Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Adaxio Shampoo for Dogs

Date Created: February 2015

Updated: March 2017

PuAR correct as of 01/06/2018 when RMS was transferred to FR. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0518/001/DC
Name, strength and pharmaceutical form	Adaxio Shampoo for Dogs
Applicant	Ceva Animal Health Ltd Unit 3, Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB
Active substance	Chlorhexidine digluconate 20 mg (equivalent to chlorhexidine 11.26 mg) Miconazole nitrate 20 mg (equivalent to miconazole 17.37 mg)
ATC Vetcode	QD08AC52
Target species	Dogs
Indication for use	For the treatment and control of seborrhoeic dermatitis associated with *Malassezia pachydermatis* and/or *Staphylococcus pseudintermedius*.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic 'hybrid' application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	18th June 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden.

I. SCIENTIFIC OVERVIEW

This was an application for a marketing authorisation for a generic 'hybrid' product, Adaxio Shampoo for Dogs, submitted in accordance with Article 13 (3) of Directive 2001/82/EC. This was a generic 'hybrid' application as it is not possible to demonstrate systemic bioavailability for a shampoo, because the active substances are not systemically active. The reference product was Sebolyse Shampoo for Cats and Dogs, marketed in the UK in August 1996. The true generic of Sebolyse was Malaseb Shampoo for Dogs and Cats, (authorised in the UK in 1997).

The product is intended to treat seborrhoeic dermatitis associated with *Malassezia pachydermatis* and/or *Staphylococcus pseudintermedius*. For cutaneous use, the product is applied after the animal's coat has been wetted in clean water, using sufficient product to raise a lather on the coat. The animal stands for ten minutes, the coat is then rinsed and the animal allowed to dry naturally in a warm, draught-free environment.

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

[1] SPC – Summary of product Characteristics.

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 CONSTITUENTS

II.A. Composition

The product contains chlorhexidine gluconate 20 mg/ml and miconazole nitrate 20 mg/ml. The excipients are methylchloroisothiazolinone, methylisothiazolinone, macrogol lauryl ether, cocamidopropyl betaine, disodium cocoamphodiacetate, cetrimonium chloride, macrogol 120 methyl glucose dioleate, magnesium chloride, sodium chloride, magnesium nitrate, citric acid monohydrate (for pH adjustement), benzoic acid (E210) and purified water.

The container/closure system consists of a white opaque polypropylene bottle with a polypropylene flip-top cap. The particulars of the containers and controls performed are provided and conform to the regulation. The pack sizes are 200 ml and 500 ml. Not all pack sizes may be marketed.

The choice of the formulation and the presence 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 process consists of mixing the product's ingredients, followed by making up to final solution with water. The product is then filled into bottles. The product is manufactured in accordance with the European Pharmacopoeia (Ph. Eur.) and relevant European guidelines.

II.C. Control of Starting Materials

The active substances are chlorhexidine digluconate and miconazole nitrate, established active substances described in the Ph. Eur. The active substances are 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. Suitable Certificates of Suitability were provided.

[2] Efficacy – The production of a desired or intended result.

Excipients monographed in the Ph. Eur are as follows:

Macrogol lauryl ether
Citric acid monohydrate
Purified water

Excipients not monographed (Certificates of analysis provided), in the Ph. Eur are as follows:

Cocoamidopropyl betaine solution
Disodium cocoamphodiacetate solution
Cetrimonium chloride solution
Preservative mixture (containing methylchloro-isothiazolinone and methylisothiazolinone)
PEG-120 methyl glucose dioleate.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product. A declaration stating that the product complies with the latest version of the CPMP/CVMP guideline on TSEs EMEA/410/01 Rev. 3 was included in the application.

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. Tests include those for appearance, density, pH, viscosity, identity of active substances, impurities, and microbiological quality.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. From one manufacturer of chlorhexidine digluconate, a retest interval of 3 years for material stored in HPDE[3] drums with an external metallic cover was approved, and 2 years for material stored in HPDE drums at a temperature not exceeding 25°C. For an

[3] HPDE – High density polyethylene.

alternative manufacturer, a retest period of 2 years for material stored in HDPE drums at a temperature not exceeding 25°C was agreed.

For miconazole nitrate, for one manufacturer a retest period of 5 years was agreed for product protected from the light, at a temperature not exceeding 25°C and in an inner polyethylene bag and outer polyethylene/aluminium bag in a fibre drum. Data supplied for an alternative manufacturer also supported a retest period of 5 years.

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 when stored under the approved conditions. A variety of data were provided for the finished product, under normal and accelerated conditions, as required.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 24 months.

Shelf-life after first opening the immediate packaging: 3 months.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

Chlorhexidine digluconate is a bis-biguanide anti-microbial, effective against Gram-positive and Gram-negative bacteria via both bacteriostatic (concentrations greater than 100 µg/ml) and bactericidal (1 - 100 µg/ml) action. The active substance is widely used in human and veterinary products as a cleansing agent for wounds and clinical equipment. The mechanisms of action are achieved via the over-riding of cell wall exclusion mechanisms and the formation of phosphate complexes.

Miconazole nitrate is widely used in human and veterinary medicine for the treatment of fungal infections. It is an imidazole agent with action against a variety of micro-organisms, but with no efficacious activity against Gram-negative rods. In the proposed product, this active substance was selected for activity against *Malassezia pachydermatis*.

Pharmacokinetics

Chlorhexidine binds strongly to mucosa and skin, and is therefore poorly absorbed by this means. Excretion is mainly via the faeces, and minimally via the urine. The active substance is not detectable in the blood plasma following treatment.

For miconazole, there is again little absorption through the skin or mucous membrane. Peak plasma concentrations may be found 4 hours after a 1 g oral dose. Above 9 mg/kg, intravenous doses generate plasma concentrations of approximately 1 µg/ml. The majority of the active substance is bound to plasma protein, with poor absorption into cerebrospinal fluid. There is a large amount of diffusion to mammalian joints, liver gastrointestinal system, adrenals and kidney. Studies in rats and mice have found that miconazole crosses the placental barrier, but does not accumulate in the foetus. The active substance is detectable in mammalian milk. The half-life of miconazole is approximately 24 hours, and it is excreted mainly unchanged in the faeces. A smaller proportion is excreted via the kidneys, in general, as metabolites of the active substance. Plasma concentrations can remain higher in subjects with impaired renal function.

Toxicological Studies

The applicant provided bibliographical data:

- Single Dose Toxicity

Chlorhexidine is of low acute toxicity. For female and male rats, the acute oral LD_{50}[4] values were identified in one study as being 2000 mg/kg and 2270 mg/kg bodyweight respectively, and in mice, 2547mg/kg and 2515 mg/kg bodyweight respectively. Parenteral administration increased the toxicity. For miconazole, the applicant provided data on acute oral LD_{50} (mg/kg) values. For mice, this was 578.1 mg/kg in one study and between 2160 - 2650 mg/kg in another study. In rats the acute oral LD_{50} value was >640 mg/kg in one study, and between 920 – 1200 mg/kg in another study. For dogs, a reported figure of >160 mg/kg bodyweight was provided.

- Repeated Dose Toxicity

Data from an MRL[5] study of chlorhexidine were provided, showing that a NOEL[6] of 0.5 mg/kg bodyweight was obtained for an oral study in dogs. Studies conducted in rats using miconazole noted adverse effects on the liver and kidneys of rats, no NOEL was provided, but doses in excess of 30 mg/kg appear to generate adverse effects in dogs. In studies conducted with miconazole administered orally to rats, effects were noted on the liver and kidneys. In one study, target organ effects were reversible 4 weeks after cessation of dosing.

[4] LD50 – Lethal dose at which 50% mortality observed.
[5] MRL – Maximum residues limit.
[6] NOEL – No observed effect limit.

No NOEL has been calculated from the results of either study, but doses over 30 mg/kg appear to give rise to adverse effects.

- Reproductive Toxicity, including Teratogenicity:

For chlorhexidine, an overall NOEL for fertility and reproduction in rats was noted as being 4.9 mg/kg bw per day, based on reduced pup weights on day 4 post-partum. There was no evidence of foetotoxicity or teratogenicity at any dose level in rat and rabbit teratology studies. Supporting data from cited maximum residues limits were provided.

It was observed that miconazole had no effects on the foetus in rat reproduction studies. No teratogenic or inhibitory effects on the growth of foetuses were seen, however, miconazole was shown to significantly prolong gestation (over 30 mg/kg/day), which could have resulted in a slight increase in the incidence of still-births (100 mg/kg/day). From rabbit studies, the maternal NOEL was 10 mg/kg/day based on reduced body weight gain and 30 mg/kg/day for foetuses, (the highest dose tested). Miconazole was not considered to be foetotoxic or teratogenic.

- Mutagenicity

No carcinogenic effects were noted for either active substance.

Observations in Humans

Both active substances have been used extensively in human medicines. Used as advised in the SPC, the proposed veterinary product is deemed safe for use. Commonly the concentration of chlorhexidine in such products is 4%, and that contained in the proposed veterinary product is 2%. Irreversible eye damage has been observed with accidental application of chlorhexidine. The SPC for the proposed product carries suitable safety warnings. Miconazole is also commonly used in human medicines, and the SPC contains sufficient information with regard to appropriate safety precautions.

Microbiological Studies

Cases of resistance to the active substances have been noted, however, this is not expected to compromise user safety.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that when used as described, warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- People with known hypersensitivity to chlorhexidine, miconazole or any of the excipients should avoid contact with the product.

- This product may cause hypersensitivity following dermal contact. If you develop symptoms following exposure such as skin rash, you should seek medical advice and show the physician the label or package leaflet.

- Accidental eye contact with undiluted product may cause serious eye irritation. Avoid contact with the eyes. In case of accidental contact with eyes, rinse with plenty of water. If irritation persists consult your physician.

- The product can be irritating to skin. Avoid prolonged contact with the shampoo by gently washing and drying hands.

- Avoid excessive handling and stroking of treated animals immediately following treatment.

Environmental Safety

Phase I:

The applicant submitted a Phase I ERA in accordance with VICH guidelines. The assessment ended at Phase I, based on use in non-food producing animals only. The disposal advice given in the SPC is in line with the Notice to Applicants and this product is not expected to pose a risk to the environment when used as directed.

Residue Studies

No residue depletion studies were conducted because the product will be used in non-food producing species.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

As previously described in the Safety section.

Pharmacodynamics

Chlorhexidine digluconate is a bis-biguanide anti-microbial effective against Gram-positive and Gram-negative bacteria via both bacteriostatic (concentrations greater than 100 a µg/ml) and bactericidal (1 - 100 µg/ml) means. The active substance is widely used in human and veterinary products as a cleansing agent for wounds and clinical equipment. The mechanisms of action are achieved via the over-riding of cell wall exclusion mechanisms and the formation of phosphate complexes.

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Tolerance in the Target Species

Although no specific tolerance studies were performed. The applicant provided data related to a clinical field trial, which compared the proposed product and Malaseb Shampoo for Dogs and Cats. Minor adverse events, which apart from one case were likely not related to treatment, were observed. The SPC carries suitable warnings in relation to the product causing possible eye irritation. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Information provided suggests that while resistance has been seen in some bacterial species, this is not thought to impact currently on the efficacy of the proposed product. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Field Trials

Two literature references and the results of a multi-centric field trial were used to evaluate efficacy and target animal safety. The two literature references supported the data collated for the field trial.

Study title	Evaluation of the clinical efficacy and safety of a miconazole chlorhexidine shampoo for the treatment and control of dermatitis associated with *Malassezia pachydermatis* overgrowth and/or *Staphylococcus pseudintermedius* overgrowth in client-owned dogs.
Objectives	Assessment of the clinical field safety and effectiveness of shampoo containing a combination of 2% chlorhexidine digluconate and 2% miconazole nitrate in the treatment and control of canine dermatitis associated with *Malassezia pachydermatis* overgrowth and/or *Staphylococcus pseudintermedius* overgrowth in client-owned dogs.
Test site(s)	Multi-centre, veterinary practices, EU countries.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP).
Test Product	Miconazole (20 mg/ml) chlorhexidine (20 mg/ml) shampoo.
Control product	Malaseb Shampoo for Dogs and Cats.
Animals	265 dogs of both sexes, neutered and entire, and spanning more than 80 breeds were recruited to the trial, but only 262 received treatment: Inclusion criteria: signs of dermatitis associated with overgrowth of *M. pachydermatis* or *S. pseudintermedius.* Shampoo alone was considered as an appropriate treatment. Exclusion criteria: signs of deep pyoderma, parasitic skin disease, leishmaniasis, auto-immune disease, endocrinopathy or neoplasia. Flea allergy dermatitis (not treatable with shampoo). Treatment with other relevant products. Known hypersensitivity to the proposed product or control. Initiation of an exclusion diet less than 3 weeks before the study. There were additionally some post-inclusion removal criteria.
Outcomes/endpoints	Primary endpoint was improvement in mean skin score index (SSI) between days 0-28.
Randomisation	Two cohorts of dogs were recruited: dogs with SSI < and >15 at day 0. These animals were then randomised

	in a block design on a 1:1 ratio, being allocated to either the proposed product or the control group. All clinical and investigating personnel were blinded, with codes provided to investigators should the blind be required to be broken in the case of an emergency.
Blinding	Blinded: investigator/other. Parallel group. Block design.
Method	Animals were examined at day 0 and appropriate scores taken for skin sores. Samples were taken for analysis of the target pathogenic species, and owners provided with a shampooing regimen for the dogs (twice weekly for two weeks). At day 14, further analyses were conducted, and if necessary the regimen changed to once a week for two weeks. Alternatively the regimen was kept as first stated, any dogs which required different treatment were regarded as having left the study. These animals were tested for the pathogenic species. Interim examinations were permitted if the owner required, or if considered appropriate. At day 28, final examinations were made, with a clinical exam performed, SSI score calculated, and body odour score and overall efficacy score were allocated. Sampling took place for the pathogenic species.
Statistical method	A number of populations were studied, including: Dogs completing 28 days of treatment. Safety population: all dogs receiving one shampoo with either product. Statistical aim was to establish non-inferiority of the proposed product as compared to the control, using a non-inferiority margin of 20%, a significance level of 5% and a power of 80%. Non inferiority was demonstrated if the lower limit of the 95% two-sided confidence interval of the difference was not below the non-inferiority limit. Qualitative variables were analysed using Chi square or Fisher exact tests and quantitative variables were analysed using student t tests.
RESULTS	
Outcomes for endpoints	Based on the mean efficacy criterion, it was shown that the proposed product was non-inferior to the control product. No statistical differences were noted for any secondary efficacy variables.
Adverse events	No significant adverse events occurred during the study.
DISCUSSION	It was concluded that the proposed product was efficacious in treating the pathogenic species cited in the indication.

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(s) is favourable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)