ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Prasequine 1 mg tablets for horses (AT, BE, DE, EE, EL, ES, FR, HU, IE, IT, LT, LV, NL, PT, SK, UK-NI)

Prasequin vet. 1 mg tablets for horses (DK, FI, NO, PL, SE)

Pras-equine 1 mg tablets for horses (CZ)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substances:
Pergolide 1.0 mg
equivalent to 1.31 mg pergolide mesilate

Excipients:

Qualitative composition of excipients and other constituents
Lactose monohydrate
Croscarmellose sodium
Povidone
Magnesium stearate
Iron oxide yellow (E172)

Off-white round and convex tablet with a cross-shaped break line on one side.
Tablets can be divided into 2 or 4 equal parts.

3. CLINICAL INFORMATION

3.1 Target species

Horses (non food-producing).

3.2 Indications for use for each target species

Symptomatic treatment of clinical signs associated with Pituitary Pars Intermedia Dysfunction (PPID) (Equine Cushing's Disease).

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or other ergot derivatives or to any of the excipients.
Do not use in horses less than 2 years of age.

3.4 Special warnings

Appropriate endocrinologic laboratory tests should be conducted as well as evaluation of clinical signs in order to establish a diagnosis of PPID.

3.5 Special precautions for use

Special precautions for safe use in the target species:
As the majority of cases of PPID are diagnosed in aged horses, other pathological processes are frequently present. For monitoring and frequency of testing, see section 3.9.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Pergolide, like other ergot derivatives, may cause emesis, dizziness, lethargy or low blood pressure. Severe adverse events such as collapse have been observed.
Ingestion may be harmful and associated with severe adverse events, especially in children or people with pre-existing heart conditions. Do not ingest this veterinary medicinal product.

In order to reduce the risk of accidental ingestion:
- Store and handle this veterinary medicinal product separately away from human medicinal products and handle it with great care. Keep the veterinary medicinal product out of reach and sight of children.
- Tablets prepared for administration should be administered immediately and not left unattended.
- Tablet parts should be returned to the open blister space. Blisters should be inserted back into the outer packaging and kept in a safe place.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Avoid driving or operating machinery following ingestion of this veterinary medicinal product.

This veterinary medicinal product may cause eye irritation, an irritating smell, or headache after dividing the tablets. Avoid contact with the eyes and inhalation when handling the tablets. Minimise exposure risks when dividing or dissolving tablets, e.g. tablets should not be crushed.
In case of contact with skin, wash exposed skin with water. In the event of eye exposure, flush the affected eye immediately with water and seek medical advice. For nasal irritation, move to fresh air and seek for medical attention if breathing difficulty develops.

This veterinary medicinal product may cause hypersensitivity (allergy) reactions. People with known hypersensitivity to pergolide or other ergot derivatives should avoid contact with the veterinary medicinal product.
This veterinary medicinal product may cause adverse effects due to decreased prolactin levels, which poses a particular risk to pregnant and lactating women. Pregnant or lactating women should avoid dermal contact or hand-to-mouth contact by wearing gloves when administering the veterinary medicinal product.

Do not eat, drink or smoke when using this veterinary medicinal product. Wash hands after use.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Horses (non food-producing):

Rare (1 to 10 animals / 10 000 animals treated):	Inappetence, Anorexia[1], Lethargy[1] Central nervous system disorder (e.g., central nervous system depression and ataxia)[2] Diarrhoea, Colic
Very rare	Increased sweating

(<1 animal / 10 000 animals treated, including isolated reports):	

[1]Transient
[2] Mild

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:
The safety of this veterinary medicinal product has not been demonstrated in pregnant mares. Laboratory studies in mice and rabbits have not produced any evidence of teratogenic effects. Reduced fertility was seen in mice at a dose of 5.6 mg/kg body weight per day. Use only according to the benefit/ risk assessment by the responsible veterinarian.

Lactation:
The use is not recommended in lactating horses, in which the safety of this veterinary medicinal product has not been demonstrated. In mice, reduced body weights and survival rates in the progeny were attributed to the pharmacological inhibition of prolactin secretion resulting in lactation failure.

3.8 Interaction with other medicinal products and other forms of interaction

Use with caution in case the veterinary medicinal product is co-administered with other drugs known to affect protein binding.
Do not administer concurrently with dopamine antagonists, such as neuroleptics (phenothiazines - e.g. acepromazine), domperidone, or metoclopramide, as these agents may reduce the effectiveness of pergolide.

3.9 Administration routes and dosage

Oral use, once daily.
To facilitate administration, the required daily dose should be placed in a small amount of water and/or mixed with molasses or other sweetener and agitated until dissolved. In this case, the dissolved tablets should be administered with a syringe. The whole amount should be administered immediately. Tablets should not be crushed, see section 3.5. When tablets are divided, the remaining tablet portion should be given at the next administration.

Starting dose
The starting dose is about 2 µg pergolide/kg (dose range: 1.7 to 2.5 µg/kg; see table below). The maintenance dose should then be titrated according to the individual response as determined by monitoring (see below), resulting in an average maintenance dose of 2 µg pergolide/kg bodyweight with a dose range of 0.6 to 10 µg pergolide/kg bodyweight.

Starting doses are recommended as follows:

Horse body weight kg	Number of tablets	Starting dose mg/horse	Dosage range µg/kg
200 - 300	½	0.50	1.7 – 2.5
301 – 400	¾	0.75	1.9 - 2.5
401 - 600	1	1.00	1.7 – 2.5
601 - 850	1 ½	1.50	1.8 – 2.5
851 - 1000	2	2.00	2.0 – 2.4

Maintenance dose
Lifelong treatment is anticipated for this disease.
Most horses respond to therapy and are stabilised at an average dose of 2 µg pergolide/kg body weight. Clinical improvement with pergolide is expected within 6 to 12 weeks. Horses may respond clinically at lower or varying doses; it is therefore recommended to titrate to the lowest effective dose per individual based on response to therapy, whether it is effectiveness or signs of intolerance. Some horses may require doses as high as 10 µg pergolide/kg body weight per day. In these rare situations, appropriate additional monitoring is advised.

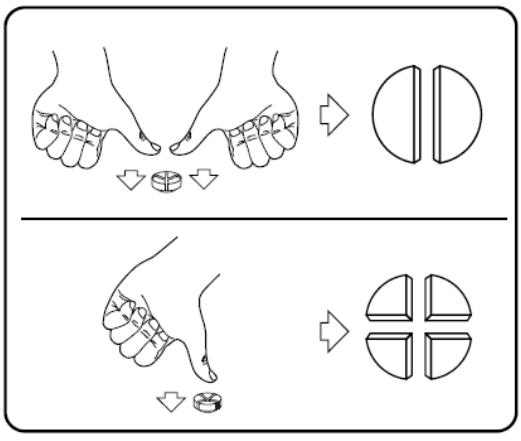
Following initial diagnosis, repeat endocrinologic testing for dose titration and monitoring of treatment at intervals of 4 to 6 weeks until stabilisation or improvement of clinical signs and/or diagnostic testing occurs.

If clinical signs or diagnostic testing have not yet improved at the first 4 to 6 week interval, the total daily dose may be increased by 0.25 - 0.50 mg. In case clinical signs have improved but are not yet normalised, the veterinarian may decide to titrate or not to titrate the dose, considering the individual's response/tolerance to the dose.

In case clinical signs are not adequately controlled (clinical evaluation and/or diagnostic testing) it is recommended to increase the total daily dose by 0.25 - 0.50 mg increments (if the drug is tolerated at that dose) every 4 to 6 weeks until stabilisation occurs.
If signs of dose intolerance develop, treatment should be stopped for 2 to 3 days and reinstated at one-half of the previous dose. The total daily dose may then be titrated back up to the desired clinical effect by 0.25 - 0.50 mg increments every 2 to 4 weeks.
If a dose is missed, the next scheduled dose should be administered as prescribed.

Following stabilisation, regular clinical assessment and diagnostic testing should be performed every 6 months to monitor treatment and dose. Where there is no apparent response to treatment, the diagnosis and/or treatment plan should be re-evaluated.

Tablets can be divided into 2 or 4 equal parts to ensure accurate dosing. Place the tablet on a flat surface, with its scored side facing up and the convex (rounded) side facing the surface.



2 equal parts: press down with your thumbs on both sides of the tablet.
4 equal parts: press down with your thumb in the middle of the tablet.

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

No information available.

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

Not applicable.

3.12 Withdrawal periods

Not authorised for use in horses intended for human consumption.
The horse must have been declared as not intended for human consumption under national horse passport legislation.
Not authorised for use in mares producing milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QN04BC02

4.2 Pharmacodynamics

Pergolide is a synthetic ergot derivative and is a potent, long-acting dopamine receptor agonist. Both *in vitro* and *in vivo* pharmacological studies have demonstrated the activity of pergolide as a selective dopamine agonist with little or no effect on norepinephrine, epinephrine or serotonin pathways at therapeutic doses. As with other dopamine agonists, pergolide inhibits the release of prolactin. In horses with Pituitary Pars Intermedia Dysfunction (PPID) pergolide exerts its therapeutic effect by stimulating dopamine receptors. Further, in horses with PPID, pergolide has been shown to decrease the plasma levels of ACTH, MSH and other pro-opiomelanocortin peptides.

4.3 Pharmacokinetics

Pharmacokinetic information in the horse is available for oral doses of 2, 4 and 10 µg pergolide/kg body weight. It has been demonstrated that pergolide is rapidly absorbed with a short time to peak concentration.

Peak concentrations (C_{max}) following the dose of 10 µg/kg were low and variable with a mean of ~ 4 ng/ml and a mean terminal half-life (T ½) of ~ 6 hours. The median time of peak concentration (T_{max}) was ~ 0.4 hours and the area under the curve (AUC) was ~ 14 ng x hours/ml.

In a more sensitive analytical assay, plasma concentrations following the dose of 2 µg pergolide/kg were very low and variable with peak concentrations ranging from 0.138 to 0.551 ng/ml. The peak concentrations occurred at 1.25 +/- 0.5 hours (T_{max}). Plasma concentrations in most horses were quantifiable for only 6 hours post dose. However, one horse had quantifiable concentrations for 24 hours. Terminal half-lives were not calculated as there was incomplete elucidation of the plasma concentration-time curve for most horses.

Peak concentrations (C_{max}) following the dose of 4 µg/kg were low and variable with a range from 0.4 – 4.2 ng/mL with a mean of 1.8 ng/mL, and a mean terminal half-life (T ½) of ~ 5 hours. The median time of peak concentration (T_{max}) was ~ 0.6 hours and the AUC_t ~ 3.4 ng x h/ml.

Pergolide mesilate is approximately 90% associated with plasma proteins in humans and laboratory animals. The route of elimination is via the kidneys.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years

5.3 Special precautions for storage

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

5.4 Nature and composition of immediate packaging

OPA/aluminium/PVC-aluminium blisters, containing 7 or 10 tablets each.
Carton box of 60, 91, 100, 160 or 240 tablets.
Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal product 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

CP-Pharma Handelsgesellschaft mbH

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}

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

{DD/MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

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

ANNEX II

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARTON BOX

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Prasequine 1 mg tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Pergolide 1.0 mg (equivalent to 1.31 mg pergolide mesilate)

3. PACKAGE SIZE

60 tablets
91 tablets
100 tablets
160 tablets
240 tablets

4. TARGET SPECIES

Horses (non food-producing)

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral use.

7. WITHDRAWAL PERIODS

Withdrawal periods:
Not authorised for use in horses intended for human consumption.
The horse must have been declared as not intended for human consumption under national horse passport legislation.
Not authorised for use in mares producing milk for human consumption.

8. EXPIRY DATE

Exp. {mm/yyyy}

9. SPECIAL STORAGE PRECAUTIONS

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.
Avoid accidental ingestion by humans. See package leaflet for user warnings.

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

CP-Pharma Handelsgesellschaft mbH

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

OPA/aluminium/PVC-aluminium blisters

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Prasequine

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Pergolide 1.0 mg

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Prasequine 1 mg tablets for horses

2. Composition

Each tablet contains:

Active substances:
Pergolide 1.0 mg
equivalent to 1.31 mg pergolide mesilate

Off-white round and convex tablet with a cross-shaped break line on one side.
Tablets can be divided into 2 or 4 equal parts.

3. Target species

Horses (non food-producing).

4. Indications for use

Symptomatic treatment of clinical signs associated with Pituitary Pars Intermedia Dysfunction (PPID) (Equine Cushing's Disease).

5. Contraindications

Do not use in cases of hypersensitivity to the active substance or other ergot derivatives or to any of the excipients. Do not use in horses less than 2 years of age.

6. Special warnings

Special warnings:
Appropriate endocrinologic laboratory tests should be conducted as well as evaluation of clinical signs in order to establish a diagnosis of PPID.

Special precautions for safe use in the target species:
As the majority of cases of PPID are diagnosed in aged horses, other pathological processes are frequently present. For monitoring and frequency of testing, see section "Dosage for each species, routes and method of administration".

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Pergolide, like other ergot derivatives, may cause emesis, dizziness, lethargy or low blood pressure.

Severe adverse events such as collapse have been observed.
Ingestion may be harmful and associated with severe adverse events, especially in children or people with pre-existing heart conditions. Do not ingest this veterinary medicinal product.

In order to reduce the risk of accidental ingestion:
- Store and handle this veterinary medicinal product separately away from human medicinal products and handle it with great care. Keep the veterinary medicinal product out of reach and sight of children.
- Tablets prepared for administration should be administered immediately and not left unattended.
- Tablet parts should be returned to the open blister space. Blisters should be inserted back into the outer packaging and kept in a safe place.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Avoid driving or operating machinery following ingestion of this veterinary medicinal product.

This veterinary medicinal product may cause eye irritation, an irritating smell, or headache after dividing the tablets. Avoid contact with the eyes and inhalation when handling the tablets. Minimise exposure risks when dividing or dissolving tablets, e.g. tablets should not be crushed.
In case of contact with skin, wash exposed skin with water. In the event of eye exposure, flush the affected eye immediately with water and seek medical advice. For nasal irritation, move to fresh air and seek for medical attention if breathing difficulty develops.

This veterinary medicinal product may cause hypersensitivity (allergy) reactions. People with known hypersensitivity to pergolide or other ergot derivatives should avoid contact with the veterinary medicinal product.
This veterinary medicinal product may cause adverse effects due to decreased prolactin levels, which poses a particular risk to pregnant and lactating women. Pregnant or lactating women should avoid dermal contact or hand-to-mouth contact by wearing gloves when administering the veterinary medicinal product.

Do not eat, drink or smoke when using this veterinary medicinal product. Wash hands after use.

Pregnancy:
Use only according to the benefit/ risk assessment by the responsible veterinarian. The safety of this veterinary medicinal product has not been demonstrated in pregnant mares. Laboratory studies in mice and rabbits have not produced any evidence of teratogenic effects. Reduced fertility was seen in mice at a dose of 5.6 mg/kg body weight per day.

Lactation:
The use is not recommended in lactating horses, in which the safety of this veterinary medicinal product has not been demonstrated. In mice, reduced body weights and survival rates in the progeny were attributed to the pharmacological inhibition of prolactin secretion resulting in lactation failure.

Interaction with other medicinal products and other forms of interaction:
Use with caution in case the veterinary medicinal product is co-administered with other drugs known to affect protein binding.
Do not administer concurrently with dopamine antagonists, such as neuroleptics (phenothiazines - e.g. acepromazine), domperidone, or metoclopramide, as these agents may reduce the effectiveness of pergolide.

Overdose:
No information available.

7. Adverse events

Horses (non food-producing):

Rare (1 to 10 animals / 10 000 animals treated):	Inappetence, Anorexia[1], Lethargy[1] Central nervous system disorder (e.g., central nervous system depression and ataxia)[2] Diarrhoea, Colic
Very rare (<1 animal / 10 000 animals treated, including isolated reports):	Increased sweating

[1]Transient
[2] Mild

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: {national system details}.

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

Oral use, once daily.

Starting dose
The starting dose is about 2 µg pergolide/kg (dose range: 1.7 to 2.5 µg/kg; see table below). The maintenance dose should then be titrated according to the individual response as determined by monitoring (see below), resulting in an average maintenance dose of 2 µg pergolide/kg bodyweight with a dose range of 0.6 to 10 µg pergolide/kg bodyweight.

Starting doses are recommended as follows:

Horse body weight kg	Number of tablets	Starting dose mg/horse	Dosage range µg/kg
200 - 300	½	0.50	1.7 – 2.5
301 – 400	¾	0.75	1.9 - 2.5
401 - 600	1	1.00	1.7 – 2.5
601 - 850	1 ½	1.50	1.8 – 2.5
851 - 1000	2	2.00	2.0 – 2.4

Maintenance dose
Lifelong treatment is anticipated for this disease.
Most horses respond to therapy and are stabilised at an average dose of 2 µg pergolide/kg body weight. Clinical improvement with pergolide is expected within 6 to 12 weeks. Horses may respond clinically at lower or varying doses; it is therefore recommended to titrate to the lowest effective dose per individual based on response to therapy, whether it is effectiveness or signs of intolerance. Some horses may require doses as high as 10 µg pergolide/kg body weight per day. In these rare situations, appropriate additional monitoring is advised.

Following initial diagnosis, repeat endocrinologic testing for dose titration and monitoring of treatment at intervals of 4 to 6 weeks until stabilisation or improvement of clinical signs and/or diagnostic testing occurs.

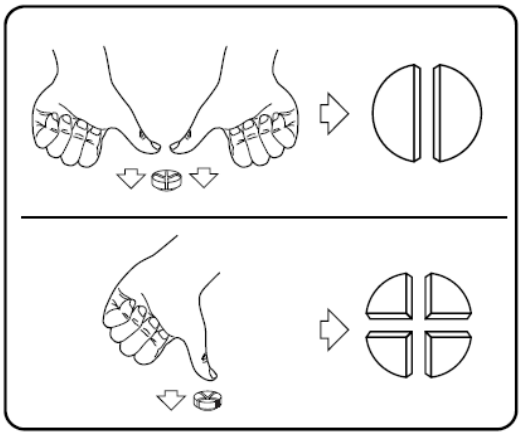
If clinical signs or diagnostic testing have not yet improved at the first 4 to 6 week interval, the total daily dose may be increased by 0.25 - 0.50 mg. In case clinical signs have improved but are not yet

normalised, the veterinarian may decide to titrate or not to titrate the dose, considering the individual's response/tolerance to the dose.

In case clinical signs are not adequately controlled (clinical evaluation and/or diagnostic testing) it is recommended to increase the total daily dose by 0.25 – 0.50 mg increments (if the drug is tolerated at that dose) every 4 to 6 weeks until stabilisation occurs.
If signs of dose intolerance develop, treatment should be stopped for 2 to 3 days and reinstated at one-half of the previous dose. The total daily dose may then be titrated back up to the desired clinical effect by 0.25 - 0.50 mg increments every 2 to 4 weeks.
If a dose is missed, the next scheduled dose should be administered as prescribed.

Following stabilisation, regular clinical assessment and diagnostic testing should be performed every 6 months to monitor treatment and dose. Where there is no apparent response to treatment, the diagnosis and/or treatment plan should be re-evaluated.

Tablets can be divided into 2 or 4 equal parts to ensure accurate dosing. Place the tablet on a flat surface, with its scored side facing up and the convex (rounded) side facing the surface.



2 equal parts: press down with your thumbs on both sides of the tablet.
4 equal parts: press down with your thumb in the middle of the tablet.

9. Advice on correct administration

To facilitate administration, the required daily dose should be placed in a small amount of water and/or mixed with molasses or other sweetener and agitated until dissolved. In this case, the dissolved tablets should be administered with a syringe. The whole amount should be administered immediately. Tablets should not be crushed, see section 6. When tablets are divided, the remaining tablet portion should be given at the next administration.

10. Withdrawal periods

Not authorised for use in horses intended for human consumption.
The horse must have been declared as not intended for human consumption under national horse passport legislation.
Not authorised for use in mares producing milk for human consumption.

11. Special storage precautions

Keep out of the sight and reach of children.
This veterinary medicinal product does not require any special storage conditions.

Do not use this veterinary medicinal product after the expiry date which is stated on the carton and the blister after Exp. The expiry date refers to the last day of that month.

12. Special precautions for disposal

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

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

UK(NI) only:
Medicines should not be disposed of via wastewater.
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.
Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Blisters, containing 7 or 10 tablets each.
Carton box of 60, 91, 100, 160 or 240 tablets.
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:
CP-Pharma Handelsgesellschaft mbH
Ostlandring 13
31303 Burgdorf
Germany
Tel: +49-(0)5136-6066-0

Local representatives and contact details to report suspected adverse events:

17. Other information