# I. INTRODUCTION

Baytril Max 10% Solution for Injection contains the active substance enrofloxacin. This product is authorised to be used in cattle for the treatment of bovine respiratory disease associated with *Mannheimia haemolytica, Pasteurella multocida, Haemophilus somnus* and Mycoplasma spp. where clinical experience, supported where possible, by sensitivity testing of the causal organism, indicates enrofloxacin as the drug of choice. The product is also indicated for the treatment of local signs (inflammation, milk quality and yield) associated with peracute/acute mastitis in lactating dairy cattle caused by *E. coli*, where herd history and previous sensitivity testing indicate enrofloxacin as the drug of choice. For respiratory infections in cattle, the recommended dose is 7.5 mg/kg bodyweight as a single dose (by subcutaneous injection) and for *E.coli* mastitis, the recommended dose is 5.0 ml per 100 kg bodyweight daily for two days.

Baytril Max 10% Solution for Injection holds a national MA in the UK and this application for a change to the existing MA is in accordance with Article 2a of Commission Regulation (EC) No.1084/2003, an extension to the Marketing Authorisation (MA) submitted under Article 12(3) of Directive 2001/82/EC, as amended.

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.

# II. QUALITY ASPECTS

## Product Development and Composition

The product contains the active substance, enrofloxacin and the excipients, benzyl alcohol, arginine, butyl alcohol and water for injection.

The product is packaged in a 100 ml amber type 1 glass vials sealed with siliconised grey rubber butyl bungs. The particulars of the containers and controls performed were provided and conform to the regulation.

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 enrofloxacin is an established active substance and supporting data have been provided. It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

## Other Substances

All excipients are supplied against Ph. Eur. monographs and are commonly used in veterinary medicines.

## Packaging Materials

The packaging materials used in the manufacture of the product comply with the requirements of the applicant's specification and meet the requirements of the European Pharmacopoeia for Type I glass containers.

## 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 manufacturing formula, method of manufacture (description and flow diagram) and in-process controls were considered appropriately described.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

## Finished Product Quality Control

The finished product specification controls the relevant parameters for the pharmaceutical form. The range of tests applied was considered appropriate for a product of this type. 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

Data have been provided and these show that the active substance is stable when stored in the appropriate container under appropriate conditions.

### Finished Product

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its 3 year shelf life

### In-Use

In-use stability testing has been carried out adequately to justify a 28 day in-use shelf life.

Other information
**Proposed Pharmaceutical Warnings:**
Do not store above 25°C
Do not freeze.
Discard if visibly contaminated.

**Shelf life**
Unopened – 3 years
Broached bottle – Following withdrawal of the first dose, use the product within 28 days. Discard unused material.

# III. SAFETY ASPECTS

## Pharmacology

As this application is for an extension to add a new route of administration (intravenous), and the currently approved route of administration (subcutaneous) is also parenteral, the applicant has not supplied any new data.

## Toxicology

As this application is for an extension to add a new route of administration (intravenous), and the currently approved route of administration (subcutaneous) is also parenteral, the applicant has not supplied any new data.

## Environmental Safety

This application for an extension is to add the intravenous route to the MA for Baytril Max. An environmental risk assessment (ERA) has been provided which concentrates solely on the risks associated with the intravenous administration of this product to cows that have mastitis caused by *E. coli*. The ERA has been carried out in accordance with VICH Phase I guidelines.

## CONCLUSIONS ON SAFETY AND RESIDUES

### Conclusions on User Safety

It is concluded that the risk to the user has not changed by the addition of this new route of administration. No new user safety warnings are proposed and this is acceptable.

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

- Baytril Max 10% solution for injection is an alkaline solution. Wash any splashes from skin or eyes immediately with water.
- Do not eat, drink or smoke whilst using the product
- Care should be taken to avoid accidental self-injection. If accidental self injection occurs seek medical advice immediately.

### Conclusions on Environmental Safety

Baytril Max 10% Solution for Injection is already authorised for use in cattle to treat respiratory disease. The environmental risk for this indication has been assessed and environmental risk is considered acceptable. This line extension seeks to add the intravenous route for treatment of mastitis caused by *E. coli* in dairy cattle. Animals will be treated in housing and the residues of enrofloxacin will reach the environment when manure from treated animals is spread onto land. Phase I environmental risk assessment has been provided for the new indication which has demonstrated that exposure of the environment will not be extensive. This is considered acceptable.

### Withdrawal periods

Based on the data provided above, withdrawal periods as indicated are justified:

Withdrawal periods after being treated with 7.5 mg/kg bodyweight, once, by subcutaneous injection are:

| | | |
|---|---|---|
| Cattle | (meat & offal): | 14 days |
| | (milk): | 84 hours |

The withdrawal periods for the proposed treatment with 5 mg/kg body weight daily for two consecutive days, by slow intravenous injection, are:

| | | |
|---|---|---|
| Cattle | (meat & offal): | 4 days |
| | (milk): | 72 hours |

## IV. CLINICAL ASPECTS

## Clinical Pharmacology

Pharmacodynamics

The applicant has cross-referred to the pharmacodynamic data submitted for the application for the extension to Baytril 10 % Solution for Injection, to add the same administration route and indication. This is considered acceptable.

Pharmacokinetics

The applicant has cross-referred to the pharmacokinetic data submitted for the application for the extension to Baytril 10 % Solution for Injection. This is considered acceptable.

## Tolerance in the Target Species

The tolerance of Baytril Max 10 % Solution for Injection in cattle has already been established where a single dose of up to 7.5 mg/kg is administered by the subcutaneous route. In addition, the applicant has cross-referred to the GLP tolerance study submitted for Baytril 10% solution for injection. This study demonstrated that Baytril 10% solution, when administered by the i/v route at a dose rate of 5 mg/kg/day for 5 days to lactating cows, produced no adverse systemic affects.

## Resistance

The applicant has cross-referred to the microbiological Expert Report submitted for the application for the extension to Baytril 10 % Solution for Injection, and the subsequent PK-PD analysis for the product submitted in responses.

Some amendments have been made in section 5.1 of the SPC, detailing the mechanisms of resistance to fluoroquinolones. This is in accordance with requirements of the guideline on the SPC for antimicrobial products, EMEA/CVMP/SAGAM/383441/2005.

## Clinical Efficacy

As Baytril Max 10 % solution for injection can be considered to be bioequivalent to Baytril 10% solution for injection for the IV administration route, the applicant has cross-referred to the clinical data submitted for the application for the extension to Baytril 10 % Solution for Injection. For Baytril 10% solution for injection, the applicant submitted one dose determination and two dose confirmation studies conducted in lactating cattle with artificially induced *E coli* mastitis. In addition, there was a clinical field study. These clinical studies provided evidence of the efficacy of Baytril 10% when administered by the proposed dose regimen in treating the local clinical signs of acute *E. coli* mastitis. In addition the applicant submitted opinions from Experts and literature references. It was concluded that the data supported the following indication: “Treatment of local signs (inflammation, milk quality and yield) associated with peracute/acute mastitis in lactating dairy cattle caused by *E. coli*, where herd history and previous sensitivity testing indicate enrofloxacin as the drug of choice.”

## CONCLUSIONS ON CLINICAL ASPECTS

As Baytril Max 10 % Solution for Injection and Baytril 10 % Solution for Injection are both aqueous solutions containing enrofloxacin 100 mg/ml as the active substance, intended to be administered by the intravenous route, they can be considered as bioequivalent for the same indication in cattle. It is therefore acceptable that the data package for Baytril 10 % should be extrapolated to Baytril Max 10 %.

However, Baytril Max 10 % contains two excipients not included in the Baytril 10 % formulation: the preservative, benzyl alcohol and L Arginine. The applicant has provided literature references to support the safety of these two excipients when administered by slow intravenous injection at the proposed dose rates and concentrations to cattle.

Some additional warnings are included in the SPC, consistent with the CVMP’s guidance regarding the prudent use of fluoroquinolones in food producing species.

# 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)