I. INTRODUCTION

Microbex contains the active substance chlorhexidine digluconate 31.2 mg. This product is authorised to be used in dogs for the treatment of *Malassezia pachydermatis* surface proliferation and the control of associated clinical signs. The product is to be applied topically three times a week for twoweeks then, if necessary, twice a week for two weeks and finally on a weekly basis. If necessary, further use may be required in accordance with the directions of and a benefit/risk assessment by the prescribing veterinarian. This product should not be used in dogs that are known to be hypersensitive to chlorhexidine or any of the other ingredients. Safety of the product has not been demonstrated in animals of less than five months of age.

This is application is made in accordance with Article 12 (3) of Directive 2001/82/EC as amended by 2004/28/EC.

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 product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC[1].

II. QUALITY ASPECTS

Product Development and Composition

The product contains the active substance chlorhexidine digluconate and the excipients lauryl glucoside, cocamidopropyl betaine, glucono δ-lactone, purified water and Ponceau 4R (E124).

The product is an established pharmaceutical form and its development has been adequately described in accordance with the relevant European guidelines.

Active Substance

The active substance is chlorhexidine digluconate which is described in the European Pharmacopoeia.

The active substance specifications are considered adequate to control the quality of the materials.

Other Substances

No European Pharmacopoeia monograph is available for glucono deltalactone. Acceptably, the applicant applies the monograph of the current USP (United States Pharmacopoeia). The European Pharmacopoeia monograph is appropriately applied in the case of purified water. A certificate of analysis for all the excipients has been provided.

Packaging Materials

The product is presented in 200-ml white high-density polyethylene bottle closed by a polypropylene disc top screw and an overcap. The secondary pack is a cardboard box. These packaging materials are stated to meet the requirements of the relevant monographs of the European Pharmacopoeia.

[1] SPC – Summary of Product Characteristics.

Manufacture of the Finished Product

The applicant has provided a description of the manufacturing process. Appropriate checks are carried out during the manufacturing process. The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

A declaration has been provided stating that no materials of animal origin are used in the manufacture of the active substances or any excipient.

Finished Product Quality Control

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 were provided.

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

Stability of the Product

Active substance

The Certificate of Suitability for chlorhexidine digluconate solution issued by EDQM states a retest interval of three years for material stored at a temperature not exceeding 25°C in HDPE drums with an external metallic cover or two years for material stored under the same conditions in HDPE drums without the metallic cover.

Finished Product

Stability data on the finished product were provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

A shelf life of 3 years was considered justified with no special storage condition.

In-Use

An in-use shelf life of 2 months was considered justified. Do not refrigerate. (Do not store at +8°C or below).

CONCLUSIONS ON QUALITY

The product is appropriately formulated and controlled. A shelf-life of 3 years in an unopened pack and in-use shelf life of 2 months was justified.

III. SAFETY ASPECTS

Introduction

Chlorhexidine, the active ingredient of the product, is a biguanide used widely in disinfectants and antiseptics for both human and veterinary use and the safety information submitted by the company therefore includes a review of published literature on the pharmacology and toxicology of chlorhexidine gluconate.

Pharmacology

The applicant provided literature references to support the pharmacokinetics of chlorhexidine. The published literature indicates that chlorhexidine is not absorbed to any significant extent from the gut or via dermal application.

Toxicology

Chlorhexidine has been found to be of fairly low acute toxicity when given to laboratory animals orally and published information on the toxicity of the chlorhexidine following repeated administration to rats, cats and dogs showed no adverse effects in any of the species. Published literature also provides adequate information on the possible effects of chlorhexidine on reproductive performances in animals. Other published literature indicates that chlorhexidine does not possess any mutagenic and carcinogenic potential. Other reports indicated that chlorhexidine possess skin and eye irritancy potential. The appropriate user warnings are included in the SPC and product literature.

Reproductive studies

The CVMP summary report shows that there is no effect on reproduction and only a slight effect on pup bodyweight after oral administration of chlorhexidine at 44.4 mg/kg.

Embryotoxicity/fetotoxicity

The applicant conducted an in-house study to determine the effects of Microbex on embryo-foetal development in the rat by oral route. The study was conducted in accordance with GLP. The results of the in-house embryotoxicity study with Microbex, coupled with the opinion of the CVMP in the Summary Report on chlorhexidine indicate that oral administration of doses up to 100 mg/kg does not elicit fetotoxicity in rats.

Mutagenicity

The published literature and in-house mutagenicity tests on Microbex indicates that chlorhexidine does not possess any mutagenic potential.

Environmental Safety

The applicant has provided environmental risk assessment which was carried out in accordance with VICH Phase I guidelines. The veterinary medicinal product will only be used in non-food animals, therefore the environmental risk assessment demonstrates that exposure of the environment will not be extensive.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

Adequate toxicity data were provided by the applicant and the necessary warnings are listed in the SPC and product literature. These are:

People with known hypersensitivity to chlorhexidine or any of the excipients should avoid contact with the veterinary medicinal product.
Avoid contact with eyes. In case of accidental eye contact, rinse with plenty of water. If irritation persists consult your doctor.
Wash hands after use.
Do not eat, drink or smoke while handling this product.
In the event of accidental ingestion, seek medical advice and show the package leaflet or the label to the doctor.

Conclusions on Consumer Safety

The product is for use in dogs only, and therefore no concerns relating to consumer safety.

Conclusions on Environmental Safety

The veterinary medicinal product will only be used in non-food animals, namely dogs. As a result exposure of the environment is not extensive. As a result of these considerations Microbex is not expected to pose a risk for the environment when used according to the SPC (or instructions on the label).

IV. CLINICAL ASPECTS

Clinical Pharmacology

The safety information submitted by the applicant includes a review of published literature on the pharmacology and toxicology of chlorhexidine gluconate. Published literature provides adequate information on the physico-chemical properties of chlorhexidine. Other reports the comparison of the rate of killing of three canine pathogens (*Staphylococcus intermedius, Pseudomonas aeruginosa and Malassezia pachydermatis*) by four canine chlorhexidine shampoos of different concentrations. A study was also conducted to determine the *in vitro* MIC and MFC of chlorhexidine digluconate against *Malassezia pachydermatis* isolated from canine clinical cases of dermatitis at a 1/5 dilution. The study has also been demonstrated at both a 1/5 dilution and a 1/25 dilution for a similar 3 % chlorhexidine digluconate shampoo. The study was conducted in accordance with the principles of ISO17025 and GLP regulations. The study concluded that the MIC and MFCs of the field strains were homogeneous and supports the existence of a fungicidal action of chlorhexidine on *M. pachydermatis.*

Pharmacokinetics

The applicant provided two literature references and two experimental studies to support the pharmacokinetics of chlorhexidine. These studies indicate that after topical administration of the product to dogs, there was little or no systemic absorption of chlorhexidine digluconate. Absorption of chlorhexidine after oral administration is also very low. The efficacy of the product is due to the high concentrations of chlorhexidine digluconate achieved on the body surface for the 10-minute period of shampooing.

Tolerance in the Target Species

The applicant provided one bibliographic reference describing a safety study in dogs and one tolerance study. A general and local tolerance study of the product was conducted on dogs after repeated topical applications at 0, 1 and 5 times the therapeutic dose. The study was conducted in accordance with Good Laboratory Practice Regulations. This study and the literature reference demonstrated that dogs receiving up to five times the recommended therapeutic dose, three days a week for four consecutive weeks, shows on occasions slight cutaneous reactions only. These reactions were transient, although they could last for several days when shampooing was ongoing. They did not require any particular treatment.

Resistance

To date no resistance to chlorhexidine has been shown for *Malassezia pachydermatis*.
Resistance to chlorhexidine is uncommon in Gram (+) bacteria but some resistant Gram (-) isolates have been described in human hospital environments (*Proteus* spp., *Pseudomonas* spp.).
When used in accordance with the recommended dose regimen the development of resistance to chlorhexidine is not expected.

Clinical Efficacy

The applicant provided two field studies to determine the efficacy of Microbex. The first study was conducted to assess the efficacy of Microbex in the treatment of dermatitis associated with *Malassezia pachydermatis* proliferation in dogs against a positive control, in normal field conditions of use. This study was conducted in accordance with Good Clinical Practice. Another study was conducted to evaluate the antimicrobial and clinical efficacy and tolerance of another product (a 3 % chlorhexidine digluconate shampoo) in the control of abnormally high *Malassezia pachydermatis* populations and the associated clinical conditions.

These studies provided evidence that Microbex can be safely used in dogs for the treatment of *Malassezia pachydermatis* surface proliferation and the control of associated clinical signs at the recommended dose rate.

PART V. OVERALL CONCLUSION ON THE PRODUCT

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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)