

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PLUSET Powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of lyophilized product contains :

Active substances:

- Follicle stimulating hormone (FSHp)500 IU
- Luteinizing hormone (LHp)500 IU

One vial of solvent contains:

- Chlorocresol0.021 g
- Sterile, pyrogen-free, normal saline to21 ml

Each ml of reconstituted solution contains:

Active substance:

Follicle stimulating hormone (FSHp)50 IU

Luteinising hormone (LHp)50 IU

Excipients:

Chlorocresol 1 mg

Sterile, pyrogen-free, normal saline to1 ml

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White to off-white lyophilised pellet and clear and colourless solution.

4. CLINICAL PARTICULARS

4.1. Target species

Bovine (reproductively mature females)

4.2. Indications for use, specifying the target species

To induce superovulation in reproductively mature heifers or cows.

4.3. Contraindications

See section 4.7.

4.4. Special warnings for each target species

None

4.5. Special precautions for use

Special precautions for use in animals

The following recommendations for the use of PLUSET for the induction of superovulation with adequate response should be followed:

- a. The donor animal must have had at least one normal oestrous cycle prior to the initiation of PLUSET treatment.
- b. The donor animal should not have any signs of clinical illness when treatment with PLUSET begins. Ovarian examination should confirm the presence of a functional corpus luteum and the absence of any pathological conditions such as cystic ovarian degeneration or adhesions around the ovaries.
- c. Treatment should be initiated between day 9 and 12 of the oestrous cycle (with day 11 generally giving best results).
- d. A luteolytic dose of prostaglandin F₂ alpha or analogue should be given intramuscularly at 60 and/or 72 hours after the beginning of superovulation treatment.
- e. Standing oestrus will take place 40-48 h after prostaglandin treatment and animals should be bred 12 h after the onset of standing heat and, again 12 h later with high quality semen.
- f. Following the non-surgical recovery of embryos on day 7, it is recommended to give the animals another prostaglandin treatment to assure a rapid return to heat; if not, animals should be examined 4 weeks after, to ascertain that normal ovarian activity has been restored. Breeding can take place at the first heat after superovulation, which normally is seen after 28 days.
- g. The effect of repeated treatments with PLUSET over long periods has not been assessed for all possible schedule treatment. Therefore it is recommended that PLUSET not be administered more than twice for superovulation and that at least one natural oestrus cycle be allowed to occur between the two superovulation treatments.
- h. The interval from calving to initiation of superovulation treatment should be at least 3 months.
- i. Individually variability of responses depending of age, breed, on reproductive status, could occur.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Care should be taken when handling the product to avoid self-injection. Accidental self-injection may cause biological effects in women and to the unborn child. In the event of accidental self-injection in women who are pregnant, or whose pregnancy status is unknown, seek medical advice.

4.6. Adverse reactions (frequency and seriousness)

Slight reduction in milk yield.

Following the treatment a delayed return to heat is possible.

Ovarian cysts may be formed as a result of induction of superovulation

4.7. Use during pregnancy, lactation or lay

Do not use during pregnancy.

A slight reduction in milk yield has been observed during superovulatory heat (as in other heats) but the production in general reaches pretreatment levels within 2 weeks.

4.8. Interaction with other medicinal products and other forms of interaction

None known

4.9. Amounts to be administered and administration route

Dissolve each vial of freeze-dried product with 10.5 ml of solvent.

Use aseptic technique during reconstitution and when removing aliquots from the vial. Adequately clean and disinfect the vial closure prior to each entry with a sterile needle.

Mix gently during reconstitution.

PLUSET is to be given by intramuscular injection only.

The following treatment schedule is recommended for the induction of superovulation in the cow:

The total recommended dose is 800 to 1000 IU in decreasing doses for 4 to 5 days. Considering the variability between animals and taking into account breed, age and reproductive status the dosing schedule should be adjusted appropriately. For heifers and beef cows a total dose of 800 IU is recommended. For dairy cows the dose could be increased to 1000 IU taking into account increasing age, parity number and dairy production.

Recommended schedule for 800 IU in 4 days:

Day 1*	08:00 hrs	3.0 i.m.	ml	(150 IU FSH + 150 IU LH)
	20:00 hrs	3.0 i.m.	ml	(150 IU FSH + 150 IU LH)
Day 2	08:00 hrs	2.5 i.m.	ml	(125 IU FSH + 125 IU LH)
	20:00 hrs	2.5 i.m.	ml	(125 IU FSH + 125 IU LH)
Day 3**	08:00 hrs	1.5 i.m.	ml	(75 IU FSH + 75 IU LH)
	20:00 hrs	1.5 i.m.	ml	(75 IU FSH + 75 IU LH)
Day 4	08:00 hrs	1.0 i.m.	ml	(50 IU FSH + 50 IU LH)
	20:00 hrs	1.0 i.m.	ml	(50 IU FSH + 50 IU LH)

Recommended schedule for 1000 IU in 5 days:

Day 1*	08:00 hrs	3.0 i.m.	ml	(150 IU FSH + 150 IU LH)
	20:00 hrs	3.0 i.m.	ml	(150 IU FSH + 150 IU LH)
Day 2	08:00 hrs	2.5 i.m.	ml	(125 IU FSH + 125 IU LH)
	20:00 hrs	2.5 i.m.	ml	(125 IU FSH + 125 IU LH)
Day 3**	08:00 hrs	2.0 i.m.	ml	(100 IU FSH + 100 IU LH)
	20:00 hrs	2.0 i.m.	ml	(100 IU FSH + 100 IU LH)
Day 4	08:00 hrs	1.5 i.m.	ml	(75 IU FSH + 75 IU LH)
	20:00 hrs	1.5 i.m.	ml	(75 IU FSH + 75 IU LH)
Day 5	08:00 hrs	1.0 i.m.	ml	(50 IU FSH + 50 IU LH)
	20:00 hrs	1.0 i.m.	ml	(50 IU FSH + 50 IU LH)

* Corresponds to the 11th day of the oestrus cycle.

** A luteolytic dose of prostaglandin F₂ alpha should be administered intramuscularly at 60 and/or 72 hours after the beginning of superovulation treatment.

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

It is not advisable to exceed the maximum recommended dose. High doses of FSH and LH could be associated with reduced fertilization rate, resulting in an increase of unfertilized embryos.

4.11. Withdrawal period

Cattle: meat and offal: Zero days

milk: Zero hours

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Gonadotrophins

ATCvet code: QG03GA

5.1. Pharmacodynamic properties

Porcine FSH and LH are glycoproteins secreted from the anterior pituitary under the influence of GnRH released from the hypothalamus. These proteins are composed of an alpha and a beta subunit; biological specificity resides in the beta unit (molecular weight = 27,000 - 34,000).

FSH and LH stimulate normal gonadal functions and sex hormones secretion in male and female mammals.

In females, during the normal oestrous cycle, FSH stimulates the development and maturation of Graafian follicles and the ovum. The follicles respond with increased oestrogen secretion from the internal thecal cells surrounding the follicle, which at mid-cycle, stimulate the release of pituitary LH by feed-back mechanism. The increased oestrogen secretion and LH from the pituitary cause the rupture of the follicle leading to ovulation. The follicle is then transformed into a progesterone-secreting corpus luteum

By administration of exogenous gonadotropin preparations containing FSH and LH it is possible to increase the ovulation rate. It is supposed that exogenous gonadotropin administration increases the number of antral follicles and reduces the number of atretic follicles. For the purpose of superovulation a proper FSH/LH ratio and an adequate treatment regimen is required. While FSH stimulates the follicular growth, a minimum LH amount has been shown to be necessary for obtaining multiple ovulations. Although the FSH/LH bioactivity ratio in PLUSET is maintained at 1:1, the activity is primarily that of follicle stimulation because of the short half-life of porcine LH.

5.2. Pharmacokinetic particulars

The gonadotropins FSH and LH have comparable molecular structures in all mammalian species with only minor structural differences. In consequence naturally occurring FSH and LH from pig origin will be metabolised and excreted like the respective endogenous gonadotropins.

Endogenous as well as exogenous FSH and LH are cleared from the body primarily by the kidneys. The renal fate of glycoprotein hormones is glomerular filtration, followed by either (a) excretion (largely unchanged) in the urine, or (b) degradation by the cells of the proximal convoluted tubule. The filtered protein hormone is reabsorbed (internalized via endocytosis) and catabolised to oligopeptides and free amino acids in the lysosomes. The released amino acids are then returned via the peritubular circulation to the bloodstream.

The kinetics of p-FSH and p-LH in cows are represented by a bio-exponential curve with an initial rapid time of disappearance ($t_{1/2\alpha}$) followed by a slow decline ($t_{1/2\beta}$) in the blood.

The half-life values of p-FSH are 2 ½ h ($t_{1/2\alpha}$) and 25 ½ h ($t_{1/2\beta}$) respectively, determined after a single i.v administration in two heifers. These values for p-LH are 40 min and 6 h respectively.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Chlorocresol
Sodium chloride
Water for injection

6.2. Incompatibilities

None known.

6.3. Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf-life after reconstitution according to directions: six days

6.4. Special precautions for storage

Store below 25°C.
Reconstituted solution: store and transport refrigerated (+2°C to +8°C) and do not freeze.
Keep the vial in the outer carton.

6.5. Nature and composition of immediate packaging

Container for the lyophilised product:

- Vial of colourless neutral glass (type 1) Capacity: 10 ml. Provided with bromobutyl and silicate stopper and aluminium cap flip off seal.

Container for the diluent:

- Vial of colourless neutral glass (type 1) Capacity: 21 ml. With rubber peni-type stopper of grey colour and aluminium cap flip off seal.

- Cardboard box with 2 glass vials of 10 ml of lyophilised product and 1 glass vial of 21 ml of diluent.

6.6. Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

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

7. MARKETING AUTHORISATION HOLDER

Kernfarm B.V.
De Corridor 14D
3621 ZB Breukelen
The Netherlands

8. MARKETING AUTHORISATION NUMBER

Vm 43877/4007

9. DATE OF FIRST AUTHORISATION

28 June 2016

10. DATE OF REVISION OF THE TEXT

June 2016

Approved: 28 June 2016

A handwritten signature in black ink, consisting of a stylized 'C' followed by a vertical line and a horizontal stroke.