I. INTRODUCTION

This product is an oral suspension containing neomycin and sulfadiazine and is indicated for treatment of diarrhoea in pre-ruminant calves associated with infections caused by organisms known to be or suspected of being susceptible to the combination of active substances. The dosage regime is 4 ml per 10 kg bodyweight twice daily for a maximum period of 5 days. This equates to 60 mg/kg Sulfadiazine and 10 mg/kg Neomycin twice daily.

This application is submitted under Article 13 (1) of the Directive 2001/82/EC as amended by Directive 2004/28/EC. The applicant has confirmed that the formulation of Bimamix Oral Suspension is identical to the formulation of an approved product and the manufacturing procedures used to formulate both products are the same, therefore no bioequivalence or bioavailability data have been presented.

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. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

Product Development and Composition

The product is supplied in high density polyethylene containers of 250 ml and one litre with tamper evident closures formed from polypropylene co-polymer. Taking into account the approximate maximum weight of a pre-ruminant calf as 45 kg, both pack sizes are appropriate to treat 13 and 55 calves respectively.

With the exception of simethicone emulsion and carmoisine, both the active substances and excipients comply with the relevant European Pharmacopoeial (Ph. Eur) monographs. Additionally, both the active substances are supplied against Ph. Eur. certificates of suitability (CEP).

The rationale for the selection of the active substances and excipients has been satisfactorily discussed. Neomycin is present in the formulation fully solvated whereas sulfadiazine is present in a suspended form. The particle size is controlled for sulfadiazine and is adequate to control the input material.

The bulking agent is kaolin which is a well known excipient and has been employed as an anti-diarrhoeal agent in many formulations. Polysorbate 20 and propylene glycol are used as dispersing and wetting agents respectively, with the povidone and xanthan gum added as suspending agents. Simethicone emulsion is employed as an anti-foaming agent, citric acid and sodium citrate as pH adjusters and carmoisine as a colouring agent. Finally, methyl and propyl hydroxybenzoates are included as preservatives at levels typically seen in this type of oral product.

Active Substance

There are two active substances in this product, neomycin sulphate and sulfadiazine.

Neomycin sulphate
This is supplied and manufactured against the current version of Ph. Eur. certificate of suitability (CEP) 1999-184-Rev-01. This includes a further test for sodium metabisulphite at not more than 0.4 %. The raw material specification of the dosage form manufacturer includes further in house particle size testing in addition to the monograph requirements. Batch analysis data demonstrating compliance with the Ph. Eur. monograph have been provided.

Sulfadiazine
This is supplied against the current version of CEP 1996-109. This includes a further test for any unspecified impurity at not more than 0.10 %. The raw material specification indicates what tests the dosage form manufacturer undertakes on receipt, if the batch is supported by a certificate of analysis from the supplier, and this is satisfactory. Batch analysis data demonstrating compliance with the Ph. Eur. monograph have been provided.

Other Substances

All the excipients comply with various pharmacopoeia and raw material specifications are provided for each one. The raw material specifications also indicate what tests the dosage form manufacturer undertakes on receipt, if the batch is supported by a certificate of analysis from the qualified supplier. A typical supplier's certificate of analysis has been provided for each excipient.

Packaging Materials

The product is presented in 250 ml and one litre bottles constructed from high density polyethylene (HDPE). The closure is formed from a polypropylene copolymer and is tamper evident. Specifications and drawings are included for each of the components. The container colour is described as 'natural' and is opaque. The closures are lined with polyethylene foam. The applicant has confirmed that all the polymers used are suitable for food contact use.

Manufacture of the Finished Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

A TSE declaration and accompanying format three table have been provided and this is satisfactory. None of the materials used in the manufacture of this product fall within the scope of the guideline.

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 have been provided.

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

Stability of the Product

Active Substance
Stability data have been provided, utilising VICH storage parameters, for both substances and these show that neomycin sulphate has a retest period of 36 months with no special storage conditions and that sulfadiazine has a retest period of 60 months if stored below 25°C.

Final Product
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.

Overall the data appear to support the proposed shelf life of 36 months and no warnings on temperature controlled storage are required. With regard to photostability studies, the applicant has certified that the containers and closures are completely opaque so, photostability studies are not required

Stability Studies – opened product
Chemical stability has been investigated and this shows that the product is likely to be adequately preserved after 28 days. The shelf life is two years.[1]

CONCLUSIONS ON QUALITY

The application is supported with respect to quality.

Shelf life
Unopened - 3 years
Opened – 28 days after first opening.

[1] Variation procedure of 17th August 2011 changed shelf-life from three years to two years.

III. SAFETY ASPECTS

Pharmacology

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity, data on pharmacodynamics and pharmacokinetics are not required. This type of product is exempt from the requirements to provide bioequivalence studies.

Toxicology

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity, data on toxicology are not required. This type of product is exempt from the requirements to provide bioequivalence studies.

User Safety

The following operator warnings are included in the SPC and product literature:

"Avoid contact with skin. Wash hands after use."

The proposed operator warnings are identical to those included in the SPC and product literature for the comparator product.

Residues

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity this information is not required.

The following withdrawal period is justified:

Meat and offal: 28 days
Not permitted for use in lactating animals producing milk for human consumption.

The following warnings are included in the SPC and product literature:

Animals intended for human consumption must not be slaughtered during treatment. Calves intended for human consumption may only be slaughtered after 28 days from the last treatment. Not intended for animals producing milk for human consumption.

The meat withdrawal period of 28 days and the contra-indication for use in animals producing milk for human consumption is identical to the comparator product and is considered satisfactory to protect consumer safety

Environmental Safety

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity, data on ecotoxicity are not required. This product is considered to be bioequivalent to the reference product and environmental safety is considered to be satisfactory.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASPECTS

Clinical Pharmacology

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity this information is not required as it has already been presented for the reference product.

Tolerance in the Target Species

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity new tolerance data is not required as it has already been presented for the reference product.

In addition PSURs[2] covering the period 1 October 1998 to 1 June 2006 have been provided and show no reports of adverse reactions.

Resistance

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity resistance data is not required as it has already been presented for the reference product.

Clinical Efficacy

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity this information is not required as it has already been presented for the reference product.

CONCLUSIONS ON EFFICACY

The pharmaceutical formulations of the reference and test product are identical with regard to the nominal content of the active ingredients. No new studies on tolerance or efficacy have been presented because of the nature of the application. The applicant has stated that the product is exempt from the conduct of bioequivalence studies because the product is to be administered orally as a solution, and it contains the same active substance and excipients in the same concentration as the reference product.

[2] PSUR = Periodic Safety Update Report

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 risk benefit 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)