ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cerenia 10 mg/ml solution for injection for dogs and cats.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
The solution for injection contains 10 mg maropitant per ml as maropitant citrate monohydrate.

Excipients:
The solution for injection contains 3.3 mg/ml metacresol (as preservative).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
A clear, colourless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs, cats

4.2 Indications for use, specifying the target species

Dogs:
- For the treatment and prevention of nausea induced by chemotherapy.
- For the prevention of vomiting except that induced by motion sickness
- For the treatment of vomiting, in combination with other supportive measures

Cats:
- For the prevention of vomiting and the reduction of nausea, except that induced by motion sickness.
  For the treatment of vomiting, in combination with other supportive measures.

4.3 Contraindications

None

4.4 Special warnings

Vomiting can be associated with serious, severely debilitating conditions including gastrointestinal obstructions; therefore, appropriate diagnostic evaluations should be employed.

Good veterinary practice indicates that antiemetics should be used in conjunction with other veterinary and supportive measures such as dietary control and fluid replacement therapy while addressing the underlying causes of the vomiting.

The use of Cerenia solution for injection against vomiting due to motion sickness is not recommended.

Dogs:
Although Cerenia has been demonstrated to be effective in both the treatment and prevention of emesis induced by chemotherapy, it was found more efficacious if used preventively. Therefore, it is recommended to administer the antiemetic prior to administration of the chemotherapeutic agent.

Cats:
The efficacy of Cerenia in reduction of nausea was demonstrated in studies using a model (xylazine-induced nausea).

4.5 Special precautions for use

Special precautions for use in animals

The safety of the veterinary medicinal product has not been established in dogs less than 8 weeks of age, or in cats less than 16 weeks of age, and in pregnant or lactating dogs and cats. Use only according to the benefit/risk assessment by the responsible veterinarian.

Maropitant is metabolised in the liver and therefore should be used with caution in patients with hepatic disease.

Cerenia should be used with caution in animals suffering from or with predisposition for cardiac diseases as maropitant has affinity to Ca- and K-ion channels. Increases of approximately 10% in the QT interval of the ECG were observed in a study on healthy beagle dogs administered 8 mg/kg orally; however, such an increase is unlikely to be of clinical significance.

Injecting the product at refrigerated temperature may reduce pain at injection.

Due to the frequent occurrence of transient pain during the injection, appropriate animal restraining measures may have to be applied.

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

Wash hands after use. In case of accidental self-injection seek medical advice immediately and show the package leaflet or the label to the physician. In laboratory studies, maropitant has been shown to be a potential eye irritant. In the case of accidental eye exposure, flush the eyes with plenty of water and seek medical attention

4.6 Adverse reactions (frequency and seriousness)

Pain at injection site may occur. In cats, moderate to severe response to injection is very commonly observed (in approximately one third of cats).

In very rare cases, anaphylactic type reactions (allergic oedema, urticaria, erythema, collapse, dyspnoea, pale mucous membranes) may occur.

4.7 Use during pregnancy, lactation or lay

Use only according to the benefit/risk assessment by the responsible veterinarian, because conclusive reproductive toxicity studies have not been conducted in any animal species.

4.8 Interaction with other medicinal products and other forms of interaction

Cerenia should not be used concomitantly with Ca-channel antagonists as maropitant has affinity to Ca-channels.

Maropitant is highly bound to plasma proteins and may compete with other highly bound medicines.

4.9 Amounts to be administered and administration route

For subcutaneous use in dogs and cats.

Cerenia solution for injection should be injected subcutaneously, once daily, at a dose of 1 mg/kg bodyweight (1 ml/10 kg bodyweight) for up to 5 consecutive days.

In dogs, Cerenia can be used to treat or prevent vomiting either as tablets or as solution for injection once daily for up to five days.

To prevent vomiting, Cerenia solution for injection should be administered more than 1 hour in advance. The effect duration is approximately 24 h and therefore treatment can be given the night before administration of an agent that may cause emesis e.g. chemotherapy.

As the pharmacokinetic variation is large and maropitant accumulates in the body after once daily repeated administration, lower doses than recommended might be sufficient in some individuals and when repeating the dose.

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

Apart from transient reactions at the injection site, Cerenia solution for injection was well tolerated in dogs and young cats injected daily with up to 5 mg/kg (5 times the recommended dose) for 15 consecutive days (3-times the recommended duration of administration). No data have been presented on overdoses in adult cats.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antiemetic, ATCvet code: QA04AD90

Maropitant is a potent and selective neurokinin (NK-1) receptor antagonist, which acts by inhibiting the binding of substance P, a neuropeptide of the tachykinin family, in the CNS.

5.1 Pharmacodynamic properties

Vomiting is a complex process coordinated centrally by the emetic centre. This centre consists of several brainstem nuclei (area postrema, nucleus tractus solitarius, dorsal motor nucleus of the vagus) that receive and integrate sensory stimuli from central and peripheral sources and chemical stimuli from the circulation and the cerebro-spinal fluid.

Maropitant is a neurokinin 1 (NK_1) receptor antagonist, which acts by inhibiting the binding of substance P, a neuropeptide of the tachykinin family. Substance P is found in significant concentrations in the nuclei comprising the emetic centre and is considered the key neurotransmitter involved in vomiting. By inhibiting the binding of substance P within the emetic centre, maropitant is effective against neural and humoral (central and peripheral) causes of vomiting.

A variety of *in vitro* assays have demonstrated that maropitant binds selectively at the NK_1 receptor with dose-dependent functional antagonism of substance P activity.

Maropitant is effective against vomiting. The anti-emetic efficacy of maropitant against central and peripheral emetics was demonstrated in experimental studies including apomorphine, cisplatin and syrup of ipecac (dogs) and xylazine (cats).
Signs of nausea in dogs including excessive salivation and lethargy might remain after treatment.

5.2 Pharmacokinetic particulars

Dogs:
The pharmacokinetic profile of maropitant when administered as a single subcutaneous dose of 1 mg/kg body weight to dogs was characterised by a maximum concentration (C_{max}) in plasma of approximately 92 ng/ml; this was achieved within 0.75 hours post-dosing (T_{max}). Peak concentrations were followed by a decline in systemic exposure with an apparent elimination half-life (t1/2) of 8.84 hours.

During clinical studies maropitant plasma levels conferred efficacy from 1 hour after administration.

The bioavailability of maropitant after subcutaneous administration in dogs was 90.7%. The volume of distribution at steady-state (Vss) determined after intravenous administration at 1 - 2 mg/kg ranged from approximately 4.4 to 7.0 L/kg. Maropitant displays linear kinetics when administered subcutaneously within the 0.5 – 2 mg/kg dose range.

Following repeated subcutaneous administration of once-daily doses of 1 mg / kg bodyweight for five consecutive days, accumulation was 146%. Maropitant undergoes cytochrome P450 (CYP) metabolism in the liver. CYP2D15 and CYP3A12 were identified as the canine isoforms involved in the hepatic biotransformation of maropitant.

Renal clearance is a minor route of elimination, with less than 1% of a 1 mg/kg subcutaneous dose appearing in the urine as either maropitant or its major metabolite. Plasma protein binding of maropitant in dogs is more than 99%.

Cats:
The pharmacokinetic profile of maropitant when administered as a single subcutaneous dose of 1 mg/kg body weight to cats was characterised by a maximum concentration (C_{max}) in plasma of approximately 165 ng/ml; this was achieved on average 0.32 hours (19 min) post-dosing (T_{max}). Peak concentrations were followed by a decline in systemic exposure with an apparent elimination half-life (t1/2) of 16.8 hours. There appears to be an age-related effect on the pharmacokinetics of maropitant in cats with kittens having higher clearance than adults.

During clinical studies maropitant plasma levels conferred efficacy from 1 hour after administration.

The bioavailability of maropitant after subcutaneous administration in cats was 91.3%. The volume of distribution at steady-state (Vss) determined after intravenous administration at 0.25 mg/kg ranged from 2.27 to 3.80 L/kg. Maropitant displays linear kinetics when administered subcutaneously within the 0.25 – 3 mg/kg dose range.

Following repeated subcutaneous administration of once-daily doses of 1 mg/kg bodyweight for five consecutive days, accumulation was 250%. Maropitant undergoes cytochrome P450 (CYP) metabolism in the liver. CYP1A and CYP3A-related enzymes were identified as the feline isoforms involved in the hepatic biotransformation of maropitant.

Renal and faecal clearances are minor routes of elimination for maropitant, with less than 1% of a 1 mg/kg subcutaneous dose appearing in the urine or faeces as maropitant. For the major metabolite

10.4% of the maropitant dose was recovered in urine and 9.3% in faeces. Plasma protein binding of maropitant in cats was estimated to be 99.1%.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulphobutyl ether β-cyclodextrin (SBECD)
Water for injections
Metacresol (as preservative)

6.2 Incompatibilities

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

6.3 Shelf life

Shelf life of the product as packaged for sale: 3 years.
Once broached, use within 28 days.

6.4. Special precautions for storage

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

6.5 Nature and composition of immediate packaging

20 ml, amber molded glass type 1 vial, chlorobutyl rubber stopper and aluminium overseal with flip-off button. Each cardboard outer contains 1 vial.

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

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/06/062/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29/09/2006
Date of last renewal: 29/09/2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) 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

D. OTHER CONDITIONS AND REQUIREMENTS OF THEMARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Global Manufacturing (PGM)
Z. I. de Pocé
29 route des Industries
F-37530 Pocé sur Cisse
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

PSURS:
With the addition of a new target species (cats), the periodic safety update report (PSUR) cycle for Cerenia has been reset at 30 June 2012 for submission of 6 monthly reports (covering all authorised presentations of the product) for the next two years, followed by yearly reports for the subsequent two years and thereafter at 3 yearly intervals.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

  Not applicable

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARDBOARD CARTON / Solution for injection

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cerenia 10 mg/ml solution for injection for dogs and cats
Maropitant

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

10 mg maropitant per ml as maropitant citrate monohydrate.
Metacresol as preservative.

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

20 ml

5. TARGET SPECIES

Dogs and cats

6. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
1 mg/kg bodyweight.

7. SPECIAL WARNING(S), IF NECESSARY

Injecting the product at refrigerated temperature may reduce pain at injection. Use appropriate animal restraining measures.

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

8. EXPIRY DATE

EXP {month/year}
Once broached, use by:……..

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

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

10. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only- to be supplied only on veterinary prescription.

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

Keep out of the reach and sight of children.

12. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

13. MARKETING AUTHORISATION NUMBER(S)

EU/2/06/062/005

14. MANUFACTURER'S BATCH NUMBER

Lot

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

GLASS VIAL / Solution for injection

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cerenia 10 mg / ml solution for injection for dogs and cats
Maropitant

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

10 mg / ml

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

20 ml

4. ROUTE(S) OF ADMINISTRATION

Subcutaneous use.

5. BATCH NUMBER

Lot

6. EXPIRY DATE

EXP {month/year}
Once broached, use within 28 days.

7. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:

Cerenia 10 mg/ml solution for injection for dogs and cats

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

Marketing Authorisation Holder:

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
UK

Manufacturing Authorisation Holder Responsible For Batch Release:

Pfizer PGM
37530 Pocé sur Cisse
France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cerenia 10 mg/ml solution for injection for dogs and cats
Maropitant

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

The solution for injection contains 10 mg maropitant per ml as maropitant citrate monohydrate as a clear, colourless to light yellow solution
It also contains metacresol (as preservative).

4. INDICATIONS

Dogs:

- For the treatment and prevention of nausea induced by chemotherapy.
- For the prevention of vomiting except that induced by motion sickness
- For the treatment of vomiting, in combination with other supportive measures

Cats:

- For the prevention of vomiting and the reduction of nausea, except that induced by motion sickness.
- For the treatment of vomiting, in combination with other supportive measures.

5. CONTRAINDICATIONS

None

6. ADVERSE REACTIONS

Pain at injection site may occur.

In cats, moderate to severe response to injection is very commonly observed (in approximately one third of cats).

In very rare cases, anaphylactic type reactions (allergic oedema, urticaria, erythema, collapse, dyspnoea, pale mucous membranes) may occur.

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

7. TARGET SPECIES

Dogs and cats.

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

For subcutaneous use in dogs and cats.

Cerenia solution for injection should be injected subcutaneously, once daily, at a dose of 1 mg/kg bodyweight (1 ml/10 kg bodyweight). Treatment may be repeated for up to five consecutive days.

In dogs, Cerenia solution for injection can be used to treat or prevent vomiting once daily for up to 5 days.

9. ADVICE ON CORRECT ADMINISTRATION

To prevent vomiting, Cerenia solution for injection should be administered more than 1 hour in advance. The effect duration is approximately 24 h and therefore treatment can be given the night before administration of an agent that may cause emesis e.g. chemotherapy.

Injecting the product at refrigerated temperature may reduce pain at injection.

Due to the frequent occurrence of transient pain during the injection, appropriate animal restraining measures may have to be applied.

10. WITHDRAWAL PERIOD

Not applicable

11. SPECIAL STORAGE CONDITIONS

Keep out of the reach and sight of children.
This veterinary medicinal product does not require any special storage conditions.
Once opened, the vial should be used within 28 days.
Do not use after the expiry date, which is mentioned on the label of the vial after EXP.

12. SPECIAL WARNINGS

Vomiting can be associated with serious, severely debilitating conditions and the cause should be investigated. Products such as Cerenia should be used in conjunction with other supportive measures such as dietary control and fluid replacement therapy, as recommended by your veterinary surgeon.

Maropitant is metabolised in the liver and therefore should be used with caution in dogs and cats with liver disease. Cerenia should be used with caution in animals suffering from or with predisposition for heart diseases.

The use of Cerenia solution for injection against vomiting due to motion sickness is not recommended.

The efficacy of Cerenia in reduction of nausea in cats was demonstrated in studies using a model (xylazine-induced nausea).

The safety of Cerenia has not been established in dogs less than 8 weeks of age, or in cats less than 16 weeks of age, and in pregnant or lactating dogs and cats. The responsible veterinarian should make a benefit-risk assessment before using Cerenia in dogs less than 8 weeks of age, or in cats less than 16 weeks of age, or in pregnant or lactating bitches and cats.

Wash hands after use. In case of accidental self injection seek medical advice immediately and show the package leaflet or the label to the physician. Maropitant has been shown to be a potential eye irritant, and in the case of accidental eye exposure, flush the eyes with plenty of water and seek medical attention.

Cerenia must not be mixed with other veterinary medicinal products in the same syringe as its compatibility with other products has not been tested.

Cerenia should not be used concomitantly with Ca-channel antagonists as maropitant has affinity to Ca-channels.

Maropitant is highly bound to plasma proteins and may compete with other highly bound drugs.

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

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

14. DATE ON WHICH PACKAGE LEAFLET WAS LAST APPROVED

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

15. OTHER INFORMATION

Cerenia 10 mg per ml solution for injection for dogs and cats is available in 20 ml amber glass vials. Each cardboard box contains 1 vial.

For any information about this veterinary medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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