ANNEX 1

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

CALIERGOLIN 50 microgram/ml oral solution for dogs and cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:

Cabergoline 50 microgram

Excipients:

Qualitative composition of excipients and other constituents
Triglycerides, medium-chain.
Nitrogen, low-oxygen

Pale yellow, viscous oily solution.

3. CLINICAL INFORMATION

3.1 Target species

Dog and cat.

3.2 Indications for use for each target species

The veterinary medicinal product is indicated for the following uses:

- Treatment of false pregnancy in bitches
- Suppression of lactation in bitches and queens: suppression of lactation may be required under certain clinical circumstances (for example following removal of puppies and kittens soon after birth, following early weaning)

3.3 Contraindications

- Do not use in pregnant animals since the veterinary medicinal product may cause abortion.

- Do not use with dopamine antagonist.
- Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
- The veterinary medicinal product may induce transient hypotension in treated animals. Do not use in animals concurrently being treated with hypotensive drugs.
- Do not use directly after surgery whilst the animal is still under the influence of the anaesthetic agents.

3.4 Special warnings

Additional supportive treatments should involve restriction of water and carbohydrate intake and increase exercise.

4.5 Special precautions for use

Special precautions for safe use in the target species

The veterinary medicinal product should be administered with caution to animals with impaired liver function.

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

Wash hand after use. Avoid contact with skin and eyes. Wash of any splashes immediately.

Care should be taken to avoid contact between the solution and women of childbearing age.

Women intending to become pregnant, pregnant or breast-feeding women should wear gloves when administering the veterinary medicinal product.

If you know you are hypersensitive to cabergoline or any of the other ingredients in the veterinary medicinal product, you should avoid contact with the product.

Do not leave unattended filled syringes in the sight and presence of children. In case of accidental ingestion, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:

Not applicable

3.6 Adverse events

Dog and cat:

Undetermined frequency:	Emesis[1]

Very rare:	Allergic conditions such as allergic oedema, urticaria and hypersensitivity reactions Transient hypotension[2] Neurological disorders such as somnolence, tremor, ataxia and seizure Hyperactivity

[1] Usually only occurs after the first administration. In this case treatment should not be stopped, since the vomiting will not reoccur after the following administrations.

[2] Might result in more significant hypotension in animals concurrently being treated with hypotensive drugs, or directly after surgery whilst the animal is under the influence of anaesthetic agents.

These adverse effects are usually of a moderate and transient nature.

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

Pregnancy:

Cabergoline has the capacity to cause abortion in the later stages of pregnancy and should not be used in pregnant animals (see section 3.3). Differential diagnosis between pregnancy and false pregnancy should be made correctly.

Lactation:

The veterinary medicinal product is indicated for the suppression of lactation: inhibition of prolactin secretion by cabergoline results in a rapid cessation of lactation and a reduction in the size of the mammary glands. The veterinary medicinal product should not be used in lactating animals unless suppression of lactation is required.

3.8 Interaction with other medicinal products and other forms of interaction

Since cabergoline exerts its therapeutic effect by direct stimulation of dopamine receptors, the veterinary medicinal product should not be administered concurrently with drugs which have dopamine antagonist activity (such as phenothiazines, butyrophenones, metoclopramide), as these might reduce its prolactin inhibiting effects.

Since cabergoline may induce transient hypotension, the veterinary medicinal product should not be used in animals concurrently treated with hypotensive drugs or directly after surgery whilst the animal is still under the influence of the anesthetic agents.

3.9 Administration routes and dosage

The veterinary medicinal product should be administered orally either directly into the mouth or by mixing with food.

The dosage is 0.1 ml/kg bodyweight (equivalent to 5 microgram/kg bodyweight of cabergoline) once daily for 4-6 consecutive days, depending on the severity of the clinical condition.

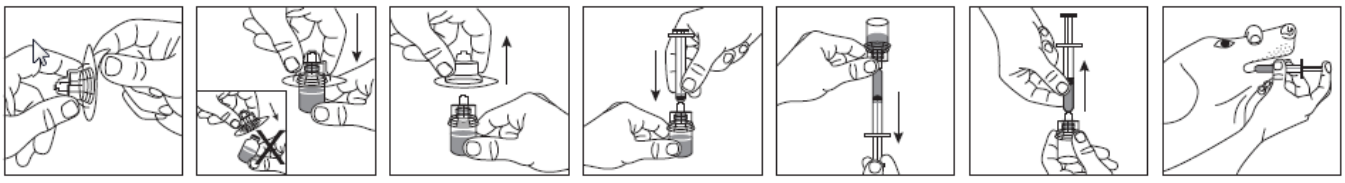
To ensure a correct dosage, body weight should be determined as accurately as possible before administration.

If the signs fail to resolve after a single course of treatment, or if they recur after the end of treatment, then the course of treatment may be repeated.

How to withdraw the recommended volume from the bottle:

a. Remove the cover from the bottle adapter package. Do not remove the bottle adapter from the blister package.
b. Attach the adapter to the bottle; use the blister pack to handle the adapter. Seat the adapter on the bottle by pushing down until the spike penetrates the stopper and the adapter snaps in place.
c. Remove and discard the blister package.
d. Attach the syringe to the adapter by firmly pressing the syringe into the bottle adapter to avoid leaking of the product when withdrawing the dose from the bottle.
e. Withdraw the drug from the bottle into the syringe holding the bottle upside down.
f. Remove the syringe from the adapter.
g. The drug is now ready for administration.

It is recommended to rinse and dry the syringe following each application.



a. b. c. d. e. f. g.

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

The experimental data indicate that a single overdose with cabergoline might result in an increased likelihood of post-treatment vomiting, and possibly an increase in post-treatment hypotension.

General supportive measures should be undertaken to remove any unabsorbed drug and maintain blood pressure, if necessary. As an antidote, the parental administration of dopamine antagonist drugs such as metoclopramide might be considered.

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

3.12 Withdrawal periods

Not applicable.

4 PHARMACOLOGICAL INFORMATION

4.1. ATC vet Code:

QG02CB03.

4.2 Pharmacodynamics

The pharmacodynamics of cabergoline have been investigated in various *in-vitro* and *in-vivo* system. The most significant findings can be summarised as follows:

- Cabergoline is a potent inhibitor of prolactin secretion by the pituitary, and as a consequence inhibits prolactin secretion dependent processes such as lactation.
- The mechanism of action of cabergoline is via direct interaction with the D-2 dopaminergic receptor on pituitary lactotroph cells; this interaction is a persistent effect.
- Cabergoline has some affinity for noradrenergic receptors but does not affect noradrenaline or serotonin metabolism.
- As for other ergoline derivatives, cabergoline has emetic effects (equivalent in potency to those of pergolide and bromocriptine).
- At high doses orally, cabergoline causes a reduction in blood pressure.

4.2. Pharmacokinetics

No pharmacokinetic data are available for the recommended dosing regimen in dogs and cats.

Pharmacokinetic studies were performed in both rats and dogs. The studies in rats were undertaken with radiolabeled cabergoline, by oral or intravenous administration, at a dose of 0.5 mg/kg bodyweight. Pharmacokinetic studies in dogs were performed with a daily dose of 80 microgram/kg bodyweight (16 times the recommended dose). Dogs were treated for 30 days; pharmacokinetic assessments were made on day 1 and 28. The source of the information given below is specified (rat data or dog data).

Absorption:

- Absorption after oral administration is nearly complete (rat data);
- T_{max} = 1 hour on day 1 and 0.5-2 hours (mean 75 minutes) on day 28;
- C_{max} ranged from 1140 to 3155 pg/ml (mean 2147 pg/ml) on day 1 and from 455 to 4217 pg/ml (mean 2336 pg/ml) on day 28 (dog data);
- $AUC_{(0\text{-}24\ h)}$ on day 1 ranged from 3896 to 10216 $pg.h.ml^{-1}$ (mean 7056 $pg.h.ml^{-1}$) and on day 28 from 3231 to 19043 $pg.h.ml^{-1}$ (mean 11137 $pg.h.ml^{-1}$) (dog data) .

Distribution:

In terms of tissue to plasma concentration ratio (AUC), the tissue uptake was very high for liver, pituitary, adrenals, spleen, kidneys, lung (260-100), followed by ovaries, uterus, heart (50-30). In the brain the levels were of the same order of magnitude as in plasma (rat data).

Biotransformation:

- Assessment of plasma metabolites consistent amounts on four metabolites (FCE 21589, FCE 21904 and two unknown) were detected in plasma in addition to unchanged cabergoline which accounted for about 26% of plasma radioactivity from 2 to 48 hours after oral administration. Large amounts of metabolites were already present at the first sampling times (0.5 and 1.0 hours) suggesting a rapid biotransformation of cabergoline even of presystemic origin (rat data);
- Assessment of excreted metabolites in the urine excreted up to 24 hours after oral and intravenous dosing, about 25% of the excreted radioactivity was represented by unchanged drug, about 50% by the metabolite 6-ADL (FCE 21589) and the remaining 25% by other currently unknown metabolites (rat data).

Elimination:

- Plasma half life in dogs t½ on day 1 ~ 19 hours; t½ on day 28 ~ 10 hours (dog data);

- Tissue half life in rats: The rate of elimination from most tissues (t½ ~ 17 hours) except for the pituitary where elimination was particularly slow (t½ ~ 60 hours) (rat data).
- Excretion route in rats: The main route of excretion was faecal; not more than 10% of the dose was recovered in the urine (rat data).

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Do not mix the veterinary medicinal product with an aqueous solution (e.g. milk)

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 first opening the immediate packaging: 14 days.

5.3 Special precautions for storage

As packaged for sale: store in a refrigerator (2ºC-8°C).

After first opening: store below 25°C.

Store in upright position.

Store in the original package in order to protect from light.

Do not freeze.

5.4 Nature and composition of immediate packaging

Amber glass bottles type III (15 ml capacity) containing 7 ml of solution, closed with a grey bromobutyl rubber stopper coated with a thin fluoropolymer layer and aluminium cap, supplied with bottle adapter and PP/HDPE dosing syringe of 1 ml, packaged in Cardboard box

Amber glass bottles type III (15 ml capacity) containing 15 ml of solution, closed with a grey bromobutyl rubber stopper coated with a thin fluoropolymer layer and aluminium cap, supplied with bottle adapter and PP/HDPE dosing syringe of 3 ml, packaged in Cardboard box

Amber glass bottles type II (30 ml capacity) containing 24 ml of solution, closed with a grey bromobutyl rubber stopper coated with a thin fluoropolymer layer and aluminium cap, supplied with bottle adapter and PP/HDPE dosing syringe of 3 ml, packaged in Cardboard box

Pack sizes:

Cardboard box with 1 bottle of 7 ml

Cardboard box with 1 bottle of 15 ml

Cardboard box with 1 bottle of 24 ml

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products 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 NUMBERS

8. DATE OF FIRST AUTHORISATION

DD/MM/YYYY

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

DD/MM/YYYY

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

ANNEX 3

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box with 1 bottle of 7, 15 or 24 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

CALIERGOLIN 50 microgram/ml oral solution

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:

Cabergoline 50 microgram/ml

3. PACKAGE SIZE

7 ml
15 ml
24 ml

4. TARGET SPECIES

Dog and cat.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral solution.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}
Once opened use within 14 days.

9. SPECIAL STORAGE PRECAUTIONS

As packaged for sale: store in a refrigerator.
After first opening: store below 25°C.
Store in upright position.
Store in the original package in order to protect from light.

Do not freeze.

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE

Read the package leaflet before use.

11. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

12. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Laboratorios Calier S.A.

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle of 7, 15 and 24 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

CALIERGOLIN 50 microgram/ml oral solution.

2. QUANTITY PATICULARS OF THE ACTIVE SUBSTANCES

Each ml contains:

Cabergoline 50 microgram/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}
Once opened use within 14 days.

B. PACKAGE LEAFLET

1. Name of the veterinary medicinal product

CALIERGOLIN 50 microgram/ml oral solution for dogs and cats

2. Composition

Each ml contains:

Active substances:

Cabergoline	50 microgram

Pale yellow, viscous oily solution

3. Target species

Dog and cat

4. Indications for use

The veterinary medicinal product under concern is indicated for the following uses:

- Treatment of false pregnancy in bitches.
- Suppression of lactation in bitches and queens: suppression of lactation may be required under certain clinical circumstances (for example following removal of puppies and kittens soon after birth, following early weaning)

5. Contraindications

- Do not use in pregnant animals since the veterinary medicinal product may cause abortion.
- Do not use with dopamine antagonist.
- Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
- The veterinary medicinal product may induce transient hypotension in treated animals. Do not use in animals concurrently being treated with hypotensive drugs.
- Do not use directly after surgery whilst the animal is still under the influence of the anesthetic agents.

6. Special warnings

Special warnings

Additional supportive treatments should involve restriction of water and carbohydrate intake and increase exercise.

Special precautions for safe use in the target animals:

The veterinary medicinal product should be administered with caution to animals with impaired liver function.

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

Wash hand after use. Avoid contact with skin and eyes wash of any splashes immediately.

Care should be taken to avoid contact between the solution and women of childbearing age. Women intending to become pregnant, pregnant or breast-feeding should wear gloves when administering the veterinary medicinal product.

If you know you are hypersensitive to cabergoline or any of the other ingredients in the product, you should avoid contact with the veterinary medicinal product.

Do not leave unattended filled syringes in the sight and presence of children. In case of accidental ingestion, particularly by a child, seek medical attention immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:

Not applicable

Pregnancy and lactation:

Pregnancy:

Cabergoline has the capacity to cause abortion in the later stages of pregnancy, and should not be used in pregnant animals (see section 5). Differential diagnosis between pregnancy and false pregnancy should be made correctly.

Lactation:

The veterinary medicinal product is indicated for the suppression of lactation: inhibition of prolactin secretion by cabergoline results in a rapid cessation of lactation and a reduction in the size of the mammary glands. The veterinary medicinal product should not be used in lactating animals unless suppression of lactation is required.

Interaction with other medicinal products and other forms of interaction:

Since cabergoline exerts its therapeutic effect by direct stimulation of dopamine receptors, the veterinary medicinal product should not be administered concurrently with drugs which have dopamine antagonist activity (such as phenothiazines, butyrophenones, metoclopramide), as these might reduce its prolactin inhibiting effects.

Since cabergoline may induce transient hypotension, the veterinary medicinal product should not be used in animals concurrently treated with hypotensive drugs or directly after surgery whilst the animal is still under the influence of the anaesthetic agents.

Overdose:

The experimental data indicate that a single overdose with cabergoline might result in an increased likelihood of post-treatment vomiting, and possibly an increase in post-treatment hypotension.

General supportive measures should be undertaken to remove any unabsorbed drug and maintain blood pressure, if necessary. As an antidote, the parental

administration of dopamine antagonist drugs such as metoclopramide might be considered.

Special restrictions for use and special conditions for use:

Veterinary medicinal product subject to prescription.

Major incompatibilities:

Do not mix the veterinary medicinal product with an aqueous solution (e.g. milk).

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

7. ADVERSE EVENTS

Dog and cat:

Undetermined frequency:	Emesis[1]
Very rare:	Allergic conditions such as allergic oedema, urticaria and hypersensitivity reactions Transient hypotension[2] Neurological disorders such as somnolence, tremor, ataxia and seizure Hyperactivity

[1] Usually only occurs after the first administration. In this case treatment should not be stopped, since the vomiting will not reoccur after the following administrations.

[2] Might result in more significant hypotension in animals concurrently being treated with hypotensive drugs, or directly after surgery whilst the animal is under the influence of anaesthetic agents.

These adverse effects are usually of a moderate and transient nature.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder or its local representative using the contact details at the end of this leaflet, or via your national reporting system:

8. Dosage for each species, routes and method of administration

The veterinary medicinal product should be administered orally either directly into the mouth or by mixing with food.

The dosage is 0.1 ml/kg bodyweight (equivalent to 5 microgram/kg bodyweight of cabergoline) once daily for 4-6 consecutive days, depending on the severity of the clinical condition.

To ensure a correct dosage, body weight should be determined as accurately as possible before administration.

If the signs fail to resolve after a single course of treatment, or if they recur after the end of treatment, then the course of treatment may be repeated.

It is recommended to rinse and dry the syringe following each application.

9. Advice on correct administration

a. Remove the cover from the bottle adapter package. Do not remove the bottle adapter from the blister package.

b. Attach the adapter to the bottle; use the blister pack to handle the adapter. Seat the adapter on the bottle by pushing down until the spike penetrates the stopper and the adapter snaps in place.

c. Remove and discard the blister package.

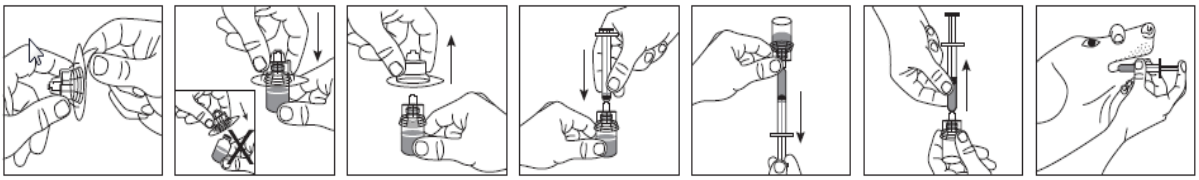
d. Attach the syringe to the adapter by firmly pressing the syringe into the bottle adapter to avoid leaking of the product when withdrawing the dose from the bottle.

e. Withdraw the drug from the bottle into the syringe holding the bottle upside down.

f. Remove the syringe from the adapter.

g. The drug is now ready for administration.

It is recommended to rinse and dry the syringe following each application.



a. b. c. d. e. f. g.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.

As packaged for sale: store in a refrigerator (2ºC-8°C).

After first opening: store below 25°C.

Shelf life after first opening the immediate packaging: 14 days.

Store in upright position.

Store in the original package in order to protect from light.

Do not freeze.

12. Special precautions for disposal

Medicines shoul

d 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 applicable national collection systems. These measures should help to protect the environment.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorization numbers and pack sizes

Pack sizes:

Cardboard box with 1 bottle of 7 ml

Cardboard box with 1 bottle of 15 ml

Cardboard box with 1 bottle of 24 ml

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{DD/MM/YYYY}

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

16. Contact details

Marketing authorisation holder and manufacturer responsible for batch release and contact details to report suspected adverse events:

Local representatives and contact details to report suspected adverse events: