



**Australian Government**  
**Australian Pesticides and  
Veterinary Medicines Authority**



## **Public release summary**

On the evaluation of the new active constituent d-cloprostenol in the product  
DALMAZIN

APVMA product number 66024

JUNE 2019

© Australian Pesticides and Veterinary Medicines Authority 2019

ISSN 1443-1335 (electronic)

### **Ownership of intellectual property rights in this publication**

Unless otherwise noted, copyright (and any other intellectual property rights, if any) in this publication is owned by the Australian Pesticides and Veterinary Medicines Authority (APVMA).

### **Creative Commons licence**

With the exception of the Coat of Arms and other elements specifically identified, this publication is licensed under a Creative Commons Attribution 4.0 Australia Licence. This is a standard form agreement that allows you to copy, distribute, transmit and adapt this publication provided that you attribute the work.



A summary of the licence terms is available from [www.creativecommons.org/licenses/by/3.0/au/deed.en](http://www.creativecommons.org/licenses/by/3.0/au/deed.en). The full licence terms are available from [www.creativecommons.org/licenses/by/3.0/au/legalcode](http://www.creativecommons.org/licenses/by/3.0/au/legalcode).

The APVMA's preference is that you attribute this publication (and any approved material sourced from it) using the following wording:

*Source: Licensed from the Australian Pesticides and Veterinary Medicines Authority (APVMA) under a Creative Commons Attribution 4.0 Australia Licence.*

In referencing this document the Australian Pesticides and Veterinary Medicines Authority should be cited as the author, publisher and copyright owner.

### **Use of the Coat of Arms**

The terms under which the Coat of Arms can be used are set out on the [Department of the Prime Minister and Cabinet website](#)).

### **Disclaimer**

The material in or linking from this report may contain the views or recommendations of third parties. Third party material does not necessarily reflect the views of the APVMA, or indicate a commitment to a particular course of action. There may be links in this document that will transfer you to external websites. The APVMA does not have responsibility for these websites, nor does linking to or from this document constitute any form of endorsement. The APVMA is not responsible for any errors, omissions or matters of interpretation in any third-party information contained within this document.

### **Comments and enquiries regarding copyright:**

Assistant Director, Communications  
Australian Pesticides and Veterinary Medicines Authority  
PO Box 6182  
KINGSTON ACT 2604 Australia

Telephone: +61 2 6210 4701

Email: [communications@apvma.gov.au](mailto:communications@apvma.gov.au).

This publication is available from the [APVMA website](#).

---

## CONTENTS

---

PREFACE	1
<b>About this document</b>	1
<b>Making a submission</b>	1
<b>Further information</b>	2
<hr/>	
<b>1 INTRODUCTION</b>	<b>3</b>
1.1 Applicant	3
1.2 Purpose of application	3
1.3 Proposed claims and use pattern	3
1.4 Mode of action	3
1.5 Overseas registrations	4
<hr/>	
<b>2 CHEMISTRY AND MANUFACTURE</b>	<b>5</b>
2.1 Active constituent	5
2.2 Formulated product	6
2.3 Recommendations	7
<hr/>	
<b>3 TOXICOLOGICAL ASSESSMENT</b>	<b>8</b>
3.1 Evaluation of toxicology	8
3.2 Health-based guidance values and poisons scheduling	10
<hr/>	
<b>4 RESIDUES ASSESSMENT</b>	<b>12</b>
<hr/>	
<b>5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD</b>	<b>14</b>
<hr/>	
<b>6 WORK HEALTH AND SAFETY ASSESSMENT</b>	<b>15</b>
6.1 Health hazards and use pattern	15
6.2 Occupational exposure	15
6.3 Public exposure	16
6.4 Recommendations	16
6.5 Conclusion	16
<hr/>	
<b>7 ENVIRONMENTAL ASSESSMENT</b>	<b>17</b>
<hr/>	
<b>8 EFFICACY AND SAFETY ASSESSMENT</b>	<b>18</b>
8.1 Proposed product use pattern	18
8.2 Efficacy and target crop/animal safety	18
8.3 Recommendations	20
<hr/>	
<b>9 LABELLING REQUIREMENTS</b>	<b>21</b>
<hr/>	
<b>ABBREVIATIONS</b>	<b>26</b>

---

GLOSSARY	28
REFERENCES	29

## LIST OF TABLES

Table 1: Nomenclature and structural formula of the active constituent (d-Cloprostenol)	5
Table 2: Key physicochemical properties of the active d-Cloprostenol	6
Table 3: Key aspects of the formulation of the product DALMAZIN	6
Table 4: Amendments to the APVMA MRL Standard	12

## PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator responsible for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia. Before approving an active constituent and/or registering a product, the APVMA must be satisfied that the statutory criteria, including the safety, efficacy, trade and labelling criteria, have been met. The information and technical data required by the APVMA to assess the statutory criteria of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined on the [APVMA website](#).

The APVMA has a policy of encouraging transparency in its activities and seeking community involvement in decision making. Part of that process is the publication of public release summaries for products containing new active constituents. This public release summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from advisory agencies, including other Australian Government agencies and State departments of primary industries. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience to encourage public comment.

### About this document

This public release summary indicates that the APVMA is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety.

Comment is sought from interested stakeholders on the information contained within this document.

### Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of the new active constituent d-cloprostenol and registration of the product DALMAZIN should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target crop or animal safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 16 July 2019 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

All personal information, and confidential information judged by the APVMA to be confidential commercial information (CCI)<sup>1</sup> contained in submissions will be treated confidentially. Unless requested by the submitter, the APVMA may release a submission, with any CCI redacted, to the applicant for comment.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the grounds for registration should be addressed in writing to:

Case Management and Administration Unit  
Australian Pesticides and Veterinary Medicines Authority  
PO Box 6182  
Kingston ACT 2604

**Phone:** +61 2 6210 4701

**Email:** [enquiries@apvma.gov.au](mailto:enquiries@apvma.gov.au).

## Further information

Further information can be obtained via the contact details provided above.

Copies of technical evaluation reports covering chemistry, efficacy and safety, toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request.

Further information on public release summaries can be found on the [APVMA website](#).

---

<sup>1</sup> A full definition of "confidential commercial information" is contained in the Agvet Code.

# 1 INTRODUCTION

## 1.1 Applicant

Ethical Agents Australia Pty Ltd.

## 1.2 Purpose of application

Ethical Agents Australia Pty Ltd has applied to the APVMA for registration of the new active constituent d-cloprostenol and registration of the new product DALMAZIN containing 75 micrograms/mL d-cloprostenol, as an injectable solution formulation.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of the new active constituent d-cloprostenol and registration of the product DALMAZIN.

## 1.3 Proposed claims and use pattern

DALMAZIN is a solution for injection for cattle (cows), pigs (sows) and horses (mares). The product will be used for the induction of oestrus in mares, synchronisation or induction of oestrus in cows and induction of parturition in cows and sows. The product is also indicated for the expulsion of mummified foetus, induction of abortion, ovarian dysfunction (persistent corpus luteum, luteal cyst) treatment, endometritis/pyometra and delayed uterine involution treatment in cows.

The proposed dose of DALMAZIN given intramuscularly (IM) is 150 µg (0.15 mg) in cattle and 75 µg (0.075 mg) in pigs and horses. This translates to 2 mL of DALMAZIN in cattle and 1 mL of DALMAZIN in pigs and horses.

## 1.4 Mode of action

DALMAZIN is a sterile aqueous solution containing 75 micrograms/mL of dextrorotatory (d)-cloprostenol, a synthetic analogue of the prostaglandin F<sub>2α</sub>. D-cloprostenol, the dextrorotatory enantiomer constitutes the biologically active component of the racemic cloprostenol molecule and results in an approximate 3.5 fold increase in activity.

Administered in the luteal phase of the oestrus cycle, d-cloprostenol induces functional and morphological regression of the corpus luteum (luteolysis) resulting in a sharp fall in progesterone levels. The increased release of the follicle stimulating hormone (FSH), induces follicular maturation followed by signs of oestrus and ovulation. In pregnant animals, parturition is induced.

## 1.5 Overseas registrations

The product is currently registered in the following countries as DALMAZIN: Albania, Algeria, Argentina (as DALAMPROST-D), Austria, Belgium, Bosnia-Herzegovina, Cyprus, Dominican Republic (as DALAMPROST-D), Estonia, France (as REPROSTENOL), Germany, Greece, Ireland, Israel, Italy, Japan, Korea, Latvia, Lebanon, Lithuania, Luxembourg, Malaysia , Mexico (as DALAMPROST-D), New Zealand, Pakistan, Poland, Portugal, Syria, Spain, Switzerland, Thailand, Turkey, Ukraine, United Kingdom and Uruguay (DALAMPROST-D). In most of the countries, it is registered for the induction of oestrus in mares, synchronisation or induction of oestrus in cows and induction of parturition in cows and sows.

## 2 CHEMISTRY AND MANUFACTURE

### 2.1 Active constituent

The active constituent d-cloprostenol is manufactured overseas. Details of the chemical name, structure, and physicochemical properties of d-cloprostenol are listed below (Tables 1–2).

The active constituent is a white to slightly yellowish very viscous oil or wax material. The d-cloprostenol is slightly soluble in water and ethyl ether, soluble in chloroform and highly soluble in 95 per cent ethanol and acetone. At -12 °C, d-cloprostenol solidifies to form a fragile vitreous mass. The substance is acidic with a pH 4.19 for an aqueous suspension (0.1095 g d-cloprostenol/ 100 mL water). It exhibits specific optical rotation of  $[\alpha]_{25}^D = +20.1^\circ$ / 95 per cent ethyl alcohol;  $c=1$  and  $[\alpha]_{25}^{365} = +61.8^\circ$ / 95 per cent ethyl alcohol;  $c=1$ .

**Table 1: Nomenclature and structural formula of the active constituent (d-Cloprostenol)**

Common name (ISO):	d-Cloprostenol
IUPAC name:	(5Z)-7-[(1R,2R,3R,5S)-2-[(1E,3R)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl]-3,5-dihydroxycyclopentyl]-hept-5-enoic acid
Chemical abstract name	5-Heptenoic acid, 7-[(1R,2R,3R,5S)-2-[(1E,3R)-4-(3-chlorophenoxy)-3-hydroxy-1-buten-1-yl]-3,5-dihydroxycyclopentyl]-, (5Z)-
CAS registry number:	54276-21-0
Molecular formula:	C <sub>22</sub> H <sub>29</sub> ClO <sub>6</sub>
Molecular weight:	424.9 g/mol
Structural formula:	

Table 2: Key physicochemical properties of the active d-Cloprostenol

Common name (ISO)	d-Cloprostenol
Physical form:	Very viscous oil or wax
Colour:	White to slightly yellowish
Melting point:	At -12 °C this substance solidifies to form a fragile vitreous mass
Solubility in water:	Slightly soluble
Organic solvent solubility:	Slightly soluble in ethyl ether, soluble in chloroform, Highly soluble in 95 % ethanol and acetone
PH:	4.19 (aqueous suspension; 0.1095 g d-cloprostenol/ 100 mL water)
Specific optical rotation	[ $\alpha$ ] <sub>25D</sub> = +20.1°/ 95 % ethyl alcohol; c=1 [ $\alpha$ ] <sub>25365</sub> = +61.8°/ 95 % ethyl alcohol; c=1

## 2.2 Formulated product

The product DALMAZIN will be manufactured overseas. Table 3 outlines some key aspects of the formulation and physicochemical properties of the product.

DALMAZIN is a parenteral solution formulation. The product will be formulated overseas, and packaged in 20 mL Type I or Type II colourless neutral glass vials with halogenobutyl based elastomer closures (Type I rubber), flip-off aluminium caps and polypropylene tamper-evident seals, or 100 mL neutral polyethylene bags closed with halogenobutyl based elastomer caps (Type I rubber) and aluminium collars fitted with tamper-proof polypropylene seals. Suitable details of the product formulation, specifications for the ingredients, formulation process and quality control, product specifications, stability data, analytical methods, and details of the packaging were evaluated.

Table 3: Key aspects of the formulation of the product DALMAZIN

Distinguishing name:	DALMAZIN
Formulation type:	Parenteral solution
Active constituent concentration/s:	d-cloprostenol (75 µg/mL)
Description	Clear colourless sterile solution with no visible particles
PH	5.5–6.5

The stability data support the nominated shelf life when the product is stored below 25 °C (air conditioning) in glass vials, or when stored below 30 °C (room temperature) in polyethylene bags. The in-use stability data

show that the product will remain within specification for at least 28 days from the day of first broaching the vial. An in-use shelf life of 28 days is therefore supported.

## 2.3 Recommendations

The APVMA has evaluated the chemistry of the active constituent d-cloprostenol and associated product DALMAZIN, including the manufacturing process, quality control procedures, stability, batch analysis results and analytical methods, and found them to be acceptable.

Based on a review of the chemistry and manufacturing details, the approval of the new active constituent d-cloprostenol and registration of the product DALMAZIN, are supported from a chemistry and manufacturing perspective.

## 3 TOXICOLOGICAL ASSESSMENT

### 3.1 Evaluation of toxicology

The toxicological data submitted on the active constituent, d-cloprostenol, were sufficient to characterise its toxicity and to establish applicable health-based guidance values for the purposes of determining the dietary risk posed by the presence of the residues in treated livestock. The toxicological dataset submitted to the APVMA consisted of acute toxicity, local tolerance, dermal sensitisation and genotoxicity.

The toxicological evaluation also relied upon the 1997 summary report of the Committee for Veterinary Products, European Medicines Agency<sup>2</sup>.

#### Mode of activity

Cloprostenol is a synthetic analogue of prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>). Cloprostenol is a racemic mixture of optically active isomers, d-cloprostenol (dextrorotatory) and l-cloprostenol (leavorotatory), at a ratio of approximately 1:1. d-Cloprostenol [or (+)-cloprostenol] is the optically active enantiomer of cloprostenol which is primarily responsible for the luteolytic activity present in racemic cloprostenol. Administration of d-cloprostenol in various animal species causes functional and morphological regression of the corpus luteum followed by return to oestrus and normal ovulation, and in pregnant animals, the induction of parturition.

#### Toxicokinetics and metabolism

d-Cloprostenol is absorbed following intramuscular (IM) administration, and rapidly distributed to tissues and excreted. Based on data for cloprostenol, it is extensively metabolised mainly by β-oxidation, with the tetranor acid being the main metabolite in most species studied eg rat, marmosets, pigs and cattle. Cloprostenol is completely excreted, with urine being the major route. No specific dermal absorption studies were submitted, but there is information to indicate that d-cloprostenol is absorbed through the skin.

#### Acute toxicity

d-Cloprostenol was of low acute toxicity when given by IM and SC routes to rats and mice and by the dermal route (formulated product) to rats. In mice, the IM LD<sub>50</sub> for d-cloprostenol was approximately 350 mg/kg bw, similar to that of cloprostenol. d-Cloprostenol has a low acute oral toxicity in rats.

#### Repeat-dose toxicity

Information on the toxicity of d-cloprostenol in repeated dose toxicity studies was limited. A published seven day study in rats using various d-cloprostenol derivatives revealed no effects of 15 mg/kg bw/d of test compounds on haematological parameters. The main data available upon which to draw conclusions as to the safety of d-cloprostenol are the data for cloprostenol, which as the racemic mixture, comprises 50 per cent d-cloprostenol. The EMEA summary (1997) refers to R-cloprostenol; this is the same as d-cloprostenol

---

<sup>2</sup> EMEA (1997). Committee for Veterinary Products. Cloprostenol and d-Cloprostenol. Summary Report. EMEA, Veterinary Medicines Evaluation Unit.

used in this report. The worst-case scenario that all the toxic effects observed for cloprostenol are due to d-cloprostenol has been assumed for the APVMA Human Health Risk Assessment.

In rats, the only toxic effect observed following repeated dosing with cloprostenol was vacuolation of the luteal cells of the corpora lutea in the ovary. This is likely to be due to the primary pharmacological activity of the drug. This effect was observed at considerably lower SC doses than oral doses, presumably due to a relatively low oral bioavailability of cloprostenol. Thus, in a three month oral study, 50 µg/kg bw/d was the NOAEL for this effect, whereas in a one month SC study, a NOAEL was not established because vacuolisation was observed at 12.5 µg/kg bw/d. As in rats, an oral NOAEL of 50 µg/kg bw/d was observed in a three month study in marmosets, although the effects observed were different (myocardial changes and an increase in testicular weights). The lowest NOAEL was therefore <12.5 µg/kg bw/d cloprostenol (and by inference, d-cloprostenol) in the one month SC rat study.

No data were available for long-term toxicity studies or carcinogenicity studies.

### Genotoxicity

An acceptable package of genotoxicity studies was submitted. d-Cloprostenol was negative in tests for point mutations and gene mutations and in an *in vivo* micronucleus test in mice. It gave a positive response in the *in vitro* assay for chromosomal aberrations in human lymphocytes (significant only in the presence of metabolic activation and at a high concentration (2320 µg/mL)). Based on the weight of evidence, d-cloprostenol is unlikely to be genotoxic *in vivo*.

### Reproductive and Developmental toxicity

In a three generation oral toxicity study in rats, the NOAEL was 15 µg/kg bw/d cloprostenol (and by inference, d-cloprostenol), with higher doses associated with neonatal viability attributable to prematurity of the offspring. Investigation of the sensitivity of the rat to termination of pregnancy resulting from luteolysis revealed that this varied according to the gestation time when cloprostenol is administered. A dose 25 µg/kg bw of cloprostenol (corresponding to 12.5 µg/kg bw d-cloprostenol, but route and period of gestation not stated) did not terminate pregnancy (EMA, 1997).

Cloprostenol was not teratogenic at oral doses of up to 100 µg/kg bw/d (corresponding to doses of up to 50 µg/kg bw/d d-cloprostenol) in rats, and at SC doses of up to 0.25 µg/kg bw/d (corresponding to doses of up to 0.125 µg/kg bw/d d-cloprostenol) in rabbits (EMA, 1997).

### Studies in humans

Neither d-cloprostenol nor cloprostenol has been developed for medical use in humans, although there is one published paper relating to its application for the treatment of glaucoma (Apostol et al, 1995)<sup>3</sup>. This paper reported on a clinical trial carried out in 23 glaucoma patients aged between 41 and 67 years (average 54 years). There was no control group. The isopropyl ester of d-cloprostenol (0.1 mg/mL eyewash in phosphate buffer solution) was administered once daily (the volume administered was not stated) for three months.

---

<sup>3</sup> Apostol, S., Gafencu, O., Carstocea, B., Selaru, D., Filip, M. and Cocu, F.G. (1995) Use of prostaglandin drugs in the treatment of glaucoma. *Oftalmologia*, XXXIX (3).

Assessment included appearance of the papilla (by direct and stereo-ophthalmoscopy) and visual accuracy which were unchanged over the treatment period. The only local reaction observed was mild hyperemia of the bulbar conjunctiva which was reported to disappear after two to three days of treatment. No systemic reactions were observed.

In *in vitro* studies, human luteal tissue slices from days 18, 21 and 25 of the menstrual cycle were superfused *in vitro* with Medium 199 alone or containing cloprostenol (1 µg/ml). Concentrations of progesterone, oestradiol-17β and prostaglandins F2α and E2 were determined in the superfusate samples. Superfusion with cloprostenol resulted in an initial depression of progesterone and oestradiol-17β but this was not maintained, levels returning to control values or showing an increase, while superfusion with cloprostenol continued. Thus, cloprostenol was not considered to be luteolytic at this dose and under these conditions for human luteal tissue *in vitro* (McDougall et al 1977)<sup>4</sup>.

### Product toxicity

The formulated product, DALMAZIN, was not irritating to the skin of rabbits, but was observed to have skin sensitising potential in the Magnusson-Kligman Maximisation test in guinea pigs. It did not cause local reactions when injected IM in target animal species (cattle and pigs). There were no data for eye irritation.

## 3.2 Health-based guidance values and poisons scheduling

### Poisons scheduling

Cloprostenol is currently listed in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). A reference to a substance in the SUSMP includes every stereoisomer of the substance, and therefore the Schedule 4 listing is applicable for d-cloprostenol.

### Acceptable Daily Intake (ADI)

The Acceptable Daily Intake (ADI) is that quantity of a chemical compound that can safely be consumed on a daily basis for a lifetime.

An Acceptable Daily Intake (ADI) for d-cloprostenol was established at 0.000075 mg/kg bw/d based on a NOAEL of 15 µg/kg bw/d in a three generation oral toxicity study of cloprostenol in rats and applying a 100-fold uncertainty factor to incorporate differences in toxicodynamics and toxicokinetics between species. An additional two fold uncertainty factor was also applied to take into account that this toxicity study used a racemic mixture of cloprostenol.

---

<sup>4</sup> McDougall, A.N., Walker, F.M. and Watson, J. (1977). The effect of cloprostenol on human luteal steroid and prostaglandin secretion *in vitro*. *Br. J. Pharmacol.* 60: 425–431.

### Acute Reference Dose (ARfD)

The Acute Reference Dose (ARfD) is the maximum quantity of a chemical that can safely be consumed over a short period of time, usually in one meal or during one day.

An Acute Reference Dose (ARfD) for d-cloprostenol was considered to be unnecessary due to its low acute toxicity.

## 4 RESIDUES ASSESSMENT

Cloprostenol is a racemic mixture of optically active isomers, d-cloprostenol and l-cloprostenol. Products containing d-cloprostenol are approved for use in the EU. The EMEA assessment of the use of d-cloprostenol in cattle and pigs concluded that MRLs were not required (EMEA/MRL/202/97-FINAL, April 1997).

The exposure of d-cloprostenol to cattle and pigs following the proposed use of DALMAZIN was not greater than that currently approved in Australia for cloprostenol. The proposed dose of d-cloprostenol (given intramuscularly) is 150 µg in cattle and 75 µg in pigs and horses. This is comparable with recommended doses of 500 µg and 175 µg IM for cloprostenol (racemic mixture) in cattle and pigs, respectively.

A non-radiometric study in cows found residues at the injection site (0.09 µg/kg), in the kidneys (0.12 µg/kg) and the liver (0.05 µg/kg) 24 hours following administration of 150 µg d-cloprostenol. Milk contained 0.033 µg/L d-cloprostenol after eight hours, and less than 0.002 µg/L d-cloprostenol after 24 hours.

A radiometric study in pigs given an intramuscular injection of <sup>14</sup>C labelled racemic cloprostenol corresponding to 100 µg/kg of d-cloprostenol found residues equivalent to a maximum d-cloprostenol concentration of 0.43 µg/kg (injection site muscle); 0.05 µg/kg (liver and kidney) and <0.04 µg/kg (muscle and fat) 24 hours after treatment.

The APVMA established an ADI of 0.000075 mg/kg bw for d-cloprostenol. In a worst case scenario, the highest level of residues observed in cattle tissues, milk and pig tissues at 24 hours after treatment is estimated to be less than one per cent of the ADI. This is based on dietary exposure estimates (National Estimated Daily Intake (NEDI) calculations using the mean Australian daily dietary consumption data).

A one day meat withholding period for cattle and pigs and a zero (0) days milk withholding period are supported noting negligible levels of d-cloprostenol were observed 24 hours after treatment and that it is unlikely that animals will be slaughtered for human consumption soon after treatment.

Considering that d-cloprostenol is rapidly eliminated from pigs and cattle and that animals are unlikely to be sent for slaughter immediately after treatment, coverage of the proposed uses in the APVMA MRL Standard as a Table 5 entry was considered appropriate. Table 5 lists uses of substances where MRLs are not necessary. MRLs are not necessary in situations where residues do not or should not occur in foods or animal feeds; or where the residues are identical to or indistinguishable from natural food components; or otherwise are of no toxicological significance.

The following changes to Table 5 of the MRL standard are recommended:

**Table 4: Amendments to the APVMA MRL Standard**

Amendments to Table 5	
Substance	Use
DELETE:	
Cloprostenol	Induction of oestrus in cattle and induction of farrowing in sows and gilts

## Amendments to Table 5

## Substance

## Use

ADD

Cloprostenol (including d-cloprostenol)

Cattle: Induction of oestrus and treatment of clinical conditions associated with the reproductive system

Pigs: Induction of farrowing in sows and gilts

## 5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Cattle meat, milk and offal as well as pig meat and offal are major export commodities.

d-Cloprostenol residues are not expected in cattle meat, offal or milk or pig meat and offal following the proposed use. As discussed above, d-cloprostenol is rapidly eliminated from pigs and cattle and therefore inclusion of d-cloprostenol in Table 5 of the APVMA MRL Standard was considered appropriate. d-Cloprostenol is approved for use in the EU where MRLs are also not required.

The APVMA considers the risk to international trade associated with the proposed use in cattle and pigs is low and not greater than what currently exists for approved products containing cloprostenol.

An Export Slaughter Interval of one day, equal to the meat withholding period, is appropriate for both cattle and pigs

## 6 WORK HEALTH AND SAFETY ASSESSMENT

### 6.1 Health hazards and use pattern

The proposed dose of d-cloprostenol (given intramuscularly (IM)) is 150 µg in cattle and 75 µg in pigs and horses. This compares with recommended doses of 500 µg and 175 µg IM for cloprostenol (racemic mixture) in cattle and pigs, respectively. DALMAZIN is a solution for IM injection and will be packaged in a 20 mL glass vial and a 100 mL plastic bag. This product like existing products containing cloprostenol will be administered principally by veterinarians, although it is expected that the product will also be used by dairy, pig and equine farmers/operators. If the latter is the case, it would be expected that these operators would also be experienced in the handling of veterinary drugs.

DALMAZIN is proposed for the synchronisation of oestrus in cows, with up to two IM doses being given 11 days apart, and for the induction of farrowing in pigs, with two IM doses being given six hours apart. DALMAZIN is also proposed for various therapeutic reproductive indications in cows, with dosing frequency ranging from a single dose to up to three doses given on consecutive days. The number of doses given will depend on the number of herds treated, herd size and frequency of dosing. For cows, synchronisation of oestrus would be expected to be done approximately once per year and for pigs, induction of farrowing would be expected to be done two to three times per year. In horses, synchronisation of oestrus would also be expected to be only done once in a year.

### 6.2 Occupational exposure

#### Exposure during use

Exposure to the product will occur when handling the product (eg when drawing up the product from the vial or bag into the syringe), when injecting the animal or by accidental spillage. The likely routes of exposure are: dermal exposure from accidental spillage, accidental needle-stick/self-injection scenario (most likely via the IM route), oral exposure (most likely by food handling or direct transfer to the mouth from contaminated hands) and ocular exposure (transfer from contaminated fingers and possible splashing following a spillage). Oral and ocular exposure would be expected to be minimal and could be further reduced by washing hands after handling the product. Inhalational exposure is not considered possible under typical conditions.

Accidental exposure events with the product are possible, in which case the entire volume of a vial or bag (up to 100 mL or 7.5 mg d-cloprostenol) could be available in the case of dermal exposure, although this extent of exposure is highly unlikely, as the volume is substantial and most of the solution would be expected to run off the exposed area of skin. The entire contents of a syringe (up to 2 mL or 150 µg d-cloprostenol) could be available in the case of self-injection, and in this scenario, it is possible for the operator to be exposed to 100 per cent of the available dose.

APVMA concluded that a single accidental exposure by either the dermal or IM route at potential worst case scenario doses would not cause adverse effects in the user unless that operator suffered from asthma or other respiratory problems or was pregnant. The label contains adequate warnings similar to other prostaglandins currently registered including those containing cloprostenol.

### Exposure during rehandling

Treatment is systemic, with the product administered IM, so post-application exposure is anticipated to occur only via urine or faeces. Excretion in milk is minimal. Farm operators (dairy cattle, pig and horse establishments) may be exposed to the compound by this means if they are splashed with urine or faeces from recently-treated animals.

d-Cloprostenol is excreted rapidly, and therefore concentrations of the drug/metabolites observed in excreta would be expected to be measurable. While there were no data for d-cloprostenol, urine was the major route of excretion of cloprostenol (50–60 per cent of administered radiolabelled d-cloprostenol). Urine is therefore the matrix expected to have the higher concentrations of drug/metabolites and workers are also more likely to be exposed to urine than faeces. However, such exposure would be expected to be low, particularly in light of the expected extensive metabolism of the drug (based on data for cloprostenol) and the lack of pharmacological activity of the metabolites. Further, such exposure is considered to be below that which may currently occur following use of currently registered products containing cloprostenol. Therefore the proposed product does not increase re-handling exposure to that which might be associated with the use of currently registered products containing cloprostenol.

## 6.3 Public exposure

The general public are not expected to use or come into contact with this product.

## 6.4 Recommendations

The following first aid instructions, safety directions and precautionary (warning) statements are recommended for the product label.

### First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131 126.

### Safety directions

Repeated exposure may cause allergic disorders. Wash hands after use.

## 6.5 Conclusion

The registration of DALMAZIN, containing 75 µg/mL d-cloprostenol for use in cattle, pigs and horses, is supported from a human health perspective.

## 7 ENVIRONMENTAL ASSESSMENT

The environmental assessment applied the standard VICH GL6 guidance for a Phase 1 assessment which applies the total residue approach. The total residue approach assumes 100 per cent of d-cloprostenol administered to the animal is excreted in the waste matrices. The assessment considered both intensively reared animals and pasture animals. Two days of treatment were assumed for cows and sows, while one day of treatment was assumed for mares.

Intensively reared animals are those which are housed indoors throughout the production cycle so treatment with DALMAZIN would be carried out in housing and d-cloprostenol would be excreted in the stable and incorporated into the manure. d-Cloprostenol would then reach the environment when the manure from the stable is spread onto land. Calculation of the potential soil concentrations for intensively reared animals is dependent on the quantity of manure containing d-cloprostenol, which can be spread onto land. The default nitrogen load of 170 kg N/ha was considered representative of the upper limit of nitrogen removal by broad acre crops in Australia. The assessment also assumed 100 per cent of dairy cows, 50 per cent of horses and 50 per cent of sows in a herd were treated. Finally, default body weights for intensively reared animals were applied in the assessment (425 kg for dairy cows, 400 kg for horses, 240 kg for sows).

Pasture animals are those which are on pasture throughout the production cycle, so treatment with DALMAZIN would be carried out in the field and the residue of d-cloprostenol would be excreted directly onto the soil. Calculation of potential soil concentrations for pasture animals is dependent on stocking densities for which default values were applied (3.5 dairy cows per ha, 3 horses per ha, 9.5 female beef cattle per ha). Finally, default body weights for pasture animals were also applied in the assessment (600 kg for dairy cows, 600 kg for horses, 330 kg for female beef cattle).

Under the most conservative methodology, predicted soil concentrations for both intensively reared and pasture animal scenarios were more than an order of magnitude lower than the VICH Phase 1 trigger value of 100 µg/kg soil. VICH guidance indicates that the trigger value of 100 µg/kg soil is considered to be below the levels shown to have ecologically relevant effects for veterinary medicine products in general. Therefore, environmental risks of the proposed use of DALMAZIN were determined to be acceptable.

## 8 EFFICACY AND SAFETY ASSESSMENT

### 8.1 Proposed product use pattern

DALMAZIN is a proposed new veterinary injectable product containing 0.075 mg/mL d-cloprostenol for various reproductive indications in cattle, pigs and horses.

The proposed claims are for induction of oestrus in mares, synchronisation or induction of oestrus in cows and induction of parturition in cows and sows. The product is also indicated for expulsion of mummified foetus, induction of abortion, ovarian dysfunctions (persistent corpus luteum, luteal cyst), treatment, endometritis/pyometra and delayed uterine involution treatment in cows.

The proposed dose of d-cloprostenol given intramuscularly (IM) is 150 µg (0.15 mg) in cattle and 75 µg (0.075 mg) in pigs and horses. This translates to 2 mL of DALMAZIN in cattle and 1 mL of DALMAZIN in pigs and horses.

DALMAZIN is proposed for the synchronisation of oestrus in cows, with up to two intramuscular (IM) doses being given 11 days apart, and for the induction of farrowing in pigs, with two IM doses being given six hours apart. DALMAZIN is also proposed for various therapeutic reproductive indications in cows, with dosing frequency ranging from a single dose to up to three doses given on consecutive days. The number of doses given will depend on the number of herds treated, herd size, frequency of dosing and the condition or disease. For cows, synchronisation of oestrus would be expected to be done approximately once per year and for pigs, induction of farrowing would be expected to be done two to three times per year. In horses, synchronisation of oestrus would also be expected to be done only once in a year.

### 8.2 Efficacy and target crop/animal safety

#### Efficacy

The efficacy data submitted and assessed included dose determination, dose confirmation and field studies.

The trial designs, treatment group sizes, ages and types of animal used, experimental conditions, administration of test and reference products, sample collection and analysis of data were considered appropriate for establishing the efficacy of the test product under normal use conditions for various reproductive indications in cattle, pigs and horses.

#### Cattle

In dose determination and confirmation studies, a dose of 0.15 mg d-cloprostenol (2 mL of DALMAZIN) given intramuscularly was chosen as an effective dose in cattle for the induction of oestrus and for the treatment of ovarian dysfunction, endometritis/pyometra and delayed uterine involution.

Doses of 0.0625, 0.125, 0.25 and 0.5 mg of d-cloprostenol were used during the dose determination trials. Monitoring of luteinising hormone levels in induced cycle in heifers' confirmed that a dose of 0.125 mg of d-cloprostenol IM elicited a similar reduction in plasma progesterone concentrations as that of a registered

product. A slightly higher dose of 0.15 mg d-cloprostenol (corresponding to 2 x 0.075 mg, ie 2 mL of DALMAZIN) was chosen as the recommended dose.

In a comparable field efficacy study, DALMAZIN demonstrated efficacy when compared to a registered product. The applicant further demonstrated the efficacy of the proposed product in three field trials conducted in cattle for all the proposed claims. Two doses, the first dose followed by a second dose 11 days later for the synchronisation of oestrus in cattle was supported by the trials submitted.

A second repeat dose after 11 days for the treatment of endometritis/pyometra and luteal cyst/persistent corpus luteum was also supported by the trials submitted.

### **Pigs**

In dose determination and confirmation studies, a dose of 0.075 mg d-cloprostenol (1 mL of DALMAZIN) given intramuscularly was chosen as an effective dose in pigs for the induction of parturition. Doses of 0.0375, 0.045 mg and 0.075 mg d-cloprostenol were used during the dose determination trials. In a comparable efficacy study, DALMAZIN demonstrated efficacy when compared to a registered product.

DALMAZIN further demonstrated the efficacy in the induction of parturition not earlier than 112 days of pregnancy in a field trial in pigs. The repetition of the dose after six hours or the injection of a myometrial stimulant (oxytocin or carazolol) after 20 hours was supported by field trials data.

### **Horses**

In dose determination, dose confirmation and field studies, a dose of 0.075 mg d-cloprostenol (1 mL of DALMAZIN) given intramuscularly was chosen as an effective dose in mares for the induction of oestrus. Doses of 0.075 mg, as well as a higher dose of 0.1 mg d-cloprostenol, was efficacious in inducing oestrus in mares. In a comparable efficacy study, DALMAZIN demonstrated efficacy when compared to a registered product.

DALMAZIN further demonstrated the efficacy in inducing oestrus in mares in field trials.

### **Animal safety**

In addition to the data discussed below for each species the applicant also submitted post-registration pharmacovigilance data (no species division) for DALMAZIN sold in Italy (1992–98; 1,167,571 doses sold (1 dose = 2 mL), Greece (1994–98; 1,500 doses sold), Spain (1998–99; 1,500 doses sold) and Portugal (1996–98; 38093 doses sold). No adverse reactions were reported in any of these countries.

### **Cattle**

In target animal safety studies in cattle, administered doses of 1X, 3X and 10X the recommended doses of 0.15 mg d-cloprostenol (2mL DALMAZIN) caused transient heart rate (HR) and leucocyte increases and small changes in differential counts were observed at 10X the recommended dose. The changes were not considered major safety concerns.

Tissue irritation studies/local tolerance tests at 3X the recommended dose were well tolerated in cattle.

No adverse events were observed in any of the efficacy studies, including studies which used higher doses than those proposed commercially.

Reproductive safety studies were not provided and none is required because pregnancy rates following treatment with d-cloprostenol did not indicate any adverse effect on fertility. There were also no reports of such adverse effects in the efficacy studies or the pharmacovigilance data provided for DALMAZIN.

### **Pigs**

In target animal safety studies in pigs, administered doses of 1X, 5X and 10X the recommended doses of 0.075 mg d-cloprostenol (1 mL DALMAZIN) caused transient leucocyte increases and small changes in differential counts were observed at 5X and 10X the recommended dose. The changes were not considered major safety concerns.

Tissue irritation studies/local tolerance tests at 3X the recommended dose were well tolerated in pigs.

No reproductive safety studies were submitted. It is noted that piglet viability following treatment with DALMAZIN was comparable to that after treatment with a registered product. Further, there were no reports of any adverse reproductive effects in the efficacy studies or the pharmacovigilance data provided for DALMAZIN.

Few adverse events were observed in one efficacy study. It was impossible to establish whether the cases were related to treatment as similar cases were observed in the other group (positive control) treated with a registered product.

### **Horses**

As in cattle and pigs, IM injections of DALMAZIN (3x the recommended dose) were well tolerated in mares, with little statistical difference between test and control groups in measured parameters.

## **8.3 Recommendations**

The APVMA has evaluated the efficacy and target animal safety data of the proposed product DALMAZIN, and found it to be acceptable. Based on a review of the data submitted, DALMAZIN would be effective and would not be likely to have an unintended effect that is harmful to the target species when used as directed.

## 9 LABELLING REQUIREMENTS

Company Name: ETHICAL AGENTS AUSTRALIA PTY LIMITED

Product Name: DALMAZIN

APVMA Approval No: 66024/52495

Date: 25 May 2019

Label Name:	DALMAZIN
-------------	----------

Signal Headings:	<p>PRESCRIPTION ANIMAL REMEDY</p> <p>KEEP OUT OF REACH OF CHILDREN</p> <p>FOR ANIMAL TREATMENT ONLY</p>
------------------	---

Constituent Statements:	75 micrograms/mL d-cloprostenol.
-------------------------	----------------------------------

Claims:	<p>Solution for injection for cattle (cows), pigs (sows) and horses (mares)</p> <p>Indications (cows) Synchronisation or induction of oestrus, induction of parturition after Day 270 of gestation. Therapeutic indications: Ovarian dysfunction (persistent corpus luteum, luteal cyst), endometritis/pyometra, delayed uterine involution, induction of abortion in the first half of pregnancy and expulsion of mummified foetuses.</p> <p>Indications (sows) Induction of parturition.</p> <p>Indications (mares) Induction of oestrus.</p>
---------	---

Net Contents:	20 mL vial and 100 mL bag.
---------------	----------------------------

Directions for Use:	
---------------------	--

Restrains:	
------------	--

Contraindications:	This product should not be used in gestating animals unless it is desirable to induce
--------------------	---

	<p>parturition or therapeutic induction of abortion.</p> <p>DO NOT inject intravenously.</p> <p>DO NOT use in sows which are expected to have dystocic parturition due to abnormal position of the foetus, mechanical obstruction etc.</p> <p>DO NOT use in animals suffering cardiovascular or respiratory disease or in animals with spastic disease of the respiratory or gastrointestinal tract.</p> <p>DO NOT administer DALMAZIN concurrently with non-steroidal anti-inflammatory (NSAID) drugs since they inhibit endogenous prostaglandin synthesis. The activity of other oxytocic agents can be increased after administration of DALMAZIN (d-cloprostenol).</p>
Precautions:	<p>Use with caution for induction of labour before the 112<sup>th</sup> day of gestation, as administration may cause mortality in piglets and an increase in the number of sows that require manual assistance.</p> <p>Use with caution, as with parenteral administration of any substance, basic antiseptic rules should be observed. The injection site must be thoroughly cleaned and disinfected in order to reduce the risk of infection with anaerobic bacteria.</p>
Side Effects:	<p>At 10 times the therapeutic dose, no adverse reactions were reported. In general, a large overdose could result in the following symptoms; increased pulse and breathing rate, bronchoconstriction, increased body temperature, increased amounts of loose faeces and urine, salivation and vomiting. As no specific antidote has been identified, in the case of overdose, symptomatic therapy is advisable.</p> <p>An overdose will not accelerate corpus luteum regression.</p> <p>Occurrence of anaerobic infection is likely if anaerobic bacteria penetrate the tissue of the injection site. This applies especially to intramuscular (IM) injection and in particular to cows.</p> <p>Typical local reactions due to anaerobic infection are swelling and crepitus at the injection site.</p> <p>When used in cows for induction of parturition and dependent on the time of treatment relative to the date of conception, the incidence of retained placenta may be increased.</p> <p>Behavioural changes seen after treatment for induction of farrowing are similar to those changes associated with natural farrowing and usually cease within one hour.</p> <p>If you notice any serious side effects or other not mentioned in this leaflet, please inform your veterinary surgeon.</p>

<p>Dosage and Administration:</p>	<p>For intramuscular (IM) administration.</p> <p>Use the contents within 28 days of first broaching of the vial. Discard the unused portion.</p> <p><u>Cows</u> Administer 2 mL of DALMAZIN, equivalent to 150 micrograms of d-cloprostenol by intramuscular (IM) injection.</p> <p>Induction of oestrus (also in cows showing weak or silent heat): Administer DALMAZIN after having established the presence of a corpus luteum (6–18<sup>th</sup> day of the cycle), heat usually appears within 48-60 hours. Proceed thereafter with insemination 72–96 hours after injection. If oestrus is not evident, administration of DALMAZIN needs to be repeated 11 days after the first injection.</p> <p>Synchronisation of oestrus: Administer DALMAZIN twice with an interval of 11 days between each dose. Proceed thereafter with two artificial inseminations at intervals of 72 and 96 hours from the second injection.</p> <p>Induction of parturition: Administer DALMAZIN after 270 days of pregnancy. Birth usually results within 30–60 hours of treatment.</p> <p>Mummified foetus: Expulsion of the foetus is observed within 3–4 days after administration of DALMAZIN.</p> <p>Induction of abortion: Administer DALMAZIN in the first half of pregnancy.</p> <p>Ovarian dysfunction (persistent corpus luteum, luteal cysts): Administer DALMAZIN, then proceed to inseminate at the first oestrus after injection. If oestrus is not evident, conduct a further gynaecological examination and repeat the injection 11 days after the first administration. Insemination must always be carried out at 72–96 hours after injection.</p> <p>Endometritis/pyometra: Administer DALMAZIN. If necessary, repeat the treatment after 10-11 days.</p> <p>Delayed uterine involution: Administer DALMAZIN and, if considered necessary, carry out one or two additional treatments at 24 hour intervals.</p> <p><u>Sows</u> Induction of parturition: Administer 1 mL of DALMAZIN, equivalent to 75 micrograms of d- cloprostenol by intramuscular (IM) injection, not earlier than 112 days of pregnancy. Repeat after 6 hours.</p>
-----------------------------------	--

	<p>Alternatively, 20 hours after the initial dose of DALMAZIN, a myometrial stimulant (oxytocin or carazolol) may be administered.</p> <p>Following the protocol of the double administration, approximately 70–80% of animals will give birth during the interval between 20–30 hours after the first administration.</p> <p><u>Mares</u> Induction of oestrus: Administer 1 mL of DALMAZIN, equivalent to 75 micrograms of d-cloprostenol by intramuscular (IM) injection when induction of oestrus is required.</p>
--	--

General Directions:	<p>DALMAZIN is a sterile aqueous solution containing 75 micrograms/mL of dextrorotatory (d)-cloprostenol, a synthetic analogue of the prostaglandin F2<math>\alpha</math>.</p> <p>Administered in the luteal phase of the oestrus cycle, d-cloprostenol induces functional and morphological regression of the corpus luteum (luteolysis) resulting in a sharp fall in progesterone levels. The increased release of the follicle stimulating hormone (FSH), induces follicular maturation followed by signs of oestrus and ovulation.</p> <p>Pharmacokinetic studies demonstrate a rapid absorption of d-cloprostenol. Following intramuscular (IM) administration of 150 micrograms of d-cloprostenol in the cow, the peak plasma level (<math>C_{max}</math>) of 1.4 micrograms/L is reached after approximately 90 minutes, while the elimination half-life (<math>t_{1/2\beta}</math>) is in the order of 1 hour 37 minutes.</p> <p>In sows, a <math>C_{max}</math> of approximately 2 micrograms /L is observed between 30–80 minutes following administration of 75 micrograms d-cloprostenol, with an elimination half-life in the order of 3 hours 10 minutes.</p>
---------------------	---

Withholding Periods:	<p>WITHHOLDING PERIODS: CATTLE &amp; PIGS MEAT: DO NOT USE less than 1 day before slaughter for human consumption. MILK: Zero (0) days. HORSES: DO NOT USE in horses that may be used for human consumption.</p>
----------------------	--

Trade Advice:	<p>EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 1 day before slaughter for export. Before using this product, confirm the current ESI from Ethical Agents Australia Pty Limited on +64 9262 1388.</p>
---------------	--

Safety Directions:	<p>Repeated exposure may cause allergic disorders. Wash hands after use.</p>
--------------------	--

First Aid Instructions:	<p>If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131 126.</p>
-------------------------	--

First Aid Warnings:	
---------------------	--

Additional User Safety:	<p><b>ADDITIONAL USER SAFETY INFORMATION</b></p> <p>Prostaglandins of the F2<math>\alpha</math> type can be absorbed through the skin and may cause bronchospasm or miscarriage.</p> <p>Care should be taken when handling the product to avoid self-injection or skin contact.</p> <p>Women of child-bearing age, asthmatics and people with bronchial or other respiratory problems should avoid contact with, or wear disposable plastic gloves when administering the product.</p> <p>Accidental spillage on the skin should be washed off immediately with soap and water.</p> <p>In case of accidental self-injection seek medical advice and show the label to the physician.</p> <p>Should shortness of breath result from accidental inhalation or injection, seek urgent medical advice.</p> <p>Do not eat, drink or smoke while handling the product.</p>
-------------------------	--

Environmental Statements:	
---------------------------	--

Disposal:	Dispose of container by wrapping with paper and putting in garbage.
-----------	---

Storage:	<p>[20 mL vial] Store below 25 °C (air conditioning). Keep container in outer carton. Protect from light. Do not freeze.</p> <p>[100 mL bag] Store below 30 °C (room temperature). Keep container in outer carton. Protect from light. Do not freeze.</p> <p>After broaching, the sample should be stored in an upright position. Use the contents within 28 days of first broaching of the vial. Discard the unused portion.</p>
----------	---

APVMA approval no:	66024/52495
--------------------	-------------

## ABBREVIATIONS

ADI	Acceptable Daily Intake (for humans)
ARfD	Acute Reference Dose
Bw	bodyweight
DT <sub>50</sub>	Time taken for 50% of the concentration to dissipate
EI	Export Interval
ESI	Export Slaughter Interval
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Haematocrit
Hb	Haemoglobin
HPLC	High Pressure Liquid Chromatography or High Performance Liquid Chromatography
id	intradermal
IM	intramuscular
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
L	Litre
LC <sub>50</sub>	concentration that kills 50% of the test population of organisms
LD <sub>50</sub>	dosage of chemical that kills 50% of the test population of organisms
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet

---

NOEC/NOEL	No Observable Effect Concentration Level
NOAEL	No Observed Adverse Effect Level
ppm	parts per million
RBC	Red Blood Cell Count
REI	Re-Entry Interval
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
µg	microgram
VICH	VICH is a trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration. Its full title is the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHP	Withholding Period

---

## 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 a material from or through 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	Repels water
Metabolism	The chemical processes that maintain living organisms
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

Apostol, S, Gafencu, O, Carstocea, B, Selaru, D, Filip, M and Cocu, F.G. 1995, *Use of prostaglandin drugs in the treatment of glaucoma*. *Oftalmologia*, XXXIX (3).

APVMA 2017, *Data Guidelines*, Australian Pesticides and Veterinary Medicines Authority, Canberra, available at [apvma.gov.au/registrations-and-permits/data-guidelines?qt-data\\_guideline\\_tabs=1#qt-data\\_guideline\\_tabs](http://apvma.gov.au/registrations-and-permits/data-guidelines?qt-data_guideline_tabs=1#qt-data_guideline_tabs).

EMA 1997, Committee for Veterinary Products. *Cloprostenol and d-Cloprostenol. Summary Report*. EMA, Veterinary Medicines Evaluation Unit.

Mcdougall, A.N., Walker, F.M. and Watson, J. 1977, *The effect of cloprostenol on human luteal ,steroid and prostaglandin secretion in vitro*. *Br. J. Pharmacol.* 60: 425–431.