ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Imrestor 15 mg solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.7 ml pre-filled syringe contains:

Active substance:
Pegbovigrastim (Pegylated bovine Granulocyte Colony Stimulating Factor [PEG bG-CSF]) 15 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless to pale yellow solution

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (dairy cows and heifers).

4.2 Indications for use, specifying the target species

As an aid in a herd management programme, to reduce the risk of clinical mastitis in periparturient dairy cows and heifers during the 30 days following calving.

4.3 Contraindications

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

4.4 Special warnings for each target species

In a European field trial, the incidence of clinical mastitis observed in the treated group was 9.1 % (113/1235) and in the control group 12.4 % (152/1230), showing a relative reduction in mastitis incidence of 26.0 % (p=0.0094). The efficacy was tested together with normal management practice. Clinical mastitis is investigated as a change in the appearance of the milk or of the quarter or of both milk and quarter.

Based on all field studies, the proportion of mastitis prevented due to herd treatment with Imrestor (Prevented Fraction) is 0.25 (with 95% confidence interval 0.14 – 0.35).

The veterinary medicinal product should only be used on the basis of a positive benefit risk assessment performed at the herd level by the responsible veterinarian.

4.5 Special precautions for use

Special precautions for use in animals

Only for subcutaneous administration.

In one safety study in Jersey cows the margin of safety of this veterinary medicinal product was 1.5x the highest recommended dose (an overdose of 60µg/kg was administered on three occasions) (see also section 4.10). Do not exceed the stated dose.

As expected from the mode of action of the active substance, safety data shows that a mild and transient rise in somatic cell counts in individual cows may be seen.

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

In the case of accidental self-injection, headache and bone and muscle pain may occur. There may also be other effects including nausea and a skin rash, hypersensitivity reactions (breathing difficulties, hypotension, urticaria and angioedema). Seek medical advice immediately and show the package leaflet or the label to the physician.

People with known hypersensitivity to pegbovigrastim should avoid contact with the veterinary medicinal product.

Personal protective equipment consisting of gloves should be worn when handling broken or damaged syringes. Remove gloves and wash hands and exposed skin after use.

4.6 Adverse reactions (frequency and seriousness)

Non-typical anaphylactoid reactions were uncommonly observed in the clinical studies. The cows presented with swelling of mucous membranes (notably vulva and eyelid), skin reactions, increased respiration rate and salivation. The animal may collapse in rare cases. These clinical signs typically appear between 30 minutes and 2 hours after the first dose and resolve within 2 hours. Symptomatic treatment may be required.

Transient local swelling at the injection site as well as inflammatory reactions which resolve within 14 days post treatment may be induced through the subcutaneous administration of the veterinary medicinal product.

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

4.7 Use during pregnancy and lactation

Can be used during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Concurrent administration of substances which alter immune function (e.g. corticosteroids or non steroidal anti-inflammatory drugs) may reduce the efficacy of the product. Concurrent use of such products should be avoided.

No information is available on the safety and efficacy of the concurrent use of this veterinary medicinal product with vaccines.

4.9 Amounts to be administered and administration route

Subcutaneous use.

The treatment regimen consists of two pre-filled syringes. The content of a single pre-filled syringe is to be injected subcutaneously to a dairy cow/heifer 7 days before the anticipated date of calving. The content of a second pre-filled syringe is to be injected subcutaneously within 24 hours after calving. The intervals between the two administrations should not be less than 3 days or more than 17 days.

A single pre-filled syringe delivers a dose of 20-40 µg/kg pegbovigrastim for most cows depending on bodyweight: e.g. a dose of 21 µg/kg bodyweight for a 700 kg cow or 33 µg/kg bodyweight for a 450 kg heifer.

Excessive shaking of the pre-filled syringe may aggregate pegbovigrastim, reducing its biological activity.
The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

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

Evidence from similar active substances in humans suggests that accidental administration of more than the recommended dose could result in adverse reactions, which are related to the activity of pegbovigrastim.

Treatment should be symptomatic. There is no known antidote.

In one safety study in Jersey cows, at overdose of 60 µg/kg, administered on three occasions (1.5x the highest recommended dose), abomasal ulcers were observed.

4.11 Withdrawal period(s)

Meat and offal: zero days.
Milk: zero days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Colony stimulating factors.
ATCvet code: QL03AA90

5.1 Pharmacodynamic properties

Pegbovigrastim is a modified form of the naturally occurring immunoregulatory cytokine, bovine granulocyte colony stimulating factor (bG-CSF). Bovine granulocyte colony stimulating factor is a naturally occurring protein produced by mononuclear leukocytes, endothelial cells and fibroblasts. Colony stimulating factors regulate the production and functional activities of immune cells. The immunoregulatory activities of granulocyte colony stimulating factor concerns notably cells of the neutrophilic granulocyte lineage which bear cell surface receptors for the protein. The product increases the number of circulating neutrophils. It has also been proved that it enhances myeloperoxidase hydrogen peroxide halide mediated microbiocidal capabilities of neutrophils. bG-CSF presents additional functions beyond its action on neutrophils and these may be direct or indirect functions on other cells/receptors and cytokine pathways.

No information is available with regard to a possible immune reaction towards the product or towards the endogenous molecule (bG-CSF) after repeated use of the product in cows.

5.2 Pharmacokinetic particulars

There is no information available about the pharmacokinetics of pegbovigrastim in cattle.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate.
Arginine hydrochloride.
Arginine.
Water for injections.

6.2 Major incompatibilities

Do not mix with any other veterinary medicinal products.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf -life after first opening the immediate packaging: use immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Sensitive to light. Store in the original packaging in order to protect from light.

The veterinary medicinal product may be stored at 25 °C for 24 hours maximum.

6.5 Nature and composition of immediate packaging

2.7 ml of solution for injection in a pre-filled polypropylene colourless syringe with siliconised chlorobutyl stopper and a stainless steel needle with needle guard.

The pre-filled syringes are packed into cardboard boxes as follows;

10 pre-filled syringes.
50 pre-filled syringes.
100 pre-filled syringes.

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.

7. MARKETING AUTHORISATION HOLDER

Elanco GmbH
Heinz-Lohmann-Str. 4
27472 Cuxhaven
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/15/193/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09/12/2015.
Date of last renewal: {DD/MM/YYYY}.

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Elanco UK AH Limited
Elanco Speke Operations
Fleming Road
Speke
Liverpool
UKL24 2LN

Elanco France S.A.S.
26 Rue de la Chapelle
68330 Huningue
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

The active substance in Imrestor 15 mg solution for injection for cattle is 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	MRL	Target tissues	Other provisions	Therapeutic classification
Pegylated bovine granulocyte colony stimulating factor	NOT APPLIABLE	Bovine	No MRL required	NOT APPLICABLE	NO ENTRY	Biological/ Immunomodulator

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 product.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cartons of 10, 50 or 100 pre-filled syringes

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Imrestor 15 mg solution for injection for cattle
pegbovigrastim

2. STATEMENT OF ACTIVE SUBSTANCES

Each 2.7 ml pre-filled syringe contains 15 mg pegbovigrastim.

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

10 pre-filled syringes
50 pre-filled syringes
100 pre-filled syringes

5. TARGET SPECIES

Cattle (dairy cows and heifers)

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal period(s):
Meat and offal: zero days
Milk: zero days

9. SPECIAL WARNING(S), IF NECESSARY

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Sensitive to light. Store in the original packaging in order to protect from light.
The veterinary medicinal product may be stored at 25 °C for 24 hours maximum.

12. SPECIAL 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

Elanco GmbH
Heinz-Lohmann-Str. 4
27472 Cuxhaven
Germany

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/15/193/001-003

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

2.7 ml pre-filled syringe

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Imrestor 15 mg injection 
pegbovigrastim

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

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

4. ROUTE(S) OF ADMINISTRATION

SC

5. WITHDRAWAL PERIOD(S)

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET
Imrestor 15 mg 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:
Elanco GmbH
Heinz-Lohmann-Str. 4
27472 Cuxhaven
Germany

Manufacturer for the batch release:
Elanco UK AH Limited
Elanco Speke Operations
Fleming Road
Liverpool
L24 9LN
United Kingdom

Or

Elanco France S.A.S.
26 Rue de la Chapelle
68330 Huningue
France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Imrestor 15 mg solution for injection for cattle
pegbovigrastim

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

The veterinary medicinal product is a clear, colourless to pale yellow solution for injection containing 15 mg pegbovigrastim (pegylated bovine colony stimulating factor) in a pre-filled syringe.

4. INDICATION(S)

As an aid in a herd management programme, to reduce the risk of clinical mastitis in periparturient dairy cows and heifers during the 30 days following calving.

5. CONTRAINDICATIONS

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

6. ADVERSE REACTIONS

Non typical anaphylactoid type reactions were uncommonly observed during the clinical field studies. The cows presented with swelling of mucous membranes (notably vulva and eyelid), skin reactions, increased respiration rate and salivation. The animal may collapse in rare cases. These clinical signs

typically appear between 30 minutes and 2 hours after the first dose and resolve within 2 hours. Symptomatic treatment may be required.

Transient local swelling at the injection site as well as inflammatory reactions which resolve within 14 days post treatment may be induced through the subcutaneous administration of the veterinary medicinal product.

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

If you notice any serious effects or other effects not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Cattle (dairy cows and heifers).

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

Subcutaneous use.

The treatment regimen consists of two syringes. The content of a single pre-filled syringe is to be injected subcutaneously to a dairy cow/heifer 7 days before the anticipated date of calving. The content of a second pre-filled syringe is to be injected subcutaneously within 24 hours after calving. The intervals between the two administrations should not be less than 3 days or more than 17 days.

A single pre-filled syringe delivers a dose of 20-40 µg/kg pegbovigrastim for most cows depending on bodyweight: e.g. a dose of 21 µg/kg bodyweight for a 700 kg cow or 33 µg/kg bodyweight for a 450 kg heifer.

9. ADVICE ON CORRECT ADMINISTRATION

Only for subcutaneous injection.

Excessive shaking of the pre-filled syringe may aggregate pegbovigrastim reducing its biological activity: The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

No information is available with regards to a possible immune reaction towards the veterinary medicinal product or towards the endogenous molecule (bG-CSF) after repeated use of the veterinary medicincal product in cows.

In one safety study in Jersey cows the margin of safety of this veterinary medicinal product was 1.5x the highest recommended dose (an overdose of 60µg/kg was administered on three occasions). Do not exceed the stated dose.

As expected from the mode of action of the active substance, safety data shows that a mild and transient rise in somatic cell counts in individual cows may be seen.

10. WITHDRAWAL PERIOD(S)

Meat and offal: zero days.
Milk: zero days.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of sight and reach of children.
Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Sensitive to light. Store in the original packaging in order to protect from light.
The veterinary medicinal product may be stored at 25 °C for 24 hours maximum.

Do not use this veterinary medicinal product after the expiry date which is stated on the carton and on the pre-filled syringe.

12. SPECIAL WARNING(S)

In animals, which have pharmaceutically altered immune function e.g. those which have recently received systemically administered corticosteroids or non-steroidal anti-inflammatory drugs the product may not be effective. Concurrent use of such products should be avoided.

The veterinary medicinal product should only be used on the basis of a positive benefit: risk assessment performed at the herd level by the responsible veterinarian.

Evidence from similar active substances in humans suggests that accidental administration to cattle of more than the recommended dose could result in adverse reactions, which are related to the activity of pegbovigrastim. Treatment should be symptomatic. There is no known antidote.

In one safety study in Jersey cows, at overdose of 60 µg/kg, administered on three occasions (1.5x the highest recommended dose), abomasal ulcers were observed.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
In the case of accidental self –injection, headache, bone and muscle pain may occur. There may also be other effects including nausea and a skin rash, hypersensitivity reactions (breathing difficulties, hypotension, urticarial and angioedema). Seek medical advice immediately and show the package leaflet to the physician.

People with known hypersensitivity to pegbovigrastim should avoid contact with the veterinary medicinal product.

Personal protective equipment consisting of gloves when handling broken or damaged syringes.
Remove gloves and wash hands and exposed skin and after use.

Pregnancy and lactation:
Can be used in pregnancy and lactation

Incompatibilities:
Do not mix with other veterinary medicinal products.
Concurrent administration of substances which alter immune function (e.g. corticosteroids or non steroidal anti-inflammatory drugs) may reduce the efficacy of the veterinary medicinal product.
Concurrent use of such products should be avoided.

No information is available on the safety and efficacy of the concurrent use of this veterinary medicinal product with vaccines.

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

Medicines should not be disposed of via wastewater or household waste.
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 veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

15. OTHER INFORMATION

There is no information about the pharmacokinetics of pegbovigrastim in cattle.

Pegbovigrastim is a modified form of the naturally occurring immunoregulatory cytokine, bovine granulocyte colony stimulating factor (bG-CSF). Bovine granulocyte colony stimulating factor is a naturally occurring protein produced by mononuclear leukocytes, endothelial cells and fibroblasts. Colony stimulating factors regulate the production and functional activities of immune cells. The immunoregulatory activities of granulocyte colony stimulating factor concerns notably cells of the neutrophilic granulocyte lineage which bear cell surface receptors for the protein. The product increases the number of circulating neutrophils. It has also been proved that it enhances myeloperoxidase hydrogen peroxide halide mediated microbiocidal capabilities of neutrophils. bG-CSF presents additional functions beyond its action on neutrophils and these may be direct or indirect functions on other cells/receptors and cytokine pathways.

In a European field trial, the incidence of clinical mastitis observed in the treated group was 9.1 % (113/1235) and in the control group 12.4 % (152/1230), showing a relative reduction in mastitis incidence of 26.0 % (p=0.0094). The efficacy was tested alongside normal dairy herd management practices. During this EU study, 312 cows were treated with Imrestor for every 10 cases of clinical mastitis that were prevented during the periparturient period.

Clinical mastitis is investigated as a change in the appearance of the milk or of the quarter or of both milk and quarter.

Based on all field studies, the proportion of mastitis prevented due to herd treatment with Imrestor (Prevented Fraction) is 0.25 (with 95% confidence interval 0.14 – 0.35).

Available in boxes of 10, 50 or 100 pre-filled syringes.
Not all pack sizes may be marketed.