SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cevaprost 250 µg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substances:

Cloprostenol 0.250 mg/ml
(as 0.263 mg/ml cloprostenol sodium)

Excipients:

Benzyl alcohol (E1519) 20 mg/ml
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle

4.2 Indications for use, specifying the target species

Cattle
- Silent heat
- Ovarian luteal cysts
- Termination of pregnancy
- Induction of parturition
- Removal of mummified foetus
- Chronic endometritis (pyometra)
- Synchronisation of oestrus (within 2 to 5 days) in groups of cyclic females treated simultaneously

4.3 Contraindications

Do not administer the product to pregnant cows unless you wish to induce parturition or therapeutic abortion, as luteolysis may result in loss of the foetus.
Do not use in animals in cases of dystocic delivery, in case of abnormal position of the foetus or of mechanical obstruction.
Do not administer to animals with known hypersensitivity to the active substance or one of the excipients.
Do not use in animals with cardiovascular, gastro-intestinal or respiratory problems.
Do not administer intravenously.

4.4 Special warnings for each target species

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

4.5 Special precautions for use

i. Special precautions for use in animals

Administer the product intramuscularly by observing normal aseptic rules to reduce the risk of anaerobic infections. Clean and disinfect the injection site prior to administration. Avoid administration through wet or dirty skin. After treatment, the animals must remain under observation to detect any adverse reaction.

In cows when used for induction of pregnancy, abortion at the most advanced stage, complications such as dystocia and increased placental retention are possible.

ii. Special Safety Precautions to be taken by the Person Administering the Medicinal Product to animals

Direct contact with skin or mucous membranes of the user should be avoided. Prostaglandins of the F2α type may 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 childbearing age, asthmatics and persons with other respiratory tract diseases should exercise caution when handling cloprostenol. Those persons should avoid contact or wear disposable gloves during administration of the product. Accidental spillage on the skin should be washed immediately with soap and water. The possible incidence of bronchospasm with the product is unknown. Should shortness of breath result from accidental inhalation or injection, seek urgent medical advice and show the doctor this warning. Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

In very rare cases, anaphylactic-type reactions can be observed which require immediate medical care. Anaerobic infection may occur if anaerobic bacteria penetrate the tissue of the injection site. Typical local reactions due to anaerobic infection are swelling and crepitus at the injection site. When used for the induction of parturition and dependent on the time of treatment relative to the date of conception, the incidence of retained placenta may be increased.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Do not administer to pregnant animals unless the objective is to terminate pregnancy.

4.8 Interactions with other medicinal products and other forms of interaction

Do not perform the treatment at the same time as non-steroidal anti-inflammatory drugs as non-steroidal anti-inflammatory drugs may inhibit the endogenous prostaglandin synthesis: concomitant administration of these compounds with the product may decrease the luteolytic effects. The activity of other oxytocin agents can be increased after the administration of cloprostenol.

4.9 Amounts to be administered and administration route

Cattle
Single or repeated 2ml doses (equivalent to 500 mcg of cloprostenol) by intramuscular injection).

Therapeutic indications:

A) Silent heat
This condition is particularly common in heavy producing dairy cows, which have normal ovarian cycles but slightly express or do not express behavioural manifestations. These animals can be treated only after checking the cycle activity and the presence of the corpus luteum. Animals treated with the product may be bred (natural service or artificial insemination) 72 and 96 hours after treatment.
If the animal has been treated in the absence of a corpus luteum, another injection of the product is required 11 days after the first injection.

B) Ovarian luteal cysts
The product has demonstrated its efficacy in restoring normal the oestrus cycle in case of absence of heat caused by ovarian cysts (characterized by the presence of persistent luteal tissue).

C) Termination of pregnancy
The condition may occur in case of immature calves.
The pregnancy can be interrupted starting from one week after its establishment until day 150 of pregnancy. Before day 100, abortion can be induced quickly and effectively while between day 100 and day 150, results may be less significant because some cows may become progressively less sensitive to the action of corpus luteum maintaining pregnancy. The animals must be kept under observation until foetus and placental membranes complete expulsion.

D) Induction of parturition
From day 270 of pregnancy, the administration of the product induces parturition 30 – 60 hours of treatment. The induction of parturition should take place as close as possible to the expected date of spontaneous parturition. The induction of parturition should not be induced before day 270 day of pregnancy. All treated animals must be kept under observation. As with all other methods of shortening the pregnancy period, placental retention rate may be increased.

E) Removal of mummified foetus
Foetus death may be followed by dehydration and degeneration. The induction of luteolysis at any stage of pregnancy causes the expulsion of mummified foetuses from the uterus to the vagina, from which it is possible to make manual removal. Usually, normal cyclic activity follows.

F) Chronic Endometritis (Pyometra)
Reproduction system lesions caused during parturition or placental retention may cause uterine inflammation and infections known as endometritis. Acute or sub-acute endometritis, which may occur shortly after parturition, may require both local and general antibiotic treatments. This condition is known as pyometra and is characterised by the absence of annual cyclic activity and the presence of a persistent corpus luteum. The condition can be successfully treated by inducing the regression of the corpus luteum. If necessary, the treatment may be repeated after 10-14 days.

Controlled breeding:

A treatment consisting of two injections of the product at 11 days interval is highly effective for oestrus synchronization in healthy cycling cows. Two artificial inseminations at 72 and 96 hours after the second injection, involve a normal fertility rate. For economic reasons, if only one insemination is performed, this must be done after 72-84 hours but this may involve fewer pregnancies. Of cause, such protocol can vary. For example, it is possible to inseminate all animals in heat after the first injection and limit the second treatment, to the cows in which the first had no effect.

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

At x5 to x10 overdose the most frequent side effect is increased rectal temperature. This is usually transient, however, and not detrimental to the animal. Limited salivation may also be observed in some animals.
Five animals treated with 40 mg cloprostenol (80 times the therapeutic dose) showed only slight symptoms of restlessness: two animals presented a slight sialorrhea and only one had diarrhoea.
These symptoms were moderate and were observed only after careful clinical examination. They disappeared definitively within 8 hours of administration.
One animal treated with 100 mg cloprostenol (200 times the therapeutic dose) by intramuscular injection showed only a slight form of transient diarrhoea, confirming that the drug presents a high safety margin.
In case of signs, a symptomatic treatment is recommended.

4.11 Withdrawal period(s):

Cattle
Meat : 1 day
Milk : zero hours

5. PHARMACOLOGICAL PROPERTIES

ATCvet Code: QG02AD90
Pharmacotherapeutic Group: prostaglandins and synthetic analogue.

Cloprostenol is a synthetic prostaglandin analogue structurally related to Prostaglandin F2α (PGF2α), for use in cattle and horses. As a potent luteolytic agent it causes functional and morphological regression of the corpus luteum (luteolysis) in cattle and horses followed by return to oestrus and normal ovulation.

Note: There is a refractory period of four to five days after ovulation when cattle and horses are insensitive to the luteolytic effect of prostaglandins. Cloprostenol has a good safety margin and does not impair fertility. No deleterious effects have been reported on the progeny conceived at the oestrus following treatment.

5.1 Pharmacodynamic properties

Cloprostenol is a synthetic prostaglandin analogue structurally related to Prostaglandin F2α (PGF2α). As a potent luteolytic agent, at dosage of only 500 micrograms, it causes functional and morphological regression of the corpus luteum (luteolysis) followed by return to oestrus and normal ovulation.
Corpus luteum regression is followed by a completely normal heat, from 2 to 4 days after administration in cows. No harmful effect has been shown on induced foetuses.

Pharmacological studies have shown that cloprostenol sodium is able to interrupt the pregnancy in rats, hamster and guinea pigs. The drug has no androgenic, estrogenic and anti-progestogen action, so its action is exclusively attributed to its luteolytic properties.
The molecule is more active when administered subcutaneously and in the most sensitive species, the pregnant hamster, it induces abortion with a dose of 1.25 mg/kg, compared to the dose of 25 mg/kg required by oral administration.
Cloprostenol sodium also induces abortion in pregnant animals with a mechanism still unknown.
At pharmacologically active doses, cloprostenol sodium does not induce symptoms of malaise in treated animals. Young rats, treated with a dose of 50 times the effective dose, presented signs of diarrhoea (adverse effects also observed in some monkeys under treatment).
Unlike other molecules similar to prostaglandins, cloprostenol sodium does not exert any thrombin-type action A2 and also does not cause platelet aggregation. Although the risk of infection at injection site caused by anaerobic bacteria may be increased due to the antithrombotic activity of some prostaglandin-similar molecules, the risk to be expected with cloprostenol sodium is that normally linked to any parenteral administration.

5.2 Pharmacokinetic particulars

Studies of metabolism, using 15-14C-cloprostenol sodium, were conducted in swine and cattle (following I.M. administration) to determine residual levels. Studies have also been conducted in rats after subcutaneous administration.
The kinetic studies of cloprostenol sodium orally have not been conducted (route not relevant).
The drug's kinetic studies, conducted in both domestic animals and laboratory species, indicate that cloprostenol sodium is rapidly absorbed from the injection site. It is then metabolised and finally excreted practically similarly between urine and stool. In cattle and pigs the majority of the administered dose is excreted within 0-4 hours after injection and in practice the whole compound is excreted and metabolised within 24 hours.
The main pathway of metabolization in all animal species appears to be that of β-oxidation with formation of the tetranor or dinor acids of cloprostenol.
The values at the peak of radioactivity in the blood are observed within 1 hour of parenteral administration of sodium cloprostenol and tend to decrease with a $T_{1/2}$ between 1 and 3 hours (depending on the animal species).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (E1519)
Sodium citrate
Citric acid anhydrous
Sodium chloride
Water for injections

6.2 Incompatibilities

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

6.3 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.

6.4 Special precautions for storage

Do not store above 25°C.
Keep vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

10 ml and 20 ml Type I colourless glass vials sealed with bromo-butyl rubber stoppers closed by aluminium flip-off caps.
Boxes with one 10 or 20ml vial.
Boxes with 10 x 20ml vials

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 if appropriate

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

7. MARKETING AUTHORISATION HOLDER

Ceva Animal Health Ltd
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8. MARKETING AUTHORISATION NUMBER

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21 September 2020

10. DATE OF REVISION OF THE TEXT

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