I. INTRODUCTION

Carprofen, the active ingredient of Norocarp Large Animal Injection belongs to the group of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs), which are used to control pain and inflammation in various disease conditions. It is a derivative of proprionic acid. Norocarp Large Animal Injection is intended to be used as an aid in the treatment of respiratory disease in young cattle.

The chemical composition of carprofen is such that the atoms in each molecule may be arranged in two different forms, known as R and S enantiomers. In Norocarp Large Animal Injection, carprofen is in the form of a mixture of these two forms and this mixture is known as a racemate.

The recommended dose is 1.4 mg carprofen per kilogram bodyweight administered by subcutaneous injection.

Carprofen has a well-established use in veterinary medicine, having been authorised for use in cattle since 1993. Because of this, a company wishing to market a product containing carprofen for use in cattle may fulfil the safety and efficacy requirements for a marketing authorisation by submitting a dossier of relevant published literature on such usage, and supplementing this with new information to fill any gaps in the published literature, as well as demonstrating that the published literature is directly relevant to their own product. This is the approach which was taken by Norbrook Laboratories when applying for a marketing authorisation for Norocarp Large Animal Injection.

II. QUALITY ASPECTS

Product Development and Composition

The product is a sterile, aqueous solution, appropriately presented in amber glass vials, sealed with a pierceable rubber stopper, allowing removal of the appropriate dose volume. The active ingredient, carprofen, is well-known in veterinary medicine and in this product is dissolved in polyethylene glycol, with the aid of the solubilising agent Lutrol F68. The pH (degree of acidity) of the solution is controlled by the addition of the amino acid L-arginine, and sodium formaldehyde sulphoxylate is added as an anti-oxidant. The solution also contains ethanol at 100 mg/ml as preservative, shown effective in controlling microbial contamination that might be introduced during removal of doses.

Active Substance

The company's dossier includes details of the manufacture and control of the active ingredient. Although there is no pharmacopoeial monograph for carprofen, the manufacturer's specification covers appropriate aspects, including appearance, identification, purity and physico-chemical properties such as melting point, pH and specific optical rotation.

This specification is in accordance with current guidelines and ensures that the material is suitable for use in an injectable product. The methods of analysis have been shown to be valid, and data obtained on several batches show that the specification is consistently met.

Other Ingredients
Where a monograph of the European Pharmacopoeia is available, this has been applied as the specification for each ingredient. In other cases, the monograph of the United States Pharmacopoeia has been cited.

Packaging materials
The product is supplied in 50 ml amber glass vials with bromo-butyl rubber bungs secured by aluminium sealing strips. The vials and rubber bungs comply with the relevant pharmacopoeial monographs for components used on injectable products.

Manufacture of the Finished Product
No ingredients of animal origin are employed in the manufacture of the product. Production of the product is in accordance with pharmaceutical Good Manufacturing Practice. The ingredients are dissolved, mixed, filtered, filled into the vials and sterilised, all under appropriate conditions. Satisfactory validation data have been provided to justify the approved batch size and further data are being generated on actual production batches.

Finished Product Quality Control
The specification for the finished product controls appropriate parameters, including appearance, pH, amounts of carprofen, ethyl alcohol and sodium formaldehyde sulphoxylate, specific optical rotation, syringeability, sterility and volume. Data have been supplied which demonstrate the suitability of the analytical methods used for testing the product.

Stability of the product

Active substance
Stability data were provided on three batches of the active ingredient stored under accelerated testing conditions and under standard test conditions. These data demonstrated satisfactory stability for the duration of the test, and justified the agreed re-test interval of 12 months.

Finished Product
The company provided data on three batches of the product subjected to accelerated testing and to long-term testing under standard test conditions. The results of 12 months testing are available. Negligible changes have been observed when the product is examined against the requirements of the end-of-life specification. Freezing and thawing the product every day for a week has shown that the product is also stable under these conditions. Long-term testing is continuing, but the data currently available justify a shelf-life of 2 years for the product when stored at temperatures of 25°C or below. Information is not available on the effect of light on the stability of the product, and it is therefore recommended that it be protected from light.

In-Use
In-use stability testing has been carried out on vials of the product subjected to storage under standard storage conditions. To simulate normal usage, doses were removed at intervals throughout the test period and the product has been shown to remain stable under these circumstances for 28 days.

CONCLUSIONS ON QUALITY

The supporting data demonstrate that the injection solution is suitably formulated and quality-controlled. A shelf-life of 2 years is justified, subject to the following storage warnings.

Do not store above 25°C. Protect from light.

III. SAFETY ASPECTS

Introduction

As indicated in part I of this document, carprofen, the active ingredient in Norocarp Large Animal Injection, has a well-established use in veterinary medicine and the safety information submitted by the company therefore includes a review of published literature on the pharmacology and toxicology of carprofen in the treatment of respiratory disease in young cattle, and new studies commissioned by themselves to fill in any gaps in the existing information. Because the pharmacological information is relevant to the clinical aspects of the product as well as the safety ones, it is summarised only once in this document, in part IV.

Toxicology

A mixture of published and new data demonstrate that carprofen was of fairly low toxicity when given to rats and mice once by mouth.

Published information on the toxicity of carprofen following repeated administration to dogs and rats was again supplemented with some newer data which were collected in accordance with Good Laboratory Practice. This information showed no adverse effects in either rats or dogs at doses of carprofen up to 2 mg/kg bodyweight. At higher doses, there was evidence of gastro-intestinal ulceration, one of the known side-effects of NSAIDs.

Published literature provides adequate information on the possible effects of carprofen on reproductive performance in animals. One of the studies described involved daily treatment of male and female rats with carprofen. Males were treated from 61 days before mating to the end of mating and females were treated from 14 days before mating, and then throughout pregnancy and lactation. No adverse effects were noted on adults or offspring at a dose of 2 mg carprofen/kg bodyweight. In another study, pregnant female rats were treated from day 5 to day 15 of pregnancy; in this case, there were no detrimental effects on the development of the young at doses up to 20 mg/kg bodyweight, although there was some evidence of adverse effects on the mothers. Information was also available to indicate a similar response in other laboratory animals.

Published literature indicates that carprofen has been tested for mutagenicity in a range of tests covering relevant end-points, and all tests produced negative results. Long-term testing in laboratory animals shows that carprofen was not carcinogenic in such animals.

Other published information relates to a lack of adverse effects on the nervous and renal systems in dogs and laboratory animals. Studies also indicated that carprofen may cause phototoxicity although photoallergy has also been suggested.

Carprofen was used in human medicines for over 10 years at doses of 150 - 600 mg/day, but has been withdrawn from the market on commercial grounds. Published literature reports adverse effects on the gastrointestinal tract, a common effect of NSAIDs. These effects are usually mild and reversible but in some cases peptic ulcers and gastrointestinal bleeding have been reported. Reports indicate that carprofen may cause photosensitisation in humans although its incidence is not known; photosensitisation has been observed with other NSAIDs and is a known effect.

User Safety

Because the product is administered by injection, the main way in which users of the product could be exposed to it are from accidental skin or eye contact or by accidental self-injection. The product is a prescription only medicine and therefore accidental exposure to children is not expected.

In the event of contact with skin, the product could cause irritation but if the area is washed immediately with water, such a reaction is unlikely.

Contact with eyes is less likely to occur but such contact is not considered to present a hazard because NSAIDs are used prophylactically in eye drops for humans before ocular surgery. Therefore the very small amount of product that could come into contact with the eye would be unlikely to cause any significant effects.

In the event of accidental self injection, it is unlikely that the entire contents of the syringe would be injected, but assuming a worse case, a syringe might contain 50 ml, which includes 500 mg of carprofen. If this were all accidentally self-injected, this would represent a dose of 8.33 mg/kg for a 60 kg adult. Since carprofen has been used as a human medicine at doses of doses of 150 - 600 mg/day, even if a full syringe was administered this would not exceed the human dose. However, a warning to avoid accidental injection is advised.

The following user warnings were agreed for the SPC and product literature:

Avoid skin contact with the product. Wash off any splashes immediately. Wash hands after use. Take care to avoid accidental self injection.

Residues

The company conducted a study in cattle to determine the amounts of carprofen in the edible parts of cattle treated with Norocarp Large Animal Injection. The study was conducted in accordance with Good Laboratory Practice. In this study twelve young cattle were treated with the recommended dose of the product and were then killed in groups of three males and three females, 7, 14 and 21 days after treatment. Samples of liver, kidney, muscle and fat, plus an additional sample taken from the exact location where the injection was given, were collected. The amount of carprofen in these samples was then measured using a method that had been shown to be fully valid.

Even at 7 days after treatment, residues of carprofen in all samples were found to be present at concentrations less than 250 µg/kg and this was lower than the maximum residue limits (MRL) permitted by EU law. In accordance with EU guidelines, a withdrawal period* of 10 days was

* The withdrawal period is the interval between the time when the last dose of the product is administered to the animal and the time when either the animal may be killed for human consumption or its produce may be used for human consumption.

agreed, based on the first time when all residues were below the MRLs, plus a “safety span” of 3 days.

All the other ingredients in Norocarp Large Animal Injection have been considered by the EU and have been deemed as not needing MRLs, as any residues resulting from their use in veterinary medicines would not cause concern from a consumer safety point of view.

The product is not intended to be used in cattle producing milk for human consumption. A milk withdrawal period is therefore not required and no information on residues in milk has been provided.

Environmental safety

Because carprofen has a well-established use in veterinary medicine, there was no requirement for the company to provide information on possible environmental effects of its use, because any such effects will have already been considered in connection with earlier products. Despite this, appropriate disposal advice is required for all veterinary medicines, and for a product such as Norocarp Large Animal Injection, this is:

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

Further guidance on these requirements is provided on the packaging of the product.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

Adequate toxicity data were provided by the company and appropriate warnings have been agreed for users of the product. User safety aspects are therefore satisfactory.

Conclusions on Consumer Safety

Data on the depletion of residues were provided by the company and an appropriate meat withdrawal period has been established. Adherence to this withdrawal period will ensure consumer safety. The product is not intended to be used in cattle producing milk for human consumption; therefore no milk withdrawal period is required.

Conclusions on Environmental Safety

No environmental assessment was required for this particular product because the active ingredient has a well-established use in veterinary medicine. Appropriate disposal advice has been agreed and environmental safety aspects are therefore satisfactory.

IV. CLINICAL ASPECTS

Introduction

As indicated earlier, carprofen has a well-established use in veterinary medicine. Thus the clinically-relevant information submitted by the company includes a review of published literature on the pharmacology, safety and efficacy of carprofen in the treatment of respiratory disease in young cattle, supplemented with new studies conducted by the company to investigate the safety of the formulated product, Norocarp Large Animal Injection, and to compare it with the already authorised product, Rimadyl Large Animal Injection.

Clinical Pharmacology

Pharmacodynamics

The company's dossier included a series of published articles describing the chemical processes that lead to the development of inflammation in response to damage to cells in the body, as may happen in the case of lung in young cattle affected by pneumonia. The damaged cells release a substance called arachidonic acid which may be converted into various other substances, such as the prostaglandins, which in turn cause an inflammatory response. These conversions are catalysed by various enzymes, one of which is called cyclo-oxygenase 2 (COX-2). It is thought that carprofen may exert its anti-inflammatory effect by inhibiting this enzyme so that the chain of reactions which leads to inflammation is broken. However, this may be only part of the mode of action; other actions, still to be elucidated, may also occur.

Another member of the cyclo-oxygenase family, COX-1, is involved in normal cellular processes and it may be that carprofen's low level of inhibition on this enzyme is the reason why it has fewer adverse effects on the gastro-intestinal system that some other NSAIDs.

Most of the anti-inflammatory action of carprofen seems to derive from the S-enantiomer.

Pharmacokinetics

Numerous published papers describing studies in various species have shown that carprofen is rapidly absorbed into the bloodstream and readily penetrates and accumulates in acute inflammatory exudate. It is removed from the bloodstream quite slowly and this is responsible for its long duration of action. It is not distributed from the blood to normal tissues to any great extent but it may be metabolised in the liver by the addition of substances called glucuronides, and from here it may be excreted via the bile and faeces.

As indicated in the introduction to this section, the company conducted a bioequivalence study, that is a study which compared Norocarp Large Animal Injection and a product that is already authorised, Rimadyl Large Animal Injection, in terms of how much of the active ingredient, carprofen, was absorbed into the bloodstream when the products were given as recommended, i.e. by subcutaneous injection. This study is described below.

The study utilised a well-accepted study design known as a "crossover" design, and involved two groups of young cattle. The first group received Norocarp Large Animal Injection at the recommended dose; after a suitable delay to allow all the carprofen to disappear from their systems, they received Rimadyl Large Animal Injection, again at the recommended dose. The second group of animal were treated in the same way except that they received Rimadyl Large Animal Injection first and Norocarp Large Animal Injection second, hence the term "crossover". Blood samples were collected from all cattle at intervals throughout the study and the amount of carprofen (racemate, R-enantiomer and S-enantiomer) in these samples was measured. When

all the measurements had been collected, a graph of the amounts at the different times was produced. From this it was possible to see that the amount of carprofen that had reached the bloodstream was similar for both products. This was confirmed by a statistical analysis of the data.

Tolerance in the Target Species

The company submitted published literature describing the use of carprofen (Rimadyl Injection) in conjunction with two different antibiotics in the treatment of respiratory disease in cattle. Carprofen was well-tolerated by the 36 animals in these studies.

The published information was supplemented with the report of a new study conducted by the company in accordance with Good Laboratory Practice. In this study, one group of cattle was given a subcutaneous injection of the recommended dose of Norocarp Large Animal Injection on two consecutive days. A second group of animals was given three times the recommended dose as a single subcutaneous injection on two consecutive days. In order to relate any possible effects to the active substance, a third group was given a single subcutaneous injection of the product but with no carprofen.

The animals were assessed for up to 21 days after the first injection. This assessment involved clinical examination, including heart rate, respiratory rate, body temperature and examination of the injection sites, plus collection of blood samples for blood cell counts, testing of clotting ability and analysis of various enzymes and other blood components.

There were no adverse effects on heart rate, respiratory rate or body temperature. There was a slight reaction at the site of injection in most animals but this had resolved by the next day. Some effects related to carprofen were noted in the levels of urea, creatinine, creatinine kinase and bilirubin but these had returned to normal by the end of the study. Changes in some of the red cell parameters (haematocrit and mean cell volume), segmented neutrophils and one of the clotting tests (activated partial prothrombin time) had also resolved by the end of the study.

It was concluded that Norocarp Large Animal Injection is well tolerated at the recommended dose rate and also at three times the recommended dose rate. This shows that the product has a good margin of safety.

Clinical Efficacy

Five published reports of the efficacy of carprofen in the treatment of bovine respiratory disease were submitted. In each case carprofen was given, at the recommended dose rate, in conjunction with a suitable antibiotic. In some studies the antibiotic was used without carprofen in order to provide a comparison of the part carprofen played in the resolution of the disease. Overall the information provided in these documents showed that carprofen quickly caused body temperature and respiratory rate to return to normal levels, and in some of the studies it was found to reduce coughing and nasal discharge. In studies where an antibiotic was used alone, the alleviation of disease signs was reduced.

Further information was also provided on the use of carprofen in other conditions, e.g. in the treatment of mastitis. In this case, it was shown to reduce temperature, heart rate and swelling of affected quarters, and also to relieve pain. Whilst not directly relevant to the use of Norocarp Large Animal Injection, these documents provide further demonstration of the anti-inflammatory and analgesic properties of carprofen.

CONCLUSIONS ON CLINICAL ASPECTS

Because carprofen has a well-established use in the treatment of respiratory disease in young cattle, the company was able to fulfil most of the data requirements for a marketing authorisation by the presentation of published literature. This literature adequately described the pharmacology of carprofen and the efficacy of the product that is already approved. It also provided some information on the safety of carprofen in cattle.

This publicly-availably information was appropriately supplemented with new information gathered from studies conducted by the company on Norocarp Large Animal Injection itself. These studies demonstrated comparable absorption of the active substance from the two products and confirmed that Norocarp Large Animal Injection has a good margin of safety, since effects in cattle treated even at three times the recommended dose were relatively minor and reversible.

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 man 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)