

**Public Release Summary  
on**

**Evaluation of the new active**

**CEPHAPIRIN**

**in the product/s**

**Metricure Benzathine cephalixin intra -uterine suspension**

**National Registration Authority  
for Agricultural and Veterinary Chemicals**

**September 2001**

**Canberra  
Australia**

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## FOREWORD

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

In undertaking this task, the NRA works in close cooperation with advisory agencies, including the Department of Health and Aged Care (Chemicals and Non-prescription Drug Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission (Worksafe Australia) and State departments of agriculture and environment.

The NRA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of public release summaries for all products containing new active ingredients and for all proposed extensions of use for existing products.

The information and technical data required by the NRA 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 NRA's publications *Vet Manual: The Requirements Manual for Veterinary Chemicals* and *Vet Requirements Series*.

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the NRA and its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

More detailed technical assessment reports on all aspects of the evaluation of this chemical can be obtained by completing the order form in the back of this publication and submitting with payment to the NRA. Alternatively, the reports can be viewed at the NRA Library Ground Floor, 22 Brisbane Avenue, Barton, ACT.

The NRA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Executive Manager—Registration, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E240, Kingston ACT 2604.



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## LIST OF ABBREVIATIONS AND ACRONYMS

<b>ac</b>	active constituent
<b>ADI</b>	Acceptable Daily Intake (for humans)
<b>AHMAC</b>	Australian Health Ministers Advisory Council
<b>ai</b>	active ingredient
<b>BBA</b>	Biologische Bundesanalstalt fur Land – und forstwirtschaft
<b>bw</b>	Bodyweight
<b>d</b>	Day
<b>DAT</b>	Days After Treatment
<b>DT<sub>50</sub></b>	Time taken for 50% of the concentration to dissipate
<b>EA</b>	Environment Australia
<b>E<sub>b</sub>C<sub>50</sub></b>	concentration at which the biomass of 50% of the test population is impacted
<b>EC<sub>50</sub></b>	concentration at which 50% of the test population are immobilised
<b>EEC</b>	Estimated Environmental Concentration
<b>E<sub>r</sub>C<sub>50</sub></b>	concentration at which the rate of growth of 50% of the test population is impacted
<b>EUP</b>	End Use Product
<b>F<sub>0</sub></b>	original parent generation
<b>g</b>	Gram
<b>GAP</b>	Good Agricultural Practice
<b>GCP</b>	Good Clinical Practice
<b>GLP</b>	Good Laboratory Practice
<b>GVP</b>	Good Veterinary Practice
<b>h</b>	Hour
<b>ha</b>	Hectare
<b>Hct</b>	Heamatocrit
<b>Hg</b>	Haemoglobin
<b>HPLC</b>	High Pressure Liquid Chromatography <i>or</i> High Performance Liquid Chromatography
<b>id</b>	Intradermal
<b>im</b>	Intramuscular
<b>ip</b>	Intraperitoneal
<b>IPM</b>	Integrated Pest Management
<b>iv</b>	Intravenous
<b>in vitro</b>	outside the living body and in an artificial environment
<b>in vivo</b>	inside the living body of a plant or animal
<b>kg</b>	Kilogram
<b>K<sub>oc</sub></b>	Organic carbon partitioning coefficient
<b>L</b>	Litre
<b>LC<sub>50</sub></b>	concentration that kills 50% of the test population of organisms
<b>LD<sub>50</sub></b>	dosage of chemical that kills 50% of the test population of organisms
<b>LOD</b>	Limit of Detection – level at which residues can be detected
<b>LOQ</b>	Limit of Quantitation – level at which residues can be dquantified
<b>mg</b>	Milligram
<b>mL</b>	Millilitre

<b>MRL</b>	Maximum Residue Limit
<b>MSDS</b>	Material Safety Data Sheet
<b>NDPSC</b>	National Drugs and Poisons Schedule Committee
<b>ng</b>	Nanogram
<b>NHMRC</b>	National Health and Medical Research Council
<b>NOEC/NOEL</b>	No Observable Effect Concentration Level
<b>OC</b>	Organic Carbon
<b>OM</b>	Organic Matter
<b>po</b>	Oral
<b>ppb</b>	parts per billion
<b>PPE</b>	Personal Protective Equipment
<b>ppm</b>	parts per million
<b>Q-value</b>	Quotient-value
<b>RBC</b>	Red Blood Cell Count
<b>s</b>	Second
<b>sc</b>	Subcutaneous
<b>SC</b>	Suspension Concentrate
<b>SUSDP</b>	Standard for the Uniform Scheduling of Drugs and Poisons
<b>TGA</b>	Therapeutic Goods Administration
<b>TGAC</b>	Technical grade active constituent
<b>T-Value</b>	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
<b>µg</b>	Microgram
<b>vmd</b>	volume median diameter
<b>WG</b>	Water Dispersible Granule
<b>WHP</b>	Withholding Period





## **INTRODUCTION**

The purpose of this document is to provide a summary of the data reviewed, and an outline of the regulatory considerations for the proposed registration of the antibiotic-containing product Metricure benzathine cephalosporin intra-uterine suspension. This information provided herein presents only the conclusions reached by the various expert reviewers after consideration of the scientific database.

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

The deadline for comment is 17 October 2001.

Comments should be sent to:

Dr Tim Dyke  
National Registration Authority  
PO Box E240  
Kingston ACT 2604.

Fax: (02) 6 272 5249

### **Applicant**

Intervet Australia Pty Limited  
91-105 Harpin St  
Bendigo East VIC 3550  
Tel: (03) 5442 5011  
Fax: (03) 5442 3162

### **Indications for use**

Metricure benzathine cephalosporin intra-uterine suspension is proposed to be used for the treatment of endometritis in individual cattle.

### **Product details**

Metricure benzathine cephalosporin intra-uterine suspension is an oily suspension of benzathine cephalosporin packaged in 19g syringes for intra-uterine use. There is 500 mg cephalosporin per syringe.

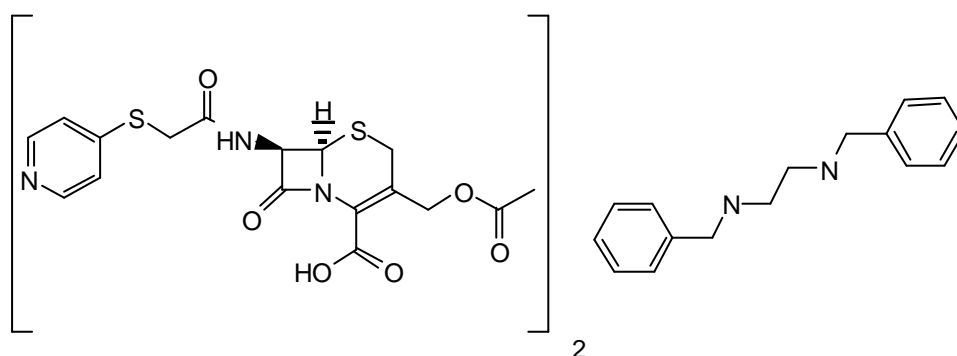
The product is manufactured overseas and imported into Australia in its final packaging. The product is registered in many countries including Japan, USA, Europe and Canada.

## CHEMISTRY AND MANUFACTURE

### Active constituent

The chemical active constituent, cephapirin, has the following properties:

Common name (ISO):	Benzathine cephapirin
Chemical name:	N,N'-dibenzyl ethylene diamine salt of 7[alpha(4-piridylthio)-acetamido]
CAS Registry Number:	21593-23-7
Empirical formula:	$[C_{17}H_{17}N_3O_6S_2]C_{16}H_{20}N_2$
Molecular weight:	1087.18
Physical form:	powder
Colour:	off- white
Structural formula:	



### Formulated product

Product name:	Metricure benzathine cephapirin intra-uterine suspension
Physical form:	suspension
Storage stability:	Data provided demonstrates that the product is stable for 36 months when stored below 25C (air conditioning) in syringes.

## TOXICOLOGICAL ASSESSMENT

The toxicological database for cephalosporins, 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 that are high compared to likely human exposures. The use of high doses increased the likelihood that potentially significant toxic effects are unlikely to occur. Such dose levels as the Lowest-Observable-Effect-Level (LOEL) are used to develop acceptable limits for dietary or other intakes at which no adverse health effects in humans would be expected.

### Acute toxicity

Acute exposure to cephalosporins via intravenous, intramuscular and intraperitoneal routes caused low toxicity in rats, rabbits and dogs. Rats exposed via the oral route to cephalosporins displayed low acute toxicity ( $LD_{50} = 14000$  mg/kg bw).

### Short-term studies

Rats were intraperitoneally injected with 0, 200, 500 or 1000 mg/kg bw cephalosporins daily for nine weeks. Treated males had slightly elevated body weight gains. Treated females had significantly heavier adrenals in relation to body weight at all doses and had an elevated liver to bodyweight ratio at 1000 mg/kg bw/day only.

Dogs were intravenously injected with 0, 200 or 500 mg/kg bw cephalosporins daily for one month. Increased incidence of vomiting was noted in 500 mg/kg bw dogs.

Dogs were intramuscularly injected with 0, 100, 200 or 400 mg/kg bw cephalosporins daily for 10 weeks. A slight reduction in food intake was noted in treated females and body weight losses occurred in treated animals. Kidney weights relative to body weights were significantly increased for 400 mg/kg bw dogs.

### Subchronic studies

Rats were fed a dietary dose of 0 or 23 mg/kg bw cephalosporins daily for 13 weeks. Significantly higher body weight gains and significantly heavier livers relative to body weight were noted in treated males.

Rats were intraperitoneally injected with 0, 200, 500 or 1000 mg/kg bw cephalosporins daily for 26 weeks. Signs of anaemia were noted in all treated groups in a dose-related manner. Cephalosporin-treated females and 1000 mg/kg bw males had slightly lower body weight gains than controls. In 1000 mg/kg bw females relative gonad weights were significantly increased.

Dogs received oral doses via capsules of 0 or 20 mg/kg bw cephalixin daily for 13.5 weeks. Treated males gained slightly more weight less than controls. An elevated incidence of vomiting was noted in treated dogs.

Dogs were intramuscularly injected with 0, 100, 200 or 400 mg/kg bw cephalixin for up to ten months. Body weight loss, decreased food intake, anorexia and anaemia were noted in some treated dogs. Reversible alterations to white blood cells were also noted. Inflammation of blood vessels in the liver, kidney and heart were noted in treated dogs.

### **Reproduction and developmental studies**

Cephalixin was administered subcutaneously to rats at 0, 200 or 500 mg/kg bw/day throughout a pre-mating period, mating, gestation and lactation. Dose relatedly greater numbers of resorption sites were found in treated females mid-way through the gestation period. The administration of cephalixin produced no other adverse responses on reproduction or foetus development.

When cephalixin was given to pregnant mice and rats throughout the period of foetal development, no adverse effects on foetal development related to cephalixin were noted at up to and including the highest dose of 500 mg/kg bw/day.

### **Genotoxicity**

Cephalixin did not show any evidence of genotoxic activity in assays for mutation in bacteria and cultured mammalian cells, and for chromosomal injury in mice.

### **Human data**

The major categories of adverse reactions towards cephalixin in humans are gastrointestinal, dermatologic, hypersensitivity, haematologic, hepatic, renal and central nervous system.

Two major studies on humans receiving either injections into muscles or veins have been performed. The most common adverse reactions were hypersensitivity reactions and alterations to liver function. Evidence of white blood cell disorders and anaemia were noted in some subjects.

## **PUBLIC HEALTH STANDARDS**

### **Poison Scheduling**

The National Drugs and Poisons Scheduling Committee (NDPSC) considered the toxicity of cephalixin in 1989 and assessed the necessary controls to be implemented under States' poisons regulations to prevent the occurrence of poisoning.

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

There are provisions for appropriate warning statements and first-aid instructions on the label of the product.

## **LOEL/ADI**

The most sensitive species was the dog, with a LOEL of 20 mg/kg bw/day. In order to calculate the acceptable daily intake (ADI) for humans, a safety factor was applied to the LOEL 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 potential hazards. Using a safety factor of 1000, an ADI of 0.02 mg/kg bw/day was established for cephapirin.

## **EVALUATION OF POTENTIAL TRANSFER OF ANTIBIOTIC RESISTANCE TO HUMANS**

The NRA sought advice from the Working Party on Antibiotics on the registration of this product containing benzathine cephapirin, a first generation cephalosporin. The Working Party on Antibiotics had no objections to the registration of the product for the treatment of single animals under the control of a veterinarian provided that its use was limited to the treatment of endometritis only in cattle. The proposed MRLs were supported by the Working Party on Antibiotics.

## **METABOLISM AND TOXICOKINETICS ASSESSMENT**

Orally administered cephapirin is poorly absorbed by humans. Following intravenous and subcutaneous injections about 90% of administered cephapirin is absorbed by humans. The main metabolite is desacetylcephapirin. The main route of elimination is via the kidneys with a half-life of 0.5 to 2 hours. Similar findings were noted in laboratory animals.

## RESIDUES ASSESSMENT

### Chemical residues in food

The residue data and use pattern supported a 2 day withholding period for meat and a NIL withholding period for milk. The data showed that when the product is used in accordance with the label, the proposed MRLs for cephalosporin should not be exceeded and consumption of tissues from treated animals is unlikely to result in dietary intake of cephalosporin exceeding the ADI.

### Metabolism studies

Two metabolism studies in cattle were presented. In other species, the major residue detected was desacetylcephalosporin.

### Analytical methods

Two methods were presented, an HPLC method for determination of cephalosporin and desacetylcephalosporin in muscle, kidney, liver, udder, fat and milk and a microbiological method for determination of cephalosporin and active metabolites in the same tissues and fluids..

### Limits of quantification

The limit of quantification in the HPLC method was 0.01 µg/g.

The limit of quantification in the microbiological method was 0.01 µg/g.

### Residue definition

The residue definition is proposed to be cephalosporin and des-acetylcephalosporin, expressed as cephalosporin.

### Residue trials

Six studies were submitted for consideration.

Milk: Cephalosporin concentrations in milk were below the limit of quantification in all milk samples when the product was given once at the recommended dose rate. At 3 times the recommended dose rate given for three days, cephalosporin concentrations in milk were below the limit of quantification by the second milking after the third dose.

Meat: and offal When the product was administered once at the recommended dose rate, finite residues were only found at 6 hours after administration in one muscle sample and in 8 out of 10 kidney samples and at 24 hours in 1 out of 4 kidney samples. Whilst finite residues were found in udder tissue at 4 days after administration of the product at the recommended dose rate, udder is not considered an edible commodity, and the withholding period was set on this basis.

### Australian MRLs

The MRLs, set at or about the limit of quantification, proposed herein for Australia are :

	Food	MRL (mg/kg)
MO 0812	Cattle, edible offal	*0.02
ML 0812	Cattle milk	*0.01
MM 0812	Cattle meat	*0.02



**Withholding period statements**

The recommended withholding period statements are:

**MILK: NIL**

**MEAT: DO NOT USE less than 2 days before slaughter for human consumption.**

**Dietary intake**

The dietary intake calculation shows that, using the total Australian population dietary intake figures, the calculated Theoretical Maximal Daily Intake (TMDI) for cephalosporin does not exceed the Australian ADI for cephalosporin of 0.02 mg / kg body weight / day, and is thus safe for human consumption.

## ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

### COMMODITIES EXPORTED

The export commodities associated with the use of this product are milk, milk products and meat from cattle.

### COUNTRIES WHERE THESE COMMODITIES ARE EXPORTED.

Meat and dairy products are exported to international markets throughout the world including Japan, Korea, USA, Europe, SE Asia, Indonesia, Egypt, the Philippines, Canada, Taiwan, and Libya.

### PROPOSED AUSTRALIAN USE OF THE PRODUCT

This product is indicated for the treatment of endometritis in cows caused by bacteria sensitive to cephalosporins, where metritis has a high prevalence (= 10%) and where an increase in early pregnancies (by 28 days after mating) is required.

The contents of one syringe should be introduced into the lumen of the uterus using the disposable catheter provided. Each 19g syringe contains 500mg of cephalosporin as an oily suspension.

### OVERSEAS REGISTRATIONS AND USE PATTERNS

This product is registered in many countries throughout the world including Japan, Korea, USA, Europe, SE Asia, Indonesia, Egypt, the Philippines, Canada, Taiwan, and Libya. The use patterns in those countries include use for the treatment and prevention of subacute/chronic endometritis in cows more than 14 days post partum.

### CODEX ALIMENTARIUS COMMISSION MRLS

No Codex MRL's have been set or are being considered.

### AUSTRALIAN MRL's AND PERMITTED LIMITS IN IMPORTING COUNTRIES.

The proposed MRL's are: 0.01µg/mL milk and 0.02µg/g meat and offal.

The withholding periods proposed are **NIL** for milk and **48 hours** for meat.

New Zealand	Cattle meat, cattle fat	0.1µg/g
	Edible offal of cattle	0.1µg/g
	Cattle milk	0.01µg/mL
USA	Cattle meat, cattle fat	0.1µg/g
	Edible offal of cattle	0.1µg/g
	Cattle milk	0.02µg/mL
EEC	Cattle	
	Muscle	0.05µg/g
	Liver	0.05µg/g
	Milk	0.01µg/g

### POTENTIAL RISK TO TRADE.

Australia exported over \$3bn in beef and veal, and over \$2bn in dairy products, in the period 1999-2000, with the major markets being USA, Japan, S. Korea, the Philippines and Saudi Arabia.

The product is registered for use in many American countries, Asia, Europe and the Middle East.

Trial work submitted in support of this application demonstrated that there were no detectable residues present at the nominated withholding periods. Therefore, there is no undue prejudice to trade when the product is used according to label directions.

### **CONCLUSIONS**

The use of this product is not likely to have any impact on trade. The product is not applied directly to edible tissues or fluids, any transfer to edible tissues is brief and is not likely to result in detectable residues in the tissues or fluids in question. Studies indicate that when used as recommended there should be no trade issues.

## **OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT**

The National Occupational Health and Safety Commission conducted an assessment on the product, and supports the registration of the product for intra-uterine treatment of cows. This recommendation was based on the product's directions for use, the product's supply in single dose syringes, the low acute oral, intramuscular and intraperitoneal toxicity of cephalixin in experimental species and poor absorption of cephalixin following oral absorption in humans. Even if the contents of an entire syringe were absorbed, the dose would be approximately 10 mg/kg body weight, lower than the 30 to 60 mg/kg body weight given as the parenteral dose in humans. Safety directions were not considered necessary due to low toxicity and minimal potential for user exposure.

## ENVIRONMENTAL ASSESSMENT

### Environmental fate

Cephapirin is largely excreted from treated cows in urine within 72 hours of treatment, much of it as residues which retain antibiotic activity, though there may be some degradation of the parent substance, particularly to desacetyl-cephapirin. Cephapirin administered by the intra-uterine method will principally reach the environment via the urine of treated cattle. The vast majority of applied cephapirin is likely to be excreted in urine within 8 h of application. Only a small percentage of cows in a herd would be likely to be treated at any one time. The urine would be distributed in patches in the area where cattle graze after treatment or possibly in dairy or yard washings.

No specific data regarding hydrolysis of cephapirin were available. However, based on evidence in the literature it is likely that the substance is susceptible to abiotic hydrolysis under appropriate conditions, at an unknown rate. On the limited evidence available, Environment Australia estimates it will be of low to moderate persistence (likely half life in the order of 14 to 180 days).

Cephapirin may be susceptible to photolysis, but further data would be needed to determine the rate at which 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 clear water. Thus direct photodegradation is unlikely to be a significant means of degradation of cephapirin eliminated from animals which has moved into soil or turbid water.

First generation cephalosporins are “relatively susceptible” to  $\beta$ -lactamase (cephalosporinase) produced by Gram-negative bacteria, whereas second and particularly third generation cephalosporins have greater stability against Gram-negative  $\beta$ -lactamases. Thus various micro-organisms present in soil and water are likely to be able to degrade cephapirin in the environment, but at an unknown rate.

No data were provided for the behaviour of cephapirin in soil. However, as it contains ionic species (a pyridylthio-N and a carboxylic group), it is likely to be adsorbed onto clay particles in the soil although the strength of adsorption is unknown.

### Environmental effects

No data were provided on the toxicity of cephapirin to birds, fish and other aquatic organisms, algae, aquatic or terrestrial plants, or terrestrial invertebrates. Environment Australia notes the lack of available data on aspects such as aquatic toxicity for this and similar antibiotics. Very low toxicity of cephapirin to mammals is indicated by its toxicity to rats, to which the acute oral LD<sub>50</sub> is  $> 10,000 \text{ mg.kg}^{-1}$ .

Cephapirin is a first generation cephalosporin and is a broad spectrum antibiotic active against gram positive organisms (including penicillinase producing Staphylococci) and with modest activity against many gram negative organisms such as *E. coli*. The application reports a range of Minimum Inhibitory Concentrations (MIC) ranging from  $0.01 \mu\text{g.mL}^{-1}$  for highly susceptible species (*Streptococcus pyogenes*) to  $>500 \mu\text{g.mL}^{-1}$  for relatively resistant organisms (*Proteus morganii*).

The effect of cephapirin on non-target organisms is harder to assess as no specific data were provided. A paper obtained by Environment Australia has demonstrated that various organisms commonly found in soil and water varied in their susceptibility to a range of

antimicrobial agents including cephalothin that is also a first generation cephalosporin with some structural similarities. Assuming this can be taken as a reliable predictor of the behaviour of cephapirin in soil or water it would appear that cephapirin residues will affect some organisms while others will be unaffected.

### **Environmental hazard**

Research cited by the applicant and experience with related antibiotics, reported in the literature, indicates the vast majority of cephapirin will be excreted unchanged in the urine. Most excretion occurs within 8 hours of application and the process of excretion will be complete by 72 hours after application. Therefore cephapirin will principally reach the external environment in urine from treated cows.

It is most likely that urine will be released onto pasture. Environment Australia estimates that in a worst case scenario the concentration of cephapirin in localised patches of soil would reach  $3.6 \mu\text{g.g}^{-1}$ . This concentration exceeds the MIC of some susceptible organisms. However, as only a small number of cows are likely to receive this treatment the impact of cephapirin in urine is likely to be highly dispersed and short term.

Where urination occurs in yards or a dairy Environment Australia has assumed the following as a worst case scenario. Five cows in a 120 cow herd have each been treated with a 500 mg dose of cephapirin. On the basis that 20% of a cows urination or defecation occurs in yards or the dairy, the equivalent of one 500 mg dose would be released in this area and be washed into the effluent stream. Based on typical dairy effluent production, this would result in 500 mg of cephapirin being diluted in ~10,000 L of effluent during the three days after treatment of the cattle. The average concentration resulting in the effluent produced in those three days would be  $\sim 50 \mu\text{g.mL}^{-1}$  which is well in excess of the MIC for some organisms. This effluent will generally be mixed with previously produced effluent in storage or holding ponds and will also be diluted further as more uncontaminated effluent is added. Cephapirin levels in stored effluent or effluent spread onto pastures or crops are therefore likely to be much lower due to the effects of dilution and degradation.

The available evidence suggests that at this concentration, residues could affect susceptible micro-organisms, but that many micro-organisms would be unaffected and able to degrade the substance. Thus microbial populations in effluent may be disrupted for a period, but susceptible strains could re-establish as residues dissipated.

Repeated treatment in succeeding months is unlikely to lead to a build-up in cephapirin, as in the interim, residues are likely to be at least partially degraded and would be diluted by large volumes of uncontaminated effluent. Furthermore, the above is very much a worst-case scenario and it is more likely that the urine would be released onto pasture.

No data are available to determine its hazard to terrestrial invertebrates or aquatic organisms but a low hazard is expected due to the low exposure.

### **Conclusion**

From the information available Environment Australia believes that the use of the product according to the label is unlikely to have an unintended effect that is harmful to animals, plants or the environment. It is recognised that the use of this and other antibiotics has possible long term consequences if resistant strains of bacteria develop. The likelihood of this occurring will be minimised due to the relatively low and isolated use and provided the product is used strictly according to the label and only when necessary.

## **EFFICACY AND SAFETY ASSESSMENT**

Four trials were submitted assessing efficacy and field safety of the product. In all trials, individual cattle were treated at least 14 days after calving for endometritis or where risk factors indicated that endometritis was likely. Scientific experts from the State Departments of Agriculture / Primary Industries assessed the submitted scientific studies and found them to be sufficient to support the proposed label claims for this product, at the recommended dose rate. Minimum inhibitory concentrations studies supported effectiveness of cephalixin against various bacterial species. No adverse reactions were recorded in field studies.

Data submitted supports that this product is to be used for the intra-uterine treatment of endometritis, caused by bacteria sensitive to cephalixin, in cattle herds in which the prevalence of endometritis is at least 10% and where an increase in early pregnancies (by 28 days after mating) is required.

## LABELLING REQUIREMENTS

### PROPOSED LABEL

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

**METRICURE™ Benzanthine  
Cephapirin intra-uterine  
suspension**

**ACTIVE CONSTITUENT PER 19 g:  
CEPHAPIRIN 500 mg**

19 g

**INTERVET AUSTRALIA PTY LIMITED  
91-105 Harpin Street  
BENDIGO EAST VIC 3550  
Phone 03 5442 5011  
Fax: 03 5442 3162**

**READ THE ENCLOSED LEAFLET BEFORE  
USING THIS PRODUCT.**

**WITHHOLDING PERIOD  
MEAT: DO NOT USE LESS THAN 2 DAYS BEFORE  
SLAUGHTER FOR HUMAN CONSUMPTION.  
MILK: NIL**

**Disposal**

Dispose of empty container by wrapping in paper and putting in garbage.

Store below 25°C (Air Conditioning)

**Batch No.:**  
**Expiry Date:**  
NRA



## PROPOSED BOX LABEL

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

**METRICURE™ Benzanthine  
Cephapirin intra-uterine  
suspension**

**ACTIVE CONSTITUENT PER 19 g:  
CEPHAPIRIN 500 mg**

Suspension for the intra-uterine treatment of metritis in herds where it is present at a high prevalence (=10%) and where an increase in early pregnancies (by 28 days after mating) is required.

10 syringes, 10 catheters and 10 gloves

**INTERVET AUSTRALIA PTY LIMITED**  
91-105 Harpin Street  
BENDIGO EAST VIC 3550  
**Phone 03 5442 5011**  
**Fax: 03 5442 3162**

**READ THE ENCLOSED LEAFLET BEFORE USING THIS PRODUCT.**

**Directions for Use**

Single dose syringe to be administered intra-uterine.

**WITHHOLDING PERIOD**

**MEAT DO NOT USE LESS THAN 2 DAYS BEFORE  
SLAUGHTER FOR HUMAN CONSUMPTION.  
MILK: NIL**

**Disposal**

Dispose of empty container by wrapping in paper and putting in garbage.

Store below 25°C (Air Conditioning)

**Batch No.:**

**Expiry Date:**

NRA

## Proposed Leaflet

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

### **METRICURE™**

Benzathine CEPHAPIRIN intra-uterine suspension.

### **Composition**

Each 19 gram syringe contains 500 mg CEPHAPIRIN (as benzathine).

### **Properties**

CEPHAPIRIN is a first generation cephalosporin; a broad-spectrum antibiotic with bactericidal action against gram-positive and gram-negative bacteria. CEPHAPIRIN is resistant to the action of penicillinase and is active in an anaerobic environment such as encountered in an infected uterus. After a single treatment with METRICURE™, concentrations of CEPHAPIRIN in endometrial tissue above the MIC of sensitive bacteria are maintained for at least 24 hours.

The suspension is well tolerated, enables good diffusion of CEPHAPIRIN into the endometrium and is easily infused.

### **Indications**

METRICURE™ is indicated for the treatment of endometritis in cows caused by bacteria sensitive to CEPHAPIRIN. Where metritis has a high prevalence (=10%) and where an increase in early pregnancies (by 28 days after mating) is required.

### **Directions for Use**

**Not recommended for use in animals known to be allergic to cephalosporins.**

The contents of one METRICURE™ syringe should be introduced into the lumen of the uterus using the disposable catheter provided.

- Fix the syringe to the catheter.
- Take the cervix of the uterus into a gloved hand introduced into the rectum.
- Introduce the catheter through the cervix into the lumen of the uterus, by gentle oscillating movements of the cervix.
- Inject METRICURE™.

One treatment of METRICURE™ is usually sufficient for a complete cure. In animals that have been inseminated, METRICURE™ may be used at one day after insemination.

In case of pyometra, pretreatment with prostaglandins is recommended in order to induce luteolysis and remove debris from the uterine cavity.

**WITHHOLDING PERIOD**

**MEAT: DO NOT USE LESS THAN 2 DAYS BEFORE SLAUGHTER FOR HUMAN CONSUMPTION.**

**MILK: NIL**

**Disposal**

Dispose of empty container by wrapping in paper and putting in garbage.

**Storage**

Store below 25°C (Air conditioning)

Distributed by:

**INTERVET AUSTRALIA PTY LIMITED**

91-105 Harpin Street

BENDIGO EAST VIC 3550

**Phone 03 5442 5011**

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## GLOSSARY

<b>Active constituent</b>	The substance that is primarily responsible for the effect produced by a chemical product.
<b>Acute</b>	Having rapid onset and of short duration.
<b>Carcinogenicity</b>	The ability to cause cancer.
<b>Chronic</b>	Of long duration.
<b>Codex MRL</b>	Internationally published standard maximum residue limit.
<b>Efficacy</b>	Production of the desired effect.
<b>Formulation</b>	A combination of both active and inactive constituents to form the end use product.
<b>Genotoxicity</b>	The ability to damage genetic material
<b>Leaching</b>	Removal of a compound by use of a solvent.
<b>Log P<sub>ow</sub></b>	Log to base 10 of octanol water partitioning co-efficient.
<b>Metabolism</b>	The conversion of food into energy
<b>Photodegradation</b>	Breakdown of chemicals due to the action of light.
<b>Photolysis</b>	Breakdown of chemicals due to the action of light.
<b>Subcutaneous</b>	Under the skin
<b>Toxicokinetics</b>	The study of the movement of toxins through the body.
<b>Toxicology</b>	The study of the nature and effects of poisons.

## References

National Registration Authority for Agricultural and Veterinary Chemicals 1996, *Vet Manual: The Requirements Manual for Agricultural Chemicals*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1997, *Vet Requirements Series: Guidelines for Registering Agricultural Chemicals*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1996, *MRL Standard: Maximum Residue Limits in Food and Animal Feedstuffs*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1997, *Vet Labelling Code—Code of Practice for Labelling Agricultural Chemical Products*, NRA, Canberra.

**NRA PUBLICATIONS ORDER FORM**

To receive a copy of the full technical report for the evaluation of cephalosporin in the product Metricure benzathine cephalosporin intra-uterine suspension, please fill in this form and send it, along with payment of \$30 to:

Ms S. Scales  
A.V.C.E.S.  
National Registration Authority for Agricultural and Veterinary Chemicals  
PO Box E240  
Kingston ACT 2604

Alternatively, fax this form, along with your credit card details, to:  
Ms S. Scales at (02) 6272 3744.

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