1. NAME OF THE VETERINARY MEDICINAL PRODUCT

AT, BG, BE, CY, CZ, DE, DK, EE, EL, ES, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PT, RO, SI, SK, UK (NI):
Bioestrovet 0.250 mg/mL solution for injection for cattle

PL:
Estrovet 0.250 mg/mL solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:

Active substance:

Cloprostenol	0.250 mg
(equivalent to Cloprostenol Sodium)	0.263 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Chlorocresol	1.00 mg
Citric Acid	
Sodium Citrate	
Sodium Chloride	
Water for Injections	

A clear colourless aqueous solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (heifers, cows).

3.2 Indications for use for each target species

Cattle (heifers, cows):
- Oestrus induction and synchronisation in cows and heifers with a functional corpus luteum.
- Induction of oestrus as an aid to management of suboestrus (‘silent heat’).
- Treatment of clinical and subclinical endometritis in the presence of a functional corpus luteum.
- Treatment of ovarian luteal cysts.
- Induction of abortion up to day 150 of gestation.
- Induction of parturition after day 270 of gestation.

3.3 Contraindications

Do not use in pregnant animals in which the induction of abortion or parturition is not intended.

Do not administer to induce parturition in animals with suspected dystocia due to mechanical obstruction or abnormal position, presentation and/or posture of the foetus.

Do not use in animals with compromised cardiovascular function, bronchospasm or gastro-intestinal dysmotility.

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

3.4 Special warnings

There is a refractory period of four to five days after ovulation when cattle are insensitive to the luteolytic effect of prostaglandins.
For the termination of gestation, best results are obtained before day 100 of gestation. Results are less reliable between day 100 and 150 of gestation.

3.5 Special precautions for use

Special precautions for safe use in the target species:

To reduce the risk of anaerobic infections arising from vasoconstriction at the injection site, injections into contaminated (wet or dirty) skin areas should be avoided.
Thoroughly clean and disinfect injection sites prior to administration.

Do not administer intravenously.

All animals should receive adequate supervision after treatment.

Induction of parturition or abortion may cause dystocia, stillbirth and/or metritis. The incidence of retained placenta may be increased depending on the time of treatment relative to the date of conception.

Injection into adipose tissue can result in incomplete absorption of the veterinary medicinal product.
Cloprostenol may cause effects related to Prostaglandin F2α activity in the smooth muscles, such as increased frequency of urination and defecation.

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

Prostaglandins of the $F2_{\alpha}$-type, such as cloprostenol, can be absorbed through the skin and may cause bronchospasm or miscarriage. Care should be taken when handling the product to avoid self-injection or skin contact.

Pregnant women, women of child-bearing age, asthmatics and people with other respiratory tract diseases should avoid any contact with the veterinary medicinal product.

Personal protective equipment consisting of impervious gloves should be worn when handling the veterinary medicinal product.

Accidental spillage on the skin should be washed immediately with soap and water.
In case of accidental self-injection or spillage onto skin, seek medical advice immediately, particularly as shortness of breath may occur, and show the package leaflet or the label to the physician.

This veterinary medicinal product may cause hypersensitive reactions. People with known hypersensitivity to chlorocresol should avoid contact with the veterinary medicinal product.

Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle (heifers, cows):

Rare (1 to 10 animals / 10 000 animals treated)	Injection site infection[1]
Very rare (<1 animal / 10 000 animals treated, including isolated reports):	Anaphylaxis[2]; Increased respiratory rate[3]; Increased heart rate[3]; Abdominal pain[3], Diarrhoea[3,5]; Incoordination[3]; Lying down[3]; Retained placenta[4], Metritis[4], Dystocia[4], Stillbirth[4]; Restlessness, Frequent urination[3,5];

[1] May occur if anaerobic bacteria enter the injection site, especially following intramuscular injection, and may become generalized. Aggressive antibiotic therapy, particularly covering clostridial species, should be employed at the first sign of infection. Careful aseptic techniques should be employed to decrease the possibility of these infections.
[2] Requiring immediate medical attention. Can be life-threatening.
[3] Cloprostenol may cause effects similar to Prostaglandin F2α activity in the smooth muscles.
[4] May be caused by induction of parturition. As part of induction of parturition, depending on the date of treatment versus the date of conception, the incidence of placental retention may be increased.
[5] In case of occurrence, these effects are observed within 15 minutes post-injection and usually disappear after one hour.

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:

Do not use in pregnant animals in which the induction of abortion or parturition is not intended.

Lactation:

The product can be used during lactation.

Fertility:

Cloprostenol has a large safety margin and does not negatively affect fertility in cattle. Nor have any harmful effects been reported in the offspring of an insemination or mating following treatment with this veterinary medicinal product for conception products obtained after treatment.

3.8 Interaction with other medicinal products and other forms of interaction

The concomitant use of oxytocin and cloprostenol increases the effects on the uterus.

Do not administer with non-steroidal anti-inflammatory drugs (NSAIDs) since they inhibit endogenous prostaglandin synthesis.

The concomitant use of progestogens decreases the effect of cloprostenol.

3.9 Administration routes and dosage

For intramuscular use.

One dose equals 0.5 mg Cloprostenol/animal corresponding to 2 mL of the veterinary medicinal product per animal.

Oestrus induction and synchronisation:
Administer one dose per animal. When no oestrus symptoms are observed, a second dose can be administered after 11 days.

Treatment of clinical and subclinical endometritis in the presence of a functional corpus luteum.:
Administer one dose per animal. If necessary, repeat the treatment 10-14 days later.

Treatment of ovarian luteal cysts:
Administer a single dose per animal.

Induction of parturition:
Administer a single dose per animal, not earlier than 10 days before the expected date of calving.

Induction of abortion up to day 150 of gestation:
Administer a single dose per animal, between the 5th and the 150th day of gestation.

It is recommended that the vial is not broached more than 10 times and that the appropriate vial size is used for prevailing usage conditions. Otherwise, automatic syringe equipment, or a suitable draw-off needle, should be used for the 50 ml and 100 ml vials to avoid excessive puncturing of the stopper.

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

At 5x to 10x overdose the most frequent side effect is increased rectal temperature. This is usually transient, however, and not detrimental to the animal. Limited salivation or transient diarrhoea may also be observed in some animals.

There are no antidotes available, treatment should be symptomatic, assuming that prostaglandin F2α influences the smooth muscle cells.

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: 1 day.

Milk: Zero hours.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QG02AD90.

4.2 Pharmacodynamics

Cloprostenol sodium, a (racemic) analogue of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), is a very potent luteolytic agent. It causes functional and morphological regression of the corpus luteum (luteolysis) in cattle followed by return to oestrus and normal ovulation.

Furthermore, this group of substances has a contractile effect on the smooth muscles (uterus, gastro-intestinal tract, respiratory tract, vascular system).

The veterinary medicinal product does not demonstrate any androgenic, oestrogenic or anti progesterone activity and its effect on pregnancy is due to its luteolytic property.

Unlike other prostaglandin analogues, cloprostenol has no thromboxane A_2 activity and does not cause platelet aggregation.

4.3 Pharmacokinetics

Metabolism studies, using $^{15-14}$C-cloprostenol have been performed in cattle (by i.m. administration) to determine residue levels.
The kinetic studies indicate that the compound is rapidly absorbed from the site of injection, is metabolised then excreted in approximately equal proportion in urine and faeces. In cattle, less than 1% of the administered dose is eliminated via milk. The major route of metabolism appears to be β-oxidation to the tetranor or dinor acids of cloprostenol. Peak values of radioactivity in blood were observed within 1 hour of a parenteral dose and declined with a t ½ of between 1 - 3 hours depending on species.

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

Keep the vial in the outer carton in order to protect from light.

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

5.4 Nature and composition of immediate packaging

Type 1 (colourless) glass vial closed with bromobutyl rubber stopper coated with a FluroTec film (ETFE) and a polypropylene flip-off cap.

Box containing 1 vial of 20 mL.
Box containing 1 vial of 50 mL.
Box containing 1 vial of 100 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.

The veterinary medicinal product should not enter water courses as cloprostenol may be dangerous for fish and other aquatic organisms.

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

{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 20, 50, 100 mL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bioestrovet 0.250 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Cloprostenol (eqivalent to Cloprostenol Sodium 0.263 mg/mL)	0.250 mg/mL

3. PACKAGE SIZE

20 mL
50 mL
100 mL

4. TARGET SPECIES

Cattle (heifers, cows)

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

i.m.

7. WITHDRAWAL PERIODS

Withdrawal periods:
Meat and offal: 1 day.
Milk: Zero hours.

8. EXPIRY DATE

Exp. {mm/yyyy}

Once broached use within 28 days.

Once broached, use by:

9. SPECIAL STORAGE PRECAUTIONS

Keep the vial in the outer carton in order to protect from light.

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 nationally]

14. MARKETING AUTHORISATION NUMBERS

[To be completed nationally]

15. BATCH NUMBER

Lot {number}

Vetoquinol logo

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Vial label 100 mL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bioestrovet 0.250 mg/mL solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Cloprostenol 0.250 mg/mL
(equivalent to Cloprostenol Sodium 0.263 mg/mL)

3. TARGET SPECIES

Cattle (heifers, cows).

4. ROUTES OF ADMINISTRATION

i.m.
Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal periods:
Meat and offal: 1 day.
Milk: Zero hours.

6. EXPIRY DATE

Exp. {mm/yyyy}

Once broached use within 28 days..

Once broached, use by:

7. SPECIAL STORAGE PRECAUTIONS

Keep the vial in the outer carton in order to protect from light.

8. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

9. BATCH NUMBER

Lot {number}

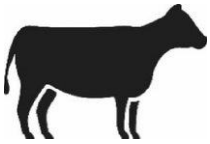
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label (20 mL – 50 mL)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bioestrovet 0.250 mg/mL solution for injection

i.m.



2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Cloprostenol 0.250 mg/mL
(eqivalent to Cloprostenol Sodium 0.263 mg/mL)

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

Once broached use within 28 days.

Once broached, use by:

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Bioestrovet 0.250 mg/mL solution for injection for cattle

2. Composition

Each mL contains:

Active substance:

Cloprostenol	0.250 mg
(equivalent to Cloprostenol Sodium)	0.263 mg

Excipient:

Chlorocresol	1.00 mg

A clear colourless aqueous solution.

3. Target species

Cattle (heifers, cows).

4. Indications for use

Cattle (heifers, cows):
- Oestrus induction and synchronisation in cows and heifers with a functional corpus luteum.
- Induction of oestrus as an aid to management of suboestrus (‘silent heat’).
- Treatment of clinical and subclinical endometritis in the presence of a functional corpus luteum (inflammation of the uterus).
- Treatment of ovarian luteal cysts.
- Induction of parturition after day 270 of gestation.
- Induction of abortion up to day 150 of gestation.

5. Contraindications

Do not use in pregnant animals in which the induction of abortion or parturition is not intended.

Do not administer to induce parturition in animals with suspected dystocia (difficult parturition) due to mechanical obstruction or abnormal position, presentation and/or posture of the foetus.

Do not use in animals with compromised cardiovascular function, bronchospasm or gastro-intestinal dysmotility.

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

6. Special warnings

Special warnings:

There is a refractory period of four to five days after ovulation when cattle are insensitive to the luteolytic effect of prostaglandins.

For the termination of pregnancy, best results are obtained before day 100 of gestation. Results are less reliable between day 100 and 150 of gestation.

Special precautions for safe use in the target species:

To reduce the risk of anaerobic infections arising from vasoconstriction at the injection site, injections into contaminated (wet or dirty) skin areas should be avoided. Thoroughly clean and disinfect injection sites prior to administration.

Do not administer intravenously.

All animals should receive adequate supervision after treatment.

Induction of parturition or abortion may cause dystocia (difficult parturition), stillbirth and/or metritis (inflammation of the uterus). The incidence of retained placenta may be increased depending on the time of treatment relative to the date of conception.

Injection into adipose tissue can result in incomplete absorption of the veterinary medicinal product. Cloprostenol may cause effects related to Prostaglandin F2α activity in the smooth muscles, such as increased frequency of urination and defecation.

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

Prostaglandins of the $F2_{\alpha}$-type, such as cloprostenol, can be absorbed through the skin and may cause bronchospasm or miscarriage. Care should be taken when handling the product to avoid self-injection or skin contact.

Pregnant women, women of child-bearing age, asthmatics and people with other respiratory tract diseases should avoid any contact with the veterinary medicinal product.

Personal protective equipment consisting of impervious gloves should be worn when handling the veterinary medicinal product.

Accidental spillage on the skin should be washed immediately with soap and water.

In case of accidental self-injection or spillage onto skin seek medical advice immediately, particularly as shortness of breath may occur, and show the package leaflet or the label to the physician.

This veterinary medicinal product may cause hypersensitive reaction. People with known hypersensitivity to chlorocresol should avoid contact with this veterinary medicinal product.

Wash hands after use.

Pregnancy:

Do not use in pregnant animals in which the induction of abortion or parturition is not intended.

Lactation:

The product can be used during lactation.

Fertility:

Cloprostenol has a large safety margin and does not negatively affect fertility in cattle. Nor have any harmful effects been reported in the offspring of an insemination or mating following treatment with this veterinary medicinal product for conception products obtained after treatment.

Interaction with other medicinal products and other forms of interaction:

The concomitant use of oxytocin and cloprostenol increases the effects on the uterus.

The concomitant use of progestogens decreases the effect of cloprostenol.

Do not administer with non-steroidal anti-inflammatory drugs (NSAIDs) since they inhibit endogenous prostaglandin synthesis.

Overdose:

At 5x to 10x overdose the most frequent side effect is increased rectal temperature. This is usually transient, however, and not detrimental to the animal. Limited salivation or transient diarrhoea may also be observed in some animals.

There are no antidotes available, treatment should be symptomatic, assuming that prostaglandin F2α influences the smooth muscle cells.

Special restrictions for use and special conditions for use:

Not applicable.

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 (heifers, cows):

Rare *(1 to 10 animals / 10 000 animals treated)*
Injection site infection[1]
Very rare *(<1 animal / 10 000 animals treated, including isolated reports):*
Anaphylaxis[2]; Increased respiratory rate[3]; Increased heart rate[3]; Abdominal pain[3], Diarrhoea[3,5]; Incoordination[3]; Lying down[3]; Retained placenta[4], Metritis[4], Dystocia[4], Stillbirth[4]; Restlessness, Frequent urination[3,5];

[1] May occur if anaerobic bacteria enter the injection site, especially following intramuscular injection, and may become generalized. Aggressive antibiotic therapy, particularly covering clostridial species, should be employed at the first sign of infection. Careful aseptic techniques should be employed to decrease the possibility of these infections.
[2] Requiring immediate medical attention. Can be life-threatening.
[3] Cloprostenol may cause effects similar to Prostaglandin F2α activity in the smooth muscles.
[4] May be caused by induction of parturition. As part of induction of parturition, depending on the date of treatment versus the date of conception, the incidence of placental retention may be increased.
[5] In case of occurrence, these effects are observed within 15 minutes post-injection and usually disappear after one hour.

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:
[To be completed nationally]

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

For intramuscular use (i.m.).

One dose equals 0.5 mg Cloprostenol/animal corresponding to 2 mL product per animal.

Oestrus induction and synchronisation:
Administer one dose per animal. When no oestrus symptoms are observed, a second dose can be administered after 11 days.

Treatment of clinical and subclinical endometritis in the presence of a functional corpus luteum.:
Administer one dose per animal. If necessary, repeat the treatment 10-14 days later.

Treatment of ovarian luteal cysts:
Administer a single dose per animal.

Induction of parturition:
Administer a single dose per animal, not earlier than 10 days before the expected date of calving.

Induction of abortion up to day 150 of gestation:
Administer a single dose per animal, between the 5th and the 150th day of gestation.

It is recommended that the vial is not broached more than 10 times and that the appropriate vial size is used for prevailing usage conditions. Otherwise, automatic syringe equipment, or a suitable draw-off needle, should be used for the 50 ml and 100 ml vials to avoid excessive puncturing of the stopper.

9. Advice on correct administration

10. Withdrawal periods

Meat and offal: 1 day.
Milk: Zero hours.

11. Special storage precautions

Keep out of the sight and reach of children.

Keep the vial in the outer carton in order to protect from light.

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

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 immediate packaging: 28 days.

When the container is broached (opened) for the first time, using the in-use shelf-life which is specified on this package leaflet, the date on which any product remaining in the carton should be discarded should be worked out. This discard date should be written in the space provided.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

The veterinary medicinal product should not enter water courses as cloprostenol may be dangerous for fish and other aquatic organisms.

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 applicable to the veterinary medicinal product concerned.

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

[To be completed nationally]

Box containing one 20 mL glass vial.
Box containing one 50 mL glass vial.
Box containing one 100 mL glass vial.

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 *or* Local representative 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

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