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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Furosivet 20 mg Tablets for Dogs and Cats

Date Created: March 2019

Updated: November 2023

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0329/001/DC
Name, strength and pharmaceutical form	Furosivet 20 mg Tablets for Dogs and Cats, Tablet
Applicant	Millpledge Europe BVBA 38 Verrekijker 8750 Wingene Belgium
Active substance(s)	Furosemide
ATC Vetcode	QC03CA01
Target species	Dogs and Cats
Indication for use	For the treatment of oedema and ascites, particularly resulting from cardiac insufficiency, renal dysfunction, or of a traumatic origin.

MODULE 2

The Summary of Product Characteristics (SPC) the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	6th February 2019
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Belgium, France, Germany, United Kingdom (Northern Ireland)

I. SCIENTIFIC OVERVIEW

This was a generic application submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended. The product is indicated for the treatment of oedema and ascites, particularly resulting from cardiac insufficiency, renal dysfunction, or of a traumatic origin. The reference product is Furosemide Tablets B.P. (Vet) 20 mg, also marketed by Millpledge Ltd, which was authorised in the UK via a National procedure in 1998.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] 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 [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains the active substance furosemide and the excipients lactose monohydrate, maize starch, pregelatinised starch and magnesium stearate.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

The product is supplied in:

- cardboard box of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 25 or 50 Aluminium-PVC foil/PVC-PVDC blisters of 10 tablets each corresponding to 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, 250 or 500 tablets per box, as well as;
- white high-density polyethylene container containing 250 tablets, with a silica gel bag desiccant, and sealed with a white, child-resistant, polypropylene closure. The particulars of the containers and controls performed are provided and conform to the regulation.

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

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of the mixing of the active substance with the excipients before compression into tablets.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

II.C. Control of Starting Materials

The active substance is furosemide, an established active substance described in the European Pharmacopoeia (Ph. Eur). 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. An acceptable certificate of suitability was provided. The excipients, and purified water used for processing, are all monographed within the Ph. Eur.

The container/closure for the active substance and the packaging for the finished product are suitably defined in the Ph. Eur. The silica gel descant sachets placed within the product tubs are in compliance with United States Food and Drug Administration (FDA) requirements.

II.C.4. Substances of Biological Origin

The only material of animal origin is lactose monohydrate and a statement from the supplier is provided, stating that it is prepared from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption, and is prepared without the use of ruminant material other than calf rennet.

A completed EMA TSE table confirming compliance with the Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products (EMEA/410/01 Rev.3) was provided.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. 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. Control tests on the finished product include those for: appearance, identification of the active substance, average weight of tablets, water content, loss on drying, thickness and hardness of tablets, dissolution, assay of related substances and microbiological purity.

II.F. 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. The retest period for the active substance is 5 years as stated on the certificate of suitability.

Data are presented to show that the tablets are chemically and physically stable for up to 60 months at 25°C/60%RH and 6 months at 40°C/75%RH and therefore support a shelf life of 5 years, provided the tablets are kept in the original container in order to protect from light.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 5 years.

Store in the original container in order to protect from light and moisture. The silica gel bag should be kept inside the container. Half tablets should be replaced back into the original container and should be given at the next administration.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

This application was for a generic product, submitted in accordance with Article13 (1) of Directive 2001/82/EC, as amended. The product has the same qualitative and quantitative composition as the reference product and therefore pharmacological and toxicological data, other than to support the URA, were not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- Furosemide has possible genotoxic properties and there is evidence of carcinogenicity in mice. Although there is inconclusive evidence relating to these effects in humans, skin contact with or accidental ingestion of the product should be avoided. Wear impervious gloves during handling and administration of the product and wash hands thoroughly afterwards.
- For the same reasons, the product is supplied in a container with a child-resistant closure. The cap of the container must be securely engaged after use. If smaller quantities are dispensed from the pack, they must be supplied in a container with a child-resistant closure. If appropriate containers are not available, the product must be supplied in the original container.
- Unused tablets or half tablets should be placed back into the container, the child-resistant closure replaced, and the product stored safely, out of the sight and reach of children.
- In case of accidental ingestion seek medical attention and show product label and/or pack insert to the doctor.
- People with known hypersensitivity to furosemide should avoid contact with the veterinary medicinal product.
- Do not handle this product if you know you are sensitive to sulphonamides as hypersensitivity to sulphonamides may lead to hypersensitivity to furosemide.
- If you develop symptoms following exposure such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines. The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required. The product is not expected to pose a risk to the environment when used as directed.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Due to the nature of the application, no data were required.

Tolerance in the Target Species

No tolerance studies were provided for this generic application. Recommendations to update appropriate data in the SPC and on the product literature as compared with the reference product were actioned. Refer to Sections 4.3, 4.4, 4.5i, 4.6, 4.7, 4.8 and 4.10 of the SPC for details.

IV.II. Clinical Documentation

No studies were required for this section as this was an application for a generic product. The indications for the product were revised for clarification purposes as compared to that of the reference product.

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 benefit/risk profile of the product is favourable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Summary of change (procedure number)	**Section updated**	**Approval date**
Change in RMS from UK (UK/V/0682/001) to NL (NL/V/0329/001).	Module 1,2,3 4	9 April 2019
NL/V/0329/001/IA/001/G C.I.9.a) Change in the QPPV and/or QPPV contact details and/or back up procedure; C.I.9.b.) Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and/or change of the site undergoing pharmacovigilance activities	Module 4	24 October 2020
NL/V/0329/001/VNRA/ 3865: B.22 Replacement of UK batch release site by EU site (Millpledge Europe BVBA) ; B.24. Replacement of a UK batch control site with a EU batch control site for a finished productB.3A Deletion of a batch control site. B.34 Immediate package change PP bottle to HDPE, HDPE closure to PP). B.27.a Change to in-process tests or limits applied during the manufacture of the finished product: — tightening of in process limits. B.27.b Change to in-process tests or limits applied during the manufacture of the finished product: — addition of a new in process test and limits B.3.n Deletion of a nonsignificant specification parameter (e.g. deletion of an obsolete parameter	Module 3,4	8 December 2022

such as odour and taste or identification test for a colouring or flavouring material) in the specification parameters or limits of the finished product] B.30.a Change in the specification parameters or limits of the finished product: -Tightening of specificaiton limits] B.44 Submission of a new or updated Ph. Eur. CEP from an already approved manufacturer for a non-sterile - active substance; - starting material, reagent or intermediate used in the manufacturing process of the active substance 3866: B.3.n Remove loss on drying from FPS, including editorial changes 3867, B.3.a Deletion of a batch control site 3868. B.3.a. Deletion of a batch control site		
NL/V/0329/001/A/002/G – F.II.d.2.b Change in test procedure for the finished product, other changes to a test procedure (*replacement)* F.II.e.1.b.1 - Change in immediate packaging of the finished product, addition of a new container for solid pharmaceutical form *(introduction of blister pack)* F.II.e.5.a. Quality changes - Finished product - Container closure system - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack outside the range of the currently approved pack sizes	Module 3,4	12 April 2023
VNRA 9855 - B.34 Change in qualitative and quantitative composition of the immediate packaging for a solid pharmaceutical form for a finished product	Module 4	30 August 2023