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

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

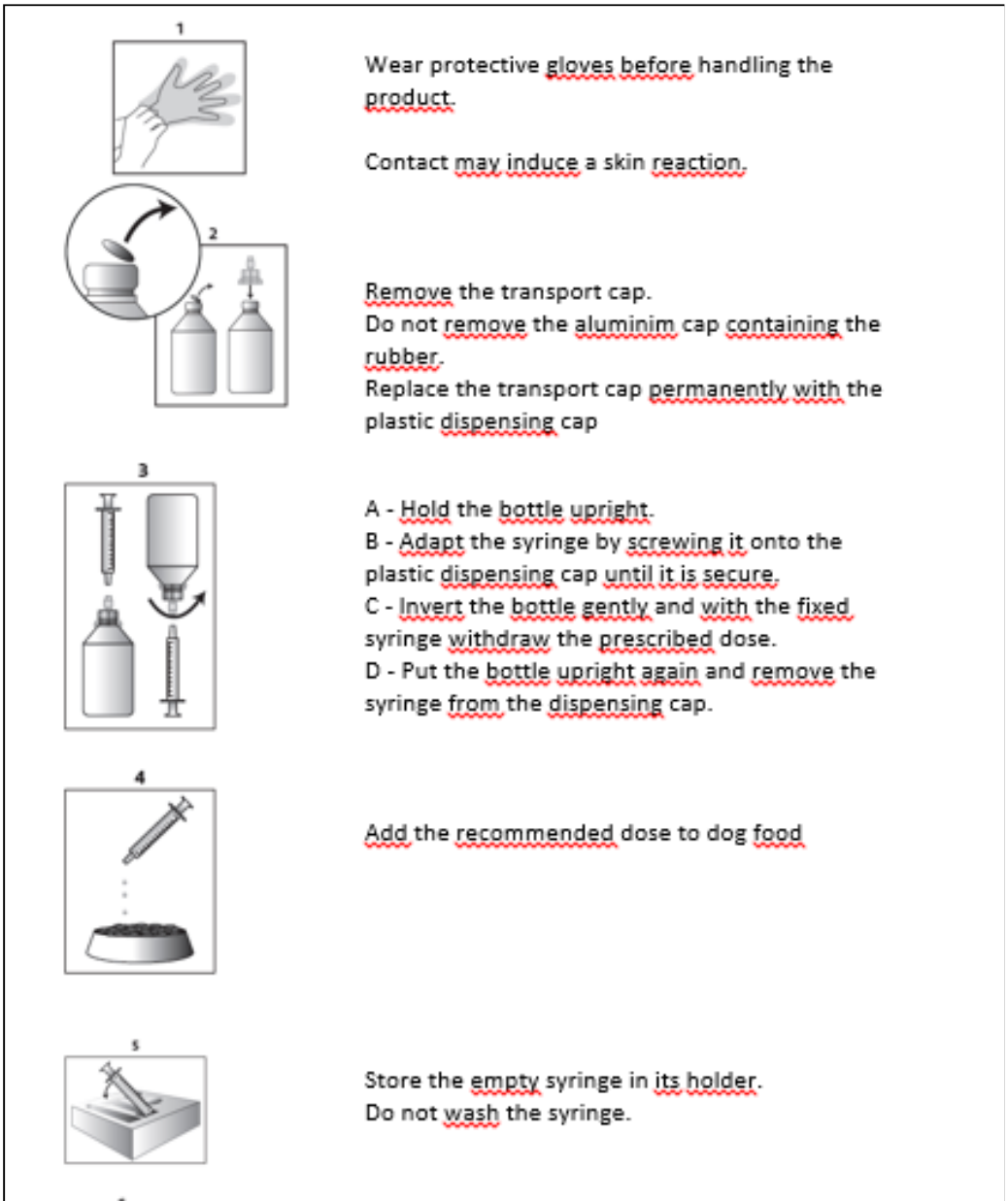
None known.

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.



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 (t½ of 160 h) and a low plasma clearance (Cl = 0.04 ml/kg/min). After repeated administrations of Milteforan at the therapeutic dose of 2 mg/ kg/ day for 28 days to fed dogs, the maximum plasma

concentration (C_{max}) is around 32582 $ng.ml^{-1}$ ± 4030 $ng.ml^{-1}$ with a mean T_{max} of 5.0 ± 2.0 h and the AUC_{0-t} is 649617 ± 94478 $ng.h.ml^{-1}$ after the last administration. The elimination half-life obtained after the last administration is long with a t½= 153 ± 13.7h. Consequently, repeated administrations of Milteforan for 28 days lead to an accumulation with a factor of 7.65 ± 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 terephtalate 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
1ère 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}