Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)
Parque Empresarial Las Mercedes
Edificio 8
C/ Campezo, 1
E - 28022 Madrid
Spain
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

MILTEFORAN

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0116/001/DC
Name, strength and pharmaceutical form	MILTEFORAN 20 mg/ml oral solution for dogs
Applicant	VIRBAC S.A. 1ère Avenue – 2065 m – I.I.D. 06516 CARROS, France
Active substance(s)	Miltefosine
ATC Vetcode	QP51D
Target species	Dogs
Indication for use	Control of canine leishmaniasis.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v) website) (www.HEVRA.org).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	2nd April 2007
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	CY, EL, IT, PT, SI

I. SCIENTIFIC OVERVIEW

For public assessment reports for the first authorisation in a range:

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the reactions observed are indicated in the SPC.
The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains miltefosine (20 mg/ml) as the active substance and excipients (hydroxypropylcellulose, propylene glycol and purified water).

The container/closure system consists of 50, 100 and 125 ml bottles of polyethylene terephthalate, a rubber stopper and an aluminium tamper-proof seal. Other devices included are: a plastic transfer device equipped with an inline non-return valve and a 3 ml Luer lock plastic graduated syringe.

The particulars of the containers and controls performed are provided and conform to the regulation.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of the formulation and the absence of preservative are justified.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The flow chart of the manufacturing process has been supplied.

The product is manufactured using conventional manufacturing techniques and consists of seven steps for formulation and sample collection, and three steps for filling.

Process validation for 3 full-scale batches has been performed. Each batch was packed in the 3 commercial containers.

C. Control of Starting Materials

The active substance is miltefosine, an established active substance that complies in-house specifications. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Hydroxypropylcellulose, propylene glycol and purified water comply with the European Pharmacopoeia monographs 01/2005:0337, 01/2005:0430 and 01/2005:0008, respectively. A certificate of analysis has been submitted for a batch of each excipient.

Certificates of analysis for packaging materials including routine controls have been attached.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (3 years) under the approved conditions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

None

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

See Part IV

Toxicological Studies

The applicant has conducted laboratory studies which show that the toxicity profile of Miltefosine after oral administration was non-specific and characterised by apathy, salivation, ruffled fur and delayed body weight gain. Gastric dilatation and a reddened intestinal mucosa revealed the gastrointestinal tract to be a specific target organ. Miltefosine is classified in Category 4 of the 423 OECD Guideline after a single administration by oral route

- Single dose toxicity

In rodent species, the LD_{50} for miltefosine after oral administration is comprised between 300 and 600 $mg.kg^{-1}$. When the finished product (Milteforan) is administered, this value is superior to 2000 $mg.kg^{-1}$. Milteforan is not suspected to cause sensisisation by skin contact, is moderately irritant for eye and is irritant for skin.

- Repeated dose Toxicity

Repeat dose toxicity studies were performed in rats and dogs. The NOEL was found to be $1mg.kg^{-1}$ in juvenil rats administered (oral route) with miltefosine for 8 consecutive weeks. Morphological eyes alterations observed at doses superior to the NOEL were found to be reversible after the end of the treatment. In dogs treated for 13 consecutive weeks, the NOEL was also $1mg.kg^{-1}$. After 52 weeks of daily oral dosing, this value was 0.422 $mg.kg^{-1}$ in rats (without eye alteration) and $<1mg.kg^{-1}$ for dogs, with signs of salivation, diarrhoea and vomiting for the latter species.

- Reproductive Toxicity including Teratogenicity:

Studies revealed that miltefosine is embryo- and foeto-toxic in rats and rabbits, and teratogenic in rats. No study of reproductive toxicity in the target species was provided. Doses that produced teratogenicity in rats are very near to the doses, which are indicated for Milteforan. Therefore, the product is contraindicated in the SPC and in the package leaflet for use in pregnant and lactating females and in breeding animals.

- Mutagenicity and Carcinogenicity

Miltefosine is devoid of mutagenic or carcinogenic properties.

Other Studies

The applicant has provided information in relation with the immunotoxic effects. There was no sensitisation produced by Milteforan in the Bülher test in the guinea pigs. The test was performed in compliance with GLP.

Observations in Humans

The applicant has provided bibliographical data which show that Miltefosine is a membrane activating alkilphospholipid originally developed as an antineoplastic agent.
Initial testing in Kala-azar (visceral leishmaniasis) patients, which was based upon solid experimental antileishmanial activity, demonstrated gastrointestinal toxicity but also obvious clinical and parasitologic effects.
Miltefosine given for 28 days at a dose of 50 mg once or twice a day (depending on a body weight <25 kg or ≥ 25 kg, respectively) induced cure rates of approximately 90-95%.
Although miltefosine shows promise as an antifungal drug and is approved for use in humans with leishmaniasis, it has disadvantages. The parent compound has, like numerous other antineoplastic agents, a high incidence of gastrointestinal side effects (anorexia, nausea, vomiting –approximately 60%- and diarrhoea –approximately 20%-); a lesser incidence of hepatotoxicity, with typically transient increases in liver enzyme levels, and occasional rashes, including rare instances of Stevens-Johnson syndrome. Nausea and vomiting precluded its long-term use in patients with cancer.
High doses are teratogenic in rats, and although congenital abnormalities have not been reported in humans when the male partner was taking miltefosine, the drug is contraindicated in pregnant women

Microbiological Studies

Miltefosine is an antileishmanial drug not known for any potential microbiological effect. This product is intended to be used only in dogs (not in food producing animals).
By consequence, no experimental data have been presented by the applicant.

User Safety

User safety has been addressed adequately.
Taking into account the pharmacological and toxicological profile of the product, the experimental exposure data and the implemented options for risk control, it is considered that the warnings in the SPC and product literature would sufficiently address any risks associated with potential oral exposure.

Ecotoxicity

An Environmental Risk Assessment was performed in the Dossier according to the legislation in force in the EEC and according to the VICH Phase I GL 6 “Guideline on environmental impact assessment (EIAs) for veterinary medicinal products – Phase I”.

According to the decision tree set in this guideline, this Environmental Risk Assessment was stopped at the question 3 related to the use of MILTEFORAN in non-food producing animals only (dogs). The decision to stop this ERA at this question is perfectly justified according to the legislation in force in the European Community. In addition, it should be born in mind that MILTEFORAN is a product intended to be used for individual treatment only. Consequently, amounts potentially released into the environment are low, and of no risk for living organism.

Miltefosine is however an anticancer drug. This leads to question about its safety when administered to dogs and therefore after being excreted into the environment.
For a better evaluation of the potential environmental contamination associated with the use of MILTEFORAN, the applicant considered a great city from South Europe. Indeed, the density population of dogs is much higher in cities than in the country, and consequently cities are the areas with maximal potential drug concentration in different compartments of the environment.

The applicant submitted an approximation for the environmental risk assessment, which, although not the usual method referred to the veterinary guidelines, could be considered more correct and, more adjusted to the practical conditions of use of the product.

After an extended approximation taking into account, the percentage of dogs which would be treated by the drug, the dosage regimen for Milteforan, the average monthly rainfalls for the city and which whole surface, the mass excretion balance and the metabolite profile of miltefosine (among other things) the applicant could finally refined the concentration potentially found into the waste water.

The calculated predicted environmental concentration ($PEC_{Surfacewater}$) for Milteforan is below the action limit of 0.01 µg/ml. There are no other environmental concerns apparent regarding the use of Milteforan.
Milteforan is unlikely to represent a risk for the environment following the prescribed usage in dogs.
It is not required therefore to perform a further environmental risk assessment according to phase II.

III.B Residues documentation

Residue Studies

No residues documentation is required because the product is for non food producing animals.

IV. CLINICAL ASSESSMENT (EFFICACY)

MILTEFORAN is a 2% solution for oral use in dogs for control of canine leishmaniasis. The product should be administered at 2 mg miltefosine/kg bw, daily for 28 days.. It is indicated for the control of canine leishmaniasis. The clinical signs are significantly reduced 2 weeks after the beginning of the treatment . These signs continue to improve for at least 4 weeks after completion of the treatment.

IV.A Pre-Clinical Studies

Pharmacology

The active substance is miltefosine, a synthetic glycerol-free phospholipid analogue (alkylphosphocholine) antiprotozoal agent, developed for use in dogs.

Miltefosine is a new active ingredient not previously assessed for veterinary use. However, miltefosine is well known in human medicine. It has been used for many years in human as topical treatment for skin metastases resulting from breast cancers and, in some countries, for the treatment of human visceral leishmaniasis.

Antileishmanial activity was assessed in vitro and in vivo in experimental models. Miltefosine exhibited its Antileishmanial effect against promastigote form and amastigote form of L.donovani and L.infantum.

Pharmacokinetic:

Several studies on the pharmacokinetic in Beagle dogs were provided. The product is well absorbed after oral administration, is moderately distributed and is slowly metabolized. A high bioavailability (F=93,6%) was determined.

Oral Bioavailability (F= 93.6 %) respect IV route was determinated after a single dose of 1 mg/kg of miltefosine General and complete information on

pharmacokinetic profile of miltefosine (with the final formulation: MILTEFORAN) at the recommended dose (2 mg/kg/day of miltefosine for 28 days) in Beagle dogs is submitted. Plasma, urine and faeces concentrations of miltefosine had been analysed. The main pharmacokinetic findings are a long elimination and terminal plasmatic half life, a low plasmatic clearance and a high accumulation factor of 7.65 which leads to achieve the steady state at the end of the treatment period. Miltefosine is mainly eliminated via the fæcal 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.

Tolerance in the Target Species

Three tolerance studies were carried out in Beagles with X, 2 X and 3X the recommended dose for a month to assess the tolerance margin and the best administration conditions. Palatability and high level dosages were tested in the two former studies.

The occurrence of GI adverse effects was observed when increasing twice the recommended dose and when the product is administered by forced intake (Study 107.00/40001). In a second study, the dose was largely increased to 3x to produce a higher rate of adverse effects and in case of bad tolerance what antiemetic should be used.

A complete tolerance study carried out with the final formulation, where clinical, electrocardiographic, ophtalmological, haematological, biochemical and micro and macro anatomy pathologic parameters were evaluated. 2mg/kg.b.w was selected as the dose with an acceptable margin of tolerance.

During the clinical studies, the main adverse events were related to gastrointestinal tract: vomiting and diarrhoea.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

Dose determination Trials

Dose determination studies were carried out in naturally infected dogs, due to a large period of manifestation of clinical signs of Leishmaniasis after infection. Three studies were carried out, in countries of Mediterranean littoral and with a similar design. Assessment of efficacy was made from clinical criteria and parasitological analysis. (serology, and myelogram).

Field Trials

A study was performed in order to assess the efficacy of the product at the recommended dose, it was a multicentric open study. Clinical, serological and parasitological (myelogram) criteria were used for diagnosis and for assessment of efficacy after two months of follow up after treatment.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target specie is favourable and the quality and safety of the product for humans and the environment is acceptable.