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NRA NATIONAL REGISTRATION AUTHORITY
FOR AGRICULTURAL AND VETERINARY CHEMICALS

Public Release Document

CLORSULON

IN THE PRODUCT
IVOMEC-PLUS INJECTION FOR CATTLE

This document is published by the
National Registration Authority for
Agricultural and Veterinary Chemicals.
For further information, please contact:

EXECUTIVE SUMMARY

Introduction

The purpose of this document is to provide a summary of the data reviewed and an outline of regulatory considerations for the proposed clearance and registration of the chemical clorsulon for use as a flukicide by injection in cattle.

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) invites public comment before deciding whether to proceed to approve this product for use in Australia.

IVOMEC-PLUS INJECTION FOR CATTLE, containing the active ingredients clorsulon and ivermectin, is to be used for the treatment of gastro-intestinal roundworms, lungworm, eyeworm, liver fluke, sucking lice, mites and ticks.

The NRA has completed an assessment of the data submitted by the applicant in support of this use of clorsulon when combined with ivermectin and has provided the following information for public comment:

Animal Production Aspects

Clorsulon is a new flukicide with a novel mode of action. It will be marketed in the product IVOMEC-PLUS INJECTION FOR CATTLE which has the same formulation as IVOMEC INJECTION FOR CATTLE containing ivermectin at 10mg/mL, with the addition of clorsulon at 100mg/mL.

Beef production is a major earner of foreign exchange and along with the dairy industry contributes significantly to Australia's economy. Liver fluke (*Fasciola hepatica*) is an economically important parasite of cattle with a widespread distribution throughout eastern Australia. Because clorsulon has a novel mode of action, it will provide an additional liver fluke control agent that will not be subject to any resistance induced through previous use of products such as the salicylanilide group.

The data package is considered adequate to indicate that IVOMEC-PLUS INJECTION FOR CATTLE will control liver fluke when used according to the directions on the label.

Target animal safety of clorsulon alone and in combination with ivermectin was demonstrated at up to 25 times the use level, with no signs of adverse effects other than injection site swellings where elevated doses were given.

The major advantage of using IVOMEC-PLUS INJECTION FOR CATTLE is that all significant internal parasites can be treated with a single dose, providing benefits in animal health and welfare.

Environmental Aspects

Clorsulon has low potential for toxicity to mammals, terrestrial invertebrates, plants and aquatic animals. Wildlife species are not likely to be affected as a result of cattle being injected subcutaneously with clorsulon at a rate of 2 mg/kg body weight. It is not expected that the avian toxicity of clorsulon would exceed that of ivermectin, the other veterinary drug in **IVOMEC-PLUS'S** formulation, which is already registered for similar uses. Once excreted onto the ground clorsulon is capable of entering the soil either by the action of rain water, by manure from treated cattle being ploughed (or trodden) into the soil or through burying by dung beetles.

Clorsulon in water is rapidly broken down by sunlight. Degradation in soil or faeces to form carbon dioxide is incomplete, but the combined effects of degradation, its moderate solubility in water and mobility in soil result in its dissipation. In the soil sub-surface of feedlots, under moist conditions the drug could enter aquatic compartments, given its stability in water in the absence of light. However, in view of the low application rate, its short half-life in light, the management practices associated with feedlots in Australia and the low potential for environmental toxicity, clorsulon residues are expected to be below levels that would be considered a hazard to the environment.

Toxicology

Clorsulon is of low acute toxicity to rats and mice. There is no evidence of potential to cause birth defects and damage to genetic material in mice only occurred at doses exceeding those demonstrated to be toxic to the bone marrow. Lifetime carcinogenicity studies in rats and mice showed no evidence of carcinogenic effect.

The formulated product is a slight eye irritant but the presentation in plastic pouches ready for injection significantly reduces the chances of exposure.

Ivermectin, the other active ingredient in IVOMEC-PLUS, is registered and on sale in Australia in formulations for sheep, horses, dogs and cattle. Extensive toxicology data in mice, rats, rabbits, dogs and rhesus monkeys was submitted in support of those registration applications.

Residues

In cattle dosed with IVOMEC-PLUS at the recommended dose rate, clorsulon residues were highest in the kidney at 0.54 ppm on day 3 after dosing. At the same time, liver averaged 0.2 ppm, muscle 0.06 ppm and fat averaged 0.02 ppm. Rapid depletion followed, resulting in average residues at or below the limit of determination of 0.1 mg/kg by day 21 for all tissues. The proposed withholding period is 42 days, based upon depletion of ivermectin which has a longer tissue residue half-life than clorsulon.

Maximum Residue limits of 0.1 mg/kg have been proposed for cattle meat and edible offal of cattle.

Occupational Health and Safety Aspects

Clorsulon and IVOMEC-PLUS present minimal safety risk to workers when handled according to instructions on the label and in the Material Safety Data Sheet (MSDS). The risk of developing significant acute and chronic health effects from occupational exposure is low. Clorsulon and IVOMEC-PLUS may produce eye irritation.

To minimise occupational exposure the safety directions on the label must be followed. A copy of the MSDS should be easily accessible to all users/handlers.

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INTRODUCTION

The purpose of this document is to provide the public with a summary of the data reviewed and an outline of regulatory considerations for the proposed use of the chemical clorsulon as a flukicide by injection in cattle, and to seek public comment prior to the chemical product being approved for use in Australia.

Comments should be received by 18 April 1994 and sent to:

[redacted]

Applicant

Merck Sharp & Dohme (Australia) Pty Limited has applied for clearance of a new veterinary drug clorsulon, a flukicide to be used in combination with the registered drug, ivermectin.

Product Details

Clorsulon will be marketed in the product IVOMEC-PLUS INJECTION FOR CATTLE which has the same formulation as IVOMEC INJECTION FOR CATTLE containing ivermectin at 10mg/mL, with the addition of clorsulon at 100mg/mL. Because clorsulon has a novel mode of action, it will provide an additional liver fluke control agent that will not be subject to any resistance induced through previous use of other products.

Except for the additional claim against adult liver fluke *Fasciola hepatica*, the claims for the product are the same as for the registered product, **IVOMEC INJECTION**.

IVOMEC-PLUS is not formulated locally but will be imported from one of four Merck, Sharp and Dohme facilities in The Netherlands, Brazil, Puerto Rico or England.

IVOMEC-PLUS will be used in areas of Australia where liver fluke in cattle is a problem, as a ready to use injection in plastic pouches.

Overseas Registration Status

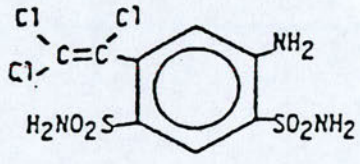
IVOMEC-PLUS is currently registered in 23 overseas countries including France, Brazil, Chile, Holland, UK., U.S.A. and New Zealand.

PROPERTIES OF THE CHEMICAL ACTIVE INGREDIENT

Clorsulon is a side chain halogenated, benzene sulphonamide compound.

CHEMICAL IDENTITY

Name (IUPAC):	4 - amino - 6 - (trichloroethenyl) - 1, 3 - benzenedisulfonamide
Common name:	Clorsulon
Manufacturers code numbers & synonyms:	MK- 0401 (MK401), L-631, 529-000U
CAS number:	60200-06-8
Molecular formula:	$C_8H_8Cl_3N_3O_4S_2$
Molecular weight:	380.66
Structural formula:	



Clorsulon

Purity of TGAC: Minimum 98%, no single impurity >0.5%

PHYSICAL-CHEMICAL PROPERTIES

Pure Active Constituent:

Appearance:	Cream to light coloured, crystalline powder
Melting Point:	Mixture - approximately 193-207 °C - capillary tube method

Vapour Pressure:	4.60 x 10-l3 atm calculated using the Clausius-Clapeyron equation
Water Solubility:	1 mg/mL (0.1%); above pH 10 solubility increases to 10 mg/mL in 0.1 N NaOH
Solubility solvents:	very soluble in many organic solvents
Hygroscopicity:	nonhygroscopic
pKa value:	0.4 ± 0.2 at 25 °C
Partition Coefficient:	pH 7: 14.4 +/- 0.1 at 25 °C
Stability:	Data indicates that clorsulon retains > 95% potency after 57 months storage at 25 °C 76% potency after 8 days in 0.1 M methanolic HCI at25°C 86% potency after 8 days in 0.1 M methanolic NaOH at 25°C

ANIMAL PRODUCTION ASSESSMENT

Justification For Use

Beef production is a major primary industry and along with the dairy industry contributes significantly to Australia's economy. Liver fluke (*Fasciola hepatica*) is an economically important parasite of cattle with a widespread distribution throughout eastern Australia. Production losses through liver damage arising from liver fluke infestation can be significant and such damage can trigger secondary conditions such as black disease. These aspects have significant animal health and welfare implications .

The major advantage of using IVOMEC-PLUS INJECTION FOR CATTLE is that all significant internal parasites can be treated with a single dose, providing benefits in animal health and welfare apart from the impact on cost of production. Because clorsulon has a novel mode of action, it will provide an additional liver fluke control agent that will not be subject to any resistance induced through previous use of products such as the salicylanilide group.

Proposed Use Pattern

Clorsulon will be administered to cattle by subcutaneous injection at a dosage of 1mL **IVOMEC-PLUS** per 50 kg body weight (equivalent to 2 mg clorsulon per kg body weight). Generally, cattle at pasture will receive 2-3 doses of the drug per year and feedlot cattle will receive only one dose upon entry to the feedlot.

Evaluation of Efficacy

Immature liver fluke have previously been shown to be less susceptible to clorsulon than are adult flukes. Initial dose titration trials established a dose rate of 2 mg/kg and this was confirmed in subsequent trials, using both naturally acquired and artificial infestations for clorsulon alone or in combination with ivermectin at 200 mcg/kg.

Trials in the U.S.,U.K. and Australia have confirmed high efficacy (generally >97%) against adult flukes. The data presented support the label claims for IVOMEC-PLUS.

Target Animal Safety

The only issue that was apparent in a range of studies where up to 25 times the normal dose rate was used, was injection site swellings in up to 10% of animals and occasionally fibrosis at the injection site. These swellings regressed with time (up to 35 days after treatment) and are not considered significant.

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL FATE

Clorsulon will be administered to cattle by subcutaneous injection at a dosage of 1 mL **IVOMEC-PLUS** per 50 kg body weight (equivalent to 2 mg clorsulon per kg body weight). Generally, cattle at pasture will receive 2-3 doses of the drug per year and feedlot cattle will receive only one dose upon entry to the feedlot.

Degradation rates and routes

Clorsulon is resistant to breakdown by combining with water but is readily broken down by light when in solution, although this may be slower in turbid water.

Limited soil/faecal metabolism studies show some degradation, the extent of which is not fully defined. Complete mineralization to carbon dioxide is low over 64 days. While this does not preclude conversion of clorsulon to stable metabolites, these have not been studied. However, simulated field results do provide some support for the relatively rapid loss of parent clorsulon due to degradation processes and its tendency to move with water through the soil profile .

In the soil/feedlot sub-surface, under moist conditions, the drug could enter the aquatic compartments of the environment (e.g. ground water); given its stability in water in the absence of light.

Metabolites

Clorsulon is excreted largely unchanged. The drug's metabolites would account for no more than 5% of the total residue.

Mobility

Following administration via sub-cutaneous injection, any clorsulon not metabolised or absorbed by the target animal will be excreted and enter the surrounding soil and water compartments of the environment only. Movement of the chemical into the atmosphere will be unlikely due to its low vapour pressure.

Adsorption/desorption data indicates that clorsulon is not very tightly bound to soil and appears to be environmentally mobile. Once excreted the drug should readily transfer into the aquatic environment, both through leaching into the soil profile and lateral flow into surface waters.

Accumulation in soils

Clorsulon's low octanol/water partition coefficient indicates aquatic bioaccumulation is not likely to occur.

ENVIRONMENTAL EFFECTS

Mammalian toxicity

Acute and short-term feeding studies on dogs, rats and rabbits indicated that clorsulon is practically non-toxic to mammals.

Although avian and dung fauna toxicity tests were not provided for clorsulon the effect that it may have on these non-target organisms is likely to be minimal when compared with the registered drug, ivermectin, in the formulated product **IVOMEC PLUS**.

Aquatic toxicity

Results from studies on freshwater fish, *Daphnia* (water flea) and algae indicate negligible toxicity to aquatic organisms.

Non-target invertebrates

Tests on earthworms and soil micro-organisms did not reveal any toxic effects of clorsulon using doses ranging between 100 and 1000 ppm & 0.05 and 0.2 ppm respectively. However, a decrease in microbial respiration became apparent at 0.2

ppm clorsulon in loamy sand soils and at 2 ppm clorsulon in loam and a decrease in nitrification at 20 ppm.

Phytotoxicity

The phytotoxicity of clorsulon was tested using eight species of plant. Clorsulon was phytotoxic to some plant species but not at levels expected in fertilised fields under typical use conditions.

ENVIRONMENTAL HAZARD

Hazard arising from use:

Aquatic and terrestrial toxicity

Terrestrial and aquatic wildlife species are not likely to be affected as a result of cattle being injected sub-cutaneously with clorsulon at a rate of 2 mg/kg body weight.

The degradation of clorsulon is rapid in sunlight. It is moderately soluble in water and highly mobile in soil. It readily leaches into the soil and moves freely through the soil profile. Once into the water compartment of the environment away from sunlight it is not expected to degrade readily.

Use of manure from treated cattle as a fertiliser

Once excreted onto the ground clorsulon is capable of entering the soil either by the action of rain water, by manure from treated cattle being ploughed (or trodden) into the soil or through burying by dung beetles. Manure from treated cattle applied to pastoral land as fertilizer would be expected to be walked into the top 1-2 cm of the soil through the grazing of free-range cattle. The moderate solubility of clorsulon in water would also result in its movement into and down through the soil profile. The spreading of manure over pastoral land at a rate of 5 tonnes/ha could result in a worst case scenario of 0.15 ppm clorsulon in the top 1 cm of soil per annum.

If it is assumed that there is no degradation of clorsulon in the faeces then, using current Australian feedlot practices, it is estimated that the maximum concentration of clorsulon could range between 0.03 and 0.08 ppm, depending on the depth to which the manure is ploughed into the soil. At these concentrations, clorsulon should not interfere with microbial respiration.

CONCLUSIONS

Clorsulon is a veterinary drug for the control of a range of internal parasites in cattle. It is moderately soluble in water, mobile and persistent in soil and water systems in the absence of light but degraded rapidly in water exposed to sunlight and will dissipate in soil and faeces.

However,in view of the low application rate, its short half-life in light, the management practices associated with feedlots in Australia and the low toxicity to terrestrial and aquatic species, clorsulon residues are expected to be below levels that would be considered a hazard to the environment.

PUBLIC HEALTH AND SAFETY ASSESSMENT

Evaluation Of Toxicology

The toxicological database for clorsulon, which consists primarily of toxicity tests conducted using animals, is adequate to assess potential risks associated with its presence in Ivomec-Plus. In interpreting these data, it should be noted that animal toxicity tests generally use doses or exposures which are high compared to likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable Effect Level (NOEL) are used to develop appropriate standards for exposures at which no adverse health effects in humans would be expected.

Clorsulon is of low acute toxicity to animals, with the LD50 for mice and rats greater than 20 g/kg and 10 g/kg respectively. There is no evidence of potential to cause birth defects and damage to genetic material in mice only occurred at doses exceeding 500 mg/kg that were demonstrated to be cytotoxic to the bone marrow. Lifetime carcinogenicity studies in rats and mice showed no evidence of carcinogenic effect at dose levels up to 49 and 300 mg/kg/day respectively.

The acute toxicity of clorsulon was low in mice and rats. IVOMEC-PLUS, the formulated injectable product containing clorsulon and ivermectin, showed relatively low acute toxicity potential. The toxic effects of the product appear to be attributable mainly to its content of ivermectin. There was no evidence for any interaction between the active ingredients. Ivomec-Plus is a slight eye irritant, but did not irritate the skin when tested in rabbits. These data indicate the need to warn against exposure of the eyes.

Short-term (up to 90 days) and long-term (1 - 2 years) administration of clorsulon to mice, rats and dogs at doses ranging up to 1000 mg/kg body wt/day indicated that mild liver toxicity and non-specific toxicity demonstrated by poor appetite, reduced growth and mild anaemia were the main adverse effects seen at high doses. In long-term studies in rats at doses of 20 mg/kg body wt/day and above, mild toxicity to several major organs was apparent, but reversible hyperplasia of urinary bladder cells and changes in urine composition were perhaps the most prominent of these effects. Like some other sulphonamides, clorsulon inhibits the enzyme carbonic anhydrase. The resultant changes in urinary acidity and electrolyte balance are thought to be contributing factors to the urinary bladder cell hyperplasia. The NOEL for this bladder change in rats was 30 mg/kg/day in a 3 month study. Rat bladder cells are particularly sensitive to this effect, but the effects are generally not seen in other species, including humans.

Rats and rabbits were the more sensitive species tested. The NOEL for kidney changes in a long-term rat feeding study was 4 mg/kg body wt/day, while the NOEL in reproductive toxicity studies was 2 mg/kg body wt/day, based on a slight increase in the length of the gestation period in rats and a reduction in maternal weight gain during the dosing period in rabbits. These effects were seen at the next highest dose (10 mg/kg body wt/day) and were probably associated with renal toxicity in the pregnant female animals. Otherwise, clorsulon did not have any significant toxic effects on reproductive performance or foetal development.

Clorsulon did not induce tumours or have toxic effects on genetic material (DNA). Overall, these studies indicate that clorsulon is a relatively non-toxic chemical.

Potential For Chemical Residues In Food

An analytical method suitable for residue analysis of clorsulon in cattle meat and offal and having an adequate level of recovery was provided. The method had a limit of determination for unchanged clorsulon of 0.1 mg/kg.

The results of two trials using cattle were evaluated. Radio labelled clorsulon (10 mg/kg body wt) was administered directly into the rumen. The radioactivity of samples of liver, kidney, fat and muscle was assessed to determine the residue profiles 7 - 21 days after dosing. The highest residue levels were detected in kidney on day 7 and were mostly unchanged clorsulon. In the second trial, clorsulon was administered by subcutaneous injection of Ivomec-Plus, using the recommended clorsulon dose rate of 2 mg/kg body wt. Liver, kidney, fat and muscle were sampled from 3 - 35 days after dosing. Both trials demonstrated that the level of clorsulon residues had fallen to below the level of analytical determination by 21 - 28 days after dosing.

It was concluded that these trials were adequate to support MRLs of *0.1 mg/kg in both cattle meat and offal. The proposed WHP of 42 days (to allow for residues of ivermectin) is more than adequate for clorsulon. No data were provided on residue

levels in cattle milk, so that an appropriate use restraint statement "WHEN MILK OR MILK PRODUCTS ARE TO BE USED FOR HUMAN CONSUMPTION, DO NOT ADMINISTER TO COWS WITHIN 28 DAYS PRIOR TO CALVING OR DURING LACTATION. " was recommended for the product label.

The following amendments to Table 1 of the MRL Standard were recommended:

Table 1

Compound	Codex Code	Food	MRL mg/kg
Add:			
clorsulon	MM 0812	Cattle meat	*0.1
	MO 0812	Cattle, Edible offal of	*0.1

* at or about the limit of analytical determination

Public Health Standards

The Drugs & Poisons Schedule Standing Committee (DPSSC) of the National Health & Medical Research Council (NHMRC) 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 human poisoning.

The DPSSC recommended that clorsulon be listed in Schedule 5 of the NHMRC Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). There are provisions for appropriate warning statements and first aid directions on the product label.

Conclusion

Based on an assessment of the toxicology and the fact that there should be no dietary intake of clorsulon residues, it was considered that there should be no adverse effects on human health.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Before end-use

As the fully formulated product will be imported into Australia, potential for exposure before use exists only for workers engaged in transport, storage and retailing. The physico-chemical and toxicological properties of clorsulon indicate that it presents low health and safety risks to workers when handled as per instructions on the label and in the MSDS. It is not flammable. Clorsulon would not be classified as a Dangerous Good.

End-use

Clorsulon has a low acute and chronic toxicity and is a moderate eye irritant. The product has a low acute toxicity but is a slight eye irritant. End-users may be exposed to clorsulon when injecting cattle.

The acute health risk on accidental self-injection is low due to the low acute toxicity of clorsulon and IVOMEC-PLUS. The likelihood of eye exposure is low due to the presentation of the product in retail packs for direct use with automatic injection equipment thus minimising worker handling.

The likelihood of chronic exposure via injection is remote. In a worker weighing 70 kg, a daily injection of approx. 3 mL IVOMEC-PLUS would be needed to approach the No Observed Effect Level of 3.8 mg/kg/day in a chronic study in animals. Clorsulon as an injectable preparation can be used safely by workers.

Recommendations for the control of worker exposure

Clorsulon and IVOMEC-PLUS are considered to be hazardous substances (based on the eye irritation properties) according to Worksafe Australia classification criteria for workplace substances.

An occupational exposure limit and health surveillance requirements are not recommended by Worksafe.

To minimise occupational exposure to clorsulon the following should be observed:

Information on the label and the MSDS should be consulted while handling clorsulon and its products.

A copy of the MSDS should be easily accessible to all users/handlers of the product. MSDSs on clorsulon and its products should meet Worksafe Australia's requirements.

Summary

Clorsulon and IVOMEC-PLUS present minimal safety risk to workers when handled according to instructions on the label and in the MSDS. The risk of developing significant acute and chronic health effects from occupational exposure is low. Clorsulon and IVOMEC-PLUS may produce eye irritation.

To minimise occupational exposure the safety directions on the label must be followed. A copy of the MSDS should be easily accessible to all users/handlers.

SUGGESTED FURTHER READING

Interim Requirements for Clearance of Agricultural and Veterinary Chemical Products (available from the NRA)

Code of Practice For Labelling Veterinary Chemical Products (available from the NRA)

MRL Standard - Maximum Residue Limits in Food and Animal Feedstuffs (NHMRC)