I. INTRODUCTION

Ivermectin Pour-On Solution for Cattle 5 mg/ml Virbacis a clear, colourless to pale yellow solution containing ivermectin. It is indicated for the treatment of gastro-intestinal nematodes, lungworms, warbles, chorioptic and sarcoptic mange mites, sucking and biting lice of beef and non-lactating dairy cattle. The dosage and route of administration is 500 µg of ivermectin per kilogram body weight (equivalent to 1 ml per 10 kg of body weight) applied topically along the mid-line of the back in a narrow strip between the withers and tailhead.

This product is authorised as a generic product submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC. The product is bioequivalent with the reference product, Ivomec Classic Pour-On for Cattle 5 mg/ml, Pour-on solution, hereafter referred to as “Ivomec”, (Vm 08327/4169) which has been authorised in the UK, since 19 May 1988.

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 contains the active substance ivermectin and excipients crodamol CAP, trolamine (triethanolamine) and isopropyl alcohol.

The product is available in either 500 ml and 1 litre packs with a squeeze measure pour system or 2.5 litre or 5.0 litre backpack with a draw-off cap. The 500 ml and 1 litre opaque high density polyethylene bottles are fitted with a child resistant cap (screw fit) internally lined with a low density polyethylene seal. These packs are supplied with a polypropylene dosing device capable of delivering doses of 10 to 25 ml, at 5 ml intervals. The 2.5 and 5 litre opaque high density polyethylene pack is fitted with a child resistant cap (screw fit) internally lined with a low density polyethylene seal. Although no dosing device is supplied with these larger pack sizes, the applicant has indicated on the SPC that a polypropylene dosing device should be used in conjunction with a dosing gun. For each pack size a plastic flask is also contained in the cardboard carton with the dosing device.

The choice of the formulation is justified. Each of the excipients contained in this product are commonly used in pour-on veterinary medicinal products. Isopropyl Alcohol acts as a solvent for the active substance and as a diluent for other formulation components. Triethanolamine is used as a buffering and alkylizing agent and Crodamol CAP as an emollient.

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 ivermectin an established active substance described in the European Pharmacopoeia. The applicant’s specification includes all of the tests and limits as specified in the European Pharmacopoeia. Tighter limits for ivermectin content are specified to those

specified in the European Pharmacopoeia monograph. An additional test for microbial limits has also been specified (European Pharmacopoeia 2.6.12). Certificates of analysis have been provided for two batches of active substance. The test results comply with the monograph for ivermectin, including acceptable test results for microbial purity.

Other Substances

Isopropyl alcohol and Trolamine (Triethanolamine) are to be of the quality required by the European Pharmacopoeia. Copies of the applicant's certificate of analysis in addition to the corresponding in house quality specifications have been provided for each excipient. The applicant also confirmed that all tests listed are conducted upon receipt of each raw material.

There is no pharmacopoeial monograph for the excipient crodamol CAP. Instead an in-house specification was developed which appropriately controls parameters including appearance, solubility (water and alcohol), identification and assay by GC[1] of components of crodamol CAP, relative density, water content, acid value, iodine value and saponification value. An in-house certificate of analysis was also provided.

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

Packaging Materials

In-house specifications for each component of the packaging material and dosing device were provided. The specification for each size of container included tests for appearance, container size (height thickness and width), screw neck size (external diameter, height and thread screw), flask weight, identity (by UV spectrophotometry) and water-tightness. The specification for each size of screw cap included tests for appearance, size (external diameter, internal diameter and height), and identity of the seal (by UV spectrophotometry). The specification presented for the 500 and 1000 ml dosing device includes tests for appearance, and size (external diameter of the screw neck, external diameter of the tank, height and height of the straw). Certificates of analysis for each component of the packaging showed that test results were in compliance with their corresponding specification.

Manufacture of the Finished Product

The applicant provided a description and a flow chart of the various steps of the manufacturing. The method of manufacture involves simple dissolution of ingredients. Initially ivermectin and isopropyl alcohol are mixed under appropriate conditions until complete dissolution is achieved. Crodamol CAP is added then added and mixed into the bulk. Triethanolamine is later added and mixed together under appropriate conditions. The process was validated with respect to homogeneity of active, physical and chemical properties and to levels of degradation products. Following manufacture and packing, each pilot batch of pour-on solution was tested for microbial quality according to European Pharmacopoeia Monograph 5.1.4 Category 2 Preparations for topical use. These data confirm satisfactory microbiological quality of the finished product. Additional basic chemical and physical data have also been presented to indicate that the quality of the pour-on solution remained unchanged with a 'holding time' between pour-on solution manufacture and filling of up to two days.

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

[1] GC = Gas chromatography, this is an analytical technique

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

No stability data were presented for ivermectin, the applicant has relied upon the certificates of suitability for the raw material. A retest period of three years when stored in a double lined polyethylene heat sealed bag placed in an aluminium tin was considered acceptable.

Finished Product

Stability data of the finished product in the smallest (500 ml) and largest (5000 ml) pack sizes was presented when stored at 25°C/60%RH[2] for up to 24 months and 40°C/75%RH for up to 6 months. An additional pack size of 2500 ml was also stored at 40°C/75%RH and additional samples were stored in ambient light for up to 30 days. The following shelf life is justified:

Shelf life of the veterinary medicinal product as packaged for sale: 2 years. Shelf life after first opening the immediate packaging: 6 months.

In-Use

In use stability testing was conducted on the 1000 ml and 5000 ml presentations when stored at 25°C/60%RH. These data support the six month in-use shelf life. The SPC contains a warning to store the product in the original container and keep tightly closed.

Stability data were also been provided for samples stored for one month at 4°C followed by exposure to -18°C, prior to being allowed to warm to ≈20°C. The clarity of the drug product remained unchanged before and after cooling to -18°C and following equilibration to room temperature. The summary of product characteristics contains a warning that if stored at low temperatures below 0°C, this product may appear cloudy. Allowing to warm to room temperature restores the normal appearance without affecting efficacy.

CONCLUSIONS ON QUALITY

The quality of the product was adequately demonstrated by the data presented in the dossier. The product is satisfactorily formulated, manufactured and controlled. Stability data justify the shelf-life of 2 years and the in-use shelf life of 6 months. Product literature bears the appropriate warnings:

Store the product in the original container and keep tightly closed. Keep the container in the outer carton in order to protect from light. The container should be stored in an upright position. If stored at low temperatures below 0°C this product may appear cloudy. Allowing to warm to room temperature will restore the normal appearance without affecting efficacy

[2] RH= relative humidity

III. SAFETY ASPECTS

Pharmacology

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

The pharmacological aspects of this product are identical to the reference product.

Warnings and precautions as listed on the product literature are the same as those of the reference product.

Toxicology

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

The toxicological aspects of this product are identical to the reference product.

Warnings and precautions as listed on the product literature are the same as those of the reference product.

User safety

The applicant provided a user risk assessment which addressed all potential routes of exposure. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. These are the same as the reference product. These are included on the SPC as follows:

The product may be irritating to human skin and eyes and the user should be careful not to apply it to himself or other persons. Operators should wear nitrile rubber gloves, rubber boots and a waterproof coat when applying the product. Protective clothing should be washed after use. If accidental skin contact occurs, wash the affected area immediately with soap and water. If accidental eye exposure occurs, flush the eyes immediately with water and get medical attention. Do not smoke, drink or eat while handling the product. Wash hands after use. Use only in well-ventilated areas or outdoors. HIGHLY FLAMMABLE.

Residues

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of residue depletion studies are not required. However, confirmatory residue depletion studies in fat and liver in the target species were provided. These studies indicated that residues in liver and peri-renal fat were below the LOQ[3] from 14 days onwards

The residues aspects of this product are identical to the reference product.

[3] LOQ = Limit of Quantification, which is the concentration the analytical method can measure with acceptable level of accuracy and precision.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to consumers.

MRLs
Ivermectin is listed in Annex I of Council Regulation 2377/90. The marker substance is 22,23-dihydro-avermectin $B1_a$

Target tissues	MRLs
Fat	100 µg/kg
Liver	100 µg/kg
Kidney	30 µg/kg

The excipients present are the same as in the reference product.

Based on the information provided, a 28 day meat withdrawal period in cattle is justified. This is the same withdrawal period as the reference product.

Environmental Safety
The product is administered to cattle on pasture or in housing at a dose of 500 µg ivermectin/kg bodyweight by topical administration. The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline. It is unlikely that the environment will be exposed as a result of direct entry and residues of ivermectin will reach the environment in excreta of treated animals. As the product is a parasiticide used on pasture a Phase II environmental risk assessment was provided. The assessment was based on information available in published scientific literature.

Fate and effect studies for ivermectin were provided. Risk to soil, surface water and groundwater, sediment and dung from exposure to ivermectin were also considered. The risks were considered acceptable and warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

CONCLUSIONS ON SAFETY
All aspects of safety were adequately addressed and the application is supported with respect to safety. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended.

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. Bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

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, this information 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. However, some information of this nature was provided. One study evaluated the influence of rainfall on the efficacy of the test product. Results showed that artificial rain applied both before and after treatment with the product had no significant effect on short-term efficacy. The second study compared the efficacy of Virbamec with that of Ivomec against a range of gastro-intestinal parasites, including those that are least sensitive to ivermectin. The findings in this dose confirmation study concluded that both Virbamec and Ivomec were virtually 100% effective against the parasites included when assessed on total worm counts at post-mortem. Thus, based on these findings, both products were considered as bioequivalent.

CONCLUSIONS ON CLINICAL ASPECTS
The company demonstrated that the product is bioequivalent to the established product Ivomec Classic Pour-On for Cattle 5 mg/ml, Pour-on solution, and provided some additional data which provided further re-assurance about the product's 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 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)