

[Version 9,03/2022]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Pergosafe 1 mg film-coated tablets for horses (AT, BE, BG, CY, CZ, DE, DK, ES, FR, HR, HU, IS, IT, LU, NL, NO, PT, RO, SI, SK)

Pergocoat 1 mg film-coated tablets for horses (EE, IE, FI, LT, LV, PL, SE, UK)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:

Pergolide 1.0 mg
equivalent to 1.31 mg pergolide mesilate

Excipients:

Qualitative composition of excipients and other constituents	Quantitative composition if that information is essential for proper administration of the veterinary medicinal product
Core:	
Lactose monohydrate	
Croscarmellose sodium	
Povidone	
Magnesium stearate	
Iron oxide yellow (E172)	0.12 mg
Coat:	
Polyvinylalcohol	
Talc	
Titanium dioxide (E171)	2.86 mg
Glycerol monocaprylocaprate	
Sodium laurilsulfate	
Iron oxide yellow (E172)	0.11 mg
Ferrosoferic oxide	25 µg
Iron oxide red (E172)	6 µg

Beige sphere shaped, film-coated tablet

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 horses with known hypersensitivity to pergolide mesilate 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:

This 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 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 and wear gloves when administering the product.

Accidental ingestion, especially by children, may cause adverse reactions such as emesis, dizziness, lethargy or low blood pressure. To avoid accidental ingestion, the blister should be replaced into the carton and carefully kept away from children. Avoid hand-to-mouth contact. Do not eat, drink or smoke when using this product. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

This product may cause eye irritation. Avoid contact with the eyes including hand-to-eye contact when handling the tablets. Minimize exposure risks when dissolving the tablets, e.g. tablets should not be crushed. In case of contact of the dissolved product with skin, wash exposed skin with water. In the event of eye exposure, flush the affected eye immediately with water and seek medical advice. Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Horses:

Rare (1 to 10 animals / 10,000 animals treated):	Inappetence, anorexia ¹ , lethargy ¹ . Central nervous system signs ² (e.g. depression ² , ataxia ²). Diarrhoea, colic.
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Sweating.

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 also section 'contact details' of the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

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.

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.

Starting dose

The starting dose is about 2 µg pergolide/kg (dose range: 1.3 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	0.5 mg tablet		1 mg tablet	2 mg tablet	Starting dose	Dosage range
200 - 400 kg					0.5 mg	1.3 – 2.5 µg/kg
401 - 600 kg					1.0 mg	1.7 – 2.5 µg/kg
or						
401 - 600 kg	 				1.0 mg	1.7 – 2.5 µg/kg
601 - 850 kg		+			1.5 mg	1.8 – 2.5 µg/kg
or						
601 - 850 kg	  				1.5 mg	1.8 – 2.5 µg/kg
851 - 1000 kg					2.0 mg	2.0 – 2.4 µg/kg
or						
851 - 1000 kg			 		2.0 mg	2.0 – 2.4 µg/kg

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 0.50 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 0.5 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 0.5 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 should be re-evaluated.

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.

Treated horses may never be slaughtered 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 ($T_{1/2}$) 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 ($T_{1/2}$) of ~ 6 hours. The median time of peak concentration (T_{\max}) was ~ 0.6 hours and the AUCt ~ 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: 30 months

5.3 Special precautions for storage

Store in the original package, in order to protect from light.

5.4 Nature and composition of immediate packaging

PVC/PE/PVDC-aluminium blister containing 10 tablets.
OPA/aluminium/PVC-aluminium blister containing 10 tablets.
Carton box of 10, 30, 60, 90, 100, 120, 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

Alfasan Nederland BV

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**

Pergosafe 1 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Pergolide 1 mg (equivalent to 1.31 mg pergolide mesilate)

3. PACKAGE SIZE

10 tablets
30 tablets
60 tablets
90 tablets
100 tablets
120 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.

Treated horses may never be slaughtered 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

Store in the original package, in order to protect from light.

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE”
--

Read the package leaflet before use.

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

Alfasan Nederland BV

14. MARKETING AUTHORISATION NUMBERS
--

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS ALUMINIUM BLISTER

1. NAME OF THE VETERINARY MEDICINAL PRODUCT
--

Pergosafe

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Pergolide 1 mg (equivalent to 1.31 mg pergolide mesilate)

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Pergosafe 0.5 / 1 / 2 mg film-coated tablets for horses

2. Composition

Each tablet contains:

Active substance:

Pergolide 0.5/1.0/2.0 mg
equivalent to 0.66/1.31/2.62 mg pergolide mesilate

Excipients:

0.5 mg tablet

Core:

Iron oxide yellow (E172) 0.064 mg

Coating:

Iron oxide yellow 22 µg

Titanium dioxide (E171) 1.5 mg

1 mg tablet

Core:

Iron oxide yellow (E172) 0.12 mg

Coating:

Iron oxide yellow (E172) 0.11 mg

Titanium dioxide (E171) 2.86 mg

Ferrosofferic oxide 25 µg

Iron oxide red (E172) 6 µg

2 mg tablet

Core:

Iron oxide yellow (E172) 0.24 mg

Coating:

Iron oxide yellow (E172) 0.66 mg

Titanium dioxide (E171) 5.06 mg

Ferrosofferic oxide 0.28 mg

Film-coated tablet

0.5 mg tablet: Off-white sphere shaped, film-coated tablet

1 mg tablet: Beige sphere shaped, film-coated tablet

2 mg tablet: Green sphere shaped, film-coated tablet

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 horses with known hypersensitivity to pergolide mesilate 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 8.

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

This 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 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 and wear gloves when administering the product.

Accidental ingestion, especially by children, may cause adverse reactions such as emesis, dizziness, lethargy or low blood pressure. To avoid accidental ingestion, the blister should be replaced into the carton and carefully kept away from children. Avoid hand-to-mouth contact. Do not eat, drink or smoke when using this product. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

This product may cause eye irritation. Avoid contact with the eyes including hand-to-eye contact when handling the tablets. Minimize exposure risks when dissolving the tablets, e.g. tablets should not be crushed. In case of contact of the dissolved product with skin, wash exposed skin with water. In the event of eye exposure, flush the affected eye immediately with water and seek medical advice.

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:

Rare (1 to 10 animals / 10,000 animals treated):	Inappetence, anorexia ¹ , lethargy ¹ . Central nervous system signs ² (e.g. depression ² , ataxia ²). Diarrhoea, colic.
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	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 the local representative of the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system.













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: 1.3 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	0.5 mg tablet		1 mg tablet	2 mg tablet	Starting dose	Dosage range
200 - 400 kg					0.5 mg	1.3 – 2.5 µg/kg
401 - 600 kg					1.0 mg	1.7 – 2.5 µg/kg
or						
401 - 600 kg	 				1.0 mg	1.7 – 2.5 µg/kg
601 - 850 kg		+			1.5 mg	1.8 – 2.5 µg/kg
or						
601 - 850 kg	  				1.5 mg	1.8 – 2.5 µg/kg
851 - 1000 kg					2.0 mg	2.0 – 2.4 µg/kg
or						
851 - 1000 kg			 		2.0 mg	2.0 – 2.4 µg/kg

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 0.50 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 0.5 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 0.5 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 should be re-evaluated.

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.

10. Withdrawal periods

Not authorised for use in horses intended for human consumption.

Treated horses may never be slaughtered 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.

Store in the original package, in order to protect from light. Do not use this veterinary medicinal product after the expiry date which is stated on the blister and carton 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.

For UK(NI) use only:

Medicines should not be disposed of via wastewater.

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

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

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Carton box of 10, 30, 60, 90, 100, 120, 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 reactions:

Alfasan Nederland BV

Kuipersweg 9

3449 JA Woerden

The Netherlands

Tel: +31 348 416945

E-mail: pharmacovigilance@alfasan.nl

Manufacturer responsible for batch release:

Lelypharma BV

Zuiveringsweg 42

8243 PZ Lelystad

The Netherlands

Local representatives and contact details to report suspected adverse reactions :

[To be completed nationally].

17. Other information