Public Release Summary
on

Evaluation of the new active

FLORFENICOL

in the product

NuFlor LA Injectable Solution

National Registration Authority
for Agricultural and Veterinary Chemicals

January 2003

Canberra
Australia

ISSN1443-1335

This document is published by the National Registration Authority for Agricultural and Veterinary Chemicals. In referencing, the NRA should be cited as both the author and publisher of this document. For further information, please contact:

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 Family Services (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.

Contents

List Of Abbreviations And Acronyms

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ADI	Acceptable Daily Intake
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Haematocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HPLC	High Performance Liquid Chromatography
id	intradermal
im	intramuscular
IM	Intramuscular
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC/MS	Liquid Chromatographic Mass Spectrometry
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
log Kow	Octanol/Water Partition Coefficient
LOQ	Limit of Quantitation – level at which residues can be dquantified

LOQ	Limit of Quantitation
µg	microgram
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SC	Subcutaneous
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TRR	Total Radioactive Residues
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
vmd	volume median diameter
WG	Water Dispersible Granule
WHO	World Health Organisation
WHP	Withholding Period

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 florfenicol for use as an antibiotic in pigs and cattle. The information provided herein presents only the conclusions reached by various reviewers after consideration of the scientific database. All trial data and methods of assessment presented for evaluation were conducted to accepted scientific principles.

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 florfenicol and now invites public comment before deciding whether to approved this product for use in Australia. The information contained in the document is provided for public comment.

The deadline for comments is 4 February 2003. Comments should be sent to:

[redacted]

Applicant's details
Schering-Plough Animal Health Limited
11 Gibbon Road
Baulkham Hills NSW 2153

Justification for use

The product Nuflor LA Injectable Solution is proposed for use in the treatment of cattle with bacterial infections susceptible to florfenicol, especially the causative organisms of pinkeye, bovine respiratory disease (BRD) and footrot, and in the treatment of pigs with swine respiratory disease.

Product details
Nuflor LA Injectable Solution contains 300 mg/mL Florfenicol and is presented as a sterile solution in glass or HDPE vials with bromobutyl rubber stoppers and aluminium seals. The formulation of the product takes place overseas.

Florfenicol has approved uses (October 2002) as an injectable for cattle in Argentina, Austria, Belgium, Brazil, Canada, Chile, Colombia, Costa Rica, Czech Republic, Denmark, Egypt, El Salvador, Finland, France, Germany, Greece, Guatemala, Hungary, Ireland, Israel, Italy, Jamaica, Jordan, Lebanon, Luxembourg, Malaysia (no registration requirement), Mexico,

Morocco, Netherlands, New Zealand, Panama, Paraguay, Peru, Poland, Portugal, Saudi Arabia, Slovak Republic, South Africa, Spain, Switzerland, Turkey, United Kingdom, USA, Uruguay and Venezuela.

Florfenicol has approved uses (October 2002) as an injectable for pigs in Austria, Belgium, Brazil, Finland, France, Germany, Greece, Italy, Japan, Luxembourg, Malaysia (no registration requirement), Mexico, New Zealand, Panama, Portugal, Spain and Venezuela. Additionally, countries with oral uses that do not have currently approved injectable uses include Denmark, Ireland, The Netherlands and the United Kingdom.

Chemistry and Manufacture

Active Constituent

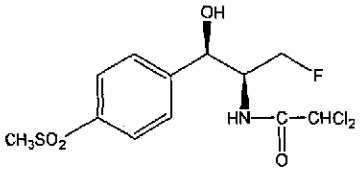
Manufacturers

Schering Corporation
1011 Morris Avenue
Union, NJ 07083
United States

Shanghai Sunve Pharmaceutical Factory
88 Bao an Road
Bao Shan
Shanghai, China

Hickson PharmaChem Ltd
Loughbeg, Ringaskiddy
County Cork, Ireland

Chemical Characteristics of the Active Constituent

Common name:	florfenicol
Chemical name:	[R-(R*,S*)]-2,2-dichloro-N-[1-(fluoromethyl)-2-hydroxy-2-[4-(methylsulfonyl)phenyl] ethyl]acetamide; D-threo-2,2-dichloro-N-[1-(fluoromethyl)-2-hydroxy-2-[4-methylsulfonyl) phenyl]ethyl]-acetamide
Manufacturer's code:	Sch 25298
Molecular formula:	$C_{12}H_{14}C_{l2}FNO_4S$
Molecular weight:	358.2
CAS Number:	73231-34-2
Chemical structure:	

Physical and Chemical Properties of Pure Active Constituent and TGAC

Appearance [1]	Fine white to off-white powder
Chemical purity [1]	99.5% (HPLC, area normalisation)
Enantiomeric purity [1]	S,R enantiomer < 0.1% (chiral HPLC)
Related compounds [1]	2 spots, total <0.5% (TLC); 3 minor peaks, total <0.5% (HPLC)
Melting point [1]	154.5-155.2°C
Specific rotation [1]	-16.7°
pH [1]	5.9
Moisture [1]	0.05% (Karl Fisher)
Heavy metals [1]	<0.001%
Residual isopropyl alcohol [1]	0.05%
Residue on ignition [1]	0.0%
Solubility [2] (mg/mL)	dichloromethane 4.8,; ethanol (USP) 31.8; ethyl acetate 22.9; methanol 86.7; 0.1N hydrochloric acid 1.3; 0.1N sodium hydroxide

	1.0; ethanol 25.8; propylene glycol 19.6; water 1.3; acetone >100; dimethylformamide >100; dimethylacetamide >100; dimethylsulfoxide >100; N-methylpyrrolidone >100
Dissociation constant [2]	No acidic or basic functional groups
Partition coefficient [2]	$K_{octanol/water} = 2.4$
Hygroscopicity [2]	Not hygroscopic, <0.5% moisture uptake after 2 weeks at 25°C/95% RH or 3 months at 35°C/75% RH.
Polymorphism [2]	Two polymorphs possible, I and II

1. Reference standard (batch 20811-31-1)
2. Batch identity not stated

Summary of the NRA's Evaluation of Florfenicol Active Constituent

The Chemistry and Residues Evaluation Section of the NRA has evaluated the chemistry aspects of florfenicol active constituent (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable. On the basis of the data provided it is proposed that the following minimum compositional standards be established for florfenicol:

Active constituent	***Specification***
florfenicol	Not less than 970 g/kg

Product

Distinguishing name:	Nuflor LA Injectable Solution
Formulation type:	Sterile injectable solution
Active constituent[s] concentration:	Florfenicol 300 mg/mL

Physical and Chemical Properties of the Product

Physical state:	Slightly viscous liquid
Colour:	Clear, light yellow to straw-coloured
Density or specific gravity:	1.161 g/mL
Storage stability:	Stability data provided by the applicant support a shelf life of 2 years when the product is stored below 25°C (air-conditioning) in glass or HDPE vials with bromobutyl rubber stoppers and aluminium seals.

Recommendation

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of Nuflor LA Injectable Solution is supported.

Toxicological Assessment

Summary
Although being a structural analog of two broad spectrum antibiotics used in human therapeutics, florfenicol is a new compound for veterinary use. Nuflor La Injectable Solution containing 300 mg/mL of florfenicol is intended for the treatment of bacterial infections in cattle and sheep.

Following ingestion, florfenicol and its metabolites were excreted in the urine and to a lesser extent in the faeces. Unchanged florfenicol and a number of metabolites were identified in the urine and faeces. Florfenicol has low acute oral and inhalational toxicity. It is not a skin irritant or sensitiser but is a slight eye irritant. Nuflor La Injectable Solution is likely to have a similar toxicity profile, however, the addition of additives in the formulation will probably cause it to be a slight skin irritant.

In repeat dose studies in rats, mice and dogs, the main adverse effects at high doses consisted of impaired red blood cell formation, increased liver weight, decreased liver enzymes/proteins, and damage to the male reproduction organs that was related to the duration of exposure. The incidence and severity of the functional changes in the testes of rats resulted in reduced male fertility.

In life-long exposure studies, a slightly higher incidence of non-malignant testicular interstitial cell tumours observed in rats was not considered to be predictive of an increased likelihood of cancer development in humans. Moreover, florfenicol was essentially negative in several special studies designed to detect its potential to damage genetic material. Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the use of Nuflor La Injectable Solution when used in accordance with the label directions.

Assessment of toxicology

The toxicological database for florfenicol 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 with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. 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 (ADI and ARfD) at which no adverse health effects in humans would be expected.

Metabolism and Toxicokinetics

When rats received oral doses for 7 days, the majority of florfenicol (52-68%) was excreted in the urine (higher in females than males) and a smaller portion (13-30%) in the faeces within 24 hour. Two hours after dosing on day 7, the highest concentrations were detected in the liver and kidneys, and the lowest in the brain. Unchanged florfenicol, florfenicol amine, florfenicol oxamic acid, and florfenicol alcohol, as well as their glucuronide conjugates and monochloroflorfenicol were identified in the urine and faeces. The metabolite profile in cattle and pigs was similar to that in rats.

Male dogs received oral doses of florfenicol at 0 or 200 mg/kg bw/day for 14 days. At 200 mg/kg bw/day, liver weights were increased. While aniline hydroxylase and benzphetamine N-demethylase activity remained unchanged, hepatic cytochrome P-450 content and 7-ethoxycoumarin o-deethylase activity were significantly lower than control.

Acute Studies

Florfenicol had low acute oral toxicity in mice and rats (LD_{50} > 2000 mg/kg bw). In an inhalation study with rats, no deaths occurred at the maximum attainable concentration of 280 mg/m^3. Florfenicol was slightly irritant to rabbit eyes, but not irritant to rabbit skin, and was not a skin sensitiser in a Maximisation test in guinea pigs.

Short-Term Studies

Rats received florfenicol at 250, 500 or 1000 mg/kg bw/day by gavage. Treatment was abandoned on day 8 because of severe toxicity at all doses. There was 1 death at 1000 mg/kg bw/day and 2 deaths at 500 mg/kg bw/day. Reduced food consumption, depressed body weight gain or weight loss, and clinical signs including defaecation, body surface staining, subdued behaviour and piloerection occurred in all groups. Severely distended abdomens and/or ataxia developed in all rats at 1000 mg/kg bw/day and in females at 500 mg/kg

bw/day. Enlarged caeca containing a green granular substance was revealed in almost all rats.

Rats received florfenicol at 50, 100 or 200 mg/kg bw/day by gavage for 14 days. Increased urination and defaecation, and head staining were observed in all groups. Reduced food intake and lower body weight gain were seen in females at 200 mg/kg bw/day. Liver weights were dose-dependently increased.

Rats received florfenicol at 0, 20, 65 or 200 mg/kg bw/day by gavage for 28 days. A dose-related incidence of piloerection, swollen abdomens and epistaxis was observed from week 2 onwards. Rats at 200 mg/kg bw/day also had dirty/sticky coats, abnormal gait, cyanosis and a lower food consumption and body weight gain. WBC count was reduced at all dose levels. Although reductions in RBC, Hb and Hct were only apparent at 200 mg/kg bw/day, cell morphology changes as shown by increases in MCV and MCH were observed in males at 65 mg/kg bw/day as well. There were higher plasma levels of urea nitrogen and cholesterol in treated males and a dose-related increase in albumin-globulin ratio in females. Plasma levels of glucose, creatinine and ALT in males, and iron and total iron binding capacity in females were reduced at all dose levels. At 200 mg/kg bw/day, small and flaccid testes with reduced weight were correlated with testicular atrophy, characterised by loss of seminiferous epithelium and/or lack of spermatogenesis in the epididymis. The incidence and severity of follicular atrophy of submandibular lymph nodes increased in a dose-related manner in treated groups and the number of reactive nodes reduced. Caecal enlargement was seen in all treated groups, and dilatation of the ileum, colon and caecum at 200 mg/kg bw/day. A mild reduction in the density of the bone marrow cells appeared at 200 mg/kg bw/day and in a single rat at 65 mg/kg bw/day.

There were no treatment related deaths in dogs given progressively increasing daily oral doses of florfenicol over 4 days (i.e. 160, 320, 640 and 1280 mg/kg bw/day). Clinical signs were limited to dogs at 1280 mg/kg bw/day in which soft stools and emesis were observed 3 to 5 hours after dosing.

Dogs received oral doses of florfenicol by capsule at 250 mg/kg bw/day for 14 days, or at 500 then 750 mg/kg bw/day for 7 days each followed by a 3-week recovery period. At 500 and 750 mg/kg bw/day, a yellow material appeared in faeces, reduced haemoglobin levels and morphological changes of red cells (anisocytosis, anisochromasia, polychromasia, normoblasts and Howell Jolly bodies) occurred, and lower levels of WBC or neutrophil counts were accompanied by myelocytes and metamyelocytes. Morphological changes of red cells were also seen at 250 mg/kg bw/day. All changes were resolved by recovery day 14.

Dogs received oral doses of florfenicol by capsule at 0, 25, 50, 100, 200 or 300 mg/kg bw/day for 28 days. Haemoglobin levels were lower at 200 and 300 mg/kg bw/day, and WBC and neutrophil counts were reduced at all dose levels. The ALT level was higher in the female at 300 mg/kg bw/day. Liver weights were increased in all treated dogs, with increased patchy hepatocyte fat accumulation in males at 200 and 300 mg/kg bw/day.

Long-term studies

Mice received florfenicol at 0, 10, 50, 200 or 400 mg/kg bw/day by gavage for 13 weeks. Mice at 400 mg/kg bw/day had increased liver weight with a higher incidence and more severe cytoplasmic vacuolation and/or haemorrhagic degeneration. Females at 400 mg/kg bw/day exhibited increased splenic weight and haematopoiesis. The only male decedent at

400 mg/kg bw/day showed congestion and necrosis of the caecal mucosa, damage to lymphocytes in the spleen and moderately severe bilateral nephropathy. No effects were observed at 200 mg/kg bw/day. Based on the limited parameters measured in this study, the establishment of a NOEL was not appropriate.

Mice received florfenicol at 0, 20, 100 or 200 mg/kg bw/day by gavage for 104 weeks. The incidence and severity of bilateral degeneration of the germinal epithelium in testes were increased at 200 mg/kg bw/day, which was associated with the reduction or absence of spermatozoa in epididymides. Focal coagulative necrosis developed in the liver with a higher incidence at 100 mg/kg bw/day and in males at 200 mg/kg bw/day. Incidences of hepatocellular adenoma and carcinoma in males at 100 and 200 mg/kg bw/day were higher than concurrent control, but within the range of historical control. The NOEL was 20 mg/kg bw/day.

Rats received florfenicol at 0, 10, 30 or 100 mg/kg bw/day by gavage for 13 weeks, with or without a following 4-week recovery period. Higher water consumption and lower body weight gain were observed at 100 mg/kg bw/day. Reduced levels of RBC, haemoglobin, WBC and neutrophils occurred in males at 100 mg/kg bw/day, along with increases in MCH and MCV. Lower plasma levels of total protein and bilirubin, and increased albumin/globulin ratio in both sexes, and lower levels of creatinine occurred in almost all treated groups. Reduced iron level and total iron binding capacity were observed in all treated female groups. At 100 mg/kg bw/day, kidney weights were increased, and in females, thyroid weights were higher and spleen weights were lower. Changes in the testes included: reduced testes weights in all treated groups; small and flaccid testes, complete atrophy of the seminiferous epithelium and absence of spermatogenesis at 100 mg/kg bw/day; and increased numbers of spermatogonia in the epididymis at 10 and 30 mg/kg bw/day. The treatment resulted in an increased incidence of follicular atrophy in submandibular lymph nodes in all treated groups, with reduced reactivity of lymph nodes in males at 100 mg/kg bw/day. Treatment also caused caecal distension at 30 and 100 mg/kg bw/day, and dilatation of ileum, caecum and colon of females at 100 mg/kg bw/day. Most of the changes were not reversed after the 4 week recovery period. A NOEL was not established. The LOEL was 10 mg/kg bw/day.

Rats received florfenicol at 0, 3, 12 or 48 mg/kg bw/day by gavage for 52 weeks. Females at 48 mg/kg bw/day showed laboured breathing and brown staining on the head/body. Food consumption and body weight gains were lower in males and females at 12 and 48 mg/kg bw/day. Slight lower RBC count, along with increases in MCH and MCV, was detected at 12 and 48 mg/kg bw/day. Neutrophil and WBC counts were sometimes lower at 12 and 48 mg/kg bw/day but with no evidence of a depression of activity in bone marrow. The total protein level was reduced at 12 (males) and 48 mg/kg bw/day, and the albumin-globulin ratio was correspondingly higher. Changes in testes included reduced weights and tubular atrophy in all treated groups and small/flaccid testes with spermatogenic cells in the epididymis at 12 and 48 mg/kg bw/day. Kidney weights were increased at 12 (females) and 48 mg/kg bw/day. No NOEL was established. The LOEL was 3 mg/kg bw/day.

Rats received florfenicol at 0, 3, 12 or 48 mg/kg bw/day by gavage for 104 weeks. Mortality in females at 48 mg/kg bw/day was higher during the first year. Red/brown staining in the head/body were more frequent at 12 (males) and 48 mg/kg bw/day. Body weight gain was lower in females at 48 mg/kg bw/day. Slightly higher levels of MCH and MCV occurred at 48 mg/kg bw/day, and neutrophil and WBC counts were lower in males at 48 mg/kg bw/day. There was no evidence of depressed activity in bone marrow. Higher incidences of pale cell

foci or patches in the liver were observed in males of all treated groups with increased severity at 48 mg/kg bw/day. The incidence of spongiosis hepatitis was higher in males at 48 mg/kg bw/day. Some females at 48 mg/kg bw/day developed progressive retinal degeneration or tracheal epithelial erosion/ulceration. Pathological changes in testes included: small/flaccid testes at 12 and 48 mg/kg bw/day; tubular atrophy and aspermatogenesis in all treated groups; spermatogenic cells in the epididymis at 12 and 48 mg/kg bw/day; interstitial cell hyperplasia at 48 mg/kg bw/day, and a higher incidence of interstitial cell tumours at all dose levels (exceeding historical control at 3 and 48 mg/kg bw/day). The presence of testicular tumours were correlated to that of tubular atrophy. No NOEL was established. The LOEL was 3 mg/kg bw/day.

Dogs received oral doses of florfenicol in capsules at 0, 10, 30 or 100 mg/kg bw/day for 13 weeks. Lower levels of haemoglobin, RBC, WBC and neutrophil counts occurred at 100 mg/kg bw/day, and to a lesser extent, at 30 and 10 mg/kg bw/day. One male at 100 mg/kg bw/day developed bone marrow hypoplasia, reduced numbers of later normoblasts and an altered myeloid : erythroid ratio. Lower plasma ALT and bilirubin levels and higher cholesterol levels were detected at 30 and 100 mg/kg bw/day. Dogs at 100 mg/kg bw/day had lower prostate weights, and lower testes weights along with tubular atrophy, epithelial vacuolation, absence of mature spermatids, and/or multinucleate cells in the lumen. Increased liver weight and hepatocyte enlargement were observed in all treated groups, and increased kidney weight was associated with slight tubular dilatation in males of all treated groups. Vacuolation was seen in the granular layer of the cerebellum at 30 and 100 mg/kg bw/day, and in the grey matter of the spinal cord in all treated groups. No NOEL was established. The LOEL was 10 mg/kg bw/day.

Dogs received oral doses of florfenicol in capsules at 0, 1, 3 or 12 mg/kg bw/day for 13 weeks with a 4-week recovery period in some dogs at 0 and 12 mg/kg bw/day. A trend towards reduction in total WBC and neutrophil counts was detected in females of treated groups, with biological significance at 12 mg/kg bw/day, and the changes were reversed by week 17. Liver weight was increased at 12 mg/kg bw/day. Testicular weight was reduced in 1 male at 12 mg/kg bw/day, with focal tubular atrophy, impaired spermatogenesis and vacuolation in the epididymal epithelium. Some dogs at 12 mg/kg bw/day had mild focal inflammatory cell infiltration in the skeletal muscle, or slight acinar atrophy in the pancreas. The NOEL was 3 mg/kg bw/day.

Dogs received oral doses of florfenicol in capsules at 0, 1, 3 or 12 mg/kg bw/day for 52 weeks. Body weight gain in males at 3 and 12 mg/kg bw/day was lower. Liver weight was increased at 3 and 12 mg/kg bw/day, and combined cytoplasmic rarefaction in the liver was increased in males at 12 mg/kg bw/day. Mild cystic epithelial hyperplasia of the gall bladder mucosa occurred at 3 and 12 mg/kg bw/day. Slight changes in the testes included unilateral localised impacted tubules, vacuolation of epididymal epithelium, and/or solitary cysts in some males of the 3 and 12 mg/kg bw/day groups. The NOEL was 1 mg/kg bw/day.

Reproduction and Developmental Studies

In a dose-finding study, male rats received 0, 10, 20, 40 or 65 mg/kg bw/day of florfenicol by gavage from 63 days prior to mating, then through 2 consecutive 7-day mating periods. The females were untreated. Body weight gain at 65 mg/kg bw/day was slightly lower. No females were impregnated at 40 and 65 mg/kg bw/day and only 1 male (8%) was able to impregnated a female in the 20 mg/kg bw/day group. Testes weight at 65 mg/kg bw/day and epididymis

weight at 20 and 65 mg/kg bw/day were lower, and enlarged and/or discoloured epididymides were seen at 20 and 40 mg/kg bw/day.

In a dose-finding study, female rats received 0, 10, 20, 40 or 65 mg/kg bw/day of florfenicol by gavage from 2 weeks prior to mating, through to lactation day 14. The males were not treated. Slightly increased body weight gains were seen in all treated groups. Pregnancy rates and gestation were unaffected. There was a trend towards a dose-related reduction of pup survival in all treated groups during lactation days 0-4, and mean pup weights at 65 and 40 mg/kg bw/day were lower during lactation week 1.

Rats received 0, 1, 3, or 12 mg/kg bw/day of florfenicol by gavage for two generations (F0; F1), each generation undergoing 2 successive breeding cycles (F1a & F1b; F2a & F2b). In F0 and F1b parents, 1-3 rats at 3 and 12 mg/kg bw/day had swollen abdomens. Body weight gain of F0 and F1b females was lower at 12 mg/kg bw/day during various stages of the study, but was higher in all treated groups during the lactation period. Water consumption for F0 males at 12 mg/kg bw/day and F1b males at 3 and 12 mg/kg bw/day was slightly higher. Epididymides weights for F0 and F1b males at 12 mg/kg bw/day were lower. Pregnancy rates were slightly reduced for F0 females at 12 mg/kg bw/day but gestation was unaffected. Treated F2a and F2b litters had a lower survival rate during lactation, without any apparent dose-relationship. F2a and F2b pup weights at 12 mg/kg bw/day were lower at birth and during lactation week 1. The NOEL was 3 mg/kg bw/day for parental and reproduction toxicity and in offspring.

In a dose-range finding study, assumed pregnant mice received oral doses of florfenicol at 0, 50, 100, 200 or 400 mg/kg bw/day during pregnancy days 6-15. Water consumption was increased at 100 mg/kg bw/day and above. Lower body weight gain foe dams at 400 mg/kg bw/day was likely attributed to increased late embryo and foetal deaths. Mean foetal weight at 400 mg/kg bw/day was also lower.

Assumed pregnant mice received oral doses of florfenicol at 0, 40, 120 or 400 mg/kg bw/day during pregnancy days 6-15. At 400 mg/kg bw/day, water consumption was increased, and body weight gain was lower due to late embryo and foetal deaths (3 litters were completely resorbed). Retarded skeletal ossification was extensive and severe at 400 mg/kg bw/day, less pronounced at 120 mg/kg bw/day, and at a slightly higher incidence than control at 40 mg/kg bw/day. The retarded litters at 120 and 400 mg/kg bw/day had lower mean foetal weights. Florfenicol did not show teratogenic effects. No NOEL for embryo and foetal toxicity was established. The LOEL was 40 mg/kg bw/day.

Assumed pregnant mice received oral doses of florfenicol at 0, 1, 3 or 60 mg/kg bw/day during pregnancy days 6-15. There were no treatment-related maternal or foetal effects at 60 mg/kg bw/day except slightly higher water consumption. No developmental effects were observed. Based on effects observed at 40 mg/kg bw/day in the above mouse study, the NOEL for developmental toxicity was 3 mg/kg bw/day.

In a dose-range finding study, assumed pregnant rats received oral doses of florfenicol on pregnancy days 6-17, at 0, 110, 150, 190 or 230 mg/kg bw/day, and 0, 20, 40, 65 or 100 mg/kg bw/day in 2 separate studies. Treatment-related deaths occurred at 190 and 230 mg/kg bw/day. Clinical signs (staining, piloerection, pale eyes or dyspnoea, gastro-intestinal disturbance and vagina bleeding) were observed at 110 mg/kg bw/day and above. In all treated groups, food consumption was reduced and water consumption was increased. Body

weight gains were lower at 65 mg/kg bw/day and above in association with death of some or all implants. No litter survived at 150 mg/kg bw/day and higher. Litters in the dose range of 40 to 110 mg/kg bw/day had lower foetal weight. No treatment-related structural changes in pups were observed. Maternal toxicity occurred at all dose levels. There were no effects on embryo development and foetal growth at 20 mg/kg bw/day.

Assumed pregnant rats received oral doses of florfenicol at 0, 4, 12 or 40 mg/kg bw/day during pregnancy days 6-17. Food consumption was reduced and water consumption was increased at 12 and 40 mg/kg bw/day at the beginning of the dosing period. At 40 mg/kg bw/day, mean foetal weight was lower. Retardation in ossification of sternebrae, metacarpals, pelvis thoracic centra and sacral and caudal vertebrae was noticed at 40 mg/kg bw/day, and to a less extent at 12 mg/kg bw/day. The NOEL was 4 mg/kg bw/day for maternal toxicity and developmental toxicity. There was no evidence of teratogenicity.

In a dose-finding study, non-pregnant female rabbits received oral doses of florfenicol at 0.5, 2 or 20 mg/kg bw/day for 13 days. Dosing at 20 mg/kg bw/day was discontinued on day 3 due to remarkably reduced food consumption and body weight gain. Almost all rabbits at 0.5 and 2 mg/kg bw/day also had reduced food consumption and body weight loss. The rabbit was not considered to be a suitable model for a teratogenicity study of florfenicol.

Genotoxicity Studies

Florfenicol was not genotoxic in a range of tests which included an Ames test; forward gene mutation tests on TK locus in L5178Y mouse lymphoma cells; an *in vivo* mouse bone marrow micronucleus test and an *in vivo* mouse bone marrow chromosome aberration assay; and an *in vitro* unscheduled DNA synthesis study in primary rat hepatocytes. In an *in vitro* chromosome aberration assay with CHO cells, florfenicol showed a clastogenic effect at 2500 □g/ml (a cytotoxic dose) and induced endoreduplication at 1250 and 2500 □g/ml, in the presence of S9 metabolic activation system.

Public Health Standards

Poisons Scheduling

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

On the basis of its toxicity and use pattern, the NDPSC has included florfenicol in schedule 4 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), which restricts its availability to supply only on the prescription of a veterinarian. There are provisions for appropriate warning statements and first-aid directions on the product label.

NOEL/ADI

The Acceptable Daily Intake is that quantity of an agricultural compound which can safely be consumed on a daily basis for a lifetime and is based on the lowest NOEL obtained in the most sensitive species. This NOEL is then divided by a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The ADI for florfenicol was established at 0.001 mg/kg bw/day based on a NOEL of 1 mg/kg bw/day in a 12-month dog study and using a safety factor of 1000. This safety factor was chosen because there was no NOEL in the 2-year study in rats. The ADI provides a safety factor of 3000 for the LOEL for testicular toxicity in rats, which is considered to provide an adequate margin of safety.

Acute Reference Dose (ARfD)

The acute reference dose is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated, event. The ARfD is derived from the lowest single or short term dose which causes no effect in the most sensitive species of experimental animal tested, together with a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

Since structural analogs of florfenicol are used in human therapeutics, there is a considerable body of information about the acute effects of antibiotics in this class. Antibiotics in this class are therapeutically administered at doses of about 50 mg/kg bw/day. Consequently, it is considered that establishing an ARfD for florfenicol is not required.

Residues Assessment

Summary

Studies of the metabolism of florfenicol in animals (rats, cattle and pigs) indicated that florfenicol, along with its metabolites florfenicol amine, florfenicol alcohol, florfenicol oxamic acid and monochloroflorfenicol were the predominant components of residues in edible commodities. A suitable analytical method was presented to enable the establishment of a residue definition incorporating all of the major components of the residue. Data concerning the metabolism of florfenicol in animals, and the occurrence of residues in edible cattle (cattle meat, cattle liver, cattle kidney and cattle fat) and pig commodities (pig meat, pig liver, pig kidney and pig fat/skin) were considered as part of the residue evaluation of the application.

Residue trial data presented for edible cattle commodities (cattle meat, cattle liver, cattle kidney and cattle fat) and edible pig commodities (pig meat, pig liver, pig kidney and pig fat/skin) allowed the recommendation of suitable MRLs.

Registration of *Nuflor™ LA Injectable Solution* is unlikely to pose an undue risk to human health.

Metabolism

Studies were presented addressing florfenicol pharmacokinetics in cattle and pigs and radioactive residue distribution and metabolite profiling in rats, cattle, and pigs. Florfenicol was rapidly excreted in urine. Florfenicol and its metabolites were widely distributed throughout the body following IM administration to cattle. In cattle and pigs, apart from residues at the injection site, most residues were found in liver. In one study with cattle and another with pigs the major metabolites found, other than parent compound were the amine, alcohol and oxamic acid of florfenicol, along with monochloroflorfenicol, indicating metabolism via oxidative, reductive and hydrolytic mechanisms. Distribution of the total radioactive residue (TRR) between metabolites varied with time in liver and kidney of both cattle and pigs. The sum of florfenicol and florfenicol amine accounted for the majority of the residue in cattle, while florfenicol alcohol and florfenicol oxamic acid were also present in significant quantities in pigs.

Analytical methods

Validated methods were presented for the quantitation of florfenicol residues in bovine and pig tissues. Those methods involved acid digestion, which quantitatively converted florfenicol and its major metabolites florfenicol alcohol, florfenicol oxamic acid and monochloroflorfenicol to florfenicol amine. Ethyl acetate extraction and clean up by solid phase extraction occurred prior to analysis by HPLC.

Data indicated that the method extracted > 70% of the TRR from all relevant tissue types. There was little effect of time after dosing on extractability. It was demonstrated that the method converted more than 89% of florfenicol and its major metabolites (florfenicol alcohol, florfenicol oxamic acid and monochloroflorfenicol) to florfenicol amine. Thus changes in partitioning of the residue between the metabolites over time will not greatly affect the utility of the method.

Experimental LOQ's of 0.10 mg/kg florfenicol amine were routinely attained in bovine and pig liver, kidney, fat and muscle tissue, and pig skin with adhering fat, although lower experimental LOQ's were attained (eg 0.025 mg/kg in liver, 0.01 mg/kg in muscle) in a number of cases.

Recoveries of florfenicol amine from fortified tissue samples were high and reproducible. Recoveries were routinely in the range of 80 – 110% in all relevant tissue types. Accuracy, precision and linearity of the method were acceptable. It was demonstrated that many common veterinary drugs and compounds related to florfenicol did not significantly interfere with the method.

A satisfactory LC/MS method was presented for confirmation of the presence of florfenicol amine in bovine and pig tissues.

The acid digestion / ethyl acetate extraction / HPLC methods presented are suitable for the quantitation of florfenicol amine in tissues from cattle and pigs.

Residue definition

After consideration of the metabolism of florfenicol and the analytical methodology, the establishment of the following residue definition for florfenicol is appropriate:

Florfenicol	Sum of florfenicol and its metabolites florfenicol alcohol, florfenicol oxamic acid, monochloroflorfenicol and florfenicol amine expressed as florfenicol amine.

Residues

Cattle

Data from 4 studies with cattle were submitted to support MRLs in cattle, 3 of those using IM (intermuscular) administration and 1 using SC (subcutaneous) administration. The applicant proposed separate withholding periods for IM and SC administration of 30 and 35 days respectively. Dual withholding periods were not considered appropriate, as the data for liver and injection sites indicate that residue decline is similar for the two administration routes. When the appropriate withholding period is in the order of weeks, the withholding period is usually established as an even number of weeks to ease management of treated stock. Thus a withholding period of either 35 or 42 days was considered.

In the case of an injectable product, residues at injection sites must be considered in addition to meat at non-injection sites. While the data indicate that at 35 days and thereafter the meat and injection site residues were below the applicants proposed MRL of 0.2 mg/kg, several injection site residues approached 0.2 mg/kg. The MRL proposal was considered appropriate from dietary intake and trade perspectives. However, at the immediately preceding sampling point in the SC trial of 28 days the maximum injection site residue was > 20 mg/kg. Hence it is considered that the sample sizes were too small to have a high degree of certainty that all injection site residues will be below the proposed MRL at 35 days. Thus *a slaughter withholding period of 42 days is appropriate for the proposed use of Nuflor injectable via either IM or SC injection.*

The highest observed injection site residue did not exhibit a large decline between day 30 and day 42, with the highest observed injection site residues at 42 days being 0.18 mg/kg, just below the proposed MRL, indicating that at a withholding period of 42 days some injection site residues will probably be greater than the proposed MRL of 0.2 mg/kg. Thus a *cattle meat*

MRL of 0.3 mg/kg is appropriate to cover residues arising from the proposed use of *Nuflor injectable* via either IM or SC injection.

The applicant proposed an *edible offal of cattle* MRL of 3.0 mg/kg, in line with the cattle liver MRLs established in other countries. The residue data indicate that a lower MRL is not appropriate, as the highest observed residue at 42 DAT was 2 mg/kg. The magnitude of the applicant's proposed MRL is acceptable. However, as the observed residues in kidney are much lower than those observed in liver, separate MRLs should be established for liver and kidney. *Thus a florfenicol MRL of 3.0 mg/kg for cattle liver is appropriate to cover residues arising from the proposed use.*

The maximum residue in kidney 42 days after SC administration was 0.19 mg/kg. To allow for biological variability *a cattle kidney MRL for florfenicol of 0.5 mg/kg is appropriate.*

Residues of florfenicol in cattle fat at the recommended withholding periods were less than the LOQ. The establishment of a florfenicol MRL in cattle fat is not required.

Milk residue data and starter culture studies have not been presented. Thus the applicants proposed milk withholding period statement (below) is appropriate.

> *MILK: DO NOT USE in female cattle which are producing or may in the future produce milk or milk products for human consumption.*

In most of the submitted studies a maximum of 10 mL of product was administered at each injection site. Thus *the label advice to limit single injections to 10 mL under SC administration should be extended to include IM administration.*

Pigs

Data were presented from 2 trials to support the use on pigs. One trial involved the analysis of pooled samples from a metabolism study and the other involved pigs dosed at varying rates (~ 13 to 20 mg/kg, *c.f.* label rate of 15 mg/kg). The applicant has proposed florfenicol MRLs of 2 mg/kg for pig meat and 3 mg/kg for edible offal with a slaughter withholding period of 6 days.

The recommended treatment for acute respiratory conditions includes the movement of the pig to a hospital pen for recovery[1]. The condition must have improved prior to sale, and, for carcass quality reasons, the industry recommends that administration of injectables should be avoided within a month of slaughter[1]. Therefore, a WHP of longer than 6 days was considered appropriate for the injectable product in pigs.

MRLs must be established at levels that do not prejudice human health. Pig meat makes a large contribution to the estimated dietary intake of florfenicol residues, and a partial NEDI (National Estimated Daily Intake) calculation, considering only pig meat containing florfenicol amine residues at the proposed MRL of 2 mg/kg, accounted for 85% of the ADI at a slaughter withholding period of 6 days. Such an MRL would preclude registration of one of the proposed uses on dietary grounds. Hence a different MRL / WHP combination was considered necessary.

At a withholding period of 15 days, the highest observed muscle residue was 0.07 mg/kg and the highest observed injection site residue was 0.19 mg/kg. Similarly, at a withholding period of 12 days, the highest observed muscle residue was 0.08 mg/kg (pooled sample) and the highest observed injection site residue was 0.23 mg/kg (injection site residues were not determined in the metabolism study). As the available dataset is limited, the dose rate variable (~ 13 to 20 mg/kg in the residues trials, *c.f.* label rate of 15 mg/kg) and sample pooling masks

[1] Pig Research and Development Corporation (1995). *The Good Health Manual for Pigs.*

variability, reasonable allowance must be made for both the variation in dose and biological variability. *A florfenicol amine MRL of 0.5 mg/kg in pig meat is appropriate to support the use of Nuflor Injectable in pigs. A slaughter withholding period of 12 days should be observed to ensure compliance of meat and injection site residues with the MRL.*

At a slaughter withholding period of 12 days, a *florfenicol amine MRL of 3 mg/kg in pig liver is appropriate to cover the residues arising from the proposed use.* Similarly, *a florfenicol amine MRL of 1 mg/kg in pig kidney is appropriate to cover the residues arising from the proposed use.*

Residue data for pig fat, pig skin, and pig skin + fat were presented. The majority of the data is skin + fat, the only data presenting skin and fat separately were from the metabolism trial where only pooled data are available. Residues in the skin + fat fraction showed no sign of depletion over the experimental period. The octanol/water partitioning coefficient suggests that florfenicol is hydrophilic and thus should not accumulate in fat, as supported by the cattle data and the data from the first pig study. Thus the residue in the skin + fat fraction is most likely associated with the skin. Pig skin with adhering fat is a commodity that moves in trade and thus MRL establishment is warranted. *A florfenicol amine MRL of 1 mg/kg in pig fat/skin is appropriate to cover the residues arising from the proposed use.*

Estimated dietary intake

The chronic dietary risk is estimated by a calculation encompassing all registered/temporary uses of the chemical and dietary intake data from the 1995 National Nutrition Survey of Australia. The NEDI (National Estimated Daily Intake) calculation is made in accordance with the Guidelines for Predicting Dietary Intake of Pesticide Residues (revised) (WHO, 1997). The calculation reflects the maximum residue levels in commodities. The NEDI for florfenicol (florfenicol amine) is equivalent to 54% of the ADI. This calculation is considered to be a gross overestimate of the actual consumption of florfenicol as it assumes all slaughtered animals are treated and contain residues at the MRL. It is concluded that the chronic dietary exposure is less than the ADI and the risk is acceptable.

Neither the Department of Health of Aged Care (TGA) nor the JECFA have set an acute reference dose (ARfD) for florfenicol. The TGA concluded that there was no requirement for the establishment of an acute reference dose as structural analogues of florfenicol have a long history of therapeutic use without acute affects. As a consequence, no assessment of the acute dietary exposure to florfenicol can be undertaken at this time.

Bioaccumulation potential

The octanol/water partitioning coefficient (Kow) of florfenicol is 2.36, giving a log Kow of 0.4, suggesting that florfenicol is hydrophilic. The residue data presented support that conclusion and florfenicol does not accumulate in fat.

Recommendations

Registration of the product

The Chemistry and Residues Program (CRP) has evaluated the residues aspects of *Nuflor™ LA Injectable Solution.* The CRP has considered the available metabolism, residue trials, analytical methodology, and fate in storage and processing data, including that submitted by Schering-Plough Animal Health Limited to support their application to register a new injectable product for use in cattle and pigs. The CRP is satisfied that the residues aspects of Section 14(5) Agricultural and Veterinary Chemicals Codes have been met for *Nuflor™ LA Injectable Solution.*

Recommended amendments to the MRL Standard

1. The following amendments to Table 1 of *The MRL Standard* are recommended:

Compound	Food	MRL (mg/kg)
ADD		
Florfenicol		
MM0182	Cattle meat	0.3
MO1280	Cattle kidney	0.5
MO1281	Cattle liver	3
MM0818	Pig meat	0.5
MO1284	Pig kidney	1
MO1285	Pig liver	3
	Pig fat/skin	1

2. The following amendment to Table 3 of *The MRL Standard* is recommended:

Compound	Residue
ADD	
Florfenicol	Sum of florfenicol and its metabolites florfenicol alcohol, florfenicol oxamic acid, monochloroflorfenicol and florfenicol amine expressed as florfenicol amine.

The following withholding period statements are recommended in relation to the above MRLs for *Nuflor™ LA Injectable Solution*.

WITHHOLDING PERIODS

CATTLE:
MILK: DO NOT USE in female cattle which are producing or may in the future produce milk or milk products for human consumption.
MEAT: DO NOT USE less than 42 days before slaughter for human consumption.

PIGS:
MEAT: DO NOT USE less than 12 days before slaughter for human consumption.

Commodities exported and markets

Cattle: In 2000 Australia produced ~2025 kt of beef and veal product with ~1329 kt of that being exported[2]. The major export destinations for Australian beef and veal are shown in Table 1 and live cattle export destinations in Table 2.

Table 1 Top ten export destinations for Australian beef and veal in 2000[2].

	kt	$m	% of total (volume)
USA	352.4	1173	39
Japan	325.7	1537	36
Korea, Rep of	73.3	221.7	8
Canada	41.5	148	5
Taiwan	28.6	117	3
Philippines	14.3	34	2
Indonesia	13.1	41	1
PNG	7.1	14	1
EU	5.6	37	1
Malaysia/Singapore	5.5	35	1
Total (all markets kt & $)	901.6	3466	

Table 2 Export destinations for Australian live (slaughter) cattle in 2000[2].

	'000	$m (fob)[a]	% of total (volume)
Indonesia	296.7	143.1	33
Philippines	223.8	117.8	25
Egypt	207.6	129.7	23
Malaysia	56.5	25.7	6
Japan	14.4	9.8	2
Other	88.2	45.6	10
Total live cattle	887	471.7	
[a] free on board			

Pigs: In 2001 Australia produced ~379 kt of pig meat with ~56 kt of that being exported with a value of about $A247 m[3]. The value of Australian pig meat exports has increased significantly in the last 10 years, from a value of ~$A 30 m in 1992. Exports of pig offal are also significant, forming ~11% of total pig product exports in 1999[4]. The major markets for Australian pig meat are summarised in Table 3, and liver and other offals in Table 4 and Table 5.

Table 3 Top ten export destinations for fresh or frozen Australian pig meat in 1997/98[5] and 2000[6].

	1997/98			2000		
	t	$m	% of total (volume)	t	$m	% of total (volume)
Japan	4676	23.29	32	6641	40.95	17
Russian Federation	2219	4.70	15			
New Zealand	1734	5.84	12	2121	5.6	5
Hong Kong	979	1.77	7	864	3.6	2
Germany	861	5.21	6	1039	5.4	3
Philippines	766	1.08	5	150	0.18	<1
France	759	4.68	5	914	4.6	2
Netherlands	529	3.64	4	297	0.28	1
China	373	0.47	3	225	0.29	1

[2] ABS. Australian Commodity Statistics 2001
[3] http://www.pork.gov.au/statistics.htm 15/11/02
[4] http://www.pork.gov.au/Pigstats/131.pdf, Pigstats '99, 15/11/02
[5] PRDC/APC, Australian Pig Industry handbook – PigStats98.
[6] ABS International Trade, Supplied by the Australian Pork Council

Republic of Korea	209	0.76	1	1067	3.6	3
Singapore				24551	90.5	63
Total (all markets t & $)	14449	55	91	39006	160	97

Table 4 Top ten export destinations for frozen Australian pig liver in 2000[6].

	t	$ '000	% of total (volume)
Philippines	169	185	40
Russian Federation	82.9	66.5	20
USA	34	61.4	8
Hong Kong	16	51.1	4
Singapore	19.3	47.3	5
Malaysia	30.4	36.4	7
Indonesia	19	20.9	4
Gabon	16.3	16.7	4
Yemen	17.5	14.9	4
Cote d'Ivoire	18	14.7	4
Total (all markets t & $)	425	518	99

Table 5 Top ten export destinations for Australian pig offal (other than liver) in 2000[6].

	t	$ '000	% of total (volume)
Hong Kong	297	412	19
Philippines	297	389	19
Russian Federation	203	733	13
Taiwan	118	272	8
Thailand	98	75	6
Cote d'Ivoire	90	85	6
Indonesia	69	200	4
Congo	52	43	3
USA	49	237	3
Samoa	33	34	2
Total (all markets t & $)	1563	2927	84

Current overseas registration status

Florfenicol has approved uses (October 2002) as an injectable for cattle in Argentina, Austria, Belgium, Brazil, Canada, Chile, Colombia, Costa Rica, Czech Republic, Denmark, Egypt, El Salvador, Finland, France, Germany, Greece, Guatemala, Hungary, Ireland, Israel, Italy, Jamaica, Jordan, Lebanon, Luxembourg, Malaysia (no registration requirement), Mexico, Morocco, Netherlands, New Zealand, Panama, Paraguay, Peru, Poland, Portugal, Saudi Arabia, Slovak Republic, South Africa, Spain, Switzerland, Turkey, United Kingdom, USA, Uruguay and Venezuela.

Table 6 International MRLs/tolerances of florfenicol amine in cattle tissue, as supplied by applicant unless otherwise noted (October 2002). The residue definition in the EU is the same as that proposed for Australia and the marker residue in the USA is florfenicol amine.

Country	MRL/Tolerance				WHP
	Muscle	Fat	Liver	Kidney	(injectable, days)
Australia	0.3	-	3	0.5	42
Argentina	0.8	-	3	0.4	
Brazil	0.3	0.5	2	0.5	28IM/38SC
Canada	-	-	2	-	
EU[a]	0.2	-	3	0.3	30IM/44SC 45 Denmark 55 The Netherlands
Mexico	0.3	0.5	2	0.5	28IM/38SC
New Zealand	0.1	0.3	3	0.3	28
Philippines	0.3	0.5	2	0.5	28IM/38SC
South Africa[b]	0.2	-	3	0.3	42
Spain	0.8	-	3	0.4	
USA[c]	0.3	-	3.7	-	28IM/38SC

[a] WHP in UK, pers. comm. C Abbott VMD
[b] pers. comm. Prof. GE Swan
[c] 63 FR 41191, Aug. 3, 1998

Florfenicol has approved uses (October 2002) as an injectable for pigs in Austria, Belgium, Brazil, Finland, France, Germany, Greece, Italy, Japan, Luxembourg, Malaysia (no

registration requirement), Mexico, New Zealand, Panama, Portugal, Spain and Venezuela. Additionally, countries with oral uses that do not have currently approved injectable uses include Denmark, Ireland, The Netherlands and the United Kingdom.

Table 7 International MRLs/tolerances of florfenicol amine in pig tissue, as supplied by applicant unless otherwise noted (October 2002). The residue definition in the EU is the same as that proposed for Australia and the marker residue in the USA is florfenicol amine.

Country	MRL/Tolerance				WHP
	Muscle	Fat/skin	Liver	Kidney	(injectable, days)
Australia	0.5	1	3	1	12
Brazil	0.3	0.5	2	0.5	9
Canada - Currently under evaluation					
EU[a]	0.3	0.5	2	0.5	14[b]
Japan	-	-	-	-	21
Mexico	0.3	0.5	2	0.5	9
New Zealand	0.1	0.3	3	0.3	7
USA - Currently under evaluation	0.2[c]	-	2.5[c]	-	11[c]

[a] Recommended by EMEA (EMEA/MRL/591/99-FINAL)
[b] Austria, Belgium, France, Finland, Germany, Greece, Italy, Luxembourg, Portugal, Spain
[c] Proposed

The use pattern is similar in all countries having approved uses, although not all indications are approved in all countries.

Codex

Application has not been made to Codex for consideration of florfenicol.

Risks to trade

Florfenicol has not been considered by Codex or JECFA. Export of treated produce containing finite (measurable) residues of florfenicol may prejudice Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

Cattle: Appropriate tolerances for florfenicol are established in the major beef export markets of the USA, Canada, the Philippines and the EU. In addition, uses of florfenicol in cattle are established in Malaysia. The major export markets of Japan, Korea, Taiwan, Indonesia and PNG are not known to have appropriate tolerances established for cattle product. The risk associated with the Japanese market is lessened somewhat by the existence of an approved use in pigs with an associated residue tolerance. However, as finite residues are expected at the proposed withholding periods the potential for undue trade prejudice exists.

Pigs: Appropriate tolerances for florfenicol are established in the major pig product export markets of Japan, New Zealand and countries of the EU. In addition, uses of florfenicol in pigs are established in Malaysia. The major export markets of the Russian Federation, Hong Kong, China and Korea are not known to have appropriate tolerances established for pig product. As finite residues are expected at the proposed withholding periods the potential for undue trade prejudice exists.

The applicant has proposed an export slaughter interval (ESI) of 15 days for pigs. It is noted, for both cattle and pigs, that data demonstrating the decline of residue concentrations to the LOQ have not been supplied for all tissues. At this stage, the pig industry has yet to accept an ESI as an effective method of managing trade risks.

Before registration of Nuflor™ LA Injectable Solution is finalised, the relevant Industry bodies will consulted to:

1. Determine the significance of the potential risks for trade in cattle and pig product, and,
2. Assess appropriate management strategies to mitigate the perceived risk associated with the use of Nuflor™ LA Injectable Solution in cattle and pigs.

Occupational Health and Safety Assessment

Both the product, Nuflor LA Injectable Solution and the active, Florfenicol are manufactured and formulated overseas. Therefore, Australian workers can only be exposed to the end-use product. These workers include veterinarians, farmers and their employees, and piggery workers.

Preparations for injection containing florfenicol are included in Schedule 4 of the *Standard for Uniform Scheduling of Drugs and Poisons*. Therefore professional advice is required prior to antibiotic administration to food-producing animals.

Based on its toxicity profile, florfenicol cannot be classified as hazardous according to NOHSC *Approved Criteria for Classifying Hazardous Substances* [NOHSC: 1008 (1999)].

Based on the concentration of the ingredient, N-methyl-2pyrrolidone, in the product, Nuflor LA Injectable Solution is classified as hazardous according to NOHSC Criteria. The following risk phrases apply to this non-active constituent: R36-38:
Irritating to eyes and skin.

The Material Safety Data Sheet should be provided to Australian workers, and should contain a statement of hazardous nature and reflect this classification.

Worker exposure has been assessed. Exposure to Nuflor LA Injectable Solution could occur if vials were broken or by accidental self-injection. Such occurrences are not considered to be likely or to present a significant risk to workers.

NOHSC supports the registration of Nuflor LA Injectable Solution containing 30% florfenicol for use in veterinary applications.

The product is to be used under the prescription of veterinarians, trained in injection techniques.

Environmental Assessment

Introduction

Schering-Plough Animal Health Limited has applied for the registration of a new product *Nuflor™ LA Injectable Solution* containing the new active constituent florfenicol. The product is proposed for use in the treatment of cattle with bacterial infections susceptible to florfenicol, especially the causative organisms of pinkeye, bovine respiratory disease (BRD) and footrot, and in the treatment of pigs with swine respiratory disease.

Florfenicol is a synthetic, broad-spectrum antibiotic against many gram-negative and gram-positive bacteria isolated from domestic animals. Florfenicol acts by inhibiting bacterial protein synthesis at the ribosomal level.

Environmental Fate

Florfenicol is proposed for use in cattle for the treatment of BRD, footrot and pink-eye by intramuscular injection of 20 mg florfenicol/kg bw twice at a 48 h interval or by a single dose of subcutaneous injection at 40 mg florfenicol/kg bw. For swine, the product is proposed to be administered by intramuscular injection of 15 mg florfenicol/kg bw twice at a 48 h interval. The main exposure will result from disposal of pigs/cattle wastes containing approximately 65% of the original dose as unchanged drug.

Animal Metabolism

Metabolism studies of florfenicol indicated that excreta will consists mainly the unchanged parent compound following intramuscular/subcutaneous injection of florfenicol to cattle and pigs. The majority of the dose is recovered in urine (63-71% in cattle; 46-62% in pigs) and faeces (6-9% in cattle; 8-14 % in pigs). The major components found in urine and faeces were florfenicol and monochloroflorfenicol, respectively. Three major metabolites were identified: florfenicol alcohol, florfenicol oxamic acid and florfenicol amine.

Photolysis

Results from the aqueous photolysis of florfenicol indicate that florfenicol is not photodegradable except at pH 9 where its half-life is determined to be 98.4 days. Photolytic half-lives for florfenicol alcohol, florfenicol oxamic acid and florfenicol indicate that these metabolites are relatively photodegradable.

Biodegradation-aerobic

The aerobic biodegradation of florfenicol in manured-amended soils indicates that florfenicol undergoes both primary biodegradation with half-lives of 1-4 weeks, and mineralisation to CO_2 with half-lives of 3-9 months. Production of volatile organic compounds did not exceed a mean cumulative % of 0.1% in any soil type. Significant residues presumably metabolites remained bound to the soils. No identification of the metabolites were performed but HPLC indicates none was >10%. Thus florfenicol will not persist in soil.

Results from the 28-day aerobic aquatic biodegradation studies with florfenicol and its metabolites indicated that complete degradation of these compounds to $^{14}CO_2$ or ^{14}C-volatile

organic products did not occur. Partial degradation was observed with the other compounds but metabolites were not identified in spite of HPLC being used. The data suggested that the amine metabolite was most readily metabolised by aerobic bacteria. Since florfenicol is considered water-soluble, was identified as the major component in the excreta, is not readily photodegradable in the presence of sunlight and not degradable in water, it is likely that once emitted in the environment, it will degrade slowly in the aquatic compartment.

Adsorption/Desorption

Adsorption/desorption studies have indicated that florfenicol and its major metabolites will be moderately to highly mobile. The results indicated that the binding of florfenicol and its metabolites to soil was low and in most cases <25% of the test compound was adsorbed using a 5:1 solution to soil ratio. Since florfenicol and its metabolites showed high mobility and are not persistent in soils, there is little potential for them to accumulate in soil.

The environmental fate data provided by the company is considered adequate for the proposed use of florfenicol in cattle and pigs. However, should environmental exposure of florfenicol increase significantly, the company should provide data on field dissipation studies.

Environmental Toxicology

Aquatic Toxicity

The acute toxicity of florfenicol and it metabolites, florfenicol alcohol, florfenicol oxamic acid and florfenicol amine to the following species: bluegill sunfish (*Lepomis macrochirus*), rainbow trout (*Oncorhynchus mykiss*), daphnids (*Daphnia magna*) and freshwater green algae (*Selenastrum capricormutum*) was investigated. The species found to be the most sensitive was the freshwater algae, *Selenastrum capricornutum* to which these were moderately to highly toxic except for florfenicol oxamic acid to which it was slightly toxic. However, the effect on this algae was found to be algistatic rather than algicidal.

For bluegill sunfish and rainbow trout, NOELs were found at the highest concentration tested (15-830 mg/L). For daphnids, no effect levels were observed at the highest concentrations tested for florfenicol amine and florfenicol oxamic acid. For florfenicol toxic effects were observed at >100 mg/L and for florfenicol alcohol, it was observed at >8.9 mg/L. In none of these cases were LC50s able to be established.

The applicant has also provided a toxicity study of florfenicol to the marine diatom (*Skeletonema costatum*). Based on the 72-h exposure algal growth inhibition study, an IC50 of 12.8 µg/L was established for the marine diatom indicating a considerably higher toxicity than freshwater green algae (*Selenastrum capricornutum*) with an MIC of 1500 µg/L.

Non-target Invertebrates (terrestrial)

The toxicity study of florfenicol to earthworms (*Eisenia foetida*) indicated that there was minimal toxicity to earthworms with LC50>1000 mg/kg and NOEC≥1000 mg/kg.

Soil micro-organisms

The toxicity of florfenicol and its metabolites florfenicol alcohol, florfenicol oxamic acid and florfenicol amine to a fungus (*Trichoderma viride*), a mould (*Aspergillus niger*), a nitrogen fixing bacteria (*Clostridium perfringens*), a soil bacteria (*Bacillus subtillis*) and a blue-green algae (*Nostoc*) was investigated. Minimum inhibitory concentrations (MIC) of florfenicol and the metabolites were determined for the series of micro-organisms in vitro.

The fungus and mould were found to be completely uninhibited by florfenicol and its metabolites whereas the three other species were affected to varying degrees. The species found to be most sensitive to florfenicol was the soil bacteria, *Bacillus subtillis* with an MIC of 0.4 mg/L. The MIC for all species tested with the metabolites was one order of magnitude greater than they were for florfenicol. Florfenicol oxamic acid was found to be inhibitory to *Nostoc* only and at concentration $\geq$ 400 mg/L. These results indicate that the parent compound is the most toxic of the four test compounds and the metabolic breakdown of florfenicol to metabolites in cattle has detoxified the drug significantly.

Phytotoxicity

On the basis of toxicity data of florfenicol to plant species such as wheat *(Triticum aestivum)*, mustard (*Brassica alba*) and cress (*Lepidium sativum*), varying toxicity was observed among the species. The most sensitive species tested was found to be cress with an EC50 for plant growth of 0.5 mg/kg compared with 6.7 mg/kg for wheat. An additional study was performed to determine the NOEC of florfenicol to cress which was found to be 0.16 mg/kg based on the weight and length of primary and secondary leaves.

Environmental Hazard

The applicant's calculations were based on the proposed EU guidelines for assessing the environmental risk of veterinary medicines. This may not be appropriate under the Australian conditions. Environment Australia has recalculated these taking local conditions and practices into account as well as the more toxic results to plants and the marine diatom subsequently provided.

Environment Australia has calculated the florfenicol concentration in soil as a result of the application of treated manure from the cattle feedlot. The results indicate that florfenicol is unlikely to pose an environmental hazard to earthworm, soil micro-organisms and plant species under the proposed use pattern when cattle manure is spread on cropland. Given a 1% run-off from a feedlot, that much of the excreta will be worked into the ground and the National Beef Cattle Feedlot Environmental Code of Practice, the environmental hazard to aquatic organisms as a result of feedlot run-off can be readily mitigated to an acceptable level. Hazard calculations in the case of run-off from the treated fertilised cropland also indicate a minimal environmental hazard to aquatic organisms.

Environment Australia's calculations indicate that in an open pasture scenario, urine from cattle discharged into soil has the potential to give rise to an environmental hazard in plants and soil micro-organisms but not earthworms though the former would be reduced by likely single animal treatment. In a scenario of discharge from cows into a stream along the pasture,

the calculation indicates that there are minimal adverse effects to aquatic organisms.

Environment Australia has calculated hazard for pig treatment at both post-weaning and fattening facilities. On the basis of the results obtained for Environment Australia's calculations, it is apparent that florfenicol concentrations in soil and effluent are unlikely to give rise to an environmental hazard for earthworms, soil micro-organisms, plant species and aquatic organisms under the proposed use pattern for pigs.

Efficacy and Safety Assessment

Scientific experts from the State Departments of Agriculture/Primary Industries and the National Registration Authority assessed the submitted scientific studies and found them to be sufficient to support the proposed label claims for this product.

NuflorTm LA Injectable Solution is a synthetic, broad spectrum antibiotic belonging to a group of compounds which includes chloramphenicol and thiamphenicol.

The applicant provided details of clinical trials which were undertaken across a wide range of geographical locations including western US, mid-western US, southern US, central Spain, south-western France, The Netherlands, Italy, UK and Western Canada and encompassed a wide range of climatic conditions.

Details of the animals used and their trial groups, the diseases under study, substances tested, length of trial, observations made, and analyses undertaken were provided in satisfactory detail.

The methodologies used were appropriate for the types of data and the conclusions drawn from such analyses appear to be valid.

To ascertain if the targeted bacterial species in Australia were as susceptible to florfenicol as bacterial species overseas, the company undertook studies confirming the susceptibility of Australian isolates to florfenicol. Proof of microbiological susceptibility was provided without clinical efficacy trials being conducted, and it was ascertained that the following selected indicator micro-organisms were sensitive to florfenicol:

Mannheimia (Pasteurella) haemolytica
Pasteurella multocida
Haemophilus somnus
Actinobacillus pleuropnuemoniae
Salmonella cholerasuis
Streptococcus suis Type 2 and
Mycoplasma bovis

Trials involving repeated and excessive dosages established the safety of the product when administered to cattle at the recommended doses into the recommended sites.

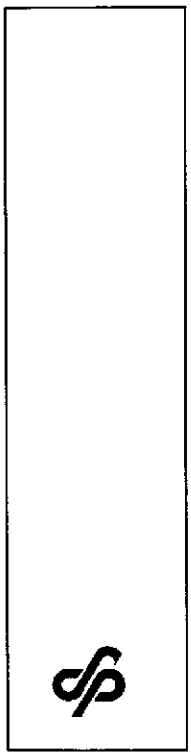
Labelling Requirements

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

NUFLOR ® LA
Injectable Solution

ACTIVE CONSTITUENT: 300 mg/mL FLORFENICOL

For the treatment of bacterial infections in cattle and pigs susceptible to florfenicol.



Schering-Plough Animal Health

20mL
50mL
100mL
250mL
500mL

READ THE ENCLOSED LEAFLET BEFORE USING THIS PRODUCT
NUFLOR® LA Injectable Solution is indicated for the treatment of **cattle** with bacterial infections susceptible to florfenicol, especially the causative organisms of pink-eye (*Moraxella bovis*), bovine respiratory disease (including *Pasteurella haemolytica, Pasteurella multocida* and *Haemophilus somnus*) and Footrot of cattle (*Fusobacterium necrophorum* and *Bacteroides melaninogenicus*), and for the treatment of **pigs** with swine respiratory disease associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Mycoplasma spp.* and *Streptococcus suis* Type 2.

DIRECTIONS FOR USE

Restraints:
DO NOT USE in female cattle which are producing or may in the future produce milk or milk products for human consumption.
DO NOT USE in calves to be processed for veal.
DO NOT USE in cattle and pigs intended for breeding.
DO NOT exceed 10mL at any one injection site (subcutaneous or intramuscular).

Contra-indications and Special Precautions for Use
Clinical improvement should be evident in most treated subjects within 24 hours initiation of therapy. If a positive response is not seen within 24 hours after the second injection, the diagnosis should be reconfirmed.

Susceptibility discs containing 30 µg of Florfenicol are available for sensitivity testing.
Mild, transient inappetence, decreased water consumption or diarrhoea may occur in cattle following treatment. Transient diarrhoea and/or perianal erythema/swelling may occur in pigs following treatment. These symptoms should return to normal shortly after treatment.
The effect of florfenicol on bovine and porcine reproductive performance and pregnancy has not been assessed.
As seen with many antibiotics high dosage and/or prolonged administration may lead to superinfections by non-sensitive organisms such as yeasts and fungi.
Intramuscular injection at sites other than the neck can cause local reaction which may result in trim loss of edible tissue at slaughter.

Dosage and Administration
CATTLE:
Intramuscular - 20 mg/kg of bodyweight (1 mL per 15 kg). A second dose should be given 48 hours later. Do not exceed 10mL at any one injection site. Inject into muscle tissue on the side of the neck. Intramuscular injection may result in local tissue reaction which persist beyond 35 days and may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck are likely to more severe.
Subcutaneous - 40 mg/kg of bodyweight (2mL per 15 kg). One subcutaneous dose ONLY. For doses that exceed 10mL, more than one injection site will be required. Inject under the skin high on the neck behind the ear.
PIGS: Intramuscular - 15 mg/kg of bodyweight (0.75 mL per 15 kg). Two injections are given 48 hours apart. Do not exceed 10mL at any one injection site. Inject into muscle tissue on side of the neck.
Intramuscular injection may result in local tissue reaction which persists for up to 21 days and may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck are likely to more severe.

WITHHOLDING PERIODS
CATTLE: **MILK: DO NOT USE in female cattle which are producing or may in the future produce milk or milk products for human consumption.**
MEAT: DO NOT USE less than 42 days before slaughter for human consumption.
PIGS: **MEAT: DO NOT USE less than 12 days before slaughter for human consumption.**

Export of Treated Produce
The withholding period stated on this label applies only to product destined for the Australian domestic market. Some export markets may apply different standards. If necessary, details of overseas standards should be obtained prior to the use of this product. Contact Schering-Plough Animal Health for further information.

First Aid: If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

For further information contact Schering-Plough Animal Health Customer Service on 1 800 226 511.

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

DISPOSE of empty container by wrapping with paper and putting in garbage. Discarded needles should immediately be placed in a designated and appropriately labelled 'sharps' container.

STORE below 30°C (Room Temperature).

BATCH

EXPIRY

NRA Approval No. 52201/_____

Schering-Plough Animal Health

Schering-Plough Animal Health
(A Division of Schering-Plough Pty Ltd)
11 Gibbon Road, Baulkham Hills NSW 2153

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

NUFLOR ® LA
Injectable Solution

ACTIVE CONSTITUENT: 300 mg/mL FLORFENICOL

For the treatment of bacterial infections in cattle and pigs susceptible to florfenicol.

Schering-Plough Animal Health

20mL
50mL
100mL
250mL
500mL

READ THE ENCLOSED LEAFLET BEFORE USING THIS PRODUCT

DIRECTIONS FOR USE

Restraints:
DO NOT USE in female cattle which are producing or may in the future produce milk or milk products for human consumption.
DO NOT USE in calves to be processed for veal.
DO NOT USE in cattle and pigs intended for breeding.
DO NOT exceed 10mL at any one injection site (SC or IM).

Dosage and Administration

CATTLE: IM - 20 mg/kg of BW (1 mL per 15 kg). 2nd dose - 48 hours later. **SC** - 40 mg/kg of BW (2mL per 15 kg). One subcutaneous dose ONLY.
PIGS: IM - 15 mg/kg of BW (0.75 mL per 15 kg). 2nd dose - 48 hours later.

WITHHOLDING PERIODS
CATTLE: **MILK: DO NOT USE in female cattle which are producing or may in the future produce milk or milk products for human consumption. MEAT: 42 days.**
PIGS: **MEAT: 12 days.**

First Aid: If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

DISPOSE of empty container by wrapping with paper and putting in garbage. Discarded needles should immediately be placed in a designated and appropriately labelled 'sharps' container.

STORE below 30°C (Room Temperature). **(B)**
EXP.

NRA Approval No. 52201/_____

Schering-Plough Animal Health

Schering-Plough Animal Health
(A Division of Schering-Plough Pty Ltd)
11 Gibbon Road, Baulkham Hills NSW 2153

PRESCRIPTION ANIMAL REMEDY

KEEP OUT OF REACH OF CHILDREN

FOR ANIMAL TREATMENT ONLY

NUFLOR® LA Injectable Solution

ACTIVE CONSTITUENT: 300 mg/mL FLORFENICOL.

Pharmacology:
Florfenicol is a synthetic, broad spectrum antibiotic active against many gram-negative and gram-positive bacteria isolated from domestic animals. Florfenicol acts by inhibiting bacterial protein synthesis at the ribosomal level.

Indications:
NUFLOR® LA Injectable Solution is indicated for the treatment of **cattle** with bacterial infections susceptible to florfenicol, especially the causative organisms of pink-eye (*Moraxella bovis*), bovine respiratory disease (including *Pasteurella haemolytica, Pasteurella multocida* and *Haemophilus somnus*) and Footrot of cattle (*Fusobacterium necrophorum* and *Bacteroides melaninogenicus*), and for the treatment of **pigs** with swine respiratory disease associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Mycoplasma spp.* and *Streptococcus suis* Type 2.

DIRECTIONS FOR USE
Restraints:
DO NOT USE in female cattle which are producing or may in the future produce milk or milk products for human consumption.
DO NOT USE in calves to be processed for veal.
DO NOT USE in cattle and pigs intended for breeding.
DO NOT exceed 10mL at any one injection site (subcutaneous or intramuscular).

Contra-indications and Special Precautions for Use
Clinical improvement should be evident in most treated subjects within 24 hours initiation of therapy. If a positive response is not seen within 24 hours after the second injection, the diagnosis should be reconfirmed.
Susceptibility discs containing 30 µg of florfenicol are available for sensitivity testing.
Mild, transient inappetence, decreased water consumption or diarrhoea may occur in cattle following treatment. Transient diarrhoea and/or perianal erythema/swelling may occur in pigs following treatment. These symptoms should return to normal shortly after treatment.
The effects of florfenicol on bovine or porcine reproductive performance, pregnancy and lactation have not been determined.
As seen with many antibiotics high dosage and/or prolonged administration may lead to superinfections by non-sensitive organisms such as yeasts and fungi.
Intramuscular injection at sites other than the neck can cause local reaction which may result in trim loss of edible tissue at slaughter.

Safety Studies
Cattle:
A 10X safety study was conducted in feeder calves. Two intramuscular injections of 200 mg/kg were administered at a 48-hour interval. The calves were monitored for 14 days after the second dose. Marked anorexia, decreased water consumption, decreased body weight and increased serum enzymes were observed following dose administration. These effects resolved by the end of the study.

A 1X, 3X and 5X (20, 60 and 100 mg/kg) safety study was conducted in calves for 3X the duration of treatment (6 injections at 48-hour intervals). Slight decrease in feed and water consumption was observed in the 1X dose group. Decreased feed and water consumption, body weight, urine pH and increased serum enzymes were observed in the 3X and 5X dose groups. Depression, soft stool consistency and dehydration were also observed in some animals (most frequently at the 3X and 5X dose levels), primarily near the end of dosing.
A 43-day controlled study was conducted in healthy cattle to evaluate the effects of Nuflor® administered at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, Nuflor® administration had no long-term effect on body weight, rate of gain or feed consumption.

Pigs:
A safety study was conducted in which cross-bred pigs were administered intramuscular injections of Nuflor® at 1X, 3X and 5X the clinical dose (15, 45 and 75 mg/kg, respectively) for 3X the recommended clinical duration of treatment (6 injections at 48-hour intervals). An additional group of animals received 10X the clinical dose (150 mg/kg) administered at the recommended clinical duration of 1 injection every 48 hours for a total of 2 injections.
The 1X group showed a minimally increased incidence of diarrhoea and injection site lesions. In the 3X and 5X groups, pigs showed a dose and time-dependent increased incidence and/or severity of diarrhoea, injection site lesions, anal erythema/swelling, decreased body weight, decreased food and water consumption, alterations in some serum electrolytes and proteins and decreased numbers of white blood cells, spleen weights and kidney weights.
Most changes in drug-related, in-life parameters did not become apparent until after dosing was extended beyond the normal clinical duration of 2 injections, 48 hours apart. Findings in pigs in the 10X group were limited to minimally increased diarrhoea and serum creatinine, and slight to moderately increased injection site lesions.

Dosage and Administration
CATTLE:
Intramuscular - 20 mg/kg of bodyweight (1 mL per 15 kg). A second dose should be given 48 hours later. Do not exceed 10mL at any one injection site. Inject into muscle tissue on the side of the neck.
Intramuscular injection may result in local tissue reaction which persist beyond 35 days and may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck are likely to more severe.

Subcutaneous - 40 mg/kg of bodyweight (2mL per 15 kg). One dose ONLY. For doses that exceed 10mL, more than one injection site will be required. Inject under the skin high on the neck behind the ear.
PIGS:
Intramuscular - **15 mg/kg of bodyweight (0.75 mL per 15 kg). Two injections are given 48 hours apart. Do not exceed 10mL at any one injection site. Inject into muscle tissue on side of the neck.**
Intramuscular injection may result in local tissue reaction which persists for up to 21 days and may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck are likely to more severe.

WITHHOLDING PERIODS
CATTLE: **MILK: DO NOT USE in female cattle which are producing or may in the future produce milk or milk products for human consumption.**
MEAT: DO NOT USE less than 42 days before slaughter for human consumption.
PIGS: **MEAT: DO NOT USE less than 12 days before slaughter for human consumption.**

Export of Treated Produce
The withholding period stated on this label applies only to product destined for the Australian domestic market. Some export markets may apply different standards. If necessary, details of overseas standards should be obtained prior to the use of this product. Contact Schering-Plough Animal Health for further information.

First Aid: If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

For further information contact Schering-Plough Animal Health Customer Service on 1 800 226 511.

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

Presentation
NUFLOR ® LA Injectable Solution is packaged in 20 mL, 50 mL, 100 mL, 250 mL and 500 mL glass sterile dose vials.

Disposal
Dispose of empty container by wrapping with paper and putting in garbage. Discarded needles should immediately be placed in a designated and appropriately labelled 'sharps' container.

Storage
Store below 30°C (Room Temperature).

NRA Approval No. 52201/_____

Schering-Plough Animal Health

Schering-Plough Animal Health
(A Division of Schering-Plough Pty Ltd)
11 Gibbon Road, Baulkham Hills NSW 2153

Glossary

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product.
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer.
Chronic	Of long duration.
Codex MRL	Internationally published standard maximum residue limit.
Desorption	Removal of an absorbed material from a surface.
Efficacy	Production of the desired effect.
Formulation	A combination of both active and inactive constituents to form the end use product.
Genotoxicity	The ability to damage genetic material
Hydrophobic	Water repelling
Leaching	Removal of a compound by use of a solvent.
Log P_{ow}	Log to base 10 of octonol water partioning co-efficient.
Metabolism	The conversion of food into energy
Photodegradation	Breakdown of chemicals due to the action of light.
Photolysis	Breakdown of chemicals due to the action of light.
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body.
Toxicology	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 Veterinary Chemical Products*, NRA, Canberra.