ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milteforan 20 mg/ml oral solution for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Miltefosine…….20 mg

Excipients:

Qualitative composition of excipients and other constituents
Hydroxypropylcellulose
Propylene glycol
Purified water

Clear colourless viscous oral solution.

3. CLINICAL INFORMATION

3.1 Target species

Dogs

3.2 Indications for use for each target species

Treatment of clinical signs of canine leishmaniasis, caused by *Leishmania infantum.*

3.3 Contraindications

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

3.4 Special warnings

The clinical signs of the disease start to decrease markedly immediately after the beginning of the treatment and are significantly reduced 2 weeks afterwards. The signs continue to improve for at least 4 weeks after completion of the treatment.

Canine leishmaniasis is a zoonosis transmitted by sandflies (*Phlebotomus* spp), in which dogs act as a reservoir. A curative effect is not achieved with this veterinary medicinal product and the parasite is not completely eliminated from the lymph nodes and other tissues of the treated dogs. Treatment does not eradicate the parasite in dogs and the disease can be fatal. Consequently, euthanasia may be recommended for an animal in poor general condition and/or when the animal is in close proximity to an immunocompromised person.

Prevention should be an integrated approach in the management of canine leishmaniasis. Long-acting topical insecticides (spot-on or collars) should be applied to dogs living in or travelling to endemic areas and should be maintained during the entire risk period of potential exposure to/or activity of sand flies.

Keeping the dog indoors during the sand fly season from dusk to dawn is also advisable.

Unnecessary use of antiprotozoal drugs or use deviating from the instructions given in the SPC may increase the resistance selection pressure and lead to reduced efficacy. The decision to use the veterinary

medicinal product should be based on confirmation of the diagnosis of leishmaniasis in the individual animal.

Resistance of *Leishmania infantum* or clinical relapses after miltefosine treatment has been reported in dogs and in humans.

In case of suspected resistance to miltefosine, the infected dog should be treated with appropriate systemic or topical insecticides if it is in an endemic area in order to reduce the risk of spreading of resistant parasites.

Cross-resistance has been shown between miltefosine and amphotericin B in *Leishmania infantum*.

The use of this veterinary medicinal product should take into account local information about susceptibility of the target parasites, where available.

It is recommended to further investigate cases of suspected resistance, using an appropriate diagnostic method (e.g. real time PCR). Confirmed resistance should be reported to the marketing authorisation holder or to the competent authorities.

3.5 Special precautions for use

Special precautions for safe use in the target species:

It is recommended to pour the veterinary medicinal product onto the animal's feed to ensure that the stomach is not empty before administration and consequently to reduce digestive adverse events.
Use in dogs suffering of severe hepatic and cardiac impairment according to the veterinarian risk/benefit assessment.
If you suspect your dog may be pregnant contact your veterinarian for advice before use.

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

This veterinary medicinal product may cause eye and skin irritation. Avoid contact with the skin, or mucous membranes (including hand-to-mouth contact), and eye contact (including hand-to-eye contact). Wear personal protective equipment consisting of impervious gloves and glasses when handling the veterinary medicinal product. In case of accidental skin or eye contact, wash and rinse with abundant quantities of water. If skin or eye irritation persists, seek medical advice and show the leaflet or the label to the physician.

Do not allow treated dogs to lick persons immediately after intake of the medication.

Miltefosine has been reported to be embryo- and foeto-toxic and teratogenic in laboratory animals.
The veterinary medicinal product should not be administered by pregnant women, by women intending to become pregnant or whose pregnancy status is unknown.

Miltefosine may cause adverse effects, particularly on the gastro-intestinal tract after ingestion.
Avoid accidental ingestion (including hand-to-mouth contact), particularly by children.
Close the bottle immediately after use to avoid the child gaining access to the contents. Do not leave a syringe containing solution in the sight and reach of children.
In order to prevent children from getting access to used syringes, immediately after use replace the syringe in the original packaging. And replace the bottle and syringe in the outer carton and store in a safe place out of the sight and reach of children.
Avoid the access of children to the dog's medicated food. In order to prevent children from getting access to the dog's medicated food, pour it over a part of the feed and wait until the animal has completely consumed the medicated feed, then administer the rest of the feed. Give the treatment out of the sight and reach of children. Any uneaten medicated food must be removed immediately and the bowl washed thoroughly. In case of accidental ingestion, seek-medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dogs:

Very common (>1 animal / 10 animals treated):	Vomiting*, diarrhoea*

*Occuring within 5 to 7 days after the beginning of the treatment and generally lasting for a period of 1 to 2 days.
These effects were reversible at the end of treatment without the need for any specific therapy.
Should these side effects appear, immediately inform the veterinarian. Simultaneous administration of antiemetics may reduce the risk of these unwanted effects.

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

Laboratory studies in rats and rabbits have produced evidence of teratogenic (rats), foetotoxic, embryotoxic and maternotoxic effects, as well as effects on males and females fertility (rats).
The safety of the veterinary medicinal product has not been established during pregnancy, lactation and in breeding animals.

Pregnancy and lactation:

Do not use during pregnancy and lactation.

Fertility:
Do not use in breeding animals.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

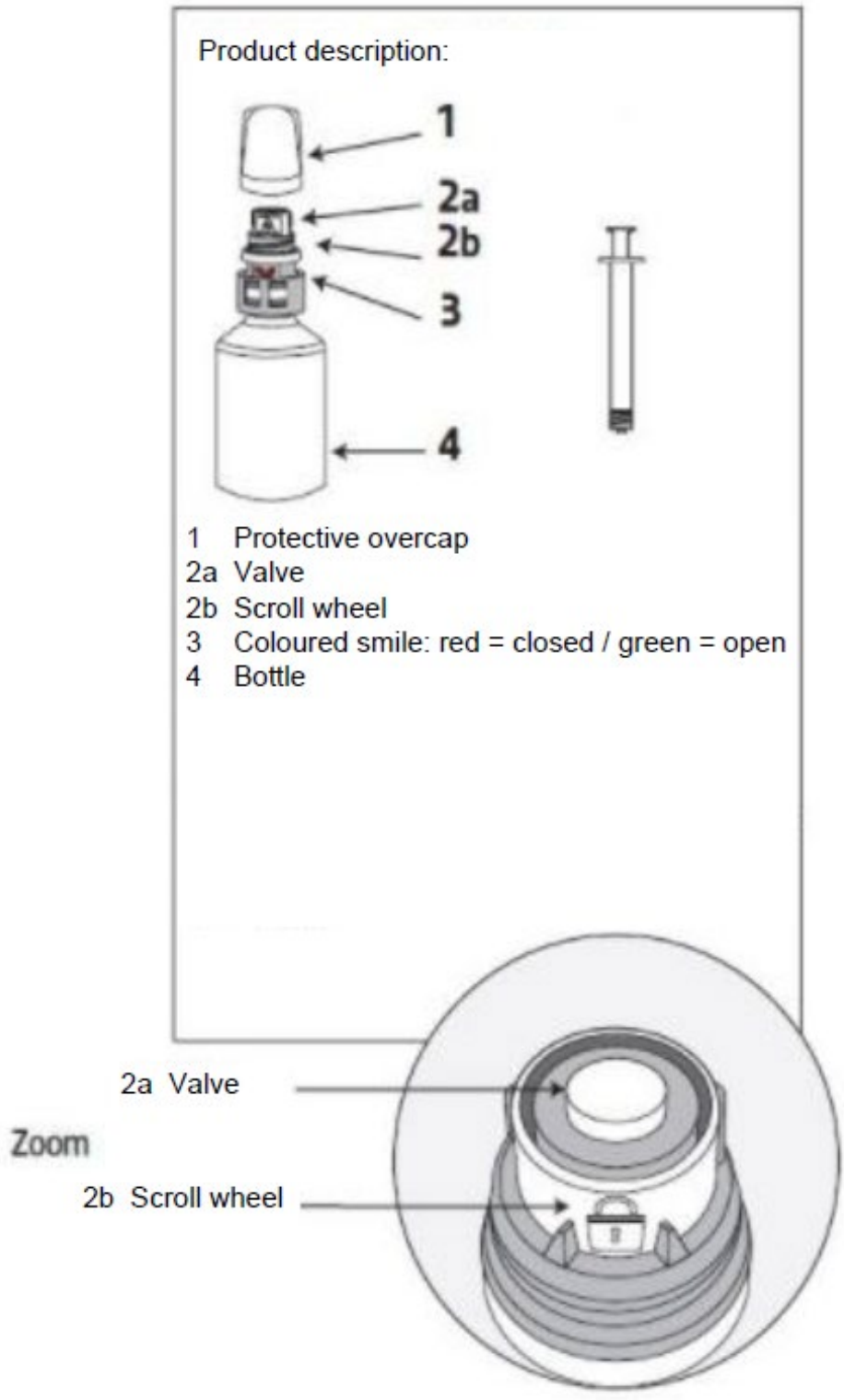
3.9 Administration routes and dosage

Oral use.

The veterinary medicinal product should be administered at 2 mg/kg bodyweight, corresponding to 1 ml of the oral solution per 10 kg b.w. The medication should be poured over a part of the feed and offered to the dog once a day for 28 days. Once the animal has completely consumed the medicated feed, the rest of the dog's meal can be offered.
The parasite being also localised within deep tissues (bone marrow, lymphatic nodes, spleen, liver), it is crucial to comply with the treatment duration (28 days) to ensure the efficacy of the veterinary medicinal product.

To ensure a correct dosage, body weight should be determined as accurately as possible prior to and during the treatment course.
Underdosing could result in ineffective use and may favour resistance development.

The oral solution is delivered through the package described below:

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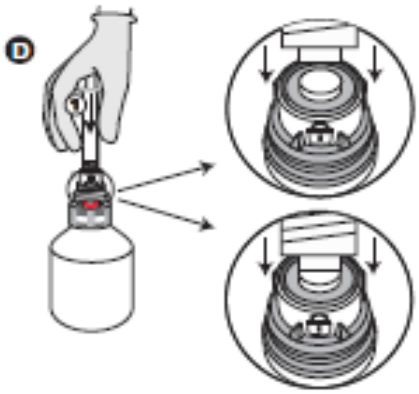
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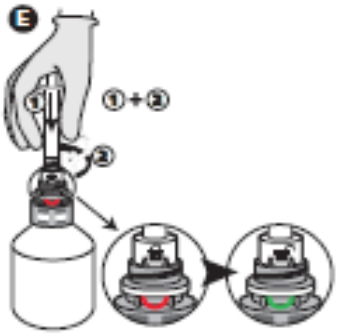
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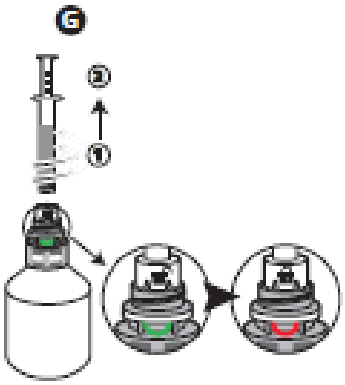
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H

A. Wear protective gloves before handling the veterinary medicinal product.
B. Shake the bottle vigorously before use.
C. Unscrew the protective overcap.
D. Insert the syringe into the upper white part of the cap (scroll wheel) by pushing firmly
E. While pushing, turn the syringe to the right (clockwise) until the green smile appears.
1 + 2 Simultaneously.
F. Draw the correct volume of the veterinary medicinal product into the syringe.
G. Unscrew the syringe from the cap without pushing by turning it to the left (counterclockwise) until the red smile appears again, then continue to turn in order to unfasten the syringe. The system can also be closed by turning the scroll wheel manually.
H. Screw the protective overcap back on. Add the recommended dose to dog food. It is recommended to pour the dose onto the dog's food over a part of the feed, to wait until the animal has completely consumed the medicated feed, and then administer the rest of the feed.

Do not wash the syringe.
Remove the protective gloves and store them properly in their holder.

To ensure a correct administration of the veterinary medicinal product, please refer to the explanatory drawings and video:
https://player.vimeo.com/video/848683785?h=863f2b2f85

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

An overdose study with up to twice the recommended dose rate for 28 days, has shown undesirable effects such as: uncontrollable vomiting.

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 applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QP51DX07

4.2 Pharmacodynamics

Miltefosine has an antileishmanial activity in-vitro and in animals models against *L. infantum*.

Miltefosine has been described to have a direct effect on the parasites by interfering with biosynthesis of phospholipids and metabolism of alkyl-lipids, affecting mitochondrial cytochrome C oxidases and inducing mitochondrial depolarization and decrease of intracellular levels of ATP, and an apoptosis-like cell death.

Resistance of *Leishmania infantum* to miltefosine has been reported in dogs and in humans. Cross-resistance has been shown between miltefosine and amphotericin B in *Leishmania infantum.*
Drug resistance could be due to a decrease in miltefosine accumulation within Leishmania parasite which is thought to be due to either an increase in drug efflux, mediated by the overexpression of the

ABC transporter P-glycoprotein and/or a decrease in drug uptake by the inactivation of the miltefosine transport machinery that consists of the miltefosine transporter and its beta subunit.
Multifactorial mechanisms are involved in natural resistance to miltefosine in *L. infantum* e.g. the absence of the 3'nucleotidase/nuclease genes *NUC1* and *NUC2*.

4.3 Pharmacokinetics

After oral administration in dogs, miltefosine is nearly completely absorbed with an absolute bioavailability of 94%. Miltefosine is characterised by a slow elimination half-life ($t_{1/2}$ of 160 h) and a low plasma clearance (Cl = 0.04 ml/kg/min). After a first therapeutic dose of 2 mg/kg bw in fed dogs, the maximum plasma concentration (C_{max}) is around 5230 ng/mL with a T_{max} of 6 h.

After repeated administrations at the therapeutic dose of 2 mg/kg bw day for 28 days to fed dogs, the C_{max} is around 32582 ng/mL and the AUC_{0-t} is 649617 ng.h/mL after the last administration. Repeated administrations of the veterinary medicinal product for 28 days lead to an accumulation with a factor of 7.65.

Miltefosine is mainly eliminated via the faecal route and about 10% of the administered dose is eliminated as the parent drug in the faeces. Elimination of miltefosine by the urine route is negligible.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 12 weeks.

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

Polyethylene terephthalate (PET) bottle equipped with a sampling polypropylene (PP) snap cap with silicone stopper and a 3 ml polypropylene (PP) syringe graduated every 0.1 ml. Carton box with one bottle of 30, 60 or 90 ml and 1 syringe.
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

VIRBAC

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

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 III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE
Carton Box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milteforan 20 mg/ml oral solution

2. STATEMENT OF ACTIVE SUBSTANCES

Miltefosine 20 mg/ml

3. PACKAGE SIZE

1x 30 ml and 1 syringe.
1x 60 ml and 1 syringe.
1x 90 ml and 1 syringe.

4. TARGET SPECIES

Dogs

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral use.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}
Once opened use within 12 weeks

9. SPECIAL STORAGE PRECAUTIONS

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

VIRBAC

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

Should not be administered by pregnant women

To ensure a correct administration of the veterinary medicinal product, please refer to the explanatory drawings and video:

https://player.vimeo.com/video/848683785?h=863f2b2f85

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE
Bottle of 60 ml
Bottle of 90 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

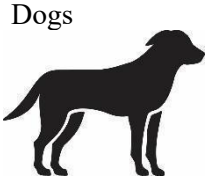
Milteforan 20 mg/ml oral solution

2. STATEMENT OF ACTIVE SUBSTANCES

Miltefosine 20 mg/ml

3. TARGET SPECIES

Dogs



4. ROUTES OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

5. WITHDRAWAL PERIODS

6. EXPIRY DATE

Exp. {mm/yyyy}
Once opened use within 12 weeks

7. SPECIAL STORAGE PRECAUTIONS

8. NAME OF THE MARKETING AUTHORISATION HOLDER

VIRBAC

9. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Bottle of 30 mL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milteforan

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Miltefosine 20 mg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Milteforan 20 mg/ml oral solution for dogs

2. Composition

Each ml contains:
Active substance:
Miltefosine……..20 mg

Clear colourless viscous oral solution.

3. Target species

Dogs.

4. Indications for use

Treatment of clinical signs of canine leishmaniasis, caused by *Leishmania infantum.*

5. Contraindications

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

6. Special warnings

Special warnings:
The clinical signs of the disease start to decrease markedly immediately after the beginning of the treatment and are significantly reduced 2 weeks afterwards. The signs continue to improve for at least 4 weeks after completion of the treatment.

Canine leishmaniasis is a zoonosis transmitted by sandflies (*Phlebotomus* spp), in which dogs act as a reservoir. A curative effect is not achieved with this veterinary medicinal product and the parasite is not completely eliminated from the lymph nodes and other tissues of the treated dogs. Treatment does not eradicate the parasite in dogs and the disease can be fatal. Consequently, euthanasia may be recommended for an animal in poor general condition and/or when the animal is in close proximity to an immunocompromised person.

Prevention should be an integrated approach in the management of canine leishmaniasis. Long-acting topical insecticides (spot-on or collars) should be applied to dogs living in or travelling to endemic areas and should be maintained during the entire risk period of potential exposure to/or activity of sand flies.

Keeping the dog indoors during the sand fly season from dusk to dawn is also advisable.

Unnecessary use of antiprotozoal drugs or use deviating from the instructions given in the SPC may increase the resistance selection pressure and lead to reduced efficacy. The decision to use the veterinary medicinal product should be based on confirmation of the diagnosis of leishmaniasis in the individual animal.

Resistance of *Leishmania infantum* or clinical relapses after miltefosine treatment has been reported in dogs and in humans.

In case of suspected resistance to miltefosine, the infected dog should be treated with appropriate systemic or topical insecticides if it is in an endemic area in order to reduce the risk of spreading of resistant parasites.

Cross-resistance has been shown between miltefosine and amphotericin B in *Leishmania infantum*.

The use of this veterinary medicinal product should take into account local information about susceptibility of the target parasites, where available.

It is recommended to further investigate cases of suspected resistance, using an appropriate diagnostic method (e.g. real time PCR). Confirmed resistance should be reported to the marketing authorisation holder or to the competent authorities.

Special precautions for safe use in the target species:
It is recommended to pour the veterinary medicinal product onto the animal's feed to ensure that the stomach is not empty before administration and consequently to reduce digestive adverse events.
Use in dogs suffering of severe hepatic and cardiac impairment according to the veterinarian risk/benefit assessment.
If you suspect your dog may be pregnant contact your veterinarian for advice before use.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
This veterinary medicinal product may cause eye and skin irritation. Avoid contact with the skin, or mucous membranes (including hand-to-mouth contact), and eye contact (including hand-to-eye contact). Wear personal protective equipment consisting of impervious gloves and glasses when handling the veterinary medicinal product. In case of accidental skin or eye contact, wash and rinse with abundant quantities of water. If skin or eye irritation persists, seek medical advice and show the leaflet or the label to the physician.

Do not allow treated dogs to lick persons immediately after intake of the medication.

Miltefosine has been reported to be embryo- and foeto-toxic and teratogenic in laboratory animals.
The veterinary medicinal product should not be administered by pregnant women, by women intending to become pregnant or whose pregnancy status is unknown.

Miltefosine may cause adverse effects, particularly on the gastro-intestinal tract after ingestion.
Avoid accidental ingestion (including hand-to-mouth contact), particularly by children.
Close the bottle immediately after use to avoid the child gaining access to the contents. Do not leave a syringe containing solution in the sight and reach of children.
In order to prevent children from getting access to used syringes, immediately after use replace the syringe in the original packaging. And replace the bottle and syringe in the outer carton and store in a safe place out of the sight and reach of children.
Avoid the access of children to the dog's medicated food. In order to prevent children from getting access to the dog's medicated food, pour it over a part of the feed and wait until the animal has completely consumed the medicated feed, then administer the rest of the feed. Give the treatment out of the sight and reach of children. Any uneaten medicated food must be removed immediately and the bowl washed thoroughly. In case of accidental ingestion, seek-medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

Pregnancy and lactation:

Laboratory studies in rats and rabbits have produced evidence of teratogenic (rats), foetotoxic, embryotoxic and maternotoxic effects, as well as effects on males and females fertility (rats).
The safety of the veterinary medicinal product has not been established during pregnancy, lactation and in breeding animals.

Do not use during pregnancy and lactation.

Fertility:

Do not use in breeding animals.

Interaction with other medicinal products and other forms of interaction:
None known.

Overdose:
An overdose study with up to twice the recommended dose rate for 28 days, has shown undesirable effects such as uncontrollable vomiting.

Major incompatibilities:
In absence of compatibility studies, it is recommended not to mix this veterinary medicinal product with other veterinary products.

7. Adverse events

Dogs:

Very common (>1 animal / 10 animals treated):	Vomiting*, diarrhoea*

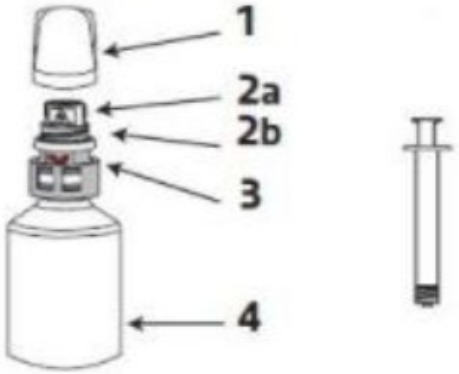
*Occuring within 5 to 7 days after the beginning of the treatment and generally lasting for a period of 1 to 2 days.
These effects were reversible at the end of treatment without the need for any specific therapy.
Should these side effects appear, immediately inform the veterinarian. Simultaneous administration of antiemetics may reduce the risk of these unwanted effects.

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.

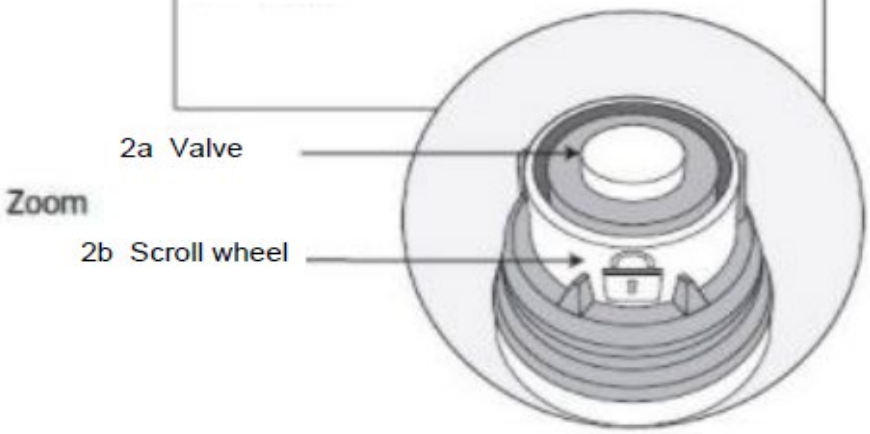
8. Dosage for each species, routes and method of administration

Oral use.
The veterinary medicinal product should be administered at 2 mg/kg bodyweight, corresponding to 1 ml of the oral solution per 10 kg b.w. The medication should be poured over a part of the feed and offered to the dog once a day for 28 days. Once the animal has completely consumed the medicated feed, the rest of the dog's meal can be offered.

Product description:



1 Protective overcap
2a Valve
2b Scroll wheel
3 Coloured smile: red = closed / green = open
4 Bottle

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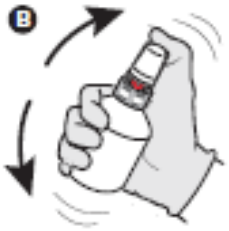
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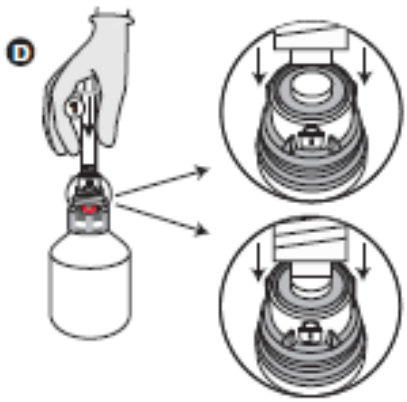
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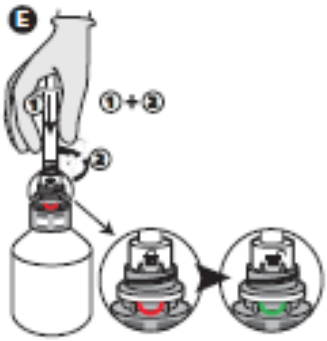
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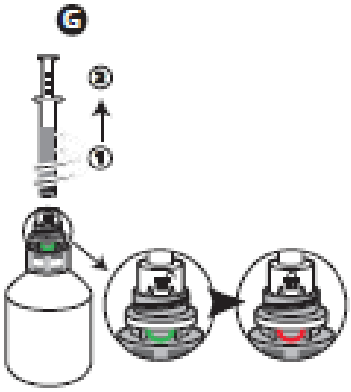
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A. Wear protective gloves before handling the veterinary medicinal product.
B. Shake the bottle vigorously before use.
C. Unscrew the protective overcap.
D. Insert the syringe into the upper white part of the cap (scroll wheel) by pushing firmly.
E. While pushing, turn the syringe to the right (clockwise) until the green smile appears.
1 + 2 Simultaneously.
F. Draw the correct volume of the veterinary medicinal product into the syringe.
G. Unscrew the syringe from the cap without pushing by turning it to the left (counterclockwise) until the red smile appears again, then continue to turn in order to unfasten the syringe. The system can also be closed by turning the scroll wheel manually.
H. Screw the protective overcap back on. Add the recommended dose to dog food. It is recommended to pour the dose onto the dog's food over a part of the feed, to wait until the animal has completely consumed the medicated feed, and then administer the rest of the feed.

Do not wash the syringe.
Remove the protective gloves and store them properly in their holder.

9. Advice on correct administration

The parasite being also localised within deep tissues (bone marrow, lymphatic nodes, spleen, liver), it is crucial to comply with the treatment duration (28 days) to ensure the efficacy of the veterinary medicinal product.
To ensure a correct dosage, body weight should be determined as accurately as possible prior to and during the treatment course.
Underdosing could result in ineffective use and may favour resistance development.

To ensure a correct administration of the veterinary medicinal product, please refer to the explanatory drawings and video:

https://player.vimeo.com/video/848683785?h=863f2b2f85

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.
This veterinary medicinal product does not require any special storage conditions.
Shelf-life after first opening the container: 12 weeks.
Do not use this veterinary medicinal product after the expiry date which is stated on the label 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 national collection systems applicable to the veterinary medicinal product concerned.

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

Polyethylene terephthalate (PET) bottle equipped with a sampling polypropylene (PP) snap cap with silicone stopper and a 3 ml polypropylene (PP) syringe graduated every 0.1 ml.
Carton box with one bottle of 30, 60 or 90 ml and 1 syringe.
Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{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

VIRBAC
1ère avenue 2065 m LID
06516 Carros
France

Local representatives and contact details to report suspected adverse reactions:

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

<17. Other information>