

[Version 8.1,01/2017]

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milteforan L 20 mg/ml oral solution for dogs (CY, IT, PT, SI)

Miltefosina Virbac 20 mg/ml oral solution for dogs (ES)

Miltefosine Virbac 20 mg/ml oral solution for dogs (EL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Miltefosine 20 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral solution

Clear colourless viscous solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

Control of canine leishmaniasis.

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

4.3 Contraindications

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

4.4 Special warnings for each target species

Underdosing should be avoided to decrease the risk of resistance development that may ultimately result in ineffective therapy.

4.5 Special precautions for use

Special precautions for use in animals

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

In case of accidental ingestion, spillage onto skin, seek medical advice immediately and show the package leaflet or the label to the physician.

People with known hypersensitivity to miltefosine should avoid contact with the veterinary medicinal product and any animal excreta (faecal matter, urine, vomiting, saliva etc) and should administer the veterinary medicinal product with caution.

The veterinary medicinal product may cause eye and skin irritation and sensitisation: personal protective equipment consisting of gloves and glasses should be worn when handling the veterinary medicinal product. In case of eye or skin contact rinse immediately with plenty of water and seek medical advice.

The veterinary medicinal product should not be administered by pregnant women, by women intending to become pregnant or whose pregnancy status is unknown.

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

Do not drink, eat or smoke when administering the product.

Do not shake the vial to avoid foaming.

4.6 Adverse reactions (frequency and seriousness)

Moderate and transient vomiting has been reported very commonly (16 % of treated dogs) and diarrhoea has been also commonly observed (12 % of treated dogs) during clinical studies.

These effects occurred on average within 5 to 7 days after the beginning of the treatment, lasting for a period of 1 to 2 days in most of the cases, however these effects might last longer, even more than seven days in some animals.

They did not affect the efficacy of the product and therefore did not require discontinuation of treatment or change in the dose regimen. These effects were reversible at the end of treatment and all dogs recovered without the need for any specific therapy.

It is recommended to pour the product onto the animal's feed to reduce digestive side effects. Should such side effects (e.g. vomiting, diarrhoea) appear, inform immediately to the veterinarian. The concurrent administration of anti-emetic products could reduce the risk of undesired effects.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy, lactation and in breeding animals.

Do not use during pregnancy, lactation and in breeding animals.

Laboratory studies in rats and rabbits have produce any evidence of a teratogenic (rats), foetotoxic, embryotoxic, maternotoxic effects.

4.8 Interaction with other medicinal products and other forms of interaction

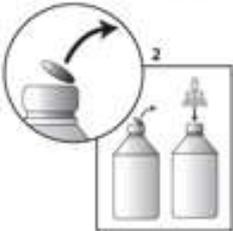
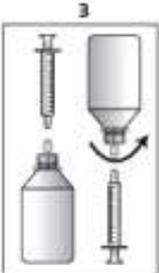
None known.

4.9 Amounts to be administered and administration route

The product should be administered at 2 mg/kg bodyweight, poured onto the food, the full meal or one part of the meal, once a day for 28 days by oral route (corresponding to 1 ml of the oral solution per 10 kg b.w.).

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 product.

The weight of the dog should be accurately estimated prior to and during the treatment course.

	<p>1 Wear protective <u>gloves</u> before handling the <u>product</u>.</p>
	<p>Contact <u>may induce</u> a <u>skin reaction</u>.</p> <p>Remove the <u>transport cap</u>. Do not <u>remove</u> the <u>aluminum cap</u> containing the <u>rubber</u>. Replace the <u>transport cap</u> <u>permanently</u> with the <u>plastic dispensing cap</u></p>
	<p>3 A - <u>Hold</u> the <u>bottle upright</u>. B - <u>Adapt</u> the <u>syringe</u> by <u>screwing it</u> onto the <u>plastic dispensing cap</u> until it is <u>secure</u>. C - <u>Invert</u> the <u>bottle gently</u> and with the <u>fixed syringe</u> <u>withdraw</u> the <u>prescribed dose</u>. D - Put the <u>bottle upright</u> again and <u>remove</u> the <u>syringe</u> <u>from</u> the <u>dispensing cap</u>.</p>
	<p>4 <u>Add</u> the <u>recommended dose</u> to <u>dog food</u></p>
	<p>5 Store the <u>empty syringe</u> in <u>its holder</u>. Do not <u>wash</u> the <u>syringe</u>.</p>
	<p>6 Remove <u>protective gloves</u> and store <u>them properly</u> in <u>their holder</u></p>
	<p>7 Wash hands <u>with soap</u> and <u>water</u>.</p>

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

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

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Agents against leishmaniosis and trypanosomosis,
ATCvet code: QP51D

5.1 Pharmacodynamic properties

Canine leishmaniasis is a lethal disease due to *Leishmania infantum* transmitted by a biting insect (*Phlebotomus* spp). Miltefosine has a marked direct antileishmanial activity in-vitro and in animal models against *L. donovani* (promastigote and amastigote test systems) and *L. infantum*.

It is likely thought that Miltefosine inhibits the penetration of *Leishmania* species into the macrophage via the interaction with glycosomes and glycosylphosphatidyl-inositol anchors (essential for the intracellular survival of *Leishmania*) and disrupts the membrane signal transduction of *Leishmania* by inhibition of phospholipase C.

5.2 Pharmacokinetic particulars

After oral administration in dogs, miltefosine is nearly completely absorbed with an absolute bioavailability of 94 % . After a therapeutic dose of 2 mg/ kg/ day, the maximum plasma concentration (C_{max}) is around 32582 ng.ml⁻¹ in fed dogs. In rats, repeated oral administration resulted in drug levels descending in the following order : kidneys, skin, adrenal glands, spleen, small intestine, fat tissue, stomach, liver, lung, serum, colon, brain, heart and muscle: most of these organs being the localisation of amastigote forms. In mice, miltefosine was almost equally distributed between plasma and erythrocytes. 24 h after intravenous injection of miltefosine in female mice, 63% of the radioactivity extractable from the liver was recovered as unchanged compound.

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 repeated administrations of Milteforan L (CY, IT, PT, SI), Miltefosina Virbac (ES), Miltefosine Virbac (EL) at the therapeutic dose of 2 mg/ kg/ day for 28 days to fed dogs, the maximum plasma concentration (C_{max}) is around 32582 ng.ml⁻¹ \pm 4030 ng.ml⁻¹ with a mean T_{max} of 5.0 \pm 2.0 h and the AUC_{0-t} is 649617 \pm 94478 ng.h.ml⁻¹ after the last administration. The elimination half-life obtained after the last administration is long with a $t_{1/2} = 153 \pm 13.7$ h. Consequently, repeated administrations of Milteforan L (CY, IT, PT, SI), Miltefosina Virbac (ES), Miltefosine Virbac (EL) for 28 days lead to an accumulation with a factor of 7.65 \pm 1.99. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose
Propylene glycol
Purified water

6.2 Major incompatibilities

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

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life after first opening the immediate packaging: 1 month.

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

Unbreakable polyethylene terephthalate vials of 30 ml, 60 ml and 90 ml hermetically closed by a rubber stopper and sealed with an aluminium cap.
Carton box with one vial, 1 medical device, 1 dosing device and 2 gloves.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

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

7. MARKETING AUTHORISATION HOLDER

VIRBAC
1^{ère} avenue 2065 m LID
06516 Carros
France

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

{DD month YYYY}

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 L 20 mg/ml oral solution for dogs (CY, IT, PT, SI)
Miltefosina Virbac 20 mg/ml oral solution for dogs (ES)
Miltefosine Virbac 20 mg/ml oral solution for dogs (EL)
miltefosine

2. STATEMENT OF ACTIVE SUBSTANCES

Miltefosine 20 mg/ml

3. PHARMACEUTICAL FORM

Oral solution

4. PACKAGE SIZE

One vial of 30 ml, 1 medical device, 1 dosing device and 2 gloves.
One vial of 60 ml, 1 medical device, 1 dosing device and 2 gloves.
One vial of 90 ml, 1 medical device, 1 dosing device and 2 gloves.

5. TARGET SPECIES

Dogs.

6. INDICATION(S)

Control of canine leishmaniasis.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

Once broached/opened, use by...

11. SPECIAL STORAGE CONDITIONS

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

VIRBAC
1^{ère} avenue 2065 m LID
06516 Carros
France

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER’S BATCH NUMBER

Batch: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL of 30 ml.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milteforan L 20 mg/ml oral solution for dogs (CY, IT, PT, SI)

Miltefosina Virbac 20 mg/ml oral solution for dogs (ES)

Miltefosine Virbac 20 mg/ml oral solution for dogs (EL)

miltefosine

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Miltefosine 20 mg / ml.

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

30 ml.

4. ROUTE(S) OF ADMINISTRATION

Oral use.

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

Batch

7. EXPIRY DATE

EXP {month/year}

Once broached/opened, use by...

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Vials of 60 ml

Vials of 90 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milteforan L 20 mg/ml oral solution for dogs (CY, IT, PT, SI)

Miltefosina Virbac 20 mg/ml oral solution for dogs (ES)

Miltefosine Virbac 20 mg/ml oral solution for dogs (EL)

miltefosine

2. STATEMENT OF ACTIVE SUBSTANCES

Miltefosine 20 mg / ml.

3. PHARMACEUTICAL FORM

4. PACKAGE SIZE

60 ml.

90 ml.

5. TARGET SPECIES

Dogs

6. INDICATION(S)

Control of canine leishmaniasis.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

Once broached/opened, use by...

11. SPECIAL STORAGE CONDITIONS

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet

13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS “KEEP OUT OF THE REACH AND SIGHT OF CHILDREN”

Keep out of the reach and sight of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

VIRBAC
1^{ère} avenue 2065 m LID
06516 Carros
France

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER’S BATCH NUMBER

Batch: {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:

Milteforan L 20 mg/ml oral solution for dogs (CY, IT, PT, SI)

Miltefosina Virbac 20 mg/ml oral solution for dogs (ES)

Miltefosine Virbac 20 mg/ml oral solution for dogs (EL)

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

Marketing authorisation holder and manufacturer responsible for batch release

VIRBAC

1^{ère} avenue 2065 m LID

06516 Carros

France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milteforan L 20 mg/ml oral solution for dogs (CY, IT, PT, SI)

Miltefosina Virbac 20 mg/ml oral solution for dogs (ES)

Miltefosine Virbac 20 mg/ml oral solution for dogs (EL)

miltefosine

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

Each ml contains:

Active substance:

Miltefosine 20 mg

List of excipients:

Hydroxypropylcellulose

Propylene glycol

Purified water

Clear colourless viscous solution.

4. INDICATION(S)

Control of canine leishmaniasis.

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

5. CONTRAINDICATIONS

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

6. ADVERSE REACTIONS

Moderate and transient vomiting has been reported very commonly (16 % of treated dogs) and diarrhoea has been also commonly observed (12 % of treated dogs) during clinical studies.

These effects occurred on average within 5 to 7 days after the beginning of the treatment, lasting for a period of 1 to 2 days in most of the cases, however these effects may last longer, even more than seven days in some animals.

They did not affect the efficacy of the product and therefore did not require discontinuation of treatment or change in the dose regimen. These effects were reversible at the end of treatment and all dogs recovered without the need for any specific therapy.

It is recommended to pour the product onto the animal's feed to reduce digestive side effects. Should such side effects (e.g. vomiting, diarrhoea) appear, inform immediately to the veterinarian. The concurrent administration of anti-emetic products could reduce the risk of undesired effects.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

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

Oral use.

The product should be administered at 2 mg/kg bodyweight, poured onto the food, the full meal or one part of the meal, once a day for 28 days by oral route (corresponding to 1 ml of the oral solution per 10 kg b.w.).

9. ADVICE ON CORRECT ADMINISTRATION

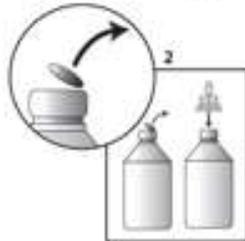
The parasite being also localised within deep tissues (bone marrow, lymphatic nodes, spleen, liver), it is crucial to comply with the treatment duration (28 days) to ensure the efficacy of the product.

The weight of the dog should be accurately estimated prior to and during the treatment course. It is recommended to pour the product onto the animal's feed to reduce digestive side effects.



Wear protective gloves before handling the product.

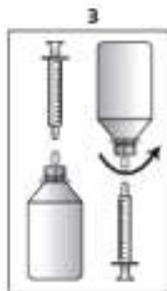
Contact may induce a skin reaction.



Remove the transport cap.

Do not remove the aluminum cap containing the rubber.

Replace the transport cap permanently with the plastic dispensing cap



A - Hold the bottle upright.

B - Adapt the syringe by screwing it onto the plastic dispensing cap until it is secure.

C - Invert the bottle gently and with the fixed syringe withdraw the prescribed dose.

D - Put the bottle upright again and remove the syringe from the dispensing cap.



Add the recommended dose to dog food



Store the empty syringe in its holder.

Do not wash the syringe.



Remove protective gloves and store them properly in their holder



Wash hands with soap and water.

10. WITHDRAWAL PERIOD(S)

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: 1 month.

Do not use this veterinary medicinal product after the expiry date which stated on the carton.

12. SPECIAL WARNING(S)

Special warnings for each target species:

Underdosing should be avoided to decrease the risk of resistance development that may ultimately result in ineffective therapy.

Special precautions for use in animals:

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:

In case of accidental ingestion, spillage onto skin, seek medical advice immediately and show the package leaflet or the label to the physician.

People with known hypersensitivity to miltefosine should avoid contact with the veterinary medicinal product and any animal excreta (faecal matter, urine, vomiting, saliva etc) and should administer the product with caution.

The product causes eye and skin irritation and sensitisation: personal protective equipment consisting of gloves and glasses should be worn when handling the veterinary medicinal product.

In case of eye or skin contact rinse immediately with plenty of water and seek medical advice.

The product should not be administered by pregnant women, women intending to become pregnant or whose pregnancy status is unknown.

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

Do not drink, eat or smoke when administering the product.

Do not shake the vial to avoid foaming.

Pregnancy and lactation:

The safety of the veterinary medicinal product has not been established during pregnancy, lactation nor in breeding animals.

Do not use during pregnancy, lactation and in breeding animals.

Laboratory studies in rats and rabbits have produce any evidence of a teratogenic (rats), foetotoxic, embryotoxic, maternotoxic effects.

Interaction with other medicinal products and other forms of interaction:

None known.

Overdose (symptoms, emergency procedures, antidotes):

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

Incompatibilities:

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

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

Medicines should not be disposed of via wastewater or household waste.

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

{DD month YYYY}

15. OTHER INFORMATION

Not all pack sizes may be marketed.