I. INTRODUCTION

Colibird 2 MIU/ml Solution for use in Drinking water for chickens, submitted as a generic application in accordance with Article 13 of Directive 2001/82/EC as amended. This product is intended to treat digestive infections caused by colistin-susceptible *Escherichia coli* (*E.coli*), in chickens. The reference product is Colistin Sulfate 2 000 000 IU/ml Buvable Veprol, not authorised for use in the UK. The active substance, colistin sulphate is a potent inhibitor of Gram-negative bacteria, especially *E.coli*. Excipients are benzyl alcohol and purified water. The product is intended for use in drinking water and contains 2 Million International Units (MIU)/ml of colistin as colistin sulphate. Colibird is authorised for use in high density polyethylene bottles, in 250 ml, 500 ml, 1L, 2L and 5L sizes. Not all pack sizes may be marketed.

The dose for chickens is 75 000 IU of colistin per kg bodyweight per day, for three to five consecutive days. The quantity of product used is deduced from the total weight of birds treated, this equates to:-

Total number of birds x average body weight in tonne x 37.5 = total volume of product (ml) to be used per day. Uptake of the product is dependant on the physiological and clinical condition of the birds to be treated.

II. QUALITY ASPECTS

Product Development and Composition

Good Manufacturing Practise (GMP) certificates were provided for both the site of manufacture and the site of batch analysis. The product possesses the same pharmaceutical form and qualitative and quantitative composition as the product Coliscour Oral Solution of Colistin Sulphate 2 MIU/ml, indicated for use in pigs. The formulation of colistin makes it freely soluble in water, and the excipients are commonly used in preparations of this type. This is a multi-dose, aqueous product, and there is a requirement for products of this type to have an antimicrobial preservative. In this case, the preservative is 1.0%wv benzyl alcohol.

Active Substance

The active substance, colistin sulphate, is mongraphed in the European Pharmacopoeia, (Ph. Eur.). An acceptable Certificate of Suitability (CEP) was provided. Certificates of analysis for three batches of the active substance, provided by the applicant, demonstrated complete compliance with the specification.

Colistin is a cyclopeptide antibiotic, belonging to the polymixin therapeutic class, that includes polymixin B. Colistin is a mixture of Colistin A and Colistin B. The active is effective against Gram-negative bacteria, with resistance to colistin being relatively unknown.

Other Substances

The excipients benzyl alcohol and purified water are monographed in the Ph. Eur. Certificates of analysis were provided for these excipients, and the applicant routinely carries out prescribed tests, adhering to specifications described in the monographs.

Packaging Materials

The product is authorised for use in 250 ml, 500 ml, 1 litre, 2 litre or 5 litre white, high density polyethylene bottles. Not all pack sizes may be marketed. The closures are white, tamper-evident caps, with a PVC/PVA seal and translucent polypropylene dosing device. The containers and lids are analysed with regard to specific components, in particular, dimensional checks are performed along with infra-red analysis of the polymers. In addition, the containers comply readily with requirements for food use.

Manufacture of the Finished Product

Manufacture is on a 1500 litre or 4000 litre scale. Potency of the finished product is analysed with regard to colistin content in an appropriate manner. Manufacture is conducted at ambient temperature, and consists of the dissolution of benzyl alcohol in purified water, followed by the addition of colistin sulphate. The product is then filtered prior to being placed in the appropriate containers.

Three pilot-scale batches of 150 litres each were validated, in addition to the analysis of ten 4000 litre commercial batches; to the Finished Product Specification.

Finished Product Quality Control

A range of tests are carried out on the finished product. These include analysis of appearance, pH, relative density, mass of content, benzyl alcohol identity, sulphate identity, colistin identity, benzyl alcohol assay, colistin sulphate assay and microbial quality. Appropriate tests for microbial contamination are carried out every eighth batch, this frequency being justified by the demonstration that three pilot batches and ten full-scale batches of product met specification limits. HPLC[1] and TLC[2] tests on appropriate parameters were deemed acceptable.

Stability of the Product

Active substance

Three full-scale commercial batches of colistin sulphate were stored in small-scale batches for twenty-four months at 25°C/60%RH, and additionally for six months at 40°C/75%RH. Appropriate, regular testing was performed, adhering to those described in the Ph. Eur. All results were acceptable. A retest interval of three years for material packaged as a commercially viable product, at no greater than 25°C/60%RH was confirmed.

[1] HPLC – High performance liquid chromatography.

[2] TLC – Thin layer chromatography.

Finished Product

Product stored over a period of time contributed to the conclusion that the shelf-life of the product as packaged for sale is thirty-six months. Shelf-life of the product after opening the immediate packaging is three months.

In-Use

Results of stability studies for three pilot batches of finished product were presented. Product was stored in opened containers for three months at ambient temperature and humidity. No significant changes were seen and the in-use shelf-life was established at three months. Further tests confirmed that the product may remain in drinking water, after reconstitution, for twenty-four hours.

CONCLUSIONS ON QUALITY

The following parameters apply to this product:-

- The shelf life is three years as packaged for sale, no special conditions of storage are required.
- Any contents remaining three months after the date on which the container was first opened should be discarded.
- Any medicated water not consumed within twenty-four hours should be discarded.

III. SAFETY ASPECTS

Introduction

This application was submitted in accordance with Article 13 of Directive 2001/82/EC, and as such, results of safety, pre-clinical and clinical tests are not required as bioequivalence is claimed with the reference product, Colistin Sulfate 2 000 000IU/ml Buvable Veprol marketed by Virbac France SAS.

Pharmacology

This application was submitted in accordance with Article 13 of Directive 2001/82/EC, and as such there is no requirement to provide results for this section as bioequivalence was demonstrated with the reference product.

Toxicology

This application was submitted in accordance with Article 13 of Directive 2001/82/EC, and as such there is no requirement to provide results for this section as bioequivalence was demonstrated with the reference product.

Residues

Residue depletion studies were provided. In the first GLP study, broiler chickens were given repeated oral administration with Colistine Ceva 2 MUI/ml, (150 000 IU/24 hours for seven days). A number of young birds were either treated orally with the final product formulation, or were not treated. Colistin levels in tissues were subsequently analysed, and although the product was administered at levels above the recommended dose, levels remained below the maximum residue limit (MRL) at all time points.

In a second, previously published study, adult birds were treated orally and via intramuscular injection, or were not treated. The dose was 90000 IU of colistin sulphate/kg/day for five days in drinking water, and a single injection administered at 50000 IU colistin sulphate. Colistin was undetectable in albumen or egg yolk after oral administration. Colistin residues were below the MRL at all time points.

MRLs

Species	Annex	Marker Residue	Tissue	MRL	Regulation
All food producing species	I	Colistin	Muscle Fat Liver Kidney Eggs	150 µg/kg 150 µg/kg 150 µg/kg 200 µg/kg 300 µg/kg	1181/2002

Environmental Safety

A Phase I Environmental Risk Assessment was provided by the applicant. The PEC_{soil} for chickens was below 100 µg/kg. This product is intended for use in the drinking water of chickens. The Phase I Environmental Risk Assessment has satisfactorily concluded that the PEC_{soil} is below 100 µg/kg, and no further evaluation is required.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

The user warnings are similar to those already applicable for Coliscour Oral Solution of Colistin Sulphate 2 MIU/ml. These are:-

- Avoid use of the product by people sensitive to polymyxins.
- When preparing the solution, wash any splashes from eyes with water.
- Wash hands and exposed skin after use.

Conclusions on Consumer Safety

The withdrawal period for meat and offal is one day. The withdrawal period for eggs is zero days.

Conclusions on Environmental Safety

The product is safe for use when administered as directed.

IV. CLINICAL ASPECTS

Introduction

As this is a generic application, there was no requirement to provide pre-clinical or clinical data.

Clinical Pharmacology

As this is a generic application, there was no requirement to provide pre-clinical or clinical data.

Tolerance in the Target Species

As this is a generic application, there was no requirement to provide tolerance data. Data on the target species safety and efficacy were requested with regard to a pre-existing European Reference Product. The applicant provided reference data which gave information on adverse reactions to colistin in humans, more recent studies suggest lower and less severe toxic reactions. A pharmacokinetic study was also referenced, in which chickens were dosed with colistin via the oral route at high dosage. It was concluded that as colistin is poorly absorbed via the oral route, there is little risk of tolerance issues occurring. The SPC contains suitable indications and warnings. No comprehensive target species tolerance has been reviewed nationally. As a result of a referral to CVMP of colistin-containing products, a decision was made that at the recommended dose rate colistin in this type of product is considered safe to the target species.

Resistance

As this is a generic application, there was no requirement to provide data on resistance.

Clinical Efficacy

As this is a generic application, there was no requirement to provide pre-clinical or clinical data.

CONCLUSIONS ON CLINICAL ASPECTS

Efficacy and target species safety are considered satisfactory based on the fact that this is a generic product of a European Reference Product, the generic product and ERP are the same and that the indication, dose rate and tolerance have been considered acceptable by the CVMP and by the Commission following an Article 35 referral. The indication for the treatment of gastrointestinal infections caused by E. coli and the dose of 75 000 IU per kilogram body weight for three to five consecutive days are considered appropriate.

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.

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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.

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