1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PLUSET 500 IU/ml + 500 IU/ml powder and solvent for solution for injection for cattle.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of lyophilisate contains:

Active substances:
Follicle stimulating hormone, porcine (FSHp).....500 IU
Luteinising hormone, porcine (LHp).....500 IU

Each vial of solvent contains:

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Chlorocresol	0.021 g
Sodium chloride	
Water for injection	

Each ml of reconstituted solution contains:
Active substances:
Follicle stimulating hormone (FSHp).....50 IU
Luteinising hormone (LHp) .....50 IU
Excipients:
Chlorocresol..... *1 mg*

Powder: White to off white hygroscopic lyophilised pellet
Solvent: Clear and colourless solution

3. CLINICAL INFORMATION

3.1 Target species

Cattle (heifer and cow)

3.2 Indications for use for each target species

To induce superovulation in reproductively mature heifers or cows.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in males and reproductively immature female cattle.

See section 3.7.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

The following recommendations for the use of this veterinary medicinal product for the induction of superovulation with adequate response should be followed:

- The donor animal must have had at least one normal oestrous cycle prior to the initiation of the treatment.
- The donor animal should not have any signs of clinical illness when treatment with the veterinary medicinal product 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.
- Treatment should be initiated between day 9 and 12 of the oestrous cycle (with day 11 generally giving best results).
- A luteolytic dose of prostaglandin F_2 alpha or analogue should be given intramuscularly at 60 and/or 72 hours after the beginning of superovulation treatment.
- 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.
- 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.
- The effect of repeated treatments with the veterinary medicinal product over long periods has not been assessed for all possible schedule treatment Therefore it is recommended not to be administered more than twice for superovulation and that at least one natural oestrus cycle be allowed to occur between the two superovulation treatments.
- The interval from calving to initiation of superovulation treatment should be at least 3 months.
- 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:

Accidental self-injection of this veterinary medicinal product may cause hormonal effects in women and may harm unborn children.
Care should be taken by those handling the veterinary medicinal product to avoid self-injection.
In the event of accidental self-injection by women who are pregnant, or whose pregnancy status is unknown, seek medical advice immediately and show the package leaflet or label to the physician.

Special precautions for the protccion of the environment:

Not applicable.

3.6 Adverse events

Cattle (heifer and cow):

Undetermined frequency (cannot be estimated from the available data):	Milk production decrease Abnormal oestrus[1] Ovarian cyst[2]

[1]Delayed return to oestrus
[2]As a result of induction of superovulation

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 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.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

Intramuscular use.

Dissolve each vial of lyophilisate 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.

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

Recommended schedule for 1000 IU in 5 days:

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

* Corresponds to the 11th day of the oestrus cycle.
** A luteolytic dose of prostaglandin F_2 alpha should be administered intramuscularly at 60 and/or 72 hours after the beginning of superovulation treatment.

Appearance of the reconstituted solution: Clear, colourless or slightly yellowish – brown solution

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

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.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

4.10 Withdrawal periods

Cattle:

Meat and offal: Zero days.
Milk: Zero hours.

4. PHARMACOLOGICAL PROPERTIES

4.1 **ATCvet code:** QG03GA90

4.2 Pharmacodynamics

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 Graffian 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 folicular growth, a minimum LH amount hs been shown to be necessary for obtaining multiple ovulations. Although the FSH/LH bioactivity ratio in the veterinary medicinal product is maintained at 1:1, the activity is primarily that of follicle stimulation because of the short half-life of porcine LH.

4.2 Pharmacokinetics

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 (t½α) followed by a slow decline (t½β) in the blood.

The half-life values of p-FSH are 2 ½ h (t½α) and 25 ½ h (t½β) respectively, determined after a single i.v administration in two heifers. These values for p-LH are 40 min and 6 h respectively.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life after reconstitution according to directions: 6 days.

5.3 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.

5.4 Nature and composition of immediate packaging

Lyophilisate product:
Colourless neutral glass Eur. Ph. type I vials closed with bromobutyl and silicate stopper and FLIP-OFF seal and aluminium caps..

Solvent:
Colourless neutral glass Eur. Ph. type 1 vials closed with rubber peni-type stopper and FLIP-OFF seal and aluminium caps.

Package sizes:
Cardboard box with 2 vials of 10 ml of lyophilisate and 1 vial of 21 ml of solvent.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Laboratorios Calier, S.A.

7. MARKETING AUTHORISATION NUMBER(S)

VPA10665/001/001

8. DATE OF FIRST AUTHORISATION

26/09/2008

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10/03/2026

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).