Public Release Summary

for

CEPHALONIUM

in the product

COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC

1997

This document is published by the National Registration Authority for Agricultural and Veterinary Chemicals

For further information, please contact:

[redacted]

ISBN 0 642 26476 7

TABLE OF CONTENTS

FOREWORD

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is an independent statutory authority with responsibility for the assessment and approval of agricultural and veterinary chemical products prior to sale and use in Australia.

In undertaking this task, the NRA works in close cooperation with advisory agencies including the Chemicals and Non-Presciption Drug Branch (CNPD) of the Commonwealth Department of Health and Family Services, Environment Australia (EA), the National Occupational Health and Safety commission (Worksafe Australia) and State Departments of Agriculture and Health.

The NRA has a policy of encouraging openness and transparency in its activities and seeking community involvement in decision making. The publication of Public Release Summaries for products containing new active constituents is a part of that process.

The information and technical data required by the NRA in order to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in the document "The Requirements Manual for Veterinary Chemicals", and related documents, which can be purchased from the Australian Government Publishing Service.

This public release summary is intended as a brief overview of the assessment that has been completed by the NRA and advisory agencies. The document has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment. Further more detailed technical reports on occupational health and safety, public health considerations and environmental impact are available from the NRA on request.

As a relatively new organisation, the NRA would welcome comment on the usefulness of this document and suggestions for further improvement. Comments should be forwarded to The National Registration Manager, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E240, Kingston, ACT, 2604.

ABBREVIATIONS AND ACRONYMS

Abiotic	Non-living
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers' Advisory Council
Biotic, Biotically	Living, acted upon by living organisms
CNPD	Chemical and Non-Prescription Drugs Branch (of the Department of Human Services and Health)
Colostrum	*Post partum* milk produced in the first few days after calving, containing high levels of protein and cells, unsuitable for human consumption
Codex MRL	International published standard MRL
d	Day
Drying off	Removal of the cow from the milking herd at the end of a lactation cycle (generally 300 days)
EA	Environment Australia
EUP	End Use Product
g	Gram
Gram-negative/Gram-positive	Classificatory terms providing a division of the bacteria: according to the ability of the bacteria to retain the violet of Gram's stains, those that do so are designed Gram-positive, those that do not Gram-negative
h	Hour
HPLC	High Performance Liquid Chromatography
hydrolysis	The splitting of a substance by molecules of water which themselves split, contributing hydrogen atoms and hydroxyl groups to the respective products
intraperitoneal	Into the peritoneum (abdominal cavity) of the body
in vitro	In the laboratory
in vivo	In the living animal
kg	Kilogram
kt	Kilotonne
L	Litre
LC-MS	Liquid chromatography mass spectrometry
LD50	Dosage of chemical that kills 50% of the test population of organisms
m	Metre
mg	Milligram
Micturition	Urination
mL	Millilitre
MRL	Maximum Residue Limit (a legal limit)
MRL Standard	Published list of MRLs
MSDS	Material Safety Data Sheet
NOEC/NOEL	No Observable Effect Concentration/Level

ABBREVIATIONS AND ACRONYMS cont.

NRA	National Registration Authority for Agricultural and Veterinary Chemicals
oral	By mouth
post partum	After giving birth
ppm	Parts per million
s	Second
subcutaneous	Under the skin
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
µg	Micrograms
w/w	Weight for weight
WHP	Withholding Periods

INTRODUCTION

The purpose of this document is to provide a summary of the data reviewed, and an outline of regulatory considerations for, the proposed registration of the chemical Cephalonium for use as an intramammary antibiotic for cows at drying off. The information provided herein presents only the conclusions reached by the various expert reviewers after consideration of the scientific database. All trial data and methods of assessment presented for evaluation were conducted according to accepted scientific principles and of a standard publishable in reputable refereed journals.

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) has completed an assessment of the data submitted by the applicant in support of this use of Cephalonium and now invites public comment before proceeding to approve this product for use in Australia. The information contained in this document is provided for public comment.

Comments should be sent to:

1. SUMMARY

APPLICANT DETAILS

Mallinckrodt Veterinary Limited
PO Box 777 (71 Epping Road)
NORTH RYDE NSW 2113

Tel: (02) 9335 4000
Fax: (02) 9335 4085

PURPOSE OF APPLICATION

This application is for the registration of a new product based on a new active constituent for use as an intramammary in cattle. The product contains 89.9g/kg of the active constituent Cephalonium (as the dihydrate), a new semi-synthetic cephalosporin antibiotic. The formulation is intended to give effective antibiotic levels in the udder of cows, and is intended for application to the cow at the time of drying off. COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC is recommended for dry cow therapy to treat existing sub-clinical infections and to prevent new infections which can occur during the dry period. Infusion at drying off also reduces the risk of mastitis which commonly occurs at calving. Cephalonium is a broad spectrum cephalosporin antibiotic which has bactericidal activity against the majority of organisms associated with bovine mastitis. The antibacterial activity is not impaired in the presence of milk. The product to be approved for use in Australia will also contain blue dye, in conformance with current regulations governing intramammary products in Australia.

PRODUCT DETAILS

COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC in the absence of the blue dye is a white to buff coloured suspension of Cephalonium. The end use product (EUP) is presented in a 3g single dose syringe for intramammary infusion. The product contains 89.9g/kg Cephalonium (as the dihydrate), equivalent to 250mg/syringe.

Formulation of the EUP takes place at the Mallinckrodt Veterinary Limited plant at Bray, County Wicklow, in the Republic of Ireland.

JUSTIFICATION FOR USE

COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC is intended for use when cows in the milking herd have completed their lactation of approximately 300 days and are about to enter their 2 month dry period (termed drying off). At the end of this period their calves will be born and the cows brought back into the milking herd.

Cephalonium is a cephalosporin antibiotic which is bactericidal by means of inhibiting bacterial cell wall synthesis. Cephalosporins differ from penicillin-type antibiotics in their ability to resist destruction by means of the enzyme penicillinase, enabling them to effectively control bacteria which are resistant to penicillin-type antibiotics.

Cephalonium has a broad spectrum of activity, including activity against some species of gram-negative bacteria, as well as most gram-positive bacteria that cause mastitis. There are a number of already approved penicillin-type intramammary antibiotics for use in Australia but Cephalonium has a broader spectrum of activity. Other combinations of antibiotics approved for use as intramammary products in Australia have a similar spectrum of activity. Cephalonium is effective against the majority of bacteria associated with bovine mastitis, including penicillin resistant strains.

Prior to the use of COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC veterinary advice will need to be sought. The consulting veterinarian will assess the need for treatment of cows against mastitis at dry off and recommend a treatment regime. Approval of Cephalonium and the product COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC is appropriate as this product will provide veterinarians with an additional therapeutic option for the purpose of controlling mastitis in cows.

EFFICACY AND SAFETY IN TARGET SPECIES

Mallinckrodt Veterinary Limited presented both data and argument in support of the efficacy of the product COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC, although direct efficacy data on product used in Australia under Australian conditions was not provided. Laboratory efficacy data, using mastitis causing organisms isolated from Australian as well as overseas mastitis cases was used to demonstrate that the active Cephalonium, at levels likely to be present in the udder of treated cows, is effective against mastitis causing bacteria, and is also effective in the presence of blue dye. Overseas efficacy data, including data on product used under New Zealand conditions, provided evidence that the product is effective under field conditions overseas. In addition, Mallinckrodt Veterinary Limited presented written relevant expert opinion in support of the argument that no additional local efficacy data under field conditions in Australia should be required.

The submission did not include direct evidence that the product will be effective in Australia against mastitis causing organisms. However, the applicant has agreed that additional "follow-up" data should be provided to validate the argument that this product will be effective under Australian conditions. A condition of registration will be that field efficacy data to confirm the efficacy of this product in Australia will be provided following registration.

The submission did not contain specific overdose target animal safety studies. However, Cephalonium has been used as an intramammary antibiotic since 1976 in many tens of thousands of cattle throughout the world including Europe, including the United Kingdom (UK), Israel, Japan and New Zealand and the applicant commented that clinical experience with the product in the UK indicated adverse reactions are not a problem. The risk of acute toxicity with Cephalonium is extremely low (given that the LD50 in laboratory species is greater than 12,000 mg/kg).

POTENTIAL FOR CHEMICAL RESIDUES IN FOOD

COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC is infused into the teat canals of dairy cows at drying off. It is formulated to achieve retention of the active ingredient, Cephalonium, at therapeutic concentrations in the udder until calving; it is then excreted predominantly in the early *post partum* milk. The latter is comprised largely of colostrum which is not permitted for human consumption. It is proposed that individual animals will be treated on veterinary advice and only if the period between drying off and calving is 56 days or longer.

Appropriate residue and metabolism studies were submitted for evaluation in accordance with the *Interim Requirements for the Registration of Agricultural and Veterinary Chemical Products* to support the use of the product. Four residue trials were conducted that addressed the proposed use pattern.

The residue data and use pattern indicate that a meat withholding period of 21 days and a milk withholding period of 96 hours (8 milkings) are appropriate. The metabolism and residue data show that under Good Agricultural Practice, the proposed MRLs should not be exceeded and consumption of tissues or milk from treated animals is unlikely to result in the ingestion of residues exceeding the established Acceptable Daily Intake (ADI).

The following additions have been recommended for the *MRL Standard*:

TABLE 1

Compound	Food	MRL (mg/kg)
ADD:		
Cephalonium		
	Cattle meat	***0.1**
	Cattle, edible offal of	***0.1**
	Cattle milk	***0.02**

NOTE: "*" indicates that the MRL has been set at or about the limit of analytical determination.

and

TABLE 3

Compound	Residue
ADD:	
Cephalonium	**Inhibitory substance, identified as Cephalonium**

EVALUATION OF TOXICOLOGY

The Commonwealth Department of Health and Family Services has completed a toxicology evaluation and has supported the proposed registration. It was recommended that the active constituent should be included under a Schedule 4 classification in the SUSDP.

Cephalonium is a first generation cephalosporin antibiotic which is active against a range of bacteria.

After intramammary infusion in cows, Cephalonium is absorbed from the udder, is excreted in the urine, and is only detected in the udder tissue and secretions (colostrum and milk).

Acute studies suggest that Cephalonium has low toxicological concern when given by the oral, subcutaneous or intraperitoneal route.

In repeat oral dose studies, Cephalonium causes, after 3 months of high dose treatment, minor kidney enlargement. No other adverse effects are seen after prolonged dosing in rats and dogs. The antibiotic does not cause birth defects in rats, and does not cause DNA damage.

No chronic/carcinogenicity studies were submitted. Cephalosporins as a class are not known to cause cancer and the available studies do not identify any pre-cancerous lesions. Therefore, the range of studies is considered acceptable for this type of compound despite these data deficiencies.

Based on an assessment of the toxicology, it is considered that there should be no adverse effects on human health from the use of this product in accordance with the label directions.

OCCUPATIONAL HEALTH AND SAFETY

COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC will be available under veterinary prescription and control only.

Cephalosporins have been used as human therapeutic agents for over 20 years. Most cephalosporins are not well absorbed by the oral route and are given parenterally. Cephalonium also has poor oral absorption. Toxicity testing indicates the oral LD50 of Cephalonium is greater than 12,000 mg/kg.

Worksafe Australia conducted a risk assessment on COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC and concluded that no safety directions are required for the product and registration is supported.

ENVIRONMENTAL SAFETY

Environment Australia has assessed the limited data available pertaining to environmental fate and toxicity of this and related antibiotics and has concluded that the use of COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC according to the label directions is unlikely to result in primary poisoning of wildlife, fish, etc. It is recognised that the use of this and other antibiotics has possible consequences in the development of resistant bacteria, but such effects will be minimised if the substance is used as directed and only when necessary.

The likely major path for elimination of Cephalonium from intramammary infusion of dry cows is the urine of treated animals. There is evidence that a high proportion of applied Cephalonium may be degraded, altered or conjugated prior to micturition, but most evidence suggests that residues in urine retain a similar degree of antibiotic activity to Cephalonium. Some abiotic hydrolysis of Cephalonium may commence in the animal, and excreted Cephalonium or substances derived from it are likely to be hydrolysed abiotically with a half-life of the order of 10–100 days, depending on

conditions. Biodegradation is likely to be more rapid, through bacteria producing β-lactamases able to degrade this particular cephalosporin or substances derived from it.

Cephalonium is a cephalosporin bactericide working by inhibition of bacterial cell wall synthesis. It has a broad spectrum of activity, including some species of Gram-negative bacteria as well as species of Gram-positive bacteria controlled by penicillin type antibiotics already in use for these purposes. Specific data for Cephalonium are not available, but evidence suggests that while some soil and water dwelling bacteria would be susceptible to Cephalonium, strains of many non-pathogenic Gram-negative bacteria would be relatively tolerant, and that *Streptomyces* bacteria, amoebae and algae would also be relatively tolerant.

Very low toxicity of Cephalonium to mammals is indicated by its toxicity to rats and mice, to which the acute oral LD50 is greater than 12,000 mg/kg. No data are available to determine its hazard to terrestrial invertebrates or aquatic organisms, but any hazard presented is not expected to be greater than from antibiotics already in use for the proposed purposes.

Worst case scenarios from intramammary treatment of dairy cows gave potential concentrations of Cephalonium in soil and water of ~2.2 ppm (generally in localised patches) and in water of ~0.6 ppm. Cephalonium concentrations of this order are above MICs for various Gram-positive bacteria and some strains of Gram-negative bacteria, but the available data suggest that they are below MICs for many strains of Gram-negative bacteria and other micro-organisms present in soil and water. It is likely that effects of Cephalonium residues on micro-organism populations would be temporary, population distributions returning to normal as residues dissipate.

Cephalonium is a broad spectrum antibiotic, but even in worst case situations based on minimal degradation before excretion and whole herd treatment, the concentrations likely to be reached in the environment are at the low end of concentrations affecting Gram-negative bacteria, below the MIC for many species. Antibiotics already in use for the proposed purpose would also be likely to cause temporary perturbations in microbial populations, the species of bacteria affected differing between antibiotics.

IMPLICATIONS FOR TRADE

The active Cephalonium is currently available in registered intramammary products in France, Greece, Ireland, Italy, Japan, South Korea, Luxembourg, Belgium, the Netherlands, New Zealand, Portugal, Spain, and the UK. The meat and milk withholding periods are 21 days and 4 days, respectively, (identical to the withholding periods proposed for Australia) in most, but not all, of these countries.

There are no Codex MRLs for Cephalonium. However, the proposed Australian MRLs are "at or about" the limits of analytical determination and detectable residues should not occur at the withholding periods proposed for tissues or milk. The dilution of milk residues which results from bulking and blending in tankers and milk factories provides an additional safety factor. Cephalonium residues do not concentrate in butter, cheese or other milk products. The likelihood of meat and/or offal from culled dairy cows that have been treated at drying off being exported is small and the risk of Cephalonium residues being detected in exported cattle meat or offal is low. It is concluded that product registration will not unduly prejudice Australia's trade.

2. CHEMICAL PROPERTIES OF THE ACTIVE CONSTITUENT

CHEMICAL IDENTITY

Approved chemical name: Cephalonium

Chemical names: (7R)-3-(4-carbomoyl-1-pyridiniomethyl)-7-[2-(2-thienyl)acteomido]-3-cephem-4-carboxylate
N-[7ß-thienyl-2-acetamido)ceph-3-em-3-ylmethyl]-4-carbamoyl pyridinium-4-carboxylate

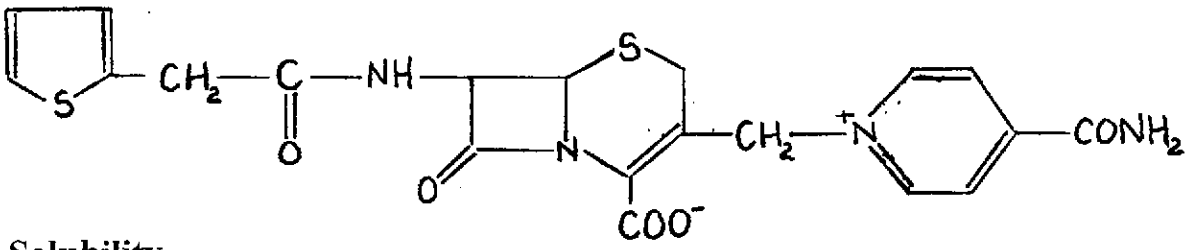
CAS Registry Number: 5575-21-3

Molecular Weight: 458.5

PHYSICAL AND CHEMICAL PROPERTIES

Physical form: A white to buff powder with a characteristic odour

Structural Formula/Diagram:



Solubility

Solvent	Amount (mL) required to dissolve 1g of Cephalonium
Acetic acid	7
Dimethyl sulfoxide	10
50% acetic acid	21
0.1N hydrochloric acid	360
Water	1,300
Methanol	2,700
Ethanol	>10,000
Acetone	>10,000
Ethyl acetate	>10,000
Chloroform	>10,000
Specific Rotation:	-50° to -56°
pH of solution:	3.5–5.0

Dangerous Goods Classification: Cephalonium is not classified as a dangerous good for the purposes of road or rail transport

Standards and Tests for Potency: Ultra-violet assay, not less than 95%

3. EFFICACY & SAFETY TO TARGET SPECIES ASSESSMENT

EFFICACY STUDIES

Efficacy studies were divided into the following sections:

- Antibacterial spectrum of Cephalonium against mastitis pathogens—UK, France, USA.
- Clinical trials—UK, Israel, Europe, NZ.
- Antibacterial spectrum of Cephalonium against mastitis pathogens—Australia.
- Blue dye depletion study—NZ.

The submission did not include clinical efficacy trials in Australia.

ANTIBACTERIAL SPECTRUM OF CEPHALONIUM

Study 8.4.1 was a determination of MICs and antibacterial activity of Cephalonium including activity in the presence of milk, by various methods. The study demonstrated the efficacy of Cephalonium at low MICs against a wide range of mastitis causing isolates in the presence of milk including isolates from sub-clinical mastitis and penicillin resistant isolates.

Study 8.4.2 was a study of the MIC for related compounds Cephalonium and Cefuroxime against 93 French isolates from clinical mastitis cases. Results of the study indicate a similar range of sensitivities to the UK study, although the range of bacterial species tested was smaller.

Study 8.4.3 was similar to study 8.4.2, using 131 US isolates, and conducted in comparison with the additional antibiotics Cephalapirin and Ceftiofur. Similar results were obtained.

CLINICAL TRIALS

Study 8.4.4 detailed field trials conducted in the UK involving 174 cows using a range of commercially available antibiotics. In the majority of cows no clinical mastitis was present at drying off. Separate analysis was undertaken on cows with infections from those without infection as determined by bacterial culture 7 days before drying off. The selection of infected animals for treatment was biased in favour of the product containing Cephalonium. Elimination of infection, prevention of infection and new infection rates were somewhat better with the product containing Cephalonium, in comparison with the other products used in the trial, although the results were not statistically significant.

Study 8.4.5 (published in the Veterinary Record (1977) **100**:557–560) was an evaluation of MICs of Cephalonium against bacteria isolated in study 8.4.4. This study demonstrated that Cephalonium is an effective antibiotic for use in dry cow therapy. Included in this paper was additional information which indicated the formulation is a non-irritant to udder tissue.

Study 8.4.6 (published in the Vet Quar (1981) **3** 2:74–79) was a comparative study of three dry cow products in Israel. The trial involved 1253 cows being treated in 14 herds. All three products tested were essentially similar in their efficacy.

Study 8.4.7 was a French comparative study in 2 herds using a product containing Cephalonium in comparison with three other products. The significant pathogens present at drying off were *Staphylococcus aureus*, *Streptococcus* spp., and *Corynebacterium pyogenes*. All products reduced the incidence of infected quarters and the rate of new infections.

Study 8.4.8 was a field trial using Cephalonium in 2901 yearling cows from 142 farms in the Netherlands undertaken in 1981. An untreated 'control' of 2805 yearling cows on 142 farms was used as a demonstration of the expected incidence of summer mastitis but due to the farm selection criteria the controls were not used in statistical analysis. The study took place in a mastitis environment uncommon in Australia. While it can be accepted that this product will aid in the prevention of summer mastitis in heifers it has little relevance in Australia.

Study 8.4.9 was a study undertaken in NZ in 1976–77 into the capacity to remove *S. aureus* infection from herds by dry cow treatment. Treatments used included Cephalonium in comparison with two other products. Cephalonium failed to remove all infection from quarters during the dry period. Heavy infection with *S. aureus* did not respond to any of the dry cow products trialed.

Study 8.4.10 was a NZ study on the treatment of dry cow mastitis for the prevention of early lactation mastitis commonly caused by *Strep. uberis* and *S. aureas*. 371 cows in 4 herds used—129 uninfected cows untreated, 139 uninfected cows treated in each quarter, 53 infected cows treated in infected quarters, 50 infected cows treated in all quarters. Cephalonium was used in all treatments. Infection status was determined in the 10 days prior to drying off. Treatment resulted in a significant cure rate of dry cow mastitis and the prevention of early lactation mastitis.

ANTIBACTERIAL SPECTRUM OF CEPHALONIUM AGAINST MASTITIS PATHOGENS

Study 8.4.11 was prepared in 1995 and examined the prevalence of the various causative agents of mastitis in Australia, mastitis control programmes in Australia, intramammary use of antibiotics in cattle, and a study into the MICs for Cephalonium and other antibiotics on Australian isolates. The relevant part of this report was the MIC study which indicated similar sensitivities to those determined in the European and US studies.

In addition, the applicant presented a NSW report on the prevalence of mastitis pathogens between 1973 and 1993 and mastitis control programmes in cattle.

Sufficient evidence was presented to indicate that products containing Cephalonium are an effective dry cow therapy for the treatment and prevention of mastitis in the UK, France, Israel and in NZ and would probably perform with a similar degree of efficacy in Australia as the range of mastitis pathogens is similar.

A study on the coexcretion of Cephalonium with blue dye provided adequate evidence to enable the reviewer to indicate the regulations regarding the inclusion of blue dye in intramammary products will be satisfied by COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC.

Confirmatory trials under Australian conditions were recommended by the reviewer in an initial report. After negotiations between the NRA and the applicant the following additional studies were agreed:

- Pre-registration: an additional *in vitro* study for any change in the efficacy of Cephalonium against typical mastitis pathogens in the presence of blue dye, and
- Post-registration: field efficacy studies of the product under Australian conditions.

A further *in vitro* study was conducted and provided evidence in support of the efficacy of the active Cephalonium in the presence of blue dye. Following evaluation of the results of this study the reviewer concluded sufficient evidence was available to enable the reviewer to recommend registration of the product COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC, subject to completion of the further post-registration studies detailed above.

4. PUBLIC HEALTH AND SAFETY ASSESSMENT

EVALUATION OF TOXICOLOGY

The toxicological database for Cephalonium which consists primarily of toxicity tests conducted using animals, is quite extensive. In interpreting the data, it should be noted that toxicity tests generally use doses which are high compared to likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes at which no adverse health effects in humans would be expected.

Toxicokinetics and Metabolism

In a study with two cows, Cephalonium was absorbed from the udder after intramammary infusion and low blood levels (<0.32 μg/mL) were detected for up to 12 hours. The antibiotic was not found in body tissues, with the exception of the udder, 3 weeks after intramammary infusion, although it was excreted in urine for up to 7–14 days.

Acute Studies

Cephalonium exhibited low acute toxicity when given by mouth (LD50 ranged from 5,000 to 20,000 mg/kg in rats and mice) or injected subcutaneously (LD50 was greater than 2,000 mg/kg in rates, and ranges from a figure greater than 2,000 to greater than 15,000 in mice) or intraperitoneally (LD50 ranged from 2,680 to 4,000 mg/kg in rats and mice).

Short-Term Studies

With the exception of minor increases in rat kidney weights, no adverse effects were seen following daily oral dosing of rats and dogs with Cephalonium for up to 3 months at doses up to 1,000 mg/kg.

Reproduction and Development Studies

No effects were seen on rat foetal development when Cephalonium was given during pregnancy at daily oral doses up to 2,000 mg/kg.

Genotoxicity

Cephalonium did not demonstrate activity in a variety of genotoxicity tests.

PUBLIC HEALTH STANDARDS

Poisons Scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of the product and its active ingredient and assessed the necessary controls to be implemented under states' poison regulations to prevent the occurrence of poisoning.

The NDPSC recommended that Cephalonium be listed in Schedule 4 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).

NOEL/ADI

The most sensitive species was the rat, with a NOEL of 39 mg/kg/day. In order to calculate the acceptable daily intake (ADI) for humans, a safety factor is applied to the NOEL in the most sensitive species. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans; variation within the human population; the quality of the experimental data; and the nature of the potential hazards. Using a safety factor of 2,000 and ADI of 0.02 mg/kg/day for Cephalonium was established.

CONCLUSION

The Commonwealth Department of Health and Family Services has completed a toxicology evaluation and has supported the proposed registration. It was recommended that the active constituent should be included under a Schedule 4 classification in the SUSDP.

Based on an assessment of the toxicology, it is considered that there should be no adverse effects on human health from the use of this product in accordance with the label directions.

5. ENVIRONMENTAL SAFETY ASSESSMENT

INTRODUCTION

Mallinckrodt Veterinary Ltd has applied for clearance and registration of the antibiotic Cephalonium (as the dihydrate) as the product COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC, for use in non-lactating dairy cattle (ie. at the end of the ~300 day lactation period, following which there is a ~60 d period before calving and recommencement of lactation). The formulation contains 89.9g/kg Cephalonium dihydrate and the product is packed in sterile syringes containing 3 g formulation.

The active ingredient is a semi-synthetic, first generation cephalosporin antibiotic. Its claimed advantages are that it has a long period of activity (up to 10 weeks) and high activity against the major causes of mastitis (*Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*), as well as providing protection against "environmental" (as opposed to "cow associated" or "contagious") organisms (eg *Streptococcus uberis* and the Gram-negative species *Escherischia coli*).

ENVIRONMENTAL FATE

Exposure of the environment to Cephalonium via animals

Two studies determining Cephalonium residues by bioassay indicate that the likely fate of a 1,000 mg Cephalonium dose infused into the teat of a cow is > 95% excreted unchanged through the treated animal's urine, largely within the first 24 h after udder infusion.

A subsequent study with ^{14}C-labelled Cephalonium and HPLC suggests that excretion of Cephalonium may take place more gradually and that some degradation may occur *in vivo*, potentially over 90% of applied Cephalonium being altered by the time it is lost in urine. However, recovery of total radioactivity in this study was incomplete, residues were not identified (except for whether or not they co-eluted with Cephalonium in two HPLC solvent systems), and the antibiotic activity of those residues in urine was not reported. This outcome is also very different to previous experience with related antibiotics. Hence, due to the lack of complete information, caution is required in interpreting the high rate of degradation indicated in these data.

Thus the likely major path for elimination and environmental impact from intramammary infusion of dry cows is the urine of treated animals. There is evidence that a high proportion of applied Cephalonium may be degraded, altered or conjugated prior to micturition, but the majority of evidence, which is based on direct bioassay, suggests that most residues in urine retain a similar degree of antibiotic activity to Cephalonium.

Abiotic hydrolysis

Of the available data in the literature, Cephalonium is most closely related to Cephaloridine and would presumably have a similar hydrolysis first order rate constant/pH profile. The evidence therefore suggests that Cephalonium should be susceptible to H^+-hydrolysis at low pH, as would occur in the stomach, or to alkaline hydrolysis at pH > 8, which could occur in urine (half-life at pH 8 and 35°C of the order of 3 d). Little acid or alkaline hydrolysis would occur at pH levels typical of blood, or of soil or water in most environments. At those pH levels, decomposition by direct

water attack or intramolecular catalysis could occur, presumably at a relatively slow rate compared to acid or alkaline hydrolysis, with a half-life of the order of 6 d in blood, and of the order of 10–100 d in soil (depending on soil pH and temperature).

COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC is supplied by the intramammary route and the applied Cephalonium is therefore likely to escape significant acid hydrolysis. The closely related cephalosporin Cephaloridine is "destroyed in the gastrointestinal tract" according to Hoover *et al.* (1975), and "poorly absorbed from the gastrointestinal tract" according to Wade and Reynolds (1977). Residues may undergo decomposition by direct water attack or intramolecular catalysis in the blood or tissue, and alkaline hydrolysis while present in urine. However, consideration of the laboratory-determined rate constant/pH profile indicates that except for the small proportion of substance not excreted in urine, the residence time in the animal will limit the extent to which abiotic hydrolysis occurs.

Thus no specific data regarding hydrolysis of Cephalonium are available, but it is likely that the substance is susceptible to abiotic hydrolysis under appropriate conditions, with a half-life of a few days in animals and of the order of 10–100 days in soil and water.

Photolysis

Photolysis of the β-lactam ring in other cephalosporins suggests that Cephalonium may also be susceptible to direct photolysis, but further data would be needed to determine whether this would occur at wavelengths present in the normal environment. The extent of exposure to effective radiation is, in any case, likely to be limited to substance present on the soil surface or in water. Thus direct photodegradation is unlikely to be a significant means of degradation of Cephalonium eliminated from animals. However, the substance may be susceptible to indirect photodegradation, eg in water in the presence of humus.

Microbial degradation

It is likely, but not demonstrated, that micro-organisms present in water or soil will include strains producing β-lactamase which can biotically hydrolyse Cephalonium, or in which production of effective β-lactamases may be induced. Thus microbial degradation would be expected, provided the concentration of antibiotic present is not inhibitory to growth of those strains. However, the rate and extent of this process which might be expected in the external environment are unclear. The effect on the biodegradation rate of the broad spectrum of Cephalonium compared to narrower spectrum antibiotics is also unclear.

Mobility

No data are available for Cephalonium. The substance is moderately soluble in water and the solubility data available suggest that it is poorly soluble in non-polar solvents. However, the n-octanol/water partition coefficient is of little relevance, as the molecule contains a number of polar groups which could bind to soil particles or organic matter. Column leaching studies would be necessary to determine mobility.

ENVIRONMENTAL EFFECTS

No data were available on the toxicity of Cephalonium to birds, fish and other aquatic organisms, algae, aquatic or terrestrial plants, or terrestrial invertebrates. Very low toxicity of Cephalonium to mammals is indicated by its toxicity to rats and mice, to which the acute oral LD50 is greater than 12,000 mg/kg.

Mode of action and toxicity to susceptible bacteria

Cephalonium is a bactericide working, like other ß-lactam antibiotics (penicillins and cephalosporins), by inhibition of bacterial cell wall synthesis. It has a broad spectrum of activity, including both Gram-negative and Gram-positive bacteria, and controls strains of some species resistant to penicillin. Data supplied by the applicant in regard to organisms known to cause mastitis indicate that Cephalonium has MICs (Minimum Inhibitory Concentrations) ranging from 0.02 ppm (µg/mL) (*Streptococcus agalactiae*) to 0.12 ppm for *Corynebacterium* spp., 0.3 ppm for *Staph. aureus*, and 1.6 ppm for *Proteus* and *Citrobacter* spp. Tests showed a wide range of MICs for some Gram-negative species, presumably due to resistance (0.8–12.5 ppm for *Enterobacter* spp. and 0.8–100 ppm for *E. coli*). Tests of isolates from the eyes of cats and dogs (Glaxo Animal Health UK data) showed MICs ranging from 0.015 ppm to 16.0 ppm for various bacterial species, with a geometric mean for MIC against those species of 0.11 ppm.

Susceptibility of non-target micro-organisms to Cephalonium

The applicant supplied a copy of a scientific paper which evaluated the relative sensitivity of typical microflora from soil and water to 21 antimicrobial compounds, including another first generation cephalosporin, Cephalothin. Although the study did not include Cephalonium, it appears reasonable to assume from the behaviour of Cephalothin that while some bacteria would be susceptible to Cephalonium contamination, strains of many non-pathogenic Gram-negative bacteria would be relatively tolerant. *Streptomyces* bacteria, amoebae and algae should also be relatively tolerant, whereas the substance has high toxicity to Gram-positive and non-resistant strains of Gram-negative bacteria isolated from cattle. Presumably Cephalonium would also have high toxicity to some soil-dwelling bacteria not tested in this study, such as soil-dwelling species of *Corynebacterium*, which are Gram-positive.

ENVIRONMENTAL HAZARD

This assessment is based on studies in animals with Cephalonium and on laboratory studies with other cephalosporins, including the closely related substance Cephaloridine.

In worst case scenarios based on simultaneous, blanket treatment of dairy herds, and assuming 95% excretion of antibiotically active Cephalonium residues, potential concentrations of Cephalonium in soil are ~2.2 ppm (generally in localised patches) and in water are ~0.6 ppm (assuming that 50% of residues excreted from 120 cows reach a 100,000 L waterbody). Cephalonium concentrations of this order are above Minimum Inhibitory Concentrations (MICs) for various pathogenic Gram-positive bacteria and some strains of Gram-negative bacteria, but available data suggest that they are below MICs for many strains of Gram-negative bacteria and other micro-organisms present in soil and water.

It is likely that effects of Cephalonium residues on micro-organism populations would be temporary, population distributions returning to normal as residues dissipate. Cephalonium is a broad spectrum antibiotic, but even in worst case situations based on minimal degradation before excretion and whole herd treatment, the concentrations likely to be reached in the environment are at the low end of concentrations affecting Gram-negative bacteria, below the MIC for many species. Antibiotics already in use for the proposed purpose would also be likely to cause temporary perturbations in microbial populations, the species of bacteria affected differing between antibiotics.

A possible concern is that while bacteria are exposed to the antibiotic, development of resistant strains may be encouraged. Furthermore, exposure to similar antibiotics might be maintained by treatment with antibiotics for other purposes (eg mastitis during milking). This concern pertains to the use of antibiotics in general and is not specific to the proposed uses or to this antibiotic.

However, the implications of such resistance developing in bacteria residing in soil and water are unclear.

Cephalonium has relatively low mammalian toxicity. No data are available to determine its hazard to terrestrial invertebrates or aquatic organisms, but any hazard presented is not expected to be greater than from antibiotics already in use for the proposed purposes.

CONCLUSION

From the information available, Environment Australia believes that the use of COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC according to the label is unlikely to result in primary poisoning of wildlife, fish etc. It is recognised that the use of this and other antibiotics has possible consequences in the development of resistant bacteria, but such effects will be minimised if the substance is used as directed and only when necessary.

REFERENCES

Hoover, J E *et al* (1975). *Remington's Pharmaceutical Sciences.* Mack Publishing Company, Easton, Pennsylvania, USA. 15th Edition.

Wade, A and Reynolds, J E F (1977). *Martindale: The Extra Pharmacopoeia.* The Pharmaceutical Press, London, UK. 27th Edition.

6. OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Worksafe Australia has conducted an occupational health and safety assessment on COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC. Worksafe Australia's recommendations were based on the following:

- The product is packaged in single dose plastets (for intramammary infusion), therefore minimising the likelihood of exposure during preparation and administration.
- The product is for single animal and herd treatment, however, only one treatment per animal is required per season and the product will be used under veterinary supervision.
- The cephalosporins are used as human therapeutics. The toxicology has been assessed by the Department of Health and Family Services. Cephalonium has low acute oral, subcutaneous and intraperitoneal toxicity. The product may be an irritant, however, exposure during use in unlikely.
- Should accidental self-injection or skin/eye contamination occur, the risk of health effects is considered to be minimal.

For the above reasons no safety directions are required.

Worksafe Australia supports the registration of Cephalonium in COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC.

7. EVALUATION FOR POTENTIAL CHEMICAL RESIDUES IN FOOD

INTRODUCTION

This section provides an outline of the evaluation of the data submitted by the applicant to support establishment of MRLs for Cephalonium in cattle meat and edible offal and cattle milk.

The applicant proposes use of an antibiotic intramammary preparation for dry cow therapy. Each udder quarter is infused with 0.25 g of Cephalonium at drying off under veterinary advice but only if the period from treatment to calving is 56 days or longer.

Metabolic studies

Refer 5.8.8: The fate of ^{14}C-labelled Cephalonium, formulated to the same standards as the COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC product, was investigated in dairy cows. Eight mastitis-free pregnant Holstein cows received a nominal 1 g dose of ^{14}C-Cephalonium; each quarter received 0.25 g of drug. Two of the animals were housed in metabolism cages and used to study pharmacokinetic properties of Cephalonium, while the remaining 6 cows were used for residue determinations. Urine, faeces and blood were collected for analysis. Liver, kidney, muscle and fat were collected from both groups at 7 days post-calving.

Levels of radioactivity present in blood peaked at 36 h after Cephalonium infusion. The milk data indicated that radioactive residue levels were very high in the first few milkings and then declined rapidly. Total radioactive residues in maternal tissues were higher in kidney than liver, and were negligible or undetectable in muscle and fat. No information on the chemical nature of these metabolites was submitted. However, a Cephalonium-specific liquid chromatography-mass spectrometry (LC-MS) assay and a microbiological assay were also used to quantify residues in milk and kidney. The LC-MS assay suggested that Cephalonium undergoes extensive degradation to a range of derivatives that accumulate in udder tissue, and are expelled only upon milking. The results obtained during analysis of milk using the microbiological assay were consistent with those obtained with the LC-MS assay which indicated that the microbiological assay is generally selective for the parent drug.

Additional information on the components of the residues present in pooled milk samples and renal tissue was gained using HPLC with radiodetection. With milk, the data indicated that degradation products are primary contributors to the high radioactive residues present in early *post partum* milk, confirming conclusions drawn on the basis of the LC-MS and microbiological assay data. Although very high in the first milking, levels of these metabolites fell very rapidly in subsequent milkings so that if the specified withholding period of 8 milkings is adhered to, Cephalonium would be the major component of the residue. Importantly, the concentrations of Cephalonium in milk were accurately quantitated using the HPLC-MS, and these results closely reflected those obtained when milk residues were quantified using the microbiological agar diffusion assay. In kidney, HPLC data indicated that parent compound comprised less than 10% of the small amount of total radioactive residues present. This finding cannot be extrapolated to 21 days post-dosing (i.e. the applicant's proposed meat withholding period). The studies demonstrated that Cephalonium does not partition into milk fat or tissue fat.

Binding of Cephalonium and/or its derivatives to kidney and milk solids was addressed using radiolabelled Cephalonium studies. The data show an acceptable recovery of total radioactivity (> 80% for milk and approximately 80% for kidney). No data were presented for liver, muscle or fat.

Residue definition

The metabolism data indicate that Cephalonium is degraded to a chemically diverse residue pool in milk. While metabolite concentrations were reported to greatly exceed the levels of the parent drug in early *post partum* milkings, these declined dramatically with subsequent milkings and at the proposed withholding period, a residue definition specifying *"inhibitory substance, identified as Cephalonium"* is appropriate. This is supported by the fact that the early *post partum* milk is not permitted for human consumption and the period of colostrum secretion approximates the proposed withholding period. The data also indicate that the residue definition is appropriate for tissues.

Analytical methods

Residues in milk and tissues were assayed using the Cephalonium-sensitive strain, *Bacillus stearothermophilus* var *calidolactus,* grown on Oxoid Antibiotic Agar No. 2. Limits of quantification were 0.015 mg/kg for milk and 0.08 mg/kg for all other tissues. Milk residues were also quantified by the Accusphere 0.01 test (which uses *Streptococcus thermophilus*) and by Delvotest P. Some milk samples were also subjected to the Yogurt Starter Culture assay which utilised *Streptococcus thermophilus* and *Lactobacillus bulgaris*.

The LC-MS method required sample extraction prior to clean-up. Recoveries ranged from 78% (10 ng/mL) to 92% (100 ng/mL); limit of detection was 5 ng/mL; and the limit of quantification was 10 ng/mL. The methodology was validated and quantified for the parent compound.

Two HPLC procedures with radioactivity detection were utilized to check the radiochemical purity of Cephalonium formulations and to resolve the radioactive residues in various biological samples into their constituents. HPLC with UV detection was used to analyse the chemical purity of Cephalonium formulations.

Residue Trials

Reference 5.8.1: In this trial two Friesian cows were dried-off using the recommended dose of product identical to COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC except that it did not contain blue dye (0.25 g/quarter). Residues in kidney, heart, liver, muscle and subcutaneous fat from both cows were all below the limit of the assay (0.08 mg/kg) at 21 days post-infusion.

Reference 5.8.2: Twenty Friesian cows from 3 commercial herds were dried-off using a product identical to COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC except it did not contain blue dye (0.25 g/quarter). The length of the dry period ranged from 29 to 97 days (12 cows had dry periods ≥ 56 days). Following calving, milk was collected from the first 22 milkings for analysis. The milk from all cows with dry periods ≥ 56 days had milk residues < 0.02 mg/kg after the eighth milking (which is the proposed milk withholding period). An additional 4 cows with dry periods < 56 days (and which therefore would not be treated under commercial practice) also had milk residues < 0.02 mg/kg after the eighth milking.

Reference 5.8.3: Ten cows from two commercial herds were dried off with 0.25 g/quarter a product identical to COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC except it did not contain blue dye. The dry periods ranged from 57 to 82 days. Milk was collected for the first 14 milkings after calving. A quantitative microbiological assay (limit of quantitation 0.04 mg/kg) detected residues of 0.04 mg/kg in the first, second and third milkings post-calving from one cow and in the first milking post-calving for two cows. Milk residues were not detected in any other samples for these cows or the remaining seven cows.

Reference 5.8.8: This study involved 8 cows whose dry periods ranged from 11 to 42 days and would therefore not be candidates for treatment in commercial practice. The milk residue data generated effectively represent a "worse case scenario". Milk residues for 5 of 6 cows were undetectable (< 0.015 mg/kg) at the ninth milking. In addition, milk samples collected from the eight cows were pooled and analysed by HPLC. Cephalonium residues reported for the third and subsequent milkings were consistently less than 0.01 mg/kg.

It was concluded that these trials were adequate to support MRLs of *0.1 mg/kg in both cattle meat and edible offal, and *0.02 mg/kg in cattle milk, and that the proposed meat withholding periods of 21 days (meat) and 96 hours or 8 milkings (milk) are appropriate. '*' denotes that the maximum residue limit (MRL) has been set at or about the limit of analytical determination.

Withholding Period Statements

Recommended label statements are:
MEAT: DO NOT USE LESS THAN 21 DAYS BEFORE SLAUGHTER FOR HUMAN CONSUMPTION

MILK: MILK FROM TREATED COWS MUST NOT BE USED FOR HUMAN CONSUMPTION OR SUPPLIED FOR PROCESSING FOR 96 HOURS (8 MILKINGS) AFTER CALVING

Dietary intake

Dietary intake calculations indicate that the theoretical maximum daily intake of Cephalonium from cattle milk, meat and offal does not exceed the Cephalonium ADI of 0.02 mg/kg/day, and is thus safe for human consumption.

8. IMPLICATIONS FOR TRADE

The export commodities associated with COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC are milk and milk products, cattle meat and offal.

The following tables illustrate the value and tonnage of these export commodities in each market:

Export of milk and milk products, 1995

Country	Quantity (kt)	% of Total
Philippines	83.0	16.3
Japan	82.8	16.2
Thailand	44.5	8.7
Malaysia	44.4	8.7
Singapore	26.0	5.1
Hong Kong	21.8	4.3
Saudi Arabia	12.3	2.4
Taiwan	9.6	1.9
USA	6.6	1.3
Indonesia	5.1	1.0
UK	4.0	0.8
Vietnam	3.0	0.6
PNG	2.4	0.5
China	2.3	0.5
Rest	162.1	31.8
Total	509.9	

Export of meat and meat products, 1995

Country	Quantity (kt)	% of Total
Japan	320.3	42.8
USA	210.7	28.1
South Korea	63.6	8.5
Canada	33.3	4.4
Taiwan	31.7	4.2
Philippines	14.9	2.0
PNG & Pacific Isles	11.6	1.5
Malaysia/Singapore	10.9	1.5
UK	6.6	0.9
Hong Kong	4.1	0.5
Rest	41.2	5.5
Total	748.9	

Source: ABARE 1995-1996 Commodity figures

Overseas Registration Status

The formulation that is intended for marketing in Australia as COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC is registered for use in various overseas countries as shown in the following table (Note that the formulation for Australia, Japan and South Korea contains blue dye; the formulation for other countries does not).

Country	First approved	Withholding Period (days)	
		Meat	Milk
France	1986	21	Nil[2]
Greece	1991	21	4[1]
Ireland	1988	21	4
Italy	1983	NA	4
Japan	1986	30	NA
South Korea	1985	21	4
Luxembourg	1991	NA	NA
Belgium	1992	21	4
Netherlands	1987	PLR	PLR
New Zealand	1977	30	4
Portugal	1991	21	4[1]
Spain	1988	21	4
United Kingdom	1981	21	4[1]

1. Provided the last treatment was > 51 days from calving.
2. 14 day withdrawal period in the case of premature calving and the dry period was less than 28 days.

PLR Product Licence Right - European Union regulatory review process
NA Not available

Codex MRLs

There are no Codex MRLs for Cephalonium for cattle meat or cattle offal, or for milk or milk products, and none are currently being considered.

Australian MRLs and Permitted Residue Levels in Importing Countries

The proposed Australian MRLs are *0.1 mg/kg for Cephalonium in cattle meat and edible offal, and *0.02 mg/kg in milk.

Overseas MRLs have not been established, but in Europe Cephalonium is undergoing the Product Licence of Right (PLR) review, which includes setting of MRLs.

Limits of quantitation

The limits of quantitation of the microbiological assay are 0.08 mg/kg for all cattle tissues and 0.015 mg/kg for cattle milk.

Risks to trade

The risk to Australian trade in either beef or dairy products would appear to be minimal for the following reasons. Variable numbers of cows will be treated at drying off depending on the individual farm circumstances, and treatment will be on the advice of a veterinary surgeon. Treated cows will be returned to the milking herd a minimum of 56 days after treatment, and following calving and observance of the milk withholding period. Milk residues are expected to be less than the MRL after this programme is followed. Any residue concentrations remaining in the milk will subsequently decrease as a result of bulking and blending on the farm of origin and at the milk collection point for the district, since not all cows on a farm or in a district will have undergone dry cow therapy at the same time with COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC. Cephalonium does not partition into milk fat on account of its physicochemical properties, and therefore residues will not concentrate in processed dairy products as compared to whole milk.

When used according to label directions tissue residues will not be detectable.

It is concluded that the registration of COOPERS CEPRAVIN DRY COW INTRAMAMMARY ANTIBIOTIC will not unduly prejudice Australia's trade.

APPENDIX 1: Draft Labels

PRESCRIPTION ANIMAL REMEDY
KEEP OUT OF REACH OF CHILDREN
FOR ANIMAL TREATMENT ONLY

COOPERS®
CEPRAVIN™ DRY COW INTRAMAMMARY ANTIBIOTIC

ACTIVE CONSTITUENT: CEPHALONIUM DIHYDRATE 89.9 g/kg

Do not use in lactating cows.
Do not use in cows with a dry period less than 8 weeks.
Use only at the time of drying off.

READ ACCOMPANYING LEAFLET BEFORE USE.

WITHHOLDING PERIODS: MEAT - 21 DAYS, MILK - DO NOT USE IN LACTATING COWS - SEE LEAFLET.

1 SYRINGE

STORE below 30°C (Room Temperature) in the closed original container in a well ventilated area. Protect from light.

BATCH
EXPIRY

MALLINCKRODT LOGO ®
Mallinckrodt Veterinary Limited
71 Epping Road, North Ryde NSW 2113

NRA Approval No. 47940/01

CEPRAVIN DRY COW LEAFLET
(FIRST PAGE)

PRESCRIPTION ANIMAL REMEDY
KEEP OUT OF REACH OF CHILDREN
FOR ANIMAL TREATMENT ONLY

COOPERS®
CEPRAVIN™ DRY COW INTRAMAMMARY ANTIBIOTIC

ACTIVE CONSTITUENT: CEPHALONIUM DIHYDRATE 89.9 g/kg

For sustained, broad spectrum control of and protection against mastitis-causing bacteria including penicillin resistant strains) in non-lactating dairy cattle.

Each single dose 3g syringe contains 250 mg cephalonium dihydrate in a long-acting base.

Claims
Coopers Cepravin Dry Cow is a long-acting intramammary cerate containing cephalonium, a semi-synthetic cephalosporin antibiotic. It is formulated to give effective antibiotic levels in the dry udder. Coopers Cepravin Dry Cow is recommended for dry cow therapy to treat existing sub-clinical infections and to prevent new infections which occur during the dry period. Infusion at drying off should be part of a mastitis control program on the advice of your veterinary surgeon and will reduce the risk of mastitis that may occur at calving.
Cephalonium is a broad spectrum cephalosporin antibiotic which has bactericidal activity against the majority of organisms associated with bovine mastitis. The antibacterial activity is not impaired in the presence of milk.
Cephalonium is active against: *Staphylococcus aureus*, including penicillin resistant strains, *Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberis, Escherichia coli Corynebacterium pyogenes* and *Corynebacterium ulcerans.* The antibiotic is also active against other organisms recovered from the bovine udder, including *Proteus* spp., *Klebsiella* spp., *Citrobacter* spp. and Enterobacter strains.

Directions for Use
Restraints
Do not use in lactating cows.
Do not use in cows with a dry period less than 8 weeks.
Use only at the time of drying off.

Use COOPERS CEPRAVIN DRY COW as directed by your veterinary surgeon as part of a mastitis control program.
The contents of one syringe should be infused into the teat canal of each quarter immediately after the last milking of the lactation. Before infusion, the teat should be thoroughly cleaned and disinfected. Care should be taken to avoid contamination of the syringe nozzle after the protective cap has been removed. After infusion it is advisable to dip the teats in an antiseptic preparation specifically designed for this purpose.

Wear rubber gloves when infusing this treatment.

COOPERS BAND LOGO

1. After milking is complete thoroughly clean and disinfect the end of the teat (eg. with cotton wool soaked in methylated spirit).

2. Hold the barrel of the syringe firmly in one hand and gently twist and pull the protective cap in a straight line to remove it. Do not bend the nozzle. Take care not to contaminate the nozzle.

3. Insert the nozzle fully into the teat canal and apply steady pressure on the syringe plunger until the full dose has been delivered. Holding the end of the teat with one hand, gently massage upwards with the other to aid dispersion of the antibiotic into the quarter.

4. Finally immerse the teats in a teat dip.

WITHHOLDING PERIODS :

MEAT - DO NOT USE LESS THAN 21 DAYS BEFORE SLAUGHTER FOR HUMAN CONSUMPTION.

MILK - DO NOT USE IN LACTATING COWS OR WITHIN 56 DAYS OF CALVING. AFTER CALVING, COLOSTRUM OR MILK FROM TREATED COWS MUST NOT BE USED FOR HUMAN CONSUMPTION OR PROCESSING FOR 96 HOURS (8 MILKINGS).

General Instructions
If the product is used in heifers during their first pregnancy the same restraints and withholding periods should be observed as in cows. Provided dry cow therapy is used, cows may be dried off safely at the end of lactation by abruptly stopping milking when the milk yield is less than 10 litres per day. A reduction in food intake may be necessary. Infusion of COOPERS CEPRAVIN DRY COW should be made, as described immediately after the last milking.

It is particularly important during the first few days following infusion that the cow should not be encouraged to 'let down' her milk as antibiotic may be lost. It is advisable, therefore, to keep recently "dried off" cows away from the milking shed to avoid stimulating the 'let down' reflex.
For further information contact Coopers Customer Service on 1-800-226-511.
Additional information is listed in the material safety data sheet.

SPECIALIST ADVICE IN EMERGENCY ONLY
Mallinckrodt Veterinary Limited
1 800 226 511 ALL HOURS - AUSTRALIA -WIDE

Warranty
Mallinckrodt Veterinary Limited (MVL) warrants that this product is of merchantable quality and fit for its intended purpose. MVL's liability for any loss, including consequential losses or injury caused by any act or omission, including negligent acts or omissions, by MVL or its agent, is limited to replacing or repairing the product at the option of MVL. If possible, a sample of any product causing concern should be retained or delivered to MVL within 30 days for a scientific examination.

DISPOSE of empty containers and outer packaging by wrapping with paper and putting in garbage.
STORE below 30°C (Room Temperature) in the closed original container in a well ventilated area. Protect from light.

Mallinckrodt Logo
Mallinckrodt Veterinary Limited
71 Epping Road
North Ryde NSW 2113

NRA Approval No. 47940/01

CEPRAVIN DRY COW CARTON
(FRONT PANEL)

PRESCRIPTION ANIMAL REMEDY
KEEP OUT OF REACH OF CHILDREN
FOR ANIMAL TREATMENT ONLY

COOPERS®
CEPRAVIN™ DRY COW
INTRAMAMMARY ANTIBIOTIC

ACTIVE CONSTITUENT: CEPHALONIUM DIHYDRATE 89.9 g/kg

For sustained, broad spectrum control of and protection against mastitis-causing bacteria (including penicillin-resistant strains) in non-lactating dairy cattle .

20 SYRINGES

COOPERS LOGO

(13.3.1997)

CEPRAVIN DRY COW CARTON
(BACK PANEL)

COOPERS® CEPRAVIN™ DRY COW INTRAMAMMARY ANTIBIOTIC
Each single dose 3g syringe contains 250 mg cephalonium dihydrate in a long-acting base.

Claims
Coopers Cepravin Dry Cow is a long-acting intramammary cerate containing cephalonium, a semi-synthetic cephalosporin antibiotic. It is formulated to give effective antibiotic levels in the dry udder.
Coopers Cepravin Dry Cow is recommended for dry cow therapy to treat existing sub-clinical infections and to prevent new infections which occur during the dry period. Infusion at drying off should be part of a mastitis control program on the advice of your veterinary surgeon and will reduce the risk of mastitis that may occur at calving.
Cephalonium is a broad spectrum cephalosporin antibiotic which has bactericidal activity against the majority of organisms associated with bovine mastitis. The antibacterial activity is not impaired in the presence of milk.
Cephalonium is active against: *Staphylococcus aureus*, including penicillin resistant strains, *Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberis, Escherichia coli, Corynebacterium pyogenes* and *Corynebacterium ulcerans*.. The antibiotic is also active against other organisms recovered from the bovine udder, including *Proteus* spp., *Klebsiella* spp., *Citrobacter* spp. and Enterobacter strains.

READ ACCOMPANYING LEAFLET BEFORE USE.

Directions for Use
Restraints
Do not use in lactating cows.
Do not use in cows with a dry period less than 8 weeks.
Use only at the time of drying off.

Use COOPERS CEPRAVIN DRY COW as directed by your veterinary surgeon as part of a mastitis control program.
The contents of one syringe should be infused into the teat canal of each quarter immediately after the last milking of the lactation. Before infusion, the teat should be thoroughly cleaned and disinfected. Care should be taken to avoid contamination of the syringe nozzle after the protective cap has been removed. After infusion it is advisable to dip the teats in an antiseptic preparation specifically designed for this purpose.

WITHHOLDING PERIODS :

MEAT : DO NOT USE LESS THAN 21 DAYS BEFORE SLAUGHTER FOR HUMAN CONSUMPTION.

MILK - DO NOT USE IN LACTATING COWS OR WITHIN 56 DAYS OF CALVING. AFTER CALVING, COLOSTRUM OR MILK FROM TREATED COWS MUST NOT BE USED FOR HUMAN CONSUMPTION OR PROCESSING FOR 96 HOURS (8 MILKINGS).

CEPRAVIN DRY COW CARTON
SIDE PANEL

General Instructions
If the product is used in heifers during their first pregnancy the same restraints and withholding periods should be observed as in cows. Provided dry cow therapy is used, cows may be dried off safely at the end of lactation by abruptly stopping milking when the milk yield is less than 10 litres per day. A reduction in food intake may be necessary. Infusion of COOPERS CEPRAVIN DRY COW should be made, as described immediately after the last milking.

It is particularly important during the first few days following infusion that the cow should not be encouraged to 'let down' her milk as antibiotic may be lost. It is advisable, therefore, to keep recently "dried off" cows away from the milking shed to avoid stimulating the 'let down' reflex.

For further information contact Coopers Customer Service on 1-800-226-511.

Additional information is listed in the material safety data sheet.

SPECIALIST ADVICE IN EMERGENCY ONLY
Mallinckrodt Veterinary Limited
1 800 226 511 ALL HOURS - AUSTRALIA -WIDE

Warranty
Mallinckrodt Veterinary Limited (MVL) warrants that this product is of merchantable quality and fit for its intended purpose. MVL's liability for any loss, including consequential losses or injury caused by any act or omission, including negligent acts or omissions, by MVL or its agent, is limited to replacing or repairing the product at the option of MVL. If possible, a sample of any product causing concern should be retained or delivered to MVL within 30 days for a scientific examination.

DISPOSE of empty containers and outer packaging by wrapping with paper and putting in garbage.
STORE below 30°C (Room Temperature) in the closed original container in a well ventilated area.
Protect from light.

BATCH

EXPIRY

Mallinckrodt Logo
Mallinckrodt Veterinary Limited
71 Epping Road
North Ryde NSW 2113

NRA Approval No. 47940/01

BAR CODE

CEPRAVIN DRY COW
INSIDE CARTON (FRONT PANEL)

PRESCRIPTION ANIMAL REMEDY
KEEP OUT OF REACH OF CHILDREN
FOR ANIMAL TREATMENT ONLY

COOPERS®
CEPRAVIN™ DRY COW
INTRAMAMMARY ANTIBIOTIC

ACTIVE CONSTITUENT:
CEPHALONIUM DIHYDRATE 89.9 g/kg

4 X 3g SYRINGES

COOPERS LOGO

IT IS ILLEGAL TO SELL THIS CARTON SEPARATELY

(13.3.1997)

CEPRAVIN DRY COW
INSIDE CARTON (REAR PANEL)

READ ENCLOSED DIRECTIONS BEFORE USE

For further information contact Coopers Customer Service on 1 800 226 511.
Additional information is listed in the Material Safety Data Sheet.

SPECIALIST ADVICE IN EMERGENCY ONLY
Mallinckrodt Veterinary Limited
1 800 226 511 ALL HOURS - AUSTRALIA -WIDE

Warranty
Mallinckrodt Veterinary Limited (MVL) warrants that this product is of merchantable quality and fit for its intended purpose. MVL's liability for any loss, including consequential losses or injury caused by any act or omission, including negligent acts or omissions, by MVL or its agent, is limited to replacing or repairing the product at the option of MVL. If possible, a sample of any product causing concern should be retained or delivered to MVL within 30 days for a scientific examination.
DISPOSE of empty containers and outer packaging by wrapping with paper and putting in garbage.
STORE below 30°C (Room Temperature) in the closed original container in a well ventilated area.
Protect from light.

Mallinckrodt Logo
Mallinckrodt Veterinary Limited
71 Epping Road
North Ryde NSW 2113

NRA Approval No. 47940/01