I. INTRODUCTION

Norocarp is a solution for injection containing 5%w/v carprofen. It has been designed for use in cattle under 12 months of age, and in horses and ponies. In cattle, it is used as a secondary therapy to control inflammation in respiratory disease. In horses and ponies it is used for pain control, as an anti-inflammatory in musculo-skeletal disorders, and after surgery. The dose for cattle is 1.4mg carprofen per kg bodyweight as a single dose. The dose for horses and ponies is 0.7mg carprofen per kg bodyweight, but this can be repeated after 24 hours. The product is presented in 50ml multi-dose vials. In cattle, the product is designed to be given subcutaneously or intravenously. In horses, Norocarp may only be delivered intravenously. The product is manufactured according to Good Manufacturing Practise, and produced in accordance with validated methods.

This application for a Marketing Authorisation was submitted under Article 13 (1) of Directive 2001/82/EC, as amended by Directive 2004/28/EC. The applicant has ensured that the product is essentially similar, (bioequivalent), to the reference product authorised for use in the UK, Rimadyl Large Animal Solution. Bioequivalence is defined as two products having the same active substance, the same dosage form, and being administered by the same route. Rimadyl Large Animal Solution was used in appropriate bioequivalence studies for Norocarp.

II. QUALITY ASPECTS

Product Development and Composition

The active ingredient in Norocarp, carprofen, is incorporated into suitable solvents, making it appropriate for use by injection. Carprofen is not in the European Pharmacopoeia (Eur.Ph.), but it is a known active substance. All other excipients are monographed in the Ph. Eur., apart from sodium formaldehyde, which is monographed in the United States National Formulary, (USNF). Norocarp is of the same composition as the reference product, Rimadyl Large Animal Solution as regards active ingredient, and both products have the same route of administration. Justification was given for the amounts and types of solvents used to dilute the carprofen, these were acceptable, and the product was also tested satisfactorily with regard to foaming and syringeability. Carprofen and all the excipients have been used in previously authorised injectable products.

Data were provided with reference to solubility, pH control, batch control and packaging. All results were satisfactory. A satisfactory TSE format 3 declaration was made. This stated that pertinent products were not of animal origin.

Active Substance

The active substance, carprofen, is a known active substance which has been used in previously authorised injectable products. Norocarp solution contains 5% w/v of racemic carprofen. Carprofen is a non-steroidal anti-inflammatory drug (NSAID), and possesses anti-inflammatory, analgesic and antipyretic activities.

Other Substances

All excipients are monographed in the Ph. Eur. with the exception of sodium formaldehyde sulphoxylate, which is monographed in the USNF. The requirements of these pharmacopoeias with regard to specification for these materials have been applied.

Packaging Materials

The product is presented in amber 50ml glass multi-dose vials with bromobutyl rubber closures. The closures are secured by a 20mm diameter aluminium sealing strip and comply with Ph. Eur. requirements.

Manufacture of the Finished Product

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

Process validation data on the product have been presented in accordance with the relevant European guidelines.

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

This source of carprofen has been used in previously authorised injectable products and has been shown to be stable. Little change occurs during the proposed shelf life.

Finished Product

Data were provided on a series of stability studies which demonstrated that the finished product was stable. Tests included an accelerated study over six months on product stored at 40°C, a long term test demonstrating that the product was stable at 25°C over 24 months, a freeze-thaw study indicating that there was no change in the product during freeze-thaw cycling and a test to show that the product was stable after repeated broaching of the vial with an 18-gauge hypodermic needle. In this last study, one batch of products was two years old.

In-Use

Shelf life after opening of the produced vial is 28 days. Shelf life of the unopened, packaged product is 2 years. The product is not to be stored above 25°C.

CONCLUSIONS ON QUALITY

All Quality considerations have been addressed and results were satisfactory.

III. SAFETY ASPECTS

Introduction

The product was shown to be bioequivalent to the reference product, Rimadyl Large Animal Solution, and as such, no new data was required with regard to safety. The main hazards associated with misuse of the product are eye irritation and sensitisation. User warnings for the reference product, (which specify any hazards and contraindications), are likewise applicable to Norocarp. The source of carprofen used in the product has already been evaluated from a safety perspective.

Pharmacology

This Marketing Authorisation is submitted under Article 13 (1) of Directive 2001/82/EC, as amended by Directive 2004/28/EC. There is therefore no requirement for pharmacological studies in this section, as the product is essentially similar to the reference product, Rimadyl Large Animal Solution.

Toxicology

This Marketing Authorisation is submitted under Article 13 (1) of Directive 2001/82/EC, as amended by Directive 2004/28/EC. There is therefore no requirement for toxicological tests in this section as the product is essentially similar to the reference product, Rimadyl Large Animal Solution.

Residues

Post-analysis residues examinations showed that Norocarp was cleared from animal systems to an acceptable level. The withdrawal period for the drug was set at 21 days for cattle meat, milk from cattle is not be used for human consumption. The product is not to be used in horses intended for human consumption.

Environmental Safety

It is concluded from a Phase 1 Environmental Risk Assessment that there will be minimal environmental impact.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

The product is essentially similar to the reference product, and previously submitted data with respect to the reference product confirm that user warnings are satisfactory. Even if the contents of a 50ml syringe were accidentally administered to the user, this would not exceed the permissible adult human dose. However, a warning to avoid accidental injection is provided due to the risk of this occurring.

Conclusions on Consumer Safety

The product is bioequivalent to the reference product and this is satisfactory with regard to consumer safety. For cattle meat, the withdrawal period is 21 days. Neither milk from treated cattle, nor any product from treated horses and ponies may be used.

Conclusions on Environmental Safety

Environmental safety data is deemed satisfactory and is in accordance with current legislation.

IV. CLINICAL ASPECTS

Introduction

This application was submitted in accordance with article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC. No pre-clinical or clinical trials are necessary under this Directive, provided bioequivalence can be demonstrated between the generic product and a reference product. Data were included for a pharmacokinetic study showing that Norocarp was bioequivalent to the reference product, Rimadyl Large Animal Solution, and also for three tolerance studies, two in cattle and one in horses. No data were required for intravenous injection as the product and reference product were shown to be bioequivalent.

Clinical Pharmacology

Pharmacodynamics

Norocarp Injection is essentially similar to the reference product, Rimadyl Large Animal Solution, therefore there was no necessity to provide pharmacodynamic data. However, a short study of the pharmacodynamic action of carprofen was provided.

Pharmacokinetics

Norocarp Injection is essentially similar to the reference product, Rimadyl Large Animal Solution, therefore there was no necessity to provide bioequivalence data for intravenous injection. Results of a pharmacokinetic study in cattle were provided. This study took the form of a crossover study, which compared the product to the reference product using subcutaneous injection. The results demonstrated that the product was bioequivalent to Rimadyl Large Animal Solution. The product may only be used intraveneously in horses and ponies, but either intravenously or subcutaneously in cattle.

Tolerance in the Target Species

Target species tolerance studies are not required for this type of application as Norocarp was shown to be bioequivalent to Rimadyl large Animal Solution. However, the applicant submitted two studies in cattle and one in horses. There was no evidence of any undue tolerance, results were satisfactory.

Resistance

Not applicable.

Clinical Efficacy

Data for efficacy was unnecessary for this application as equivalence with the reference product, Rimadyl Large Animal Solution, was demonstrated according to Directive 2001/82/EC Article 13 (1), as amended by Directive 2004/82/EC.

CONCLUSIONS ON CLINICAL ASPECTS

Satisfactory information regarding the pharmacodynamic action and the pharmokokinetic properties of carprofen were given by the applicant. Target species tolerance was determined as being within acceptable levels.

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)