1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Estrumate 250 micrograms/ml Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Cloprostenol 250 micrograms
(equivalent to 263 micrograms cloprostenol sodium)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl alcohol	20.00 mg
Citric acid	
Sodium citrate dihydrate	
Sodium chloride	
Water for injections	

Clear, colourless solution, practically free from particles.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (cows and heifers), goats (does), horses (mares), donkeys (jennies), pigs (sows and gilts).

3.2 Indications for use for each target species

Cattle (cows and heifers):
- 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 parturition after day 270 of gestation.
- Induction of abortion up to day 150 of gestation.

Goats (does):
- Oestrus induction and synchronisation in does with a functional corpus luteum during the breeding season.

Horses (mares):
- Oestrus induction and synchronisation in mares with a functional corpus luteum.
- Termination of early pregnancy between day 5 and day 120 of gestation.

Donkeys (jennies):
- Oestrus induction in jennies with a functional corpus luteum.

Pigs (sows and gilts):
- Induction of farrowing one or two days before the estimated date of parturition.

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 gastrointestinal 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 several days after ovulation (e.g. four to five days in cattle and horses), when females are insensitive to the luteolytic effect of prostaglandins.
For the termination of gestation in cattle, best results are obtained before day 100 of gestation. Results are less reliable between day 100 and 150 of gestation.
The response of sows and gilts to induction of parturition may be influenced by the physiological state and the time of treatment. The vast majority of animals, 95%, will commence farrowing within 36 hours of treatment. The majority of animals can be expected to respond within the period of 24+/- 5 hours following the injection, except in those cases where spontaneous parturition is imminent.

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.
Premature induction of farrowing will reduce the piglet's birth weight and increase the number of stillborn piglets and non-viable and immature born piglets. It is essential that the mean length of gestation is calculated on each farm from past records and not to anticipate the term of gestation by more than two days.
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 F2α type, such as cloprostenol, may be absorbed through the skin and may cause bronchospasm or miscarriage. Care should be taken when handling the veterinary medicinal product to avoid self-injection or skin contact.

Pregnant women, women of childbearing age, asthmatics and persons with other respiratory tract diseases should avoid contact when handling this 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 the skin seek medical advice immediately, particularly as shortness of breath may occur, and show the package leaflet or label to the physician.

This veterinary medicinal product may cause hypersensitive reactions. People with known hypersensitivity to benzyl alcohol 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 (cows and heifers):

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 or abortion. 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.

Goats (does)

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];

[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.

Horses (mares):

Uncommon (1 to 10 animals / 1,000 animals treated)	Abnormal oestrus[1];
Rare	Injection site infection[2]

(1 to 10 animals / 10,000 animals treated)	
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Anaphylaxis[3]; Increased respiratory rate[4]; Increased heart rate[4]; Increased sweating[4,5]; Abdominal pain[4], Colic[6], Diarrhoea[4,8]; Incoordination[4], Muscle tremor[5]; Lying down[4], Decreased body temperature[4]; Retained placenta[7], Metritis[7], Dystocia[7], Stillbirth[7]; Restlessness, Frequent urination[4,8];

[1] Haemorrhagic (anovular) follicles and multiple ovulations are reported in literature for horses treated with cloprostenol.
[2] 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.
[3] Requiring immediate medical attention. Can be life-threatening.
[4] Cloprostenol may cause effects similar to Prostaglandin F2α activity in the smooth muscles.
[5] Appears to be transient and resolves without any treatment.
[6] Mild.
[7] May be caused by termination of gestation, depending on the date of treatment versus the date of conception, the incidence of placental retention may be increased.
[8] In case of occurrence, these effects are observed within 15 minutes post-injection and usually disappear after one hour.

Donkeys (jennies):

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]; Increased sweating[3,4]; Abdominal pain[3], Colic[5], Diarrhoea[3,7]; Incoordination[3], Muscle tremor[4]; Lying down[3], Decreased body temperature[3], Anorexia; Retained placenta[6], Metritis[6], Dystocia[6], Stillbirth[6], Restlessness, Frequent urination[3,7];

[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] Appears to be transient and resolves without any treatment.
[5] Mild.
[6] May be caused by induction of parturition or abortion. 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.
[7] In case of occurrence, these effects are observed within 15 minutes post-injection and usually disappear after one hour.

Pigs (sows and gilts):

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.
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.

3.9 Administration routes and dosage

Intramuscular use.

Cattle (cows and heifers):
One dose equals 500 micrograms of cloprostenol per animal, corresponding to 2 ml of the veterinary medicinal product.

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 5^{th} and the 150^{th} day of gestation.

Goats (does):
One dose equals 100 – 125 micrograms of cloprostenol per animal, corresponding to 0.4 – 0.5 ml of the veterinary medicinal product.

Oestrus induction:
Administer one dose per animal.

Synchronisation of oestrus:
Administer a second dose per animal 10 – 12 days after the first dose.

Horses (mares):
Ponies and horses weighing less than 500 kg bodyweight:
One dose equals 125 – 250 micrograms of cloprostenol per animal, corresponding to 0.5 – 1 ml of the veterinary medicinal product.
Horses weighing more than 500 kg bodyweight:
One dose equals 250 – 500 micrograms of cloprostenol per animal, corresponding to 1 – 2 ml of the veterinary medicinal product.

Oestrus induction and synchronisation:
Administer a single dose per animal.

Termination of early gestation between day 5 and day 120:
Administer a single dose per animal, not earlier than 5 days after ovulation.

Donkeys (jennies):
One dose equals 125 - 250 micrograms of cloprostenol per animal, corresponding to 0.5 - 1 ml of the veterinary medicinal product, depending upon bodyweight and size.
A lower dose, down to 37.5 micrograms cloprostenol per animal, corresponding to 0.15 ml of the veterinary medicinal product, might be required for small framed jennies to reduce adverse reactions.
The dose to be applied in general should be as low as possible due to the risk of adverse events (see section 3.6).

Oestrus induction:
Administer a single dose per animal.

Pigs (sows and gilts):

One dose equals 175 micrograms of cloprostenol per animal, corresponding to 0.7 ml of the veterinary medicinal product.

Induction of farrowing:
Administer a single dose per animal one or two days before the estimated date of parturition (see also warnings in section 3.5).
To be administered by deep intramuscular route with a needle at least 4 cm long.

The stopper may be safely punctured up to 10 times. 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)

Cattle: 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.
Horses: The most frequently observed side effects are sweating and decreased rectal temperatures. These are usually transient, however, and not detrimental to the animal. Other possible reactions are increased heart rate, increased respiratory rate, abdominal discomfort, locomotor incoordination and lying down. If these occur, they are likely to be seen within 15 minutes of injection and disappear within 1 hour. Mares usually continue to eat throughout.
Pigs: In general, an overdose can lead to the following symptoms: increased heart and respiratory rate, bronchoconstriction, increased body temperature, increased amounts of faeces and urine, salivation, nausea and vomiting. In worse cases transient diarrhoea may occur.

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

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

Goats, horses, donkeys:
Meat and offal: 2 days
Milk: 24 hours

Pigs:
Meat and offal: 1 day

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) 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 pigs and cattle (by IM 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: 2 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.
Do not freeze.

5.4 Nature and composition of immediate packaging

Colourless type I glass vials, closed with ethylene tetrafluoroethylene (ETFE)-coated bromobutyl stoppers and aluminum collars with red flip-caps.

1 x 10 ml bottle
1 x 20 ml bottle

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

Intervet Ireland Limited

7. MARKETING AUTHORISATION NUMBER(S)

VPA10996/227/001

8. DATE OF FIRST AUTHORISATION

14/10/2011

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

17/12/2025

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).