ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Velactis 1.12 mg/ml solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Cabergoline ..... 1.12 mg

Excipients:
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection.
Clear pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (dairy cows)

4.2 Indications for use, specifying the target species

For use in the herd management programme of dairy cows as an aid in the abrupt drying-off by reducing milk production to:
- reduce milk leakage at drying off,
- reduce the risk of new intramammary infections during the dry period,
- reduce discomfort.

4.3 Contraindications

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

4.4 Special warnings

Velactis should be used as part of a comprehensive mastitis and milk quality control program under veterinarian advice, which might include the need to use intramammary treatment.

For cows considered likely to be free of subclinical mastitis at drying off, in which antibiotic use is not justified/permitted, Velactis can be used as a dry cow treatment. The cows should be diagnosed to be free of subclinical mastitis by using suitable criteria such as bacterial examination of milk, somatic cell count or other recognized tests.

In a multicentric randomized clinical trial where dairy cows with no intramammary infections at the time of drying-off were administered either Velactis or placebo at the time of drying-off, the incidence of new intramammary infections within 7 days after subsequent calving was significantly lower among udder quarters of cows treated with Velactis (20.5%) as compared to placebo (26.0%). The difference in percentage of new intramammary infections during the dry period between Velactis treated animals and the placebo group was 5.5% (95% confidence interval 0.5-10.4%). The efficacy of Velactis in reducing the risk of new intramammary infections during the dry period when administered

concomitantly with antimicrobial treatment to cows with intramammary infections has not been investigated compared to antimicrobial treatment alone.

In the same study, incidence of milk leakage was significantly lower among Velactis treated animals (2.0%) as compared to placebo treated animals (10.7%). The difference between groups was 8.7% (95% confidence interval 4.9-12.6%). This was confirmed in another multicentric randomized clinical trial where incidence of milk leakage was significantly lower among Velactis treated animals (3.9%) as compared to placebo treated animals (17.6%). The difference between groups was 13.7% (95% confidence interval 6.4-21%).

In a randomized and placebo controlled clinical study Velactis treated cows presented less signs of udder pain in comparison with controls on the first two days after drying-off. The difference in occurrence of pain was 9.9% (95% confidence interval 4.0-15.8%) between the Velactis treated cows compared to placebo treated animals. In a randomized and placebo controlled clinical study, reduced discomfort was demonstrated during the first day after drying-off by increasing daily lying time by 143 +/- 17 minutes in Velactis treated animals in comparison with untreated controls.

4.5 Special precautions for use

Special precautions for use in animals
Normal aseptic procedures for administration of an intramuscular injection should be followed.
Only use a dry sterile needle and avoid the introduction of humidity/water during use.

The product should only be used in dairy cows at the time of drying-off.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
The veterinary medicinal product may cause skin sensitization. Persons with a known hypersensitivity to cabergoline or any of the excipients should avoid contact with the veterinary medicinal product.
Administer the veterinary medicinal product with caution to avoid self-injection. In case of accidental self-injection, seek medical advice, and show the package leaflet or the label to the physician.
Wash hands after use.

Studies in laboratory animals have shown a risk for embryonic death following repeat oral exposure to cabergoline. In the absence of data on pregnancy outcome in humans following injection of cabergoline, pregnant women and women attempting to conceive should avoid contact with the product. Due to its pharmacological effect (inhibition of lactation) breastfeeding women should avoid contact with the product.

Other precautions
Cabergoline should not enter surface waters as it has harmful effects on aquatic species. Therefore, Velactis-treated cows should not be allowed to have access to open water, and should not contaminate watercourses with faeces until at least 5 days after administration.

4.6 Adverse reactions (frequency and seriousness)

Slight injection site reactions (mostly swellings) were commonly observed after injection of the product and may persist for at least 7 days.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Can be used during pregnancy
Velactis reduces milk production. Therefore, the product should only be administered to dairy cows at the time of drying-off.

4.8 Interaction with other medicinal products and other forms of interaction

In vitro, some macrolide antibiotics, like erythromycin, inhibited the activity of bovine Cytochrom P 450-enzymes (CYP3A4-subclass). This could theoretically decrease the metabolisation of cabergoline, and prolong its persistence in plasma from cows treated concomitantly with Velactis and such products. However, administration of tylosin concomitantly with Velactis in cows did not show any changes of cabergoline pharmacokinetic properties.

4.9 Amounts to be administered and administration route

Intramuscular use.

The recommended dose is 5.6 mg of cabergoline (corresponding to 5 ml of solution for injection) per animal in one single injection at the day of drying-off after the last milking. The product should be administered within 4 hours after the last milking.

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

Overdoses resulted in some cases in slight and transient decrease of appetite. This was observed following 1.5-2 times of the recommended dose and was more pronounced at higher doses.
The administration of three or five times the recommended dose for 3 consecutive days (*i.e.* corresponding to 9 and 15 times the recommended dose, respectively) resulted in addition in some cases in transient and reversible digestive signs such as diarrhoea. At 9 times the recommended dose a decrease in ruminal activity may be observed. Fatal meteorism has been observed in a single cow following a second administration of 5 times the recommended dose. Three consecutive administrations of 1, 3 or 5 times the recommended dose may result in transient and reversible slight elevation of plasma glucose levels.

4.11 Withdrawal period(s)

Meat and offal: 23 days
Milk:

- Zero hours after calving when the dry period length is 32 days or more.
- 4 days (8 milkings) after calving when the dry period length is less than 32 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other gynaecologicals, prolactin inhibitors, cabergoline
ATCvet code: QG02CB03

5.1 Pharmacodynamic properties

Cabergoline is a synthetic ergot derivative, which is a potent dopamine receptor agonist on D_2 receptors. It acts on dopamine receptors of prolactin producing cells in the pituitary gland suppressing the prolactin production and leading to the inhibition of prolactin secretion dependent process. Consequently, cabergoline administration induces a reduction of milk production leading to a reduction in udder engorgement and intramammary pressure. Subsequently udder pain and discomfort are reduced at one and two days after drying off, respectively.

5.2 Pharmacokinetic particulars

After intramuscular administration in cattle, the systemic absorption of cabergoline is rapid and important (bioavailability over 90%), with a peak concentration observed around 3 h after administration and followed by a high tissue distribution.
More than 74% of cabergoline is bound to plasma protein.
Cabergoline is rapidly metabolized principally by liver, and is eliminated with a mean half-life of about 20 h.
Approximately 66% of the administered dose is eliminated by faeces. Urine is the second pathway of elimination.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethyl sulfoxide
Triglycerides, medium-chain

6.2 Incompatibilities

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

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf-life after first opening the immediate packaging: 28 days.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage condition.

6.5 Nature and composition of immediate packaging

Brown glass vials closed by bromobutyl stoppers and crimped with aluminium and plastic flip capsules.

Pack sizes:
Cardboard box with 1 vial of 5 ml, 25 ml or 50 ml, or 5 vials of 5 ml.
Not all pack sizes may be marketed.

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.
Velactis should not enter water courses as this may be dangerous for fish and other aquatic organisms.

7. MARKETING AUTHORISATION HOLDER

Ceva Santé Animale
10 av. de La Ballastière
33500 Libourne
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/15/192/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09/12/2015

10 DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE
B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
C. STATEMENT OF THE MRLs

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Ceva Santé Animale
10 av. de La Ballastière
33500 Libourne
FRANCE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

The active substance in Velactis is cabergoline, an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Cabergoline	Cabergoline	Bovine	0.10 µg/kg 0.25 µg/kg 0.50 µg/kg 0.15 µg/kg 0.10 µg/kg	Fat Liver Kidney Muscle Milk	NO ENTRY	Prolactin inhibitor

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required, or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this veterinary medicinal product.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box of 5 ml vial
Cardboard box of 25 ml vial
Cardboard box of 50 ml vial
Cardboard box of 5x5 ml vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Velactis 1.12 mg/ml solution for injection
cabergoline

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

1 ml contains 1.12 mg of cabergoline.

3. PHARMACEUTICAL FORM

Solution for injection.

4. PACKAGE SIZE

5 ml
25 ml
50 ml
5 x 5 ml

5. TARGET SPECIES

Cattle (dairy cows)

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period:
Meat and offal: 23 days
Milk: - zero hours after calving when the dry period length is 32 days or more.
- 4 days (8 milkings) after calving when the dry period length is less than 32 days

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use

10. EXPIRY DATE

EXP (month/year)
For the 25 ml, 50 ml and the 5x5ml only: Once broached, use within 28 days.

11. SPECIAL STORAGE CONDITIONS

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

Disposal: read package leaflet

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

For animal treatment only. To be supplied only on 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

Ceva Santé Animale
10 av. de La Ballastière
33500 Libourne
FRANCE

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/15/192/001
EU/2/15/192/002
EU/2/15/192/003
EU/2/15/192/004

17. MANUFACTURER'S BATCH NUMBER

Lot

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Label of 5 ml vial
Label of 25 ml vial
Label of 50 ml vial

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Velactis 1.12 mg/ml solution for injection for cattle (dairy cows).
cabergoline

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

1.12 mg/ml

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

5 ml
25 ml
50 ml

4. ROUTE(S) OF ADMINISTRATION

IM

5. WITHDRAWAL PERIOD

Withdrawal period: See box

6. BATCH NUMBER

Lot

7. EXPIRY DATE

EXP

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR
Velactis 1.12 mg/ml solution for injection for cattle.

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

Marketing authorisation holder and manufacturer responsible for batch release:
Ceva Santé Animale
10 av. de La Ballastière
33500 Libourne
FRANCE

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Velactis 1.12 mg/ml solution for injection for cattle.
cabergoline

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

Each ml contains 1.12 mg of cabergoline.
Clear pale yellow solution.

4. INDICATION

For use in the herd management programme of dairy cows as an aid in the abrupt drying-off by reducing milk production to:
- reduce milk leakage at drying off,
- reduce the risk of new intramammary infections during the dry period,
- reduce discomfort.

5. CONTRAINDICATIONS

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

6. ADVERSE REACTIONS

Slight injection site reactions (mostly swellings) were commonly observed after injection of the product and may persist for at least 7 days.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

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

7. TARGET SPECIES

Cattle (dairy cows)

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

Intramuscular use.

The recommended dose is 5.6 mg of cabergoline (corresponding to 5 ml of Velactis) per animal in one single injection at the day of drying-off after the last milking. The product should be injected within 4 hours after the last milking.

9. ADVICE ON CORRECT ADMINISTRATION

Normal aseptic procedures for administration of an intramuscular injection should be followed.
Only use a dry sterile needle and avoid the introduction of humidity/water during use.

10. WITHDRAWAL PERIOD

Meat and offal: 23 days
Milk: - zero hours after calving when the dry period length is 32 days or more.
- 4 days (8 milkings) after calving when the dry period length is less than 32 days

11. SPECIAL STORAGE CONDITIONS

Keep out of the sight and reach of children.

Do not use after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This veterinary medicinal product does not require any special storage condition.
Shelf-life after first opening the immediate packaging: 28 days.

12. SPECIAL WARNING(S)

Velactis should be used as part of a comprehensive mastitis and milk quality control program under veterinarian advice which might include the need to use intramammary treatment.

For cows considered likely to be free of subclinical mastitis at drying off, in which antibiotic use is not justified/permitted, Velactis can be used as a dry cow treatment. The cows should be diagnosed to be free of subclinical mastitis by using suitable criteria such as bacterial examination of milk, somatic cell count or other recognized tests.

Special precautions for use in animals
The product should only be used in dairy cows at the time of drying-off.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
The veterinary medicinal product may cause skin sensitisation and persons with a known hypersensitivity to cabergoline or any of the excipients should avoid contact with it.

Pregnant or breastfeeding women and women attempting to conceive should avoid contact with the solution and should be prevented from an accidental self-injection. (There are no data on pregnancy outcome in humans following injection of cabergoline, but studies in laboratory animals have shown a risk for embryonic death following repeat oral exposure to cabergoline.)

Administer the veterinary medicinal product with caution to avoid self-injection. In case of accidental self-injection, seek medical advice, and show this package leaflet or the label to the physician.
Wash hands after use.

Other precautions
Cabergoline should not enter surface waters as it has harmful effects on aquatic species. Therefore, Velactis-treated cows should not be allowed to have access to open water, and should not contaminate watercourses with faeces until at least 5 days after administration.

Use during pregnancy, lactation or lay
Can be used during pregnancy. Velactis reduces milk production. Therefore, the product should only be administered to dairy cows at the time of drying-off.

Interactions with other medicinal products and other forms of interaction
In vitro, some macrolide antibiotics like erythromycin inhibited the activity of bovine Cytochrom P 450-enzymes (CYP3A4-subclass). This could theoretically decrease the metabolisation of cabergoline, and prolong its persistence in plasma from cows treated concomitantly with Velactis and such products. However, administration of tylosin concomitantly with Velactis in cows did not show any changes of Velactis pharmacokinetic properties.

Overdose (symptoms, emergency procedures, antidotes), if necessary
Overdoses resulted in some cases in slight and transient decrease of appetite. This was observed following 1.5-2 times of the recommended dose and was more pronounced at higher doses.
The administration of three or five times the recommended dose for 3 consecutive days (*i.e.* corresponding to 9 and 15 times the recommended dose, respectively) resulted in addition in some cases in transient and reversible digestive signs such as diarrhoea. At 9 times the recommended dose a decrease in ruminal activity may be observed. Fatal meteorism has been observed in a single cow following a second administration of 5 times the recommended dose. Three consecutive administrations of 1, 3 or 5 times the recommended dose may result in transient and reversible slight elevation of plasma glucose levels.

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

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

Medicines should not be disposed of via wastewater or household waste. Velactis should not enter water courses as this may be dangerous for fish and other aquatic organisms.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

15. OTHER INFORMATION

In a multicentric randomized clinical trial where dairy cows with no intramammary infections at the time of drying-off were administered either Velactis or placebo at the time of drying-off, the incidence of new intramammary infections within 7 days after subsequent calving was significantly lower among udder quarters of cows treated with Velactis (20.5%) as compared to placebo (26.0%). The difference percentage of new intramammary infections during the dry period between Velactis treated animals and the placebo group was 5.5% (95% confidence interval 0.5-10.4%). The efficacy of Velactis in reducing the risk of new intramammary infections during the dry period when administered concomitantly with antimicrobial treatment to cows with intramammary infections has not been investigated compared to antimicrobial treatment alone.

In the same study, incidence of milk leakage was significantly lower among Velactis treated animals (2.0%) as compared to placebo treated animals (10.7%). The difference between groups was 8.7% (95% confidence interval 4.9-12.6%).This was confirmed in another multicentric randomized clinical trial where incidence of milk leakage was significantly lower among Velactis treated animals (3.9%) as compared to placebo treated animals (17.6%). The difference between groups was 13.7% (95% confidence interval 6.4-21%).

In a randomized and placebo controlled clinical study Velactis treated cows presented less signs of udder pain in comparison with controls on the first two days after drying-off. The difference in occurrence of pain was 9.9% (95% confidence interval 4-15.8%) between the Velactis treated cows compared to placebo treated animals. In a randomized and placebo controlled clinical study, reduced discomfort was demonstrated during the first day after drying-off by increasing daily lying time by 143 +/- 17 minutes in Velactis treated animals in comparison with untreated controls.

Pack sizes

Cardboard box with 1 vial of 5 ml, 25 ml or 50 ml, or 5 vials of 5 ml.
Not all pack sizes may be marketed.