ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Librela 5 mg solution for injection for dogs
Librela 10 mg solution for injection for dogs
Librela 15 mg solution for injection for dogs
Librela 20 mg solution for injection for dogs
Librela 30 mg solution for injection for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each vial of 1 ml contains:

bedinvetmab*: 5 mg
10 mg
15 mg
20 mg
30 mg

* canine monoclonal antibody expressed through recombinant techniques in Chinese hamster ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

For the alleviation of pain associated with osteoarthritis in dogs.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in dogs under 12 months.
Do not use in animals intended for breeding.
Do not use in pregnant or lactating animals.

4.4 Special warnings for each target species

This veterinary medicinal product may induce transient or persistent anti-drug antibodies. The induction of such antibodies is uncommon and may have no effect or may result in a decrease in efficacy in animals that responded to treatment previously.
If no or limited response is observed within one month after initial dosing, an improvement in response may be observed after administration of a second dose one month later. However, if the

animal does not show a better response after the second dose, the veterinary surgeon should consider alternative treatments.

4.5 Special precautions for use

Special precautions for use in animals

None.

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

Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection. Repeated self-administration may increase the risk of hypersensitivity reactions.

The importance of Nerve Growth Factor in ensuring normal foetal nervous system development is well-established and laboratory studies conducted on non-human primates with human anti-NGF antibodies have shown evidence of reproductive and developmental toxicity. Pregnant women, women trying to conceive and breastfeeding women should take extreme care to avoid accidental self-injection.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

Mild reactions at the injection site (e.g. swelling and heat) may uncommonly be observed. Hypersensitivity-type reactions have been reported very rarely. In case of such reactions, appropriate symptomatic treatment should be administered.

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, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation or in breeding dogs. Laboratory studies with human anti-NGF antibodies in cynomolgus monkeys have shown evidence of teratogenic and foetotoxic effects.

Pregnancy and lactation
Do not use in pregnant or lactating animals.

Fertility
Do not use in breeding animals.

4.8 Interaction with other medicinal products and other forms of interaction

In a laboratory study over a 2-week period in young, healthy dogs without osteoarthritis, this veterinary medicinal product had no adverse effect when concomitantly administered with a non-steroidal anti-inflammatory product (carprofen).

There are no safety data on the concurrent long-term use of NSAIDs and bedinvetmab in dogs. In clinical trials in humans, rapidly progressive osteoarthritis has been reported in patients receiving

humanised anti-NGF monoclonal antibody therapy. The incidence of these events increased with high doses and in those human patients that received long-term (more than 90 days) non-steroidal anti-inflammatory drugs (NSAIDs) concomitantly with an anti-NGF monoclonal antibody.

Dogs have no reported equivalent of human rapidly progressive osteoarthritis.

No other laboratory studies on the safety of concomitant administration of this veterinary medicinal product with other veterinary medicinal products have been conducted. No interactions were observed in field studies where this veterinary medicinal product was administered concomitantly with veterinary medicinal products containing parasiticides, antimicrobials, topical antiseptics with or without corticosteroids, antihistamines and vaccines.

If a vaccine(s) is to be administered at the same time as treatment with this veterinary medicinal product, the vaccine(s) should be administered at a different site to that of Librela's administration, to reduce any potential impact on immunogenicity of the vaccine.

4.9 Amounts to be administered and administration route

Subcutaneous use.

Dosage and treatment schedule:

The recommended dose is 0.5-1.0 mg/kg bodyweight, once a month.

Dogs weighing <5.0 kg:
Aseptically withdraw 0.1 ml/kg from a single 5 mg/ml vial and administer subcutaneously.
For dogs between 5 and 60 kg administer the entire content of the vial (1 ml) according to the table below:

	LIBRELA strength (mg) to be administered				
Bodyweight (kg) of dog	**5**	**10**	**15**	**20**	**30**
5.0-10.0	**1 vial**				
10.1-20.0		**1 vial**			
20.1-30.0			**1 vial**		
30.1-40.0				**1 vial**	
40.1-60.0					**1 vial**
60.1-80.0				**2 vials**	
80.1-100.0				**1 vial**	**1 vial**
100.1-120.00					**2 vials**

For dogs above 60 kg, the contents of more than one vial are required to administer a single dose. In those cases, withdraw the content from each required vial into the same syringe and administer as a single subcutaneous injection (2 ml).

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

No adverse reactions, except mild reactions at the injection site, were observed in a laboratory overdose study when Librela was administered for 7 consecutive monthly doses at 10 times the maximum recommended dose.
In case of adverse clinical signs after an overdose the dog should be treated symptomatically.

4.11 Withdrawal period(s)

Not applicable.

5. IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other analgesics and antipyretics
ATC vet code: QN02BG91

Mechanism of action
Bedinvetmab is a canine monoclonal antibody (mAb) targeting Nerve Growth Factor (NGF). The inhibition of NGF mediated cell signalling has demonstrated to provide relief from pain associated with osteoarthritis.

Pharmacokinetics
In a 6-month laboratory study of healthy, adult Beagles administered bedinvetmab every 28 days at doses ranging from 1-10 mg/kg, AUC and C_{max} increased nearly in proportion to dose and steady-state was achieved after approximately 2 doses. In a laboratory pharmacokinetic study at the clinical label dose (0.5-1.0 mg/kg bw), peak serum drug levels (C_{max}) of 6.10 µg/ml were observed at 2-7 days (t_{max} = 5.6 days) after subcutaneous dosing, the bioavailability was approximately 84%, the elimination half-life was approximately 12 days, and the mean $AUC_{0-\infty}$ was 141 µg x d/ml.

In a field effectiveness study at the label dose in dogs with osteoarthritis, the terminal half-life averaged 16 days. Steady state was achieved after 2 doses.

Bedinvetmab, like endogenous proteins, is expected to be degraded into small peptides and amino acids via normal catabolic pathways. Bedinvetmab is not metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Immunogenicity
The presence of binding antibodies to bedinvetmab in dogs was assessed using a multitier approach. In field studies of dogs with osteoarthritis receiving bedinvetmab once monthly, the appearance of anti-bedinvetmab antibodies was infrequent. None of the dogs exhibited any adverse clinical signs considered to be associated with binding antibodies to bedinvetmab.

Field trials
In field studies lasting up to 3 months, treatment of dogs with osteoarthritis was demonstrated to have a favourable effect on the reduction of pain assessed by the Canine Brief Pain Inventory (CBPI). CBPI is an assessment by the animal owner of an individual dog's response to pain treatment as assessed by pain severity (scale of 0 to 10, where 0 = no pain and 10 = extreme pain), interference of pain with the dog's typical activities (scale of 0 to 10, where 0 = no interference and 10 = completely interferes) and quality of life. In the pivotal EU multicentre field study, 43.5% of the Librela-treated dogs and 16.9% of the placebo-treated dogs demonstrated treatment success, defined as a reduction of ≥1 in pain severity score (PSS) and ≥2 in pain interference score (PIS), on day 28 after the first dose. An onset of efficacy was demonstrated at 7 days post administration, with treatment success demonstrated in 17.8% of the Librela-treated dogs and 3.8% of the placebo-treated dogs. Treatment with bedinvetmab has demonstrated a positive effect on all three components of the CBPI. Data from an uncontrolled follow-up study lasting up to 9 months indicated sustained efficacy of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate

Disodium edetate
Methionine
Poloxamer 188
Water for injections

6.2 Major incompatibilities

Do not mix with any other veterinary medicinal product.

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 and transport refrigerated (2 °C - 8 °C).
Do not freeze.
Store in the original package.
Protect from light.

6.5 Nature and composition of immediate packaging

Clear glass type I vials with fluorobutyl rubber stopper.

Pack sizes:

Cardboard box with 1 vial of 1 ml
Cardboard box with 2 vials of 1 ml
Cardboard box with 6 vials of 1 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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zoetis Belgium SA
Rue Laid Burniat 1
1348 Louvain-la-Neuve
BELGIUM

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/20/261/001-015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10/11/2020.

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/).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Zoetis Inc
601 West Cornhusker Highway
68521 Lincoln, Nebraska
UNITED STATES

Name and address of the manufacturer responsible for batch release

Zoetis Belgium SA
Rue Laid Burniat 1
1348 Louvain-la-Neuve
BELGIUM

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARDBOARD BOX

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Librela 5 mg Solution for injection for dogs.
Librela 10 mg Solution for injection for dogs.
Librela 15 mg Solution for injection for dogs.
Librela 20 mg Solution for injection for dogs.
Librela 30 mg Solution for injection for dogs.
bedinvetmab

2. STATEMENT OF ACTIVE SUBSTANCES

Each 1 ml contains 5 mg bedinvetmab.
Each 1 ml contains 10 mg bedinvetmab.
Each 1 ml contains 15 mg bedinvetmab.
Each 1 ml contains 20 mg bedinvetmab.
Each 1 ml contains 30 mg bedinvetmab.

3. PHARMACEUTICAL FORM

Solution for injection.

4. PACKAGE SIZE

1 x 1 ml
2 x 1 ml
6 x 1 ml

5. TARGET SPECIES


Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once broached use immediately.

11. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.
Store in the original package.
Protect from light.

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

Zoetis Belgium SA
Rue Laid Burniat 1
1348 Louvain-la-Neuve
BELGIUM

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/20/261/001 5 mg 1 vial
EU/2/20/261/002 5 mg 2 vials
EU/2/20/261/003 5 mg 6 vials
EU/2/20/261/004 10 mg 1 vial
EU/2/20/261/005 10 mg 2 vials
EU/2/20/261/006 10 mg 6 vials
EU/2/20/261/007 15 mg 1 vial
EU/2/20/261/008 15 mg 2 vials
EU/2/20/261/009 15 mg 6 vials

EU/2/20/261/010 20 mg 1 vial
EU/2/20/261/011 20 mg 2 vials
EU/2/20/261/012 20 mg 6 vials
EU/2/20/261/013 30 mg 1 vial
EU/2/20/261/014 30 mg 2 vials
EU/2/20/261/015 30 mg 6 vials

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL – 1 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Librela 5 mg Solution for injection for dogs
Librela 10 mg Solution for injection for dogs
Librela 15 mg Solution for injection for dogs
Librela 20 mg Solution for injection for dogs
Librela 30 mg Solution for injection for dogs
bedinvetmab

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

bedinvetmab 5 mg
bedinvetmab 10 mg
bedinvetmab 15 mg
bedinvetmab 20 mg
bedinvetmab 30 mg

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

1 ml

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:
Librela 5 mg solution for injection for dogs
Librela 10 mg solution for injection for dogs
Librela 15 mg solution for injection for dogs
Librela 20 mg solution for injection for dogs
Librela 30 mg solution for injection for dogs

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:

Zoetis Belgium SA
Rue Laid Burniat 1
1348 Louvain-la-Neuve
BELGIUM

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Librela 5 mg solution for injection for dogs
Librela 10 mg solution for injection for dogs
Librela 15 mg solution for injection for dogs
Librela 20 mg solution for injection for dogs
Librela 30 mg solution for injection for dogs
bedinvetmab

3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENTS

Active substance:

Each vial of 1 ml contains 5 mg, 10 mg, 15 mg, 20 mg or 30 mg bedinvetmab*.

* Bedinvetmab is a canine monoclonal antibody expressed through recombinant techniques in Chinese hamster ovary (CHO) cells.

4. INDICATION(S)

For the alleviation of pain associated with osteoarthritis in dogs.

5. CONTRAINDICATIONS

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in dogs under 12 months.
Do not use in animals intended for breeding.
Do not use in pregnant or lactating animals.

6. ADVERSE REACTIONS

Mild reactions at the injection site (e.g. swelling and heat) may uncommonly be observed.

Hypersensitivity-type reactions have been reported very rarely. In case of such reactions, appropriate symptomatic treatment should be administered.

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).

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 inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

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

Subcutaneous use.

Dosage and treatment schedule:

The recommended dose is 0.5-1.0 mg/kg bodyweight, once a month.

Dogs weighing <5.0 kg:
Aseptically withdraw 0.1 ml/kg from a single 5 mg/ml vial and administer subcutaneously.

For dogs between 5 and 60 kg administer the entire content of the vial (1 ml) according to the table below:

	LIBRELA strength (mg) to be administered				
Bodyweight (kg) of dog	**5**	**10**	**15**	**20**	**30**
5.0-10.0	**1 vial**				
10.1-20.0		**1 vial**			
20.1-30.0			**1 vial**		
30.1-40.0				**1 vial**	
40.1-60.0					**1 vial**
60.1-80.0				**2 vials**	
80.1-100.0				**1 vial**	**1 vial**
100.1-120.00					**2 vials**

For dogs above 60 kg, the contents of more than one vial are required to administer a single dose. In those cases, withdraw the content from each required vial into the same syringe and administer as a single subcutaneous injection (2 ml).

9. ADVICE ON CORRECT ADMINISTRATION

The product should appear clear to slightly opalescent without any visible particles.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Store and transport refrigerated (2 °C – 8 °C).
Do not freeze.
Store in the original package.
Protect from light.
Do not use this veterinary medicinal product after the expiry date which stated on the label after EXP.

Shelf life after first opening the container: use immediately.

12. SPECIAL WARNING(S)

Special warnings for each target species:

This veterinary medicinal product may induce transient or persistent anti-drug antibodies. The induction of such antibodies is uncommon and may have no effect or may result in a decrease in efficacy in animals that responded to treatment previously.

If no or limited response is observed within one month after initial dosing, an improvement in response may be observed after administration of a second dose one month later. However, if the animal does not show a better response after the second dose, the veterinary surgeon should consider alternative treatments.

Special precautions for use in animals:

None

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

Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection. Repeated self-administration may increase the risk of hypersensitivity reactions.

The importance of Nerve Growth Factor in ensuring normal foetal nervous system development is well-established and laboratory studies conducted on non-human primates with human anti-NGF antibodies have shown evidence of reproductive and developmental toxicity. Pregnant women, women trying to conceive and breastfeeding women should take extreme care to avoid accidental self-injection.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy and lactation:

The safety of the veterinary medicinal product has not been established during pregnancy and lactation or in breeding dogs. Laboratory studies with human anti-NGF antibodies in cynomolgus monkeys have shown evidence of teratogenic and foetotoxic effects.

Do not use in pregnant or lactating animals.

Fertility:
Do not use in breeding animals.

Interaction with other medicinal products and other forms of interaction:

In a laboratory study over a 2-week period in young, healthy dogs without osteoarthritis, this veterinary medicinal product had no adverse effect when concomitantly administered with a non-steroidal anti-inflammatory product (carprofen).

There are no safety data on the concurrent long-term use of NSAIDs and bedinvetmab in dogs. In clinical trials in humans, rapidly progressive osteoarthritis has been reported in patients receiving humanised anti-NGF monoclonal antibody therapy. The incidence of these events increased with high doses and in those human patients that received long-term (more than 90 days) non-steroidal anti-inflammatory drugs (NSAIDs) concomitantly with an anti-NGF monoclonal antibody.

Dogs have no reported equivalent of human rapidly progressive osteoarthritis.

No other laboratory studies on the safety of concomitant administration of this veterinary medicinal product with other veterinary medicinal products have been conducted. No interactions were observed in field studies where this veterinary medicinal product was administered concomitantly with veterinary medicinal products containing parasiticides, antimicrobials, topical antiseptics with or without corticosteroids, antihistamines and vaccines.

If a vaccine(s) is to be administered at the same time as treatment with this veterinary medicinal product, the vaccine(s) should be administered at a different site to that of Librela's administration, to reduce any potential impact on immunogenicity of the vaccine.

Overdose (symptoms, emergency procedures, antidotes):

No adverse reactions, except mild reactions at the injection site, were observed in a laboratory overdose study when Librela was administered for 7 consecutive monthly doses at 10 times the maximum recommended dose.

In case of adverse clinical signs after an overdose the dog should be treated symptomatically.

Incompatibilities:

Do not mix with any other veterinary medicinal product.

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

Clear glass Type I vials with fluorobutyl rubber stopper.

Secondary packaging: cardboard box.

Pack sizes:
Cardboard box with 1, 2 or 6 vials of 1 ml

Not all pack sizes may be marketed.