I. INTRODUCTION

The product is indicated for the treatment of brachyspira, in particular haemorrhagic enteritis caused by *Brachyspira hyodysenteriae*. It is also indicated to treat enzootic pneumonia caused by *Mycoplasma hyopneumoniae*, even in the presence of pathogens such as *Mycoplasma hyorhinis*, *Pasteurella* sp, *Haemophilus* sp, or *Actinobacillus pleuropneumoniae*. The product will reduce lesions, maintaining the zootechnic performance.

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 Tiamvet Solution 12.5 % Solution is a generic of an approved product.

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 slight reactions observed are indicated in the SPC. 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 efficacy of the product was demonstrated according to the claims made 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 a solution, for oral administration to pigs, and contains the active substance tiamulin hydrogen fumerate and excipients benzyl alcohol, ethanol and purified water.

It is presented in 500 ml, 1 litre, 2 litre and 5 litre white high-density polyethylene bottles fitted with a white polypropylene, tamper-evident closure and a translucent polypropylene dosing device. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and 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.

Active Substance

The active substance is tiamulin hydrogen fumerate an established active substance described in the European Pharmacopoeia. Supporting data have been provided in the form of a European Drug Master File (EDMF). It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified. Each batch of tiamulin hydrogen fumarate is subjected to full testing on receipt to the requirements of an in house specification. This is adapted from the specifications included in the EDMFs and that in the European Pharmacopoeia monograph. The active substance specification is considered adequate to control the quality of the material.

Other Substances

Benzyl alcohol, ethanol 96 % and purified water are stated to comply with the relevant monographs in the latest edition of the European Pharmacopoeia. No specifications for the excipients are included, although copies of certificates of analysis issued by the dosage form manufacturer are provided. All of the tests of the monograph are routinely carried out on these excipients.

Packaging Materials

The product is presented in 500 ml, 1 litre, 2 litre and 5 litre white, high-density polyethylene

bottles all using the same closure. This is a white polypropylene tamper-evident screw cap with a polyvinyl chloride/polyvinyl acetate seal and a translucent polypropylene dosing device. The dosing device is a measuring cylinder affixed to the inside of cap of the bottle.

Specifications for the individual components include dimensional checks and an identification of the polymers by infrared spectroscopy. Data on the polymers are supplied, including information on compliance with requirements for food contact use. The applicant has confirmed that all of the tests of the specifications are routinely carried out on each of the packaging materials.

Manufacture of the Finished Product

The manufacturing formula and method of manufacture (description and flow diagram) are fully described. In-process controls include appearance, density, pH and fill quantity and are considered satisfactory.

The validation data supplied for three 500 litre batches, one eighth of maximum batch size, filled into all four proposed pack sizes are considered adequate to cover the proposed batch sizes. Samples from the bulk and four bottles from each pack size were examined. Degradation is not expected to occur during manufacture and this conclusion is supported by results showing no quantifiable increase in degradation products during manufacture.

Scientific data have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

Finished Product Quality Control

The range of tests is considered to include appropriate parameters for a product of this type. Tests include appearance, pH, relative density; fill volume, identity, assays of active ingredient and benzyl alcohol and microbial quality. The absence of a test for degradation products is acceptable since it has been shown that there is no quantifiable increase in degradation products during manufacture. 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<s> have been provided demonstrating compliance with the specification.

Control Tests on Intermediate Products

Not applicable as there are no intermediate products.

Stability of the Product

Active substance

Appropriate 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. Results of a study to investigate the stability of this product when exposed to light are also presented. The study, which was carried out in accordance with the ICH guideline, “Photostability Testing of New Active Substances and Medicinal Products.” This demonstrates

that the product is slightly sensitive to light, but that the packaging provides adequate protection.

In-Use
In-use stability testing was carried out over a three month period. The results show no significant change in any parameter of the finished product specification and support the claimed in-use shelf life of three months.

After reconstitution
Stability data are also presented after reconstitution in drinking waters at different dilutions. Drinking waters of a range of pH, hardness and held in a range of container types were used. Stability showed losses of less than 5 %, and the data support the 24 hour life for product reconstituted in drinking waters at these concentrations.

CONCLUSIONS ON QUALITY
The application is supported with respect to quality.

Proposed Pharmaceutical Warnings:
Any contents remaining 3 months after the date on which the container was first opened should be discarded.
Any medicated water not consumed within 24 hours should be discarded

Shelf life
Of the product as packaged for sale – 3 years
Of the product after first opening – 3 months
After dilution in drinking water – 24 hours

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 being a generic of a reference medicinal product, data on pharmacodynamics and pharmacokinetics are not required.

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 being a generic of a reference medicinal product, data on toxicology are not required.

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

Do not eat, drink or smoke whilst using this product
When mixing, direct contact with the skin and eyes should be avoided by wearing impermeable rubber gloves and safety glasses.
In case of accidental eye contact, irrigate the eyes thoroughly with clean running water immediately. Seek medical advice if irritation persists.
Contaminated clothing should be removed and any splashes on to the skin should be washed off immediately.
Wash hands after use.

The applicant has also submitted a user risk assessment, which indicates that the above warnings may be appropriate.

Environmental Safety

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 being a generic of a reference medicinal product. This product is considered to be bioequivalent to the reference product. Its environmental safety is considered to be satisfactory. Ecotoxicity data were not required for this type of product (Generic/Essentially similar) when the application was accepted by the VMD.

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

Any unused product or waste material should be disposed of in accordance with national requirements.

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 being a generic of a reference medicinal product, this information is not required.

MRLs

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues
Tiamulin	Sum of metabolites that may be hydrolysed to 8-α-hydroxytiamulin	Porcine	100 µg/kg 500 µg/kg	Muscle Liver

All the excipients are either in Annex II of Regulation 2377/90 or out of scope of this Regulation.

Based on the above the withdrawal period for pigs' meat is 2 days is justified. The UK reference product has a 2-day withdrawal period and the applicant is exempt from submitting a new residue study as this product fulfils section 4 (e) of EC Guideline EMEA/CVMP/016/00 – Guidelines for the conduct of bioequivalence studies for veterinary medicinal products. This application is acceptable with respect to consumer safety.

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 being a generic of a reference medicinal product, 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 being a generic of a reference medicinal product, new tolerance data is not required as it has already been presented for the reference product.

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 being a generic of a reference medicinal product, 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 being a generic of a reference medicinal product, 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 in the same concentration as the reference product, Tiamutin Solution, and does not contain an inactive substance that could significantly affect the absorption of the active substance.

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 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)