Parnell® Fertility Suite

GONAbreed® (gonadorelin acetate)

Time-Tested, Proven Fertility Hormone

- The highest concentration of gonadorelin available (100mcg/mL)
- GONAbreed contains gonadorelin acetate, which has demonstrated superior ovulation and pregnancy outcomes when compared to gonadorelin hydrochloride[1]
- Provides more doses per vial, for fewer vial switch-outs
- Available in 20 mL vial (20 doses) and 100 mL vial (100 doses)

GONAbreed is a high concentration 1mL dose.

estroPLAN® (cloprostenol sodium)

The Tried and True Prostaglandin

- estroPLAN is FDA-approved for use to induce luteolysis in dairy cattle to manipulate the estrous cycle
- estroPLAN, as part of the Parnell PROcept™ Protocol, is the only PGF2α proven to increase pregnancies by a relative 14% in cows in second and third lactation[2]
- Contains cloprostenol sodium (250mcg/mL)
- Available in 20 mL vial (10 doses) and 100 mL vial (50 doses)

estroPLAN is a convenient 2mL dose.

Please contact your Parnell Territory Manager or Distribution Sales Representative for Additional Information.

References: 1. Souza AH, Cunha AP, Silva EPB, et al. (2009). Comparison of gonadorelin products in lactating dairy cows; Efficiency based on induction of ovulation of an of an accessory follicle and circulator luteinizing hormone profiles. *Theriogeniology*. 2009;72(2):271-279. **2.** Wiltbank M, Baez G., Cochrane F, Barletta R, Trayford C, Joseph R. Effect of second treatment with prostaglandin F22 during the Ovsynch protocol on luteolysis and pregnancy in dairy cows. *J Dairy Sci*. 2015;98:8644-8654.

PRECAUTIONS: FOR ANIMAL USE ONLY, NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. Women of child-bearing age, asthmatics and persons with bronchial and other respiratory problems should exercise extreme caution when handling this product. In the early stages, women may be unaware of their pregnancies. estroPLAN is readily absorbed through the skin and may cause abortion and/or bronchospasms. Direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

Distributed by: Parnell U.S. 1, Inc. 7015 College Blvd., Level 6, Overland Park, KS 66211.
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MKT-18-001 PA US

PARNELL®
living SCIENCE

ANADA 200-541. Approved by FDA

GONAbreed®
(gonadorelin acetate)

Equivalent to 100 mcg gonadorelin/mL
Sterile solution

For the treatment of cystic ovaries in dairy cattle.

For use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows.

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

GONAbreed is a sterile solution containing 100 micrograms of gonadorelin (GnRH) as gonadorelin acetate per milliliter suitable for intramuscular or intravenous administration according to the indication. Gonadorelin is a decapeptide composed of the sequence of amino acids –

5-oxoPro-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 -

a molecular weight of 1182.32 and empirical formula $C_{55}H_{75}N_{17}O_{13}$. The acetate salt has a molecular weight of 60.05 and an empirical formula $C_{55}H_{75}N_{17}O_{13}.C_2H_4O_2$.

Gonadorelin is the hypothalamic releasing factor responsible for the release of gonadotropins (e.g., LH, FSH) from the anterior pituitary. Synthetic gonadorelin is physiologically and chemically identical to the endogenous bovine hypothalamic releasing factor.

PHARMACOLOGY AND TOXICOLOGY:

Endogenous gonadorelin is synthesized and/or released from the hypothalamus during various stages of the bovine estrous cycle following appropriate neurogenic stimuli. It passes via the hypophyseal portal vessels, to the anterior pituitary to effect the release of gonadotrophins (e.g. LH, FSH). Synthetic gonadorelin administered intravenously or intramuscularly also causes the release of endogenous LH or FSH from the anterior pituitary.

Gonadorelin acetate has been shown to be safe. The LD_{50} for mice and rats is greater than 60 mg/kg, and for dogs, greater than 600 mcg/kg, respectively. No untoward effects were noted among rats or dogs administered 120 mcg/kg/day or 72 mcg/kg/day intravenously for 15 days.

It has no adverse effects on heart rate, blood pressure, or EKG to unanesthetized dogs at 60 mcg/kg. In anesthetized dogs it did not produce depression of myocardial or system hemodynamics or adversely affect coronary oxygen supply or myocardial oxygen requirements.

The intravenous administration of 60 mcg/kg/day of gonadorelin acetate to pregnant rats and rabbits during organogenesis did not cause embryotoxic or teratogenic effects.

The intramuscular administration of 1,000 mcg to normally cycling dairy cattle had no effect on hematology or blood chemistry.

Further, gonadorelin acetate does not cause irritation at the site of intramuscular administration in dogs. The dosage administered was 72 mcg/kg/day for seven (7) days.

INDICATIONS AND DOSAGE:

Cystic Ovaries

GONAbreed is indicated for the treatment of ovarian follicular cysts in dairy cattle. Ovarian cysts are non-ovulated follicles with incomplete luteinization which result in nymphomania or irregular estrus.

Historically, cystic ovaries have responded to an exogenous source of luteinizing hormone (LH) such as human chorionic gonadotrophin. GONAbreed initiates release of endogenous LH to cause ovulation and luteinization

The recommended intravenous or intramuscular dosage of GONAbreed is 100 mcg (1 mL) per cow.

Reproductive Synchrony

GONAbreed is indicated for use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows.

The recommended intramuscular dosage of GONAbreed is 100 mcg (1 mL) per cow, used in reproductive synchrony programs similar to the following:

Administer the first GONAbreed injection (1 mL) at Time 0. Administer 500 mcg cloprostenol (as cloprostenol sodium) by intramuscular injection 6 to 8 days after the first GONAbreed injection.
Administer the second GONAbreed injection (1 mL) 30 to 72 hours after the cloprostenol sodium injection.
Perform FTAI 0 to 24 hours after the second GONAbreed injection, or inseminate cows on detected estrus using standard herd practices.

TARGET ANIMAL SAFETY:

In addition to the target animal safety information presented in the section addressing pharmacology and toxicology, target animal safety of, and injection site reactions to, GONAbreed when used with cloprostenol sodium were evaluated during the conduct of the effectiveness field studies. The incidence of health abnormalities was not significanty greater in cows administered GONAbreed than cows administered a placebo injection.

EFFECTIVENESS:

The effectiveness of GONAbreed (gonadorelin acetate) for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in lactating dairy cows was demonstrated in a field study at 10 different locations in the U.S. Four of the locations represented conditions that would typically cause heat stress in lactating cows. A total of 1607 healthy, non-pregnant, primiparous or multiparous lactating dairy cows within 40-150 days postpartum were enrolled in the study. A total of 805 cows were administered GONAbreed (1 mL; 100 mcg gonadorelin as the acetate salt) and 802 cows were administered an equivalent volume of water for injection as an intramuscular injection twice in the following regimen:

Day 0: 1 mL GONAbreed or sterile water for injection
Day 7: 500 mcg cloprostenol (as cloprostenol sodium)
Day 9: 1 mL GONAbreed or sterile water for injection

Fixed time AI was performed on Day 10, approximately 11 - 31 hours after the Day 9 injection. Cows were evaluated for pregnancy on Day 45 ± 5 days by trans-rectal ultrasound or rectal palpation. Pregnancy rate to FTAI was significantly higher ($P < 0.0001$) in cows treated with GONAbreed (33.4%) than the pregnancy rate to FTAI in cows treated with water (13.6%). The environmental condition (heat stress or not heat stress) did not affect the conclusion of effectiveness.

The effectiveness of GONAbreed (gonadorelin acetate) for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in beef cows was demonstrated in a field study at 10 different locations in the U.S. A total of 706 healthy, non-pregnant, primiparous or multiparous beef cows within 40-150 days postpartum were enrolled in the study. A total of 364 cows were administered GONAbreed (1 mL; 100 mcg gonadorelin as the acetate salt) and 342 cows were administered an equivalent volume of water for injection as an intramuscular injection twice in the following regimen:

Day 0: 1 mL GONAbreed or sterile water for injection
Day 7: 500 mcg cloprostenol (as cloprostenol sodium)
Day 9: 1 mL GONAbreed or sterile water for injection

Fixed time AI was performed immediately after the Day 9 injection. Cows were evaluated for pregnancy on Day 55 ± 5 days by trans-rectal ultrasound. Pregnancy rate to FTAI was significantly higher ($P = 0.0006$) in rows treated with GONAbreed (21.7%) than the pregnancy rate to FTAI in cows treated with water (7.4%).

Each mL of GONAbreed contains:
Gonadorelin (as gonadorelin acetate) 100 mcg
Benzyl alcohol 10 mg
Sodium chloride 7.47 mg
Sodium phosphate monobasic 8.3 mg
Sodium phosphate dibasic 4.8 rrg
Water for injection, USP, q.s.
pH adjusted with hydrochloric acid or sodium hydroxide

PRECAUTIONS:

Not for use in humans.
Keep this and all drugs out of reach of children.

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To obtain an MSDS or for technical assistance, contact Parnell at 1-800-88-PARNELL (1-800-887-2763). To report suspected adverse drug experiences, contact Parnell at 1-800-88-PARNELL (1-800-887-2763). For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or http://www.fda.gov/AnimalVeterinary.

Discard remaining product 180 days after first use. Once broached, product may be stored at temperatures up to 25°C (77°F)

KEEP UNOPENED VIALS REFRIGERATED:
2° - 8°C (36° - 46°F).

HOW SUPPLIED:

GONAbreed is available in a concentration of 100 mcg gonadorelin/mL as gonadorelin acetate.
GONAbreed is supplied in multidose vials containing 20 ml and 100 mL of sterile solution.

Manufactured by:
PARNELL TECHNOLOGIES PTY. LTD.
4/476 Gardeners Road
Alexandria NSW 2015 Australia
Owner of the trademark GONAbreed

Distributed by:
PARNELL U.S. 1, Inc.
7015 College Boulevard, Level 6
Overland Park, KS 66211

ANADA 200-541. Approved by FDA

20 mL: 50297b-05-November 14
100 mL: 50303b-03-November 14

ANADA 200-310, Approved by FDA estroPLAN

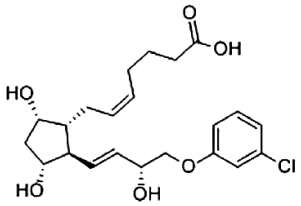
estroPLAN®
(cloprostenol sodium)

Prostaglandin Analogue For Cattle
Equivalent to 250 mcg cloprostenol/mL

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

estroPLAN (cloprostenol sodium) is a synthetic prostaglandin analogue structurally related to prostaglandin F2 α (PGF2 α). Each mL of the colorless aqueous solution contains 263 mcg of cloprostenol sodium (equivalent to 250 mcg of cloprostenol), chlorocresol 1.0 mg as a bactericide, citric acid anhydrous 0.66 mg, sodium citrate 5.03 mg, sodium chloride 6.76 mg. The pH is adjusted, as necessary, with sodium hydroxide or citric acid.



ACTION:

estroPLAN causes functional and morphological regression of the corpus luteum (luteolysis) in cattle. In normal, nonpregnant cycling animals this effect on the life span of the corpus luteum usually results in estrus 2 to 5 days after treatment. In animals with prolonged luteal function (pyometra, mummified fetus, 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.

INDICATIONS:

For intramuscular use to induce luteolysis in beef and dairy cattle. The luteolytic action of estroPLAN can be utilized to manipulate the estrous cycle to better fit certain management practices, to terminate pregnancies resulting from mismatings, and to treat certain conditions associated with prolonged luteal function.

RECOMMENDED USES:

Unobserved or Non-detected Estrus

Cows which are not detected in estrus, although ovarian cyclicity continues, can be treated with estroPLAN if a mature corpus luteum is present. Estrus is expected to occur 2 to 5 days following injection, at which time animals may be inseminated. Treated cattle should be inseminated at the usual time following detection of estrus. If estrus detection is not desirable or possible, treated animals may be inseminated twice at about 72 and 96 hours postinjection.

Pyometra Or Chronic Endometritis

Damage to the reproductive tract at calving or postpartum retention of the placenta often leads to infection and inflammation of the uterus (endometritis). Under certain circumstances, this may progress into chronic endometritis with the uterus becoming distended with purulent matter. This condition, commonly referred to as pyometra, is characterized by a lack of cyclical estrus behavior and the presence of a persistent corpus luteum. Induction of luteolysis with estroPLAN usually results in evacuation of the uterus and a return to normal cyclical activity within 14 days after treatment. After 14 days post treatment, recovery rate of treated animals will not be different than that of untreated cattle.

Mummified Fetus

Death of the conceptus during gestation may be followed by its degeneration and dehydration. Induction of luteolysis with estroPLAN usually results in expulsion of the mummified fetus from the uterus. (Manual assistance may be necessary to remove the fetus from the vagina.) Normal cyclical activity usually follows.

Luteal Cysts

A cow may be noncyclic due to the presence of a luteal cyst (a single, anovulatory follicle with a thickened wall which is accompanied by no external signs and by no changes in palpable consistency of the uterus). Treatment with estroPLAN can restore normal ovarian activity by causing regression of the luteal cyst.

Pregnancies From Mismating

Unwanted pregnancies can be safely and efficiently terminated from 1 week after mating until about 5 months of gestation. The induced abortion is normally uncomplicated and the fetus and placenta are usually expelled about 4 to 5 days after the injection with the reproductive tract returning to normal soon after the abortion. The ability of estroPLAN to induce abortion decreases beyond the fifth month of gestation while the risk of dystocia and its consequences increases. estroPLAN has not been sufficiently tested under feedlot conditions; therefore recommendations cannot be made for its use in heifers placed in feedlots.

Controlled Breeding

The luteolytic action of estroPLAN can be utilized to schedule estrus and ovulation for an individual cycling animal or a group of animals. This allows control of the time at which cycling cows or heifers can be bred. estroPLAN can be incorporated into a controlled breeding program by the following methods:

1. Single estroPLAN

Injection Only animals with a mature corpus luteum should be treated to obtain maximum response to the single injection. However, not all cycling cattle should be treated since a mature corpus luteum is present for only 11 to 12 days of the 21-day cycle.

Prior to treatment, cattle should be examined rectally and found to be anatomically normal, be non-pregnant and have a mature corpus luteum. If these criteria are met, estrus is expected to occur 2 to 5 days following injection, at which time animals may be inseminated. Treated cattle should be inseminated at the usual time following detection of estrus. If estrus detection is not desirable or possible, treated animals may be inseminated either once at about 72 hours or twice at about 72 and 96 hours postinjection.

With a single injection program, it may be desirable to assess the cyclicity status of the herd before estroPLAN treatment. This can be accomplished by heat detecting and breeding at the usual time following detection of estrus for a 6-day period, all prior to injection. If by the sixth day the cyclicity status appears normal (approximately 25 - 30% detected in estrus), all cattle not already inseminated should be palpated for normality, non-pregnancy, and cyclicity, then injected with estroPLAN. Breeding should then be continued at the usual time following signs of estrus on the seventh and eighth day.

On the ninth and tenth day breeding may continue at the usual time following detection of estrus or all cattle not already inseminated may be bred either once on the ninth day (at about 72 hours post injection) or on both the ninth and tenth day (at about 72 and 96 hours postinjection).

2. Double estroPLAN Injections

Prior to treatment, cattle should be examined rectally and found to be anatomically normal, non-pregnant, and cycling (the presence of a mature corpus luteum is not necessary when the first injection of a double injection regimen is given). A second injection should be given 11 days after the first injection. In normal, cycling cattle, estrus is expected 2 to 5 days following the second injection. Treated cattle should be inseminated at the usual time following detection of estrus. If estrus detection is not desirable or possible, treated animals may be inseminated either once at about 72 hours or twice at about 72 and 96 hours following the second estroPLAN injection.

Many animals will come into estrus following the first injection; these animals can be inseminated at the usual time following detected estrus. Animals not inseminated should receive a second injection 11 days after the first injection. Animals receiving both injections may be inseminated at the usual time following detection of estrus or may be inseminated either once at about 72 hours or twice at about 72 and 96 hours post second injection.

Any controlled breeding program recommended should be completed by either:
- Observing animals (especially during the third week after injection) and inseminating or hand mating any animals returning to estrus, or
- Turning in clean-up bull(s) 5 to 7 days after the last injection of estroPLAN to cover any animals returning to estrus.

REQUIREMENTS FOR CONTROLLED BREEDING PROGRAMS:

A variety of programs can be designed to best meet the 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 operation's breeding history, herd health and nutritional status and agree that a controlled breeding program is practical in the producer's specific situation. For any successful controlled breeding program:
- cows and heifers must be normal, nonpregnant, and cycling (rectal palpation should be performed).
- cattle must be in a fit and thrifty breeding condition and on an adequate or increasing plane of nutrition.
- proper program planning and record keeping are essential.
- if artificial insemination is used, it must be performed by competent inseminators using high quality semen.

It is important to understand that estroPLAN is effective only in animals with a mature corpus luteum (ovulation must have occurred at least 5 days prior to treatment). This must be considered when breeding is intended following a single estroPLAN injection.

SAFETY AND TOXICITY:

At 50 and 100 times the recommended dose, mild side effects may be detected in some cattle. These include increased uneasiness, slight frothing, and milk let-down.

CONTRAINDICATIONS:

estroPLAN should not be administered to a pregnant animal whose calf is not to be aborted.

WARNINGS:

For animal use only.

Women of child-bearing age, asthmatics, and persons with bronchial and other respiratory problems should exercise extreme caution when handling this product. In the early stages women may be unaware of their pregnancies.

estroPLAN injection is readily absorbed through the skin and may cause abortion and/or bronchospasms; direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

PRECAUTIONS:

There is no effect on fertility following the single or double dosage regimen when breeding occurs at induced estrus or at 72 and 96 hours post treatment. Conception rates may be lower than expected in those fixed time breeding programs which omit the second insemination (i.e. the insemination at or near 96 hours). This is especially true if a fixed time insemination is used following a single estroPLAN injection.

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

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To obtain an MSDS or for technical assistance, contact Parnell at 1-800-88-PARNELL (1-800-887-2763). To report suspected adverse drug experiences, contact Parnell at 1-800-88-PARNELL (1-800-887-2763). For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or http://www.fda.gov/AnimalVeterinary.

DOSAGE AND ADMINISTRATION:

Two mL of estroPLAN injection (500 mcg of cloprostenol) should be administered by INTRAMUSCULAR INJECTION for all indications in both beef and dairy cattle.

Discard remaining product 180 days after first use.

STORAGE CONDITIONS:

1. Protect from light.
2. Store in carton.
3. Store at controlled room temperature 20°-25°C (68°-77°F).

HOW SUPPLIED:

20 mL and 100 mL multidose vials

Made in Australia

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ANADA 200-310, Approved by FDA

20mL: 50299b-04-November 14
100mL: 50301b-03-November 14