SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

estroPLAN injection, (250 μg/ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Constituents

Cloprostenol sodium equivalent to 250 micrograms/ml cloprostenol

Other Constituents

Sodium Chloride,
Sodium Citrate Dihydrate,
Citric Acid,
Chlorocresol,
Sodium Hydroxide
Water for Injections

3. PHARMACEUTICAL FORM

A colourless, buffered, sterile aqueous solution for injection.

4. CLINICAL PARTICULARS

4.1. Target Species

Cattle
Horses

4.2. Indications for Use

Cattle

Suboestrus or non-detected oestrus
Induction of parturition
Termination of normal pregnancy
Termination of abnormal pregnancy: mummified foetushydrops of the foetal membranes
Chronic endometritis (pyometra)
Ovarian luteal cysts
Controlled breeding

Horses

Induction of luteolysis following early foetal death and resorption
Termination of persistent dioestrus
Termination of pseudopregnancy
Treatment of lactation anoestrus
Establishing oestrous cycles in barren/maiden mares
As an aid to stud management

4.3. Contraindications

None.

4.4. Special warnings for each target species

On rare occasions, severe life-threatening local bacterial infections may occur associated with clostridial proliferation at the injection site. It is important to keep treated animals under observation and if such infection occurs, aggressive antibiotic therapy, particularly covering clostridial species should be employed as a matter of urgency. Careful aseptic techniques should be employed to decrease the possibility of these infections.

4.5. Special Precautions for Use

(i) Special precautions for use in animals.

Do not administer intravenously.

Due to the possibility of post-injection bacterial infections, careful aseptic techniques should be employed.

(ii) Special precautions to be taken by the person administering the medicinal product to animals.

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

4.6. Adverse Reactions

On rare occasions, severe life-threatening local bacterial infections may occur associated with clostridial proliferation at the injection site.
Occasional side effects have been observed following intramuscular administration of PG. Such effects are generally transient and have little detrimental effect on the animal.

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.

4.7. Use During Pregnancy, Lactation and 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

None described.

4.9. Amounts to be Administered and Administration Route

Cattle

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

Therapeutic Indications

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

Horses
Ponies and Donkeys: single dose of 0.5 - 1 ml (equivalent to 125 - 250 μg cloprostenol) by intramuscular injection.
Thoroughbreds, hunters and heavy horses: 1 - 2 ml (equivalent to 250 - 500 μg cloprostenol) by intramuscular injection.

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.

4.10. Overdose

Cattle

At 5 to 10 times 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. Experimental administration of 50 - 100 times the recommended dose to cattle resulted in signs of uneasiness, salivation and milk let-down, but no other adverse effects.

Horses

Various side effects have usually resulted from doses in excess of that recommended. 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.

4.11. 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.

5. PHARMACOLOGICAL PROPERTIES

Active substance: Cloprostenol
ATC vet code: QG02AD90

5.1. Pharmacodynamic Properties

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.

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. In horses oestrus commences 2 - 5 days following treatment with cloprostenol, with normal ovulation occurring 8 - 12 days after treatment.

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. estroPLAN 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.

5.2. Pharmacokinetic Properties

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 μg 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 μg/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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sodium Chloride,
Sodium Citrate Dihydrate,
Citric Acid,
Chlorocresol,
Sodium Hydroxide
Water for Injections

6.2. Major Incompatibilities

Strong acid / alkaline products

6.3. Shelf-Life

Unbroached vial:	3 years
Broached vial:	Following withdrawal of the first dose, use the product within 28 days. Discard unused material.

6.4. Special Precautions for Storage

Do not store above 25°C. Protect from light.
Keep out of reach of children.

6.5. Nature and Contents of Immediate Packaging

Clear glass vial (Type I), with chlorobutyl rubber stopper and aluminium tear off cap. containing 20ml of solution.

6.6. Special Precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products, if appropriate.

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

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8. Marketing Authorisation Number

Vm 18731/4000

9. Date of Renewal of the Authorisation

August 2006

10. Date of Revision of Text

January 2009