PARTICULARS TO APPEAR ON THE OUTER AND IMMEDIATE PACKAGE {NATURE/TYPE}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

estroPLAN injection, (250 mg/ml)

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Active Constituent

Cloprostenol sodium equivalent to 250 micrograms/ml cloprostenol

Preservative: Chlorocresol 1 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

20 ml

5. TARGET SPECIES

Cattle and horses

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Cattle: Single or repeated 2ml doses by intramuscular injection.

Horses: Ponies and Donkeys: single dose of 0.5 - 1 ml by intramuscular injection.

Thoroughbreds, hunters and heavy horses: 1 - 2 ml by intramuscular injection.

8. WITHDRAWAL PERIOD

Cattle

Meat: 24 hours

Milk: Zero hours

Horses

Not to be used in horses intended for human consumption. Treated horses may never be slaughtered for human consumption. The horse must have been declared as not intended for human consumption under national horse passport legislation.

9. SPECIAL WARNING(S), IF NECESSARY

Do not administer to pregnant animals if abortion is not the objective.

USER WARNINGS: Prostaglandins of the F2α type can be absorbed through the skin and may cause bronchospasm or miscarriage. See package leaflet for full user warnings

10. EXPIRY DATE

11. SPECIAL STORAGE CONDITIONS

Keep the container in the outer carton.

Do not store above 25°C. Protect from light.

Following withdrawal of the first dose, use the product within 28 days. Discard unused material.

12. SPECIFIC 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 *[Distribution category]*

POM-V

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

Parnell Technologies (UK) Ltd
Belmont House
Shrewsbury Business Park
Shrewsbury
Shropshire
SY2 6LG

16. MARKETING AUTHORISATION NUMBER(S)

Vm 18731/4000

17. MANUFACTURER'S BATCH NUMBER

MINIMUM PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING UNITS {NATURE/TYPE}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

estroPLAN injection, (250 mg/ml)

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Active Constituents

Cloprostenol sodium equivalent to 250 micrograms/ml cloprostenol

Preservative: Chlorocresol 1 mg/ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

20 ml

4. ROUTE(S) OF ADMINISTRATION

For intramuscular injection

5. WITHDRAWAL PERIOD

Cattle

Meat: 24 hours

Milk: Zero hours

Horses

Not to be used in horses intended for human consumption. Treated horses may never be slaughtered for human consumption. The horse must have been declared as not intended for human consumption under national horse passport legislation.

6. BATCH NUMBER

7. EXPIRY DATE

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only

USER WARNINGS: Prostaglandins of the F2α type can be absorbed through the skin and may cause bronchospasm or miscarriage. See package leaflet for full user warnings

POM – V To be supplied only on veterinary prescription

Keep out of reach of children. Do not store above 25°C. Protect from light. Keep container in the outer carton.

Following withdrawal of the first dose, use the product within 28 days. Discard unused material.

PACKAGE LEAFLET FOR:

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

Parnell Technologies (UK) Ltd
Belmont House
Shrewsbury Business Park
Shrewsbury
Shropshire
SY2 6LG

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

estroPLAN injection, (250 μg/ml)

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

Active Constituents

Cloprostenol sodium equivalent to 250 micrograms/ml cloprostenol

Preservative: Chlorocresol 1 mg/ml

4. INDICATION(S)

COWS

Suboestrus (or non-detected oestrus)
After diagnosing the presence of a corpus luteum - by rectal palpation - treat with estroPLAN and inseminate those animals showing heat. Those animals which do not show heat are re-examined 11 days later and may receive a second injection of estroPLAN and be bred at oestrus or at fixed times; once at 72 - 84 hours or twice at 72 and 96 hours.

Induction of parturition
estroPLAN induces parturition in the period around normal term. Induction should take place as close to the predicted calving date as possible and not more than 10 days before. Induction should not be attempted before day 270 of gestation measured from the confirmed day of conception, except in pathological conditions. All treated animals must receive adequate supervision. In common with other methods of shortening the gestation period a higher than usual incidence of retention of the foetal membranes is to be expected.

Termination of normal pregnancy

Normal pregnancy can be terminated in cattle from one week after conception until the 150th day of gestation. Best results are obtained during the first 100

days. Treated animals should be kept under observation until expulsion of the foetus and placenta is complete.

Termination of abnormal pregnancy

Mummified Foetus: Induction of luteolysis at any stage of pregnancy will usually result in the expulsion of the mummified foetus from the uterus into the vagina from which manual removal may be necessary. Normal cyclical activity should then follow.

Hydrops of the foetal membrane: Pathological accumulation of placental fluids can cause severe physiological complications and death. Surgical drainage is not usually successful in alleviating the condition. In such cases, a single dose of estroPLAN may be used to induce parturition.

Chronic endometritis (pyometra)
Treat with a single dose of estroPLAN. In long-standing cases treatment may be repeated after 10 - 14 days.

Ovarian luteal cysts

Where cystic ovaries associated with persistent luteal tissue and absence of heat are diagnosed, estroPLAN has proved to be effective in correcting the condition and bringing about a return to cyclicity.

Other Indications

Controlled breeding
Examples of programmes which have been used are:

i. A single treatment of cattle with palpable evidence of a corpus luteum, followed by breeding on detection of the subsequent oestrus.

ii. Detection of oestrus for 6 days, breeding those animals seen in heat; a single treatment is given to all non-served animals on the 6th day and these cattle are bred at subsequent oestrus.

iii. Two injections 11 days apart, breeding at oestrus or at fixed times (see below).

iv. As iii. above, but breeding any animals showing oestrus before the second injection. Thus the second dose of estroPLAN is given only to those cattle not seen in oestrus during that time and is followed by breeding either on signs of oestrus or at fixed times (see below).

Cattle which respond to a single prostaglandin injection will normally do so within 6 days of treatment. The response time after two injections is more rapid. Animals may be inseminated on detection of oestrus in any of the estroPLAN programmes. However, fixed time insemination should only be used following the second of a two injection programme (ie. examples iii. and iv.). In the latter case insemination should be performed either once at 72 - 84 hours or twice at 72 and 96 hours after the second injection, as preferred.

Double 'fixed-time' insemination may give superior results to a single insemination. However, economic factors in the particular herd may outweigh such a benefit.

For successful treatment, animals should be cycling normally. Rectal examination before treatment should avoid the disappointment of treating non-cycling (anoestrous) or pregnant animals.

Attention should be directed to the diet and condition of the treated animals. Sudden changes in feeding levels, in feed constituents and in housing, etc should be avoided around the time of the breeding programme, as should any other factor, such as regrouping, which could reasonably be expected to lead to stress.

If artificial insemination is to be used, the quality of semen and insemination technique should be assured beforehand.

A recommended guideline for use of estroPLAN in dairy cows is as follows:

After the first injection of estroPLAN, inseminate any cows showing signs of heat. Animals that do not show signs of heat should be injected 11 days after the first injection and then inseminated 72 - 96 hours later.

Control of the oestrous cycle is of value in:

1. The dairy herd:

    a. To control oestrus in the individual animal giving better control of the individual calving index and reducing the number of cows culled as barren

    b. To control oestrus in groups of cows to promote management of the herd in groups of suitable size and facilitate the maintenance of a seasonal calving pattern

    c. To permit the use of artificial insemination (AI) in dairy heifers

2. The beef herd:

    a. To facilitate the use of AI to obtain better progeny by use of high quality bulls

    b. To enable the most effective use of available bulls where natural service is preferred

    c. To permit better herd management at conception and calving

<u>Requirements for controlled breeding programs</u>

A variety of programs can be designed to best meet he needs of individual management systems. A controlled breeding program should be selected which is appropriate for the existing circumstances and management practices.

Before a controlled breeding program is planned the producer's objectives must be examined and he must be made aware of the projected results and limitations. The producer and his consulting veterinarian should review the operations breeding history, herd health and nutritional status and agree that a controlled breeding program is practical in the producer's specific situation.

To achieve good results with planned mating programs, several key factors must be given adequate consideration.

1. A high proportion of cows in the herd need to be cycling normally, as PGs are only effective in cows with mature corpus lutera. This may not be the case in herds in which there are many first calvers, late calvers or cows in poor condition.
2. Cows must be in a fit and healthy breeding condition and on an adequate and increasing plane of nutrition.
3. Proper program planning and record keeping are essential
4. Oestrus detection needs to be of a high standard
5. If artificial insemination is being used, a competent technician using high quality semen must perform insemination

Provision must be made to supervise the calving of a large number of cattle over a short period of time.

Mares

Induction of luteolysis following early foetal death and resorption

About 8 - 10 % of all mares which conceive lose the conceptus during the first 100 days of pregnancy. Persistence of luteal function in the ovary precludes an early return to oestrus.

Termination of persistent dioestrus

Non-pregnant mares frequently and spontaneously go into and out of periods of prolonged dioestrus. A very high proportion of mares in this category ie. not cycling, are in prolonged dioestrus rather than anoestrus, particularly in the latter part of the breeding season.

Termination of pseudopregnancy

Some mares which are covered at normal oestrus and subsequently found to be empty (but not having lost or resorbed a conceptus) display clinical signs of pregnancy. These animals are said to be 'pseudopregnant'.

Treatment of lactation anoestrus

Failure of lactating mares to cycle again for several months after exhibiting an early 'foal heat' can be avoided.

Establishing oestrous cycles in barren/maiden mares

Some maiden or barren mares may be found, on examination, to have a functional corpus luteum and are suffering from abnormal persistence of luteal

function or are simply failing to exhibit normal oestrus. Suboestrus has a higher incidence in maiden mares early in the breeding season. Treatment with estroPLAN enables prediction of the time of onset of oestrus, allowing optimum utilisation of teasing and stallion resources.

As an aid in stud management
Mares may be brought into oestrus on a planned timing schedule (singly or in groups), to facilitate more efficient use and management of stallions during the breeding season.

5. CONTRAINDICATIONS

6. ADVERSE REACTIONS

On rare occasions, severe life-threatening local bacterial infections may occur associated with clostridial proliferation at the injection site. 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.

Cattle

Increased body temperature and salivary secretion have been reported, usually associated with the administration of 5 - 10 times the recommended dose.

Horses

Sweating, increased respiratory and heart rates, ataxia, watery diarrhoea and signs of mild abdominal pain have been observed. Such reactions have usually resulted from doses in excess of that recommended, and are generally mild and transient.

7. TARGET SPECIES

Cattle and horses

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

Cattle: Single or repeated 2ml doses by intramuscular injection.

Horses: Ponies and Donkeys: single dose of 0.5 - 1 ml by intramuscular injection.

Thoroughbreds, hunters and heavy horses: 1 - 2 ml by intramuscular injection.

9. ADVICE ON CORRECT ADMINISTRATION

Do not administer to pregnant animals unless abortion is the objective.

Do not administer intravenously

As with all parenteral products, careful aseptic techniques should be employed to decrease the possibility of post injection bacterial infection. Antibiotic therapy should be employed at the first sign of infection.

10. WITHDRAWAL PERIOD(S)

Cattle

Meat: 24 hours

Milk: Zero hours

Horses

Not to be used in horses intended for human consumption. Treated horses may never be slaughtered for human consumption. The horse must have been declared as not intended for human consumption under national horse passport legislation.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of reach of children. Do not store above 25°C. Protect from light. Keep container in the outer carton

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 container should be discarded should be determined. This discard date should be written in the space provided. Following withdrawal of the first dose, use the product within 28 days. Discard unused material.

12. SPECIAL WARNING(S)

Prostaglandins of the F2α type 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.

Women of child-bearing age, asthmatics and persons with bronchial or other respiratory problems should avoid contact with, or wear disposable plastic gloves when administering the product.

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

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

Wash hands after use.

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.

For Animal Treatment Only

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

Discard unused material. Dispose of any unused product and empty containers in accordance with guidance from your local waste regulation authority.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

POM –V To be supplied only on veterinary prescription

Vm 18731/4000

PHARMACOLOGY

Cloprostenol is a synthetic prostaglandin analogue structurally related to Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), 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.

All indications for use of estroPLAN are essentially a physiological function of the luteolytic activity of chloprostenol.

In non-pregnant cycling cattle luteolysis is usually followed by ovarian follicular development and a return to oestrus with normal ovulation in 2 - 5 days following treatment. The early corpus luteum is insensitive to the effects of PG: in cattle this refractory period spans the forst 4-5 days post ovulation. In animals with prolonged luteal function (pyometra, mummified foetus and luteal cysts) the induced luteolysis usually results in resolution of the condition and return to cyclicity. Pregnant animals may abort depending on the stage of gestation.

Cloprostenol causes regression of the corpus luteum in mares except during the refractory period spanning the first 4-5 days after ovulation. Oestrus commences 2-5 days following estroPLAN administration, with normal ovulation occurring 8-12 days after treatment. Conception rates at the induced oestrus are normal, and there are no deleterious effects on foals born as result of cycle manipulation.

PHARMACOKINETICS

After its administration by injection, cloprostenol is metabolised to 9, 11, dihydroxy-15-cetoprost-5-enoic acid and 9, 11, 15-trihydroxyprost-5-enoic acid which rapidly disappears from the blood, being excreted via the urine in 5 - 6 hours.

Radiolabelled studies show blood levels between 0.0014 and 0.002 mg per ml at 20 minutes - 2 hours after its administration. Subsequently, blood levels fall rapidly, having an apparent half life of 1 - 3 hours, falling below 0.00004 mg/ml at 8 hours. No significant concentrations are found at 24 hours in the liver, muscle, heart, kidneys, uterus, ovaries, skin, brain and fat, nor in milk after 4 hours.

Approved: 10/01/2018