I. INTRODUCTION

This application for Bimectin Plus Solution for Injection for Cattle was made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, for a generic application. The reference product is Ivomec Super Injection for Cattle. Bimectin Plus Solution for Injection for Cattle is intended for the treatment of mixed trematode and nematode or arthropod infestations in cattle as follows: Gastrointestinal roundworms (adult and fourth larval stages*), Ostertagia ostertagi*, *Ostertagia lyrata*, *Haemonchus placei*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Cooperia oncophora*, *Cooperia punctata*, *Cooperia pectinata*, *Bunostomum phlebotomum*, *Oesophastamum radiatum*, *Strongyloides papillosus*, *Nematodirus spathiger*, *Nematodirus helvetianus* and *Trichuris* spp. Treatment of the lungworm *Dictylocaulus viviparous* is also indicated, as is treatment of the liver fluke, *Fasciola hepatica*. The eye worm *Thelazia* spp. may be treated with this product, also the warble fly larvae *Hypoderma bovis* and *Hypoderma lineatum*. Mange mites *Psoroptes bovis* and *Sarcoptes scabiei* var. *bovis* may be treated, as may sucking lice spp. *Linognathus vituli*, *Haematopinus eurysternus* and *Solenoptes capillatus*. Bimectin Plus Solution for Injection for Cattle may also be used to treat for biting lice and mange mites *Damalina bovis* and *Chorioptes bovis* respectively, however complete elimination may not occur with these arthropods.

A single dose of 1 ml per 50 kg bodyweight, which equates to 200 µg ivermectin and 2 mg clorsulon per kg bodyweight is given. The product is administered to cattle as a subcutaneous injection with doses in excess of 10 ml being divided and administered over different injection sites.

Bimectin Plus Solution for Injection for Cattle, when given at the recommended dose, may be used to control re-infection with *Haemonchus placei*, *Cooperia* spp., and *Trichostrongylus axei* acquired up to fourteen days post treatment. The product may also be used to treat *Ostertagia ostertagi* and *Oesophagostomum radiatum* acquired up to twenty-one days post treatment, and *Dictocaulus viviparous* acquired up to twenty-eight days post treatment.

The active substances are 10 mg/ml ivermectin and 100 mg/ml clorsulon, and the excipients are glycerol formal, propylene glycol and monoethanolamine.

II. QUALITY ASPECTS

Product Development and Composition

The concentration of the active substances conform to those of the reference product, and the absence of an anti-microbial preservative was justified. The active substances in Bimectin Plus Solution for Injection for Cattle are ivermectin 10 mg/ml and clorsulon 100 mg/ml, and the excipients are glycerol formal, propylene glycol and monoethanolamine. The product is sterilised by filtration, due to the unsuitability of ivermectin for heated sterility processes.

All holding equipment and rubber closures are sterilised in an autoclave, while high density polyethylene containers are sterilised by gamma irradiation.

In-process controls include visual inspection, filter integrity and pH analysis. Two pilot scale batches of product were examined for compliance with the specification for the finished product, for homogeneity and for fill volume. Related substances analyses were consistent with those

permitted, and mixing regimens have been established to ensure homogeneity for production scale batches. All validation data were acceptable.

Active Substance

Active substance 1

Ivermectin utilised in this product complies with the monograph in the European Pharmacopoeia (Ph. Eur) and conforms to a satisfactory Certificate of Suitability (CEP). No testing is required in addition to adherence to the monograph. Batch analysis data for three batches of ivermectin are analysed on receipt of the active substance from the manufacturer. Each batch is tested for microbial purity, chemistry requirements, identity and solubility. Thereafter, each delivery of ivermectin is tested with regard to description, identity and solubility and one batch per year is subjected to complete testing.

Active substance 2

Clorsulon does not have a Ph. Eur monograph. However, an acceptable monograph from the United States Pharmacopoeia was presented, against which this active substance is tested.

Other Substances

The excipients are glycerol formal, propylene glycol and monoethanolamine. For propylene glycol, a Ph. Eur monograph exists and the British Pharmacopoeial monograph for ethanolamine is used for monoethanolamine. Glycerol formal does not have a pharmacopoeial monograph, an in-house specification was developed for this excipient.

Packaging Materials

The containers for Bimectin Plus Solution for Injection for Cattle are composed of high density polyethylene and are of a 50 ml, 250 ml or 500 ml size. The containers are sealed with siliconised, grey, bromobutyl rubber stoppers complying with the European Pharamcopoeial (Ph. Eur) requirement for Type I rubber closures. Aluminium overseals conform to acceptable parameters for appearance, dimensions and effectiveness of fit. The containers are checked for appearance and dimensions and are subject to an infra-red identification test. Certificates provided by the supplier assure compliance of the resins used in the manufacture of the containers with European and USA requirements for pharmaceutical and food use. The bottles are subject to periodic sterility checks.

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 applicant has provided details of the stages of, and method of manufacture. In process controls have also been described. Process validation data on the product have been presented in accordance with the relevant European guidelines. A format 3 TSE declaration states that no materials used in the finished product are relevant to the guideline on transmissible spongiform encephalopathies. Only materials of vegetable or synthetic origin are used in the manufacture of Bimectin Plus Solution for Injection for Cattle.

Finished Product Quality Control

The finished product is tested against the following parameters: appearance of product, container and closure, pH, moisture, identity of active substances and impurities.

Stability of the Product

Active substances

A certificate of suitability (CEP) for ivermectin states a retest interval of three years when stored in a double-lined heat-sealed polyethylene bag within an aluminium tin. Data regarding the stability of clorsulon are provided in an EDMF (European Drug Masterfile) provided by the manufacturer. For clorsulon, data were included on three batches prepared by different means, stored for six months and twenty-four months at 40°C/75% RH, and at thirty-six months at 25°C/60% RH. Containers were representative of commercial packaging. Data were satisfactory and a retest interval of two years was justified.

Finished Product

Two batches of finished product contained in each proposed pack size were subjected to testing under VICH* long term and accelerated conditions. Conditions were 25°C/60% RH and 40°C/75% RH. Some sensitivity to light was detected with regard to ivermectin, thus it is recommended in the SPC that the product is protected from light and stored in the outer carton. The shelf-life of the finished product as packaged for sale is three years.

In-Use

Data were provided on one batch of Bimectin Plus Solution for Injection for Cattle in 50 ml packs, and on two batches of product contained in 500 ml packs. Stability studies demonstrated that no deterioration in the product was seen that would curtail the proposed twenty-eight day in-use shelf life. Any unused product should be discarded.

CONCLUSIONS ON QUALITY

The application was supported with regard to quality.

* International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

III. SAFETY ASPECTS

Introduction

Bimectin Plus Solution for Injection for Cattle is a generic product based on the reference product Ivomec Super Injection for Cattle.

Pharmacology

This was a generic application in accordance with Directive 2004/82/EC as amended, and as such there was no requirement to submit data for this section.

Toxicology

This was a generic application in accordance with Directive 2004/82/EC as amended, and as such there was no requirement to submit data for this section.

Residues

The CVMP have adopted an opinion following an article 35 referral for injectable medicinal products with regard to the withdrawal period for injectable products containing ivermectin in combination with clorsulon. With regard to this Commission decision, reference to a residue study was not required.

Maximum Residue Limits (MRL) permitted for ivermectin and corsulon

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissue	Other provisions
Ivermectin	22,23-Dihydroavermectin B1a	All food producing mammals	100 ug/kg 30 ug/kg 100 ug/kg	Liver Kidney Fat	Not for use in animals producing milk for human consumption
Clorsulon	Clorsulon	Bovine	200 ug/kg 100 ug/kg 35 ug/kg	Kidney Liver Muscle	

Environmental Safety

Bimectin Plus Solution for Injection for Cattle is an injectable solution containing 10 mg/ml ivermectin and 100 mg/ml clorsulon. The product is most likely to be used as a single treatment in mid-winter, when cattle are contained in housing. This may be followed by a second dose at turnout in May; however, a second dose is considered a worst case scenario and would be unlikely to occur unless there was a problem on a specific farm. A Phase II risk assessment was required because the product is offered as an anti-parasitic for use in pasture animals. Ivermectin and clorsulon residues reach the environment via the manure from housed animals, which is spread onto pasture.

Ivermectin is poorly metabolised and is excreted mainly in the faeces, which in this case is spread onto soil. The applicant provided published data with regard to the effect of ivermectin on non-target species. In addition, PEC[1] values for a variety of parameters were provided by the applicant, with subsequent PNEC[2] values provided for soil, earthworms, algae, soil micro-organisms, fish sediment organisms, dung fly and dung beetle larvae. Comparison of PNECs using the worst case scenario PECS demonstrated that ivermectin does not pose a threat to the environment at Tier A. There is however a risk to aquatic organisms. The PEC_{soil} was calculated for animals in housing, and was deemed to be 1.5 ug/kg where 0.2 mg/kg/bodyweight ivermectin is given as a single administration. Tier B assessment of dung beetles suggests that as cattle are housed when treated, there is not a direct threat to these organisms, which do not generally reside within housing. Suitable wording in the Summary of Product Characteristics (SPC) ensures the protection of fish and aquatic life.

Clorsulon is also poorly metabolised in cattle, with the majority of the active substance being excreted in the faeces after seven days. PNEC values for clorsulon, provided for algae, fish, daphnia, dung fly larvae and earthworms are within the acceptable range, with comparison of PNECs using the worst case scenario PEC values all giving <1. Thus clorsulon is not expected to pose an environmental risk. Again, supplemental data in the form of referenced material provided supporting data for the use of clorsulon in Bimectin Plus Solution for Injection for Cattle.

Finally, the risk of using both compounds together was evaluated and found to be acceptable.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

Safety warnings for this product are the same as for the reference product, and are as follows:

- Do not smoke or eat while handling the product.
- Wash hands after use, take care to avoid self-injection.
- The product may cause local irritation and/or pain at the injection site.

Conclusions on Consumer Safety

[1] Predicted Environmental Concentration.
[2] Predicted No Effect Concentration.

A withdrawal period of sixty-six days was stipulated for meat and offal. The product is not to be used in cattle producing milk for human consumption, and is not to be used in non-lactating dairy cows including pregnant heifers within sixty days of calving.

Conclusions on Environmental Safety

Suitable data were presented which confirmed that Bimectin Plus Solution for Injection for Cattle is appropriate for use with regard to environmental safety.

IV. CLINICAL ASPECTS

Introduction

Bioequivalence of Bimectin Plus Solution for Injection for Cattle with Ivomec Super Injection for Cattle was claimed. A bioequivalence study was presented conforming to Good Laboratory Practice (GLP), which compared Ivomec Super Injection for Cattle and Bimectin Plus Solution for Injection for Cattle.

Clinical Pharmacology

Pharmacodynamics

Pharmacodynamic data for the two active substances of Bimectin Plus Solution for Injection for Cattle were not required. Relevant information for the reference product, submitted by the applicant, were considered appropriate.

Pharmacokinetics

A two-way, single dose GLP compliant bioequivalence study compared Bimectin Solution for Injection for Cattle with Ivomec Super Injection for Cattle. Both products were administered by subcutaneous injection. A suitable number of cattle were divided into treatment groups and subsequently injected with either the test product or the reference product at a rate of 0.2 mg/kg ivermectin and 2.0 mg/kg clorsulon per dose. Prior to administration, the animals were acclimatised and examined, then subjected to baseline blood testing and weighing. Blood sampling was also performed during the trial, with plasma levels of both test and reference product being compared with regard to active substances and residues content. Primary parameters used in statistical evaluation were AUC_t[3] and C_{max}[4]. Bioequivalence was established with a 90% confidence interval for the combined, standard equivalence limits of between 80%-125% for both AUC_t and C_{max}. The level of significance was established as being $p< 0.05$. Pharmacokinetic parameters were established via analysis of variance (ANOVA), and a 90% confidence interval based on Wilcoxon's Rank Sum Test was calculated for T_{max}.

No adverse reactions were noted during the trial; however some slight swelling occurred around the injection sites. Plasma levels of ivermectin and clorsulon for Bimectin Plus Solution for

[3] AUC_t - Area under the curve with respect to time.

[4] C_{max} – Peak serum concentration of the therapeutic drug.

Injection for Cattle during and after treatment closely reflected those of the reference product. Bimectin Plus Solution for Injection for Cattle and Ivomec Super Injection for cattle were therefore considered to be bioequivalent with regard to pharmacokinetic parameters.

Tolerance in the Target Species

A study on tolerance in the target species was supplied by the applicant. Overdose and repeat dose studies were performed using Bimectin Plus Solution for Injection for Cattle, and compared to the reference product, Ivomec Super injection for Cattle. This was a single-phase study conducted to GLP in which a suitable number of cattle were injected with either saline, 0.2 mg/kg ivermectin and 2.0 mg/kg clorsulon (Bimectin Plus Solution for Injection for Cattle), 1.0 mg/kg ivermectin and 10 mg/kg clorsulon or Ivomec Super Injection for Cattle, (at 1.0 mg/kg ivermectin and 10/0 mg/kg clorsulon). The cattle were treated daily for three days. Animals were acclimatised before being divided into four groups. Blood sampling, clinical examination and injection site examination were performed at various time points through out the trial, followed by post-mortem examinations on two groups. No adverse reactions were observed in any group, and no significant differences were noted between product treatment groups.

Resistance

Not applicable.

Clinical Efficacy

Bimectin Plus Solution for Injection for Cattle was established as being bioequivalent to the reference product, Ivomec Super Injection for Cattle. The efficacy of the generic product was therefore determined with no requirement by the applicant to provide further toxicological or pharmacological tests. Contraindications and warnings are the same as those provided in the SPC for the reference product.

CONCLUSIONS ON CLINICAL ASPECTS

It has been confirmed that bioequivalence has been demonstrated between Bimectin Plus Solution for Injection for Cattle and Ivomec Super Injection for Cattle. Therefore, this application for Bimectin Plus Solution for Injection for Cattle was supported with regard to efficacy.

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)