For Veterinary Use Only,

PGS®

Solution for Injection

Hormone - Prostaglandin F2 – alpha analogue

COMPOSITION: PGS is a colorless solution for injection containing in each ml 263 µg cloprostenol sodium equivalent to 250 µg cloprostenol and 0.1 % w/v chlorocresol as bactericide.

PHARMACOLOGIC PROPERTIES: Cloprostenol is a functional analogue of prostaglandin F2 α having a specific luteolytic effect. It is a strong luteolytic agent causing functional and morphological regression of luteolysis of corpus luteum in cattle and horses. Cloprostenol shows its luteolytic effect on corpus luteum by instantly decreasing the amount of luteinizing hormone receptors (LH) in ovaries during luteinization phase of oestrus cycle, by causing a rapid decrease in progesterone levels and helping the development of vasoconstriction in utero-ovarian veins. Therefore FSH hormone release increases in anterior lobe of pituitary gland, and normal oestrus and ovulation can be achieved following the formation of a new follicle. When administered as injection in animals during luteal period of rutting, it reduces the luteal phase and helps rutting and ovulation following rapid absorption and regression of yellow corpus. It has a rutting preparatory effect in animals that do not show oestrus. It therefore acts on treatment of this condition in animals that shows no or ambiguous oestrus(suboestrus). It facilitates excretion of mummified fetus and treatment of pyometra due to regression of yellow corpus. Infected fluid accumulated in uterus undergoes resolution in 2 to 6 days. It causes contractions in uterus and therefore abort in early phases of pregnancy and initiation of parturition at the end of pregnancy. It also induces bronchoconstruction in bronchi. Serum half-life of cloprostenol in cows is 3 hours. It is not orally active. It is absorbed by vaginal mucosa. It undergoes a substantial metabolic transformation within the body. It decomposes at a rate of approximately 95% during first transition through lungs. It is excreted in urine within 5 - 6 hours.

AREA OF USE/INDICATIONS: PGS is used intramuscularly in cattle and horses.

In cattle

- ●Treatment of suboestrus (hidden or non-recognized rutting)
- ●Development of abort (undesired pregnancies)
- ●Acceleration of parturition (Termination of pregnancy)
- ●For controlled breeding
- ●Treatment of lteal cysts in ovary.
- ●Chronic endometritis, pyometra and discharge of uterus content in mummified (macerated) fetus

In horses

- ●Early fetal death and initiation of luteolysis after resorption
- ● In termination of permanent dioestrus cases
- ● Anoestrus treatment in lactating mares
- ● Treatment of pyometra and endometritis
- ● Acceleration of parturition (Termination of pregnancy)
- ● Termination of pseudopregnancy
- ● Used for controlled breeding.

USAGE AND DOSAGE

Unless recommended otherwise by veterinary surgeon,

In Cattle: Administered in a pharmacologic dose of 500 µg cloprostenol. Single or repeated doses of 2 ml are given through intramuscular injection.

In horses: It is administered with a dose of 125 - 250 µg cloprostenol in horses up to 400 kg, and 250 - 500 µg cloprostenol in horses heavier than 400 kg. **Up to 400 kg:** 0.5-1.0 ml **400 kg and more:**1.0-2.0 ml single intramuscular injection is administered.

● Area of administration should be clean and dry.

Administration in Cattle:

1. Treatment of suboestrus: This is insufficient or no indications of rutting in highly efficient cows during peak lactation periods although cycle is normal. After determination of corpus luteum through rectal palpation, PGS injection is administered in such animals and oestrus is monitored closely. Insemination is applied in the ones showing rutting. Though a single, intramuscular dose would generally be sufficient, it might be administered in some animals during refractor period and therefore such animals might not respond to treatment. In animals not showing rutting, another single injection should be administered 11-13 days after the first injection and breeding should be carried out after 72-96 hours.

Acceleration of parturition: Initiation of parturition should be carried out at a date close to estimated parturition date so as not to be 10 days before the normal date, if possible. Parturition should not be initiated before day 270 of pregnancy specified upon confirmation of insemination. Any administered animal should be monitored closely. As a general rule, possibility of remainder of fetal membranes can be expected to be more than normal during shortened pregnancy period. As a result of premature parturition, it is considered that a decrease in survival rate of new-born calves can be observed. Any animal and broods undergoing such an administration requires special care and observation.

2. Abort: Undesired pregnancies can be terminated from week 1 to day 150. Abort can be carried out rapidly and effectively before day 100 of pregnancy. If applied between day 100 and 150 of pregnancy, results would be less reliable. As the pregnancy period progresses, dependence of some cows on corpus luteum is estimated to be reduced. Abort should not be carried out after day 150 of pregnancy. As metritis may occur following abort though rarely seen, animals administered with PGS should be kept under observation until fetus and placental membranes completely fall. Abort is formed within 2-7 days after administration; a second injection should be given in case the animal did not have an abort until day 8. A second injection may be needed in twin pregnancies. Within a few days following the administration, a flow of purulent fluid and/or fetal material from vagina occurs. The animal should be kept under observation while inducing this material to be excreted. Administration can be repeated after 11-13 days. It would be useful to perform an appropriate antibacterial treatment. Insemination should not be carried out until uterus takes is normal form.

3. Termination of abnormal pregnancy:

a) Removal of mummified fetus:

Upon the death of the fetus, dehydration and degeneration begin. Initialization of luteolysis in any phase of pregnancy may result with excretion of the mummified fetus from uterus to vagina. Manual intervention through vagina may be required. After this phase, normal cycle activity in the animal continues.

b) Hydrops of fetal membranes: Pathologic accumulation of placental fluids (hydramnios or hydrallantios) may cause serious physiological complications and death. Operative drainage cannot always be successful in regression

of this condition. PGS may be used for initiating parturition in such cases by administration of a single dose.

5. Luteal cysts of ovary: In case cystic ovary is caused by permanent corpus luteum, PGS administration helps to start normal cycle activity. Accurate diagnosis is imperative in order to obtain satisfying results at the end of the therapy.

6 Chronic endometritis (Pyometra): Damage occurring during parturition in reproductive system or non-excretion of placenta in postpartum period often cause infections and inflammation in uterus. Acute or subacute endometritis occurring in a short time after parturition may generally recover with antibiotic treatment, however endometritis may continue during a few weeks postpartum under certain conditions. Uterus swells and takes a slight doughy form. It is full of inflamed drift. Such a uterus is characterized by chronic lack of oestrus cycle and permanent presence of corpus luteum in cows. This condition can be treated successfully by initiation of luteal regression. Treatment can be repeated with an interval of 10-14 days if necessary.

7. Ovarian luteal cysts: Permanent luteal tissue related to non-existence of oestrus can be diagnosed by examination of cystic ovaries. PGS is effective on correction of this condition and return to normal cycle. Accurate diagnosis is imperative in order to obtain satisfying results at the end of the therapy.

8. Controlled Artificial Insemination Programs in Cattle: Luteolytic activity of PGS can be used for control of cattle breeding model. There are several treatment regimen that facilitates selection of the most appropriate one for properties and intentions of each group or herd

1 ››››	Rutting control is carried out for 6 days and artificial insemination is applied on the ones showing rutting.	**day 6:** PGS is injected in animals that are not applied with artificial insemination.	* Depending on rutting control, artificial insemination should be applied within normal period, or * within about 72-96 hours upon injection; or * after 72 hours collectively; Artificial Insemination should be repeated for the ones showing rutting within the next 2-3 days.	
2 ››››	Rectal palpation is performed.	PGS is injected in any animal determined during rectal palpation to have corpus luteum in ovaries.	* Depending on rutting control, artificial insemination should be applied within normal period, or * within about 72-96 hours upon injection; or * after 72 hours collectively; Artificial Insemination should be repeated for the ones showing rutting within the next 2-3 days.	
3 ››››	**day 1:** PGS is injected.	**day 11:** PGS is injected.	* Depending on rutting control, artificial insemination should be applied within normal period, or * within about 72-96 hours upon injection; or * after 72 hours collectively; Artificial Insemination should be repeated for the ones showing rutting within the next 2-3 days.	
4 ››››	**day 1:** PGS is injected.	Rutting control is carried out and Artificial Insemination is applied.	**day 11:** PGS is injected in animals that are not applied with artificial insemination.	* Depending on rutting control, artificial insemination should be applied within normal period, or * within about 72-96 hours upon injection; or * after 72 hours collectively; Artificial Insemination should be repeated for the ones showing rutting within the next 2-3 days.

PGS can be used for both introducing oestrus and programming of artificial insemination season without any information on oestrus control. Recommended 4 programs are presented in the table above.

Note:

- Best results can be obtained in herds undergoing rutting determination.
- It is important to identify the animals.
- Pregnancy rate decreases by about 20% in case Artificial Insemination is carried out 72 hours after injection.

-**Dairy Type Herds** It provides better control of calving index in animals because it allows artificial insemination without oestrus determination. Accordingly, number of cows separated due to non-retention of offspring can be decreased. For cow groups separated appropriately for feeding, artificial insemination and termination of milking, more efficient dispatch and administration can be achieved by synchronization of oestrus. It creates a complete opportunity of parturition season in the season and therefore number of cows that do not show offspring retention can be reduced as a result of insemination program. Artificial insemination program can be accelerated by means of PGS.

-**Meat Type Herds** It facilitates use of Artificial Insemination for development of future generations by means of use of genetically superior bulls. It prevents potential problems related to rutting control and makes application of insemination program practical by preparing cattle groups instead of single animals. It helps pregnancy and parturition to be directed better. Uniform calves can be obtained by performing the parturition in a desired period. As maintenance and management of calves having similar properties of age and weight, time and workforce can be saved.

Administration in horses PGS Solution for injection should be used with a dose of 0.5 -1 ml in horses of Pony breed and donkeys and with a dose of 1-2 ml (250 - 500 µg) in large horse species. 2-4 days after administration in mares, fertile oestrus is observed following luteolysis of corpus luteum. As a strong luteolytic agent, PGS causes regression of corpus luteum in mares in various conditions. Lutelolysis is followed by initiation of oestrus and ovulations within 2-4 days upon the treatment. In mares treated with PGS, it should be noted that there is a refractor period of 4-5 days after ovulation during dioestrus being progestational phase of oestrus cycle, where there is no respond against luteolytic activity of prostaglandins. PGS has a wide safety margin and has no harmful effects on mares being pregnant during oestrus induced by medication and new-born foals. In the following clinic conditions, PGS shortens the life period of corpus luteum due to such effects:

1. Early fetal death and initiation of luteolysis upon resorption:
Approximately 8-10% of pregnant mares abort within the first 100 days of pregnancy. Continuance of luteal function in the ovary prevents early return to oestrus. Treatment is recommended before day 45.
2. Termination of permanent dioestrus cases: Non-pregnant mares go into an irregular dioestrus period during which no frequent or maximum rutting can be observed. Such mares are seen with a high rate. They are in a long dioestrus phase, rather than anoestrus not showing a cycle, and such a condition is often seen in the last stages of breeding season.
3. Termination of pseudopregnancy: Some mares having normal oestrus, but then understood to be empty (without abort or fetus resorption) show clinic indications of pregnancy. Such animals are called pseudopregnant.
4. Treatment of anoestrus during lactation: It can be used in mares that cannot enter the cycle again for months after premature parturition. However it should be kept in mind that this problem may be due to various reasons.
5. Young mares not retaining offspring: It can be used in certain animals that are determined in the examination to have functional corpus lutea and to suffer from permanent luteal function or that do not display normal rutting behavior (quiet rutting).

6 Synchronization of oestrus:

It can be a desired tool under certain circumstances for dispatch and management of horses. Treatment during dioestrus generally initiates oestrus within 2-4 days upon ovulation occurring 8-12 days after the treatment.

7 Treatment of pyometra and endometritis: Presence of corpus luteum is frequently observed in such diseases. Administration should be performed in combination with appropriate antibacterial therapy.

9.**Acceleration of parturition**: If loosening occurred in pelvic ligaments of mares with functional udders having colostrums after day 330 of pregnancy, parturition will take place within a few hours after single administration.

SPECIFIC CLINICAL PARTICULARS/WARNINGS FOR TARGET SPECIES:

It should be remembered that prostaglandins are effective only in presence of corpus luteum. In cattle not sensitive to luteolytic effect of prostaglandin, there is a refractory period of 4-5 days, which means PGS will not be effective if used within 5 days after ovulation.

- A luteal tissue should exist in ovaries for PG's to be effective in pyometra cases developed in cows and mares.

-Luteal cysts are ovarian cysts that are generally seen clinically together with anoestrus. They should be distinguished from follicular cysts as PG's do not effect on follicular cysts.

-The reason for non-response against PGS may be the fact that mares are in real anoestrus or presence of formations such as cysts or neoplasm in uterus.

-Animals should have a normal cycle for a successful cycle control and synchronization. Rectal examination before drug administration can eliminate the risk of insemination of pregnant animals or animals in anoestrus period. Special attention should be paid to nutrition and condition of animals under treatment.

Stressing factors such as instant changes in feed follow-up or feeding order or changes in groups should be avoided during the application of programs. If artificial insemination will be applied, it should be ensured that right quality of semen and right insemination method are selected.

- Waste of a part of the solution during injection or injection of the drug into fatty tissue may play a role in undesired results.

-PGS has a good safety margin and has no negative effects of fertility. No harmful effect is reported on the brood during pregnancy occurring within oestrus period following the treatment.

UNDESIRED/SIDE EFFECTS: It has no known side effects in doses recommended for cattle. Temperature disorders, abdominal pain and diarrhea can be seen in mares.

DRUG INTERACTIONS: It should not be used with non-steroid anti-inflammatory drugs as they inhibit endogen prostaglandin synthesis.

SYMPTOMS OF OVERDOSE, PRECAUTIONS and ANTIDOTE:

In cattle, no undesired effects are observed in administrations up to 80 times of effective dose of 500 µg cloprostenol. When very high doses are applied accidentally, undesired effects such as sweating (occurring within about first 20 minutes of the treatment) increased respiration and heart beat, indications of abdominal disorders, aqueous diarrhea and asthenia can occur in horses. However, undesired reactions are generally slight and temporary. No specific clinical application is recommended.

CONTRAINDICATIONS: PGS should not be injected intravascularly. Cloprostenol should not be administered in following cases;

-In mares with acute or subacute gastrointestinal system disorders,

-In mares with acute or subacute respiratory track diseases (this is an important criterion as prostaglandin injections

can result with acute respiratory problems in certain animal species), as death may occur due to tear of uterus in cases that cervical dilatation does not occur. Use during pregnancy: Luteolysis may cause loss of fetus in certain periods of pregnancy. Therefore PGS should not be used in pregnant cows and mares except undesired pregnancies or stimulation of voluntary parturition in the last stage of pregnancy.

WARNINGS FOR DRUG RESIDUES IN FOOD:

Cattle should not be sent for slaughtering during treatment and before 1 day after the last drug administration.

Residue purification time for milk is "0" days.

PRECAUTIONS TO BE TAKEN BY THE USER AND WARNINGS FOR VETERINARY SURGEONS:

PGS is absorbed through skin, therefore especially women of procreative age, pregnant women and asthma patients should be careful while using the product. It should be rinsed with soap and water in case of accidental contact with skin. F2 α type prostaglandins may cause bronchospasm in humans. In case of respiratory difficulties due to accidental inhalation or injection, bronchodilators such as isoprenaline or salbutamol should be taken immediately through inhalation.

GENERAL WARNINGS:

Consult your veterinary surgeon before using and in case an unexpected effect is observed. Keep out of reach of children and away from food products. Do not purchase and use products with expired shell life and damaged packages.

STORAGE CONDITIONS AND SHELL LIFE

Protect from light. Store in its package in room temperature below 25 ℃ (4 -25 ℃). Shell life is 2 yea rs from production date.

COMMERCIAL PRESENTATION FORM: Offered for market as 4 ml x 10 pieces of 10,20, 50 ml colorless glass vials in cardboard boxes.

PLACE AND CONDITIONS OF SALE: Can be sold only to veterinary surgeons upon veterinary surgeon's prescription (VSP) in veterinary clinics and pharmacies .

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