consecutive days.

9. ADVICE ON CORRECT ADMINISTRATION

10. WITHDRAWAL PERIOD(S)

Meat and offal: 1 day
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 temperature storage precautions.
Store in the original package in order to protect from light. Do not use this veterinary medicinal product after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
Shelf life after first opening the container: 56 days.

12. SPECIAL WARNING(S)

Special precautions for use in animals

Do not administer via subcutaneous route.
Although intravenous administration has an immediate therapeutic effect, it can have excitatory effects on the CNS. Consequently, administer slowly and interrupt administration for a few minutes if necessary, when using this route.

User warnings
Chlorphenamine can cause sedation. Wash splashes from skin and eyes immediately. Precautions should be taken to avoid accidental self-injection with this drug. Preferably use a guarded needle until the moment of injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician. DO NOT DRIVE.

Use during pregnancy and lactation:
The safety of the 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 interactions
Concomitant use of other antihistamines or barbiturates may boost the sedative effect of chlorphenamine. The use of antihistamines may conceal early signs of ototoxicity caused by some antibiotics (i.e. aminoglycosides and macrolides) and may shorten the effect of oral anticoagulants.

Overdose (symptoms, emergency procedures, antidotes):
Doses up to four times the therapeutic dose have been well tolerated. In very rare cases, local reactions were observed at the injection site. All the reactions were transient and resolved spontaneously.

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Xxxxxx

15. OTHER INFORMATION

Clear Type II glass vials and polypropylene vials containing 100 ml or 250 ml, closed with a coated bromobutyl rubber stopper and aluminium cap in a carton box.
Not all pack sizes may be marketed.

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