SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PLUSET Powder and solvent for solution for injection.
PLUSET 500 IU/500 IU powder and solvent for solution for injection for cattle [PL]
PLUSET vet 500 IU/500 IU Powder and solvent for solution for injection for bovine [FI]
PLUSET 500 IU/500 IU Powder and solvent for solution for injection
Follicle stimulating hormone (FSHp) , Luteinizing hormone (LHp) [DE]

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:
- Chlorocresol .....0.021 g
- Sterile, pyrogen-free, normal saline to .....21 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 to .....1 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

Cattle (reproductively mature females)

4.2. Indications for use, specifying the target species

To induce superovulation in reproductively mature heifers or cows.

4.3. Contraindications

Do not use in case of hypersensitivity to the active substance or to any of the excipients.
Do not use in males and reproductively immature female cattle.
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 this product 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 the treatment.
b. The donor animal should not have any signs of clinical illness when treatment with the 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.
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 F_2 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 the 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.

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

Accidental self-injection of this product may cause hormonal effects in women and may harm unborn children.
Care should be taken by those handling the 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.

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.
This product 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 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.*

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: Sex hormones and modulators of the genital system. Gonadotrophins
ATCvet code: QG03GA90

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 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 product 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 (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.

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: 6 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

LABORATORIOS CALIER, S.A.
C/ Barcelonés, 26 (Plá del Ramassá)
LES FRANQUESES DEL VALLES
Barcelona (Spain)

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE
Under veterinary prescription

PACKAGE LEAFLET

PLUSET
Powder and solvent for solution for injection

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Laboratorios Calier, S.A.
Barcelonès, 26 (Pla del Ramassà)
Les Franqueses del Vallès (Barcelona)
SPAIN

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

PLUSET Powder and solvent for solution for injectionPLUSET 500 IU/500 IU powder and solvent for solution for injection for cattle [PL]
PLUSET vet 500 IU/500 IU Powder and solvent for solution for injection for bovine [FI]
PLUSET 500 IU/500 IU Powder and solvent for solution for injection for bovine
Follicle stimulating hormone (FSHp) , Luteinizing hormone (LHp) [DE]

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

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

One vial of lyophilised product contains:
Active substances:
- Follicle stimulating hormone (FSHp) ..... 500 IU
- Luteinizing hormone (LHp) ..... 500 IU

One vial of solvent contains:
- Chlorocresol ..... 0.021 g
- Sterile, pyrogen-free, normal saline to..... 21 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 to ..... 1 ml

4. INDICATIONS

To induce superovulation in reproductively mature heifers or cows.

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to the active substance or to any of the excipients.

Do not use in males and reproductively immature female cattle.

6. ADVERSE REACTIONS
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
If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES
Cattle (reproductively mature females)

8. DOSAGE FOR EACH SPECIES, ROUTE AND METHOD OF ADMINISTRATION

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.
The product is to be given by intramuscular injection only.

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.

9. ADVICE ON CORRECT ADMINISTRATION

None

10. WITHDRAWAL PERIOD

Cattle: meat and offal: Zero days, milk: Zero hours

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children
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.

Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
Shelf-life after reconstitution according to directions: 6 days

12. SPECIAL WARNINGS

The following recommendations for the use of this product 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 the treatment.
b. The donor animal should not have any signs of clinical illness when treatment with this 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.
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 this 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.

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.

User warnings

Accidental self-injection of this product may cause hormonal effects in women and may harm unborn children. Care should be taken by those handling the 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.

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.

Overdose (symptoms, emergency procedures, antidotes)

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

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

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PLUSET Powder and solvent for solution for injection
PLUSET 500 IU/500 IU powder and solvent for solution for injection for cattle [PL]
PLUSET vet 500 IU/ 500 IU Powder and solvent for solution for injection for bovine [FI]
PLUSET 500 IU/500 IU Powder and solvent for solution for injection
Follicle stimulating hormone (FSHp) , Luteinizing hormone (LHp) [DE]

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One vial of lyophilised product contains:
- Follicle-stimulating hormone (FSH)..... 500 IU
- Luteinising hormone (LH) ..... 500 IU

One vial of solvent contains:
- Chlorocresol ..... 0.021 g
- Sterile, pyrogen-free, normal saline to..... 21 ml

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. PACKAGE SIZE

2 x 10 ml vial, lyophilised FSHp + LHp. 1 x 21 ml vial solvent (sterile)

5. TARGET SPECIES

Cattle (reproductively mature females)

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Cattle: meat and offal: Zero days
milk: Zero hours

9. SPECIAL WARNING(S), IF NECESSARY

User warnings
Read the package leaflet before use

10. EXPIRY DATE

EXP

11. SPECIAL STORAGE CONDITIONS

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.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

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

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only

Under veterinary prescription

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LABORATORIOS CALIER, S.A.
C/ Barcelonès, 26 (Pla del Ramassà)
LES FRANQUESES DEL VALLÈS (Barcelona) SPAIN

16. MARKETING AUTHORISATION NUMBER(S)

17 MANUFACTURER'S BATCH NUMBER

Batch:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LYOPHILISED VIAL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PLUSET Powder for solution for injection
PLUSET 500 IU/500 IU Powder for solution for injection (DE)

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

- Follicle-stimulating hormone (FSH).....500 IU
- Luteinizing hormone (LH) .....500 IU

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

10 ml

4. ROUTE(S) OF ADMINISTRATION

Only by intramuscular route

5. BATCH NUMBER

Batch:

7. EXPIRY DATE

Exp.:
Once reconstituted use by ……
Shelf-life after reconstitution: 6 days

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PLUSET Solvent for solution for injection.

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

- Chlorocresol ..... 0.021 g
- Sterile, pyrogen-free, normal saline to..... 21 ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

21 ml

4. ROUTE(S) OF ADMINISTRATION

Only by intramuscular route

5. BATCH NUMBER

Batch:

7. EXPIRY DATE

Exp.:
Once reconstituted use by ……
Shelf life after reconstitution: 6 days

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.