Australian Government

Australian Pesticides and Veterinary Medicines Authority

Public Release Summary

on the evaluation of the new active constituent oestradiol cypionate in the product CIPIOSYN

APVMA product number 85382

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This publication is available from the APVMA website.

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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 CIPIOSYN 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 6 October 2020 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 organisation name (if relevant)
- email or postal address (if available)
- the date you made the submission.

Please note: submissions will be published on the APVMA's website, unless you have asked for the submission to remain confidential, or if the APVMA chooses at its discretion not to publish any submissions received (refer to the public consultation coversheet).

Please lodge your submission using the public consultation coversheet, which provides options for how your submission will be published.

Note that all APVMA documents are subject to the access provisions of the *Freedom of Information Act 1982* and may be required to be released under that Act should a request for access be made.

Unless you request for your submission to remain confidential, the APVMA may release your submission to the applicant for comment.

Written submissions should be addressed to:

Case Management and Administration Unit

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Sydney NSW 2001

Phone: +61 2 6770 2300

Email: 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.

1 INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of CIPIOSYN, and approval of the new active constituent, oestradiol cypionate.

1.1 Applicant

SYNTEX S.A.

1.2 Purpose of application

SYNTEX S.A. has applied to the APVMA for registration of the new product CIPIOSYN, as an injectable solution, containing 0.5 mg/mL of the new active constituent oestradiol cypionate.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of the product CIPIOSYN, and approval of the new active constituent oestradiol cypionate.

1.3 Proposed claims and use pattern

CIPIOSYN (0.5 mg/mL oestradiol cypionate) is a solution for injection, to induce oestrus and ovulation in cattle as part of a reproductive management programme. The product will be administered by intramuscular injection at the doses of 1 to 2 mL per animal (0.5–1.0 mg oestradiol cypionate).

1.4 Mode of action

Estradiol is the most potent form of the mammalian estrogenic steroids and acts as the major female sex hormone. Oestradiol cypionate diffuses through the cell membrane and binds to and subsequently activates the nuclear estrogen receptor found in the reproductive tract, breast, pituitary, hypothalamus, liver, and bone. The activated complex binds to the estrogen response element on the DNA and activates the transcription of genes involved in the functioning of the female reproductive system and secondary sex characteristics.

1.5 Overseas registrations

The product is currently registered in Argentina, Bolivia, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru and Uruguay.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

The active constituent oestradiol cypionate will be manufactured overseas. Details of the chemical name, structure, and physicochemical properties of oestradiol cypionate are listed below (Tables 1–2).

Oestradiol cypionate is a white or almost white, odourless crystalline powder. It is insoluble in water, slightly soluble in chloroform, dioxane and soluble in acetone. It is sparingly soluble in ethanol and vegetable oil.

Table 1: Nomenclature and structural formula of the active constituent oestradiol cypionate

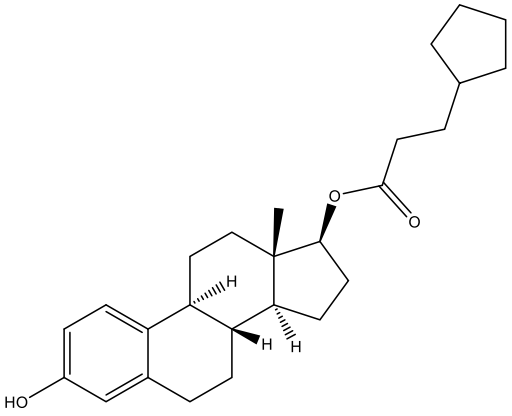
Common name (ISO):	Oestradiol cypionate
IUPAC name:	[(8*R*,9*S*,13*S*,14*S*,17*S*)-3-hydroxy-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthren-17-yl] 3-cyclopentylpropanoate
CAS registry number:	313-06-4
Molecular formula:	$C_{26}H_{36}O_3$
Molecular weight:	396.57 g/mol
Structural formula:	

Table 2: Key physicochemical properties of the active constituent oestradiol cypionate

Appearance:	White or almost white, odourless crystalline powder (purified active: 97.0–103.0% purity)
Melting point:	Between 149°C–153°C
Stability:	At long-term storage conditions (25°C /60% RH), oestradiol cypionate is stable for at least 36 months and at accelerated conditions (40°C / 75% RH) for up to 6 months and is unlikely to be adversely affected under stress conditions (high humidity, moisture content and light exposure) for up to 10 days.
Safety properties:	Not considered flammable. Not explosive.
Solubility in water:	Insoluble in water
Organic solvent solubility:	Slightly soluble in chloroform and dioxane. Sparingly soluble in ethanol and vegetable oil and soluble in acetone.
UV/VIS absorption spectra:	λ_{max} 251–281 nm
Optical rotation:	+39° – +44°

2.2 Formulated product

The product CIPIOSYN will be manufactured overseas. Tables 3 and 4 outline some key aspects of the formulation and physicochemical properties of the product.

CIPIOSYN will be available in 50 mL and 100 mL amber glass type II vials.

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

Distinguishing name:	CIPIOSYN
Formulation type:	Solution for injection
Active constituent concentration/s:	0.5 mg/mL

Table 4: Physicochemical properties of the product CIPIOSYN

Physical form:	Pale yellow oily liquid
Density:	0.900–0.940
Safety properties:	Not explosive
Storage stability:	There was sufficient data to conclude that the product is expected to remain within the nominated shelf life when stored below 25°C (air conditioning).

2.3 Recommendations

The APVMA has evaluated the chemistry of the active constituent oestradiol cypionate and associated product CIPIOSYN, including the manufacturing process, quality control procedures, physicochemical properties, spectra, stability, batch analysis results and analytical methods, and found them to be acceptable. The available storage stability data indicate that the formulated product is expected to remain stable for the nominated shelf life when stored below 25°C.

The registration of CIPIOSYN, and approval of the active constituent oestradiol cypionate, are supported from a chemistry perspective.

3 TOXICOLOGICAL ASSESSMENT

3.1 Evaluation of toxicology

It is considered that the human health risk posed is acceptable according to the safety criteria stipulated in Section 5A of the *Agricultural and Veterinary Chemicals Code Act (1994).*

Chemical class

Oestradiol cypionate is a new type of oestradiol ester for induction of oestrus in cattle.

Pharmacokinetics

Following oral dosing, oestradiol is inactivated in the intestinal tract or in the liver. In the bloodstream, oestradiol is bound to plasma proteins, and oestrogens are eliminated in faeces and urine.

Acute toxicity (active constituent)

Oestradiol is of low acute oral toxicity.

Acute toxicity (product)

CIPIOSYN is of low acute oral toxicity.

Repeat-dose toxicity

Repeat dose toxicity is related to the physiological function of oestradiol, and adverse effect seen in animals are associated with oestrogenic activity. Hormonal effects are seen at much lower doses than other toxicological responses.

Chronic toxicity and carcinogenicity

As steroid hormones promote cell proliferation, they can facilitate carcinogenicity in target tissues.

Reproductive and developmental toxicity

Adverse effects on reproduction were observed in rats, related to the hormonal effects of oestradiol.

Genotoxicity

There is no adequate evidence that 17β-oestradiol is mutagenic in bacterial or mammalian cell test systems.

Mode of action (toxicology)

Repeat dose toxicity is related to the physiological function of oestradiol, and adverse effect seen in animals are associated with oestrogenic activity.

Reports related to human toxicity

Oestrogens are used routinely as oral contraceptives and for hormone replacement in humans. They are among the most commonly prescribed drugs and include the parent molecule, its esters, and other synthetic steroidal and non-steroidal derivatives. Estrogens can be delivered orally, by intramuscular injection, or percutaneously. The main concern associated with use of estrogens for these purposes is a possibly increased risk for cancer; other side-effects may include hypertension, thromboembolic and other vascular diseases, breakthrough bleeding, gall-bladder disorders, nausea, migraine, and mood changes. The progestational component of combined hormonal therapy may be responsible for some of these effects.

3.2 Health-based guidance values and poisons scheduling

Poisons standard

Estradiol (cross referenced as oestradiol) is in Schedule 4 and 5 of the SUSMP. It is in Schedule 5 when in implant preparations for growth promotion in animals and in Schedule 4 for all other uses. Estradiol is also included in Appendix G for dilute preparations. Schedule 4 is relevant for the proposed product.

Health-based guidance values

Acceptable daily intake

The establishment of an ADI for 17β-oestradiol and its esters has been considered to be unnecessary because residues from treatment are not distinguishable from naturally occurring levels.

Acute reference dose

The establishment of an ARfD for 17β-oestradiol and its esters has been considered to be unnecessary because residues from treatment are not distinguishable from naturally occurring levels.

3.3 Recommendations

There are no concerns on human health grounds to the registration of the product CIPIOSYN, containing 0.5 mg/mL of oestradiol cypionate when the product CIPIOSYN is used as directed on the label.

4 RESIDUES ASSESSMENT

The metabolism of oestradiol cypionate and other oestradiol salts (which are approved in Australia) has been described in lactating and non-lactating beef and dairy cattle, with and without presence of endogenous oestradiol-17β produced by ovarian follicles. These studies were conducted in multiparous, and primiparous, lactating and non-lactating, dairy cattle. The comparative metabolism of oestradiol cypionate in lactating and non-lactating animals can be expected to be the same as other oestradiol salts.

The available information indicates that the level of 17β-oestradiol in cattle tissues from the proposed use oestradiol cypionate should not be greater than that expected in untreated cattle. The APVMA Health Assessment Team concluded that the establishment of an ADI or ARfD for 17β-oestradiol and its esters has been considered to be unnecessary because residues from treatment are not distinguishable from naturally occurring levels.

Table 5 of the APVMA MRL standard 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. As residues are indistinguishable from natural food components, a Table 5 entry for oestradiol cypionate ‘for reproductive management in cattle’ is considered appropriate.

A meat withholding period (WHP), export slaughter interval (ESI) and milk withholding period of zero days is acceptable for the proposed use as residues are indistinguishable from natural food components. It is noted that while a zero day withholding period and ESI is supported, it is considered unlikely that treated animals will be slaughtered for human consumption, or will be milked, soon after treatment given the proposed claim is to induce oestrus and ovulation in cattle as part of a reproductive management program.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Given that residues of oestradiol cypionate are indistinguishable from naturally occurring levels in cattle meat, offal and milk, the risk to international trade associated with the proposed use of oestradiol cypionate for reproductive management is considered to be low.

6 WORK HEALTH AND SAFETY ASSESSMENT

6.1 Health hazards

Since the active constituent is a hormone intended to be injected, no toxicity studies involving oral, inhalation or dermal routes of exposure were submitted.

6.2 Occupational exposure

Exposure during use

The product will be injected intramuscularly into cows either by a registered veterinary surgeon or under their supervision. As an injectable product, an exposure to the product via oral or dermal route is unlikely to occur.

The user of the product may, however, be exposed if accidental self-injection (needle stick injury) which can lead to internal/subcutaneous exposure to the product. The exposure in this case is likely to be a very minute amount and infrequent.

Exposure during re-entry or rehandling

As the product is intended for intramuscular injection, no exposure is anticipated from rehandling treated animals.

6.3 Public exposure

The product is not intended for use by members of the public, and the method of administration will not result in bystander exposure.

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 131126; New Zealand 0800 764 766.

Safety directions

Nil

Precautionary (warning) statements

Nil

7 ENVIRONMENTAL ASSESSMENT

7.1 Fate and behaviour in the environment

Based on excretion data and field monitoring data from manure storage structures on feedlots, it has been determined that the principal metabolite of CIPIOSYN found in beef cattle manure is oestradiol-17α. However, minor amounts of the other metabolites (oestradiol-17β and estrone) are also excreted. In addition, oestradiol-17α is expected to be rapidly transformed in the soil and aquatic environments to estrone, and minor amounts of the 17β isomers. Thus, the environmental risks of the primary metabolites were assessed. Because the structures and many of the physical-chemical properties of the oestradiol metabolites are quite similar, it was assumed that they will be transported, transformed, and degraded similarly in the environment. Thus, a single surrogate oestradiol compound was defined and modelled in the exposure assessment and used for characterizing risk.

Because the metabolites of oestradiol occur naturally and have been shown to be metabolized rapidly by mammals and fish, bioaccumulation is not expected to occur for oestradiol metabolites. Reported partition coefficients (log K_{ow}) values ranged 3.1 to 3.7. Furthermore, the bioconcentration factor (BCF) in fish was determined to be 336–624, which is well below the trigger of 2,000 for PBT (persistent, bioaccumulative, and toxic) substances. As such, oestradiol cypionate and its metabolites are not classified as PBT substances.

7.2 Effects and associated risks to non-target species

Oestradiol-17β appears to have no significant effects on aquatic invertebrates at concentrations <0.00040 mg/L, while effects on the sex ratio and onset of metamorphosis in amphibians can occur at concentrations ≤0.00020 mg/L. A lowest observable effect concentration (LOEC) associated with fish reproduction endpoints was reported at 0.0000087 mg/L of oestradiol-17β. Therefore, based on available literature data, fish are the most sensitive sentinel taxonomic group of aquatic organisms to evaluate the effects of exposure to oestradiol. Further, oestradiols are known to affect the endocrine system, and reproduction-related endpoints (eg, fecundity, sex ratio, embryo fertilization, etc) are the most sensitive endpoints available indicative of potential population-level impacts. Biomarkers, such as vitellogenin (VTG), are often sensitive measures of exposure, but these endpoints are not necessarily predictive of reproduction and/or population-level effects at any particular concentration. The risk assessment therefore focused on the potential for effects on fish reproductive-related endpoints following chronic exposure to the active metabolites of concern (oestradiol-17β, oestradiol-17α, estrone, estriol) excreted from cattle following the use of CIPIOSYN. Based on the regulatory acceptable concentrations established for each of the metabolites of concern, runoff risks were determined to be acceptable following use in dairy cattle at the screening level (tier 1) and in beef cattle at the ‘edge of field’ (tier 2).

7.3 Recommendations

The risk assessment had regard to the toxicity of the constituents and its residues, including metabolites and degradation products, in relation to ecosystems and relevant organisms. Based on the outcome of the risk assessment, the APVMA can be satisfied under s 14 of the *Agricultural and Veterinary Chemicals Code Act 1994* that the proposed use of CIPIOSYN meets the safety criteria with respect to s 5A(1)(c), and the label meets the labelling criteria under s 5D(1), with respect to environmental considerations.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product use pattern

CIPIOSYN (0.5 mg/mL oestradiol cypionate) is a proposed new veterinary injectable product containing new active constituent oestradiol cypionate to induce oestrus and ovulation in cattle as part of a reproductive management programme.

The proposed claims are for induction of oestrus and ovulation in cattle as part of a regimen to synchronise oestrus. The product is intended as an alternative to oestradiol benzoate as the oestradiol cypionate is proposed to have a longer duration of action, eliminating the need for an additional yarding of cattle at 24 to 48 hours after removal of the progesterone intravaginal device.

The product will be administered by intramuscular (IM) injection at the doses of 1 to 2 mL per animal (0.5–1.0 mg oestradiol cypionate).

Mode of action related to the efficacy of the product

The data provided supported a lower Cmax, a longer Tmax and a comparable AUC for 1.0 mg oestradiol cypionate IM compared to 1.0 mg oestradiol benzoate IM in the lactating Holstein dairy cow. Accordingly, the data thus demonstrated that oestradiol cypionate had a longer onset of action, a lower peak effect and a longer duration of action than oestradiol benzoate in terms of producing a luteinising hormone (LH) surge. Induction of ovulation is achieved by removing the source of progesterone (eg progesterone intravaginal device) or waiting for progesterone levels to decrease after injection, followed by administration of an agent/agents to stimulate ovulation.

Administration of oestradiol during the pro-oestrus phase induced by progesterone priming in cattle (eg following removal of the intravaginal insert containing progesterone), induces the release of endogenous gonadotrophins, particularly. This results in both stimulation and acceleration of the developing and maturing dominant follicle, and oestrus and ovulation to follow. Therefore, the intramuscular injection of oestradiol cypionate at the time of removal of progesterone intravaginal device increases the expression of oestrus, facilitates synchronisation of oestrus and fixed-time artificial insemination (FTAI), eliminating the need for an additional yarding of animals for oestradiol benzoate injection 24 to 48 hours after removal of the progesterone intravaginal device prior to FTAI.

Protocol for Synchronization of oestrus:

A DIB-H (progesterone 0.5 g/device) or DIB-V (progesterone 1 g/device) is inserted. The cow is injected with 2 mg of oestradiol benzoate at insertion. Removal of the device (DIB-H or DIB-V) is done at seven days after insertion and a cow injected with PGF2α (or analogue) at manufacturer's recommended dose and 1–2 mL oestradiol cypionate based on the bodyweight/body condition score (BCS).

If fixed time artificial insemination (AI) is to be used then it should be carried out at 48 hours after device removal.

8.2 Efficacy and target crop/animal safety

Efficacy

The efficacy data submitted and assessed included published studies on the use of the applicant's proposed product and active constituent (oestradiol cypionate) in beef and dairy cattle.

Adequate published data was provided to support the proposed product claim: 'To induce oestrus and ovulation in cattle as part of a reproductive management programme' when the applicant formulation was administered as a single dose of 0.5–1.0 mg per dose IM. Studies (dose confirmation and field) were conducted overseas in beef and dairy cattle breeds that are represented in Australia. Management systems were similar to those that are found in Australia. The proposed product formulation and another oestradiol cypionate formulation were used in reproductive protocols in female cattle that were intended to synchronise oestrus within a herd to facilitate fixed time artificial insemination (FTAI), or fixed time embryo transfer (FTET).

The data supports that the proposed product has a longer half-life and a longer duration of action than the reference product containing oestradiol benzoate. The applicant provided acceptable scientific argument whenever an alternative formulation was used in the efficacy studies. The data provided demonstrated that synchronization regimen using oestradiol benzoate requires the animals to be yarded and handled four times; insertion of PID, removal of PID, administration of oestradiol benzoate 24 hours later, and FTAI. This is compared to the synchronization regimen using oestradiol cypionate that requires the animals to be yarded and handled three times: insertion of PID, removal of PID together with oestradiol cypionate administration and then FTAI.

Animal safety

The published data provided documented use of the oestradiol cypionate formulation in Holstein dairy cattle in the USA given at five to eight days post parturition at an overdose of 4 or 10 mg IM in primiparous and multiparous cows. A delay in time to first ovulation was observed and this was consistent with the expected pharmacological effects of oestradiol cypionate. Lower conception rates were observed in multiparous cows receiving 4 mg oestradiol cypionate. No adverse effects on the incidence of mastitis or milk yield were observed. No other adverse effects were reported in cattle that were treated with 4 or 10 mg of the formulation. The applicant provided acceptable scientific arguments to indicate that the formulation differences between the proposed product and the formulation used in the safety study would not have an impact on safety.

The safety of the proposed product was also supported by a number of efficacy studies where no adverse events were observed.

The APVMA confirmed that no adverse events have been reported in applicant's reference product containing another oestradiol ester product with a comparable formulation. Based on the data provided including efficacy, the applicant's formulation is unlikely to cause any adverse events if used according to label directions.

The use of this product is not likely to have an unintended effect that is harmful to the target animals. This product is not intended for use in pregnant animals and a contraindication statement will be included on the label.

8.3 Recommendations

The APVMA has evaluated the efficacy and target animal safety data of the proposed product CIPIOSYN, and found it to be acceptable. Based on a review of the data submitted, CIPIOSYN 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: SYNTEX S.A

Product Name: CIPIOSYN

APVMA Approval No: 85382 / 113108

Date: 02 September 2020

Label Name:	CIPIOSYN

Signal Headings:	PRESCRIPTION ANIMAL REMEDY KEEP OUT OF REACH OF CHILDREN FOR ANIMAL TREATMENT ONLY

Constituent Statements:	0.5 mg/mL oestradiol cypionate

Claims:	To induce oestrus and ovulation in cattle as part of a reproductive management programme.

Net Contents:	50 mL 100 mL

Directions for Use:	

Restraints:	

Contraindications:	This product should not be used in pregnancy, as administration of high doses to pregnant cattle may cause abortion.

Precautions:	Concomitant use of corticosteroid agents can cause an increase in glucocorticoid effects.
Side Effects:	
Dosage and Administration:	Use the contents within 24 hours of first broaching of the vial. Discard the unused portion.

	Administer by intramuscular injection. Administer a dose of 1-2 mL per animal (corresponding to 0.5 -1.0 mg oestradiol cypionate) as part of a reproductive management programme. The product needs to be injected at the time of removal of progesterone intravaginal device. Protocol for Synchronization of oestrus: Insert DIB-H (progesterone 0.5 g/device) or DIB-V (progesterone 1 g/device). Inject the cow with 2 mg of oestradiol benzoate at insertion. Remove the device (DIB-H or DIB-V) 7 days after insertion and inject cow with PGF2α (or analogue) at manufacturer's recommended dose and 1-2 mL oestradiol cypionate based on the bodyweight/BCS. If fixed time AI is to be used then it should be carried out at 48 hours after device removal.
General Directions:	This product is indicated as an alternative to oestradiol benzoate as ovulation inducer. The second injection of oestardiol benzoate in the oestrus synchronisation protocol 24-48 h after removal of intravaginal device is replaced with an injection of oestradiol cypionate at the time of removal of the device.
Withholding Periods:	MEAT: Zero (0) days. MILK: Zero (0) days.
Trade Advice:	EXPORT SLAUGHTER INTERVAL (ESI): Zero (0) days. Before using this product, confirm the current ESI from the distributor, Minitube Australia Pty Limited on 0353428688 or the APVMA website (www.apvma.gov.au/residues)
Safety Directions:	
First Aid Instructions:	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131 126.
First Aid Warnings:	
Additional User Safety:	

Environmental Statements:	Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers.
Disposal:	DO NOT dispose of unused product in any way other than surrender to an approved retailer or wholesaler. Dispose of empty container by wrapping with paper and putting in garbage. Discarded needles should immediately be placed in a designated ‘sharps’ container.
Storage:	Store below 25 ºC (Air conditioning). Protect from light. Do not freeze.

ABBREVIATIONS

ACCS/ACMS	Advisory Committee for Chemicals Scheduling/Advisory Committee for Medicines Scheduling
ADI	Acceptable daily intake (for humans)
AI	Artificial insemination
ARfD	Acute reference dose
AUC	Area under the curve
BCF	Bioconcentration factor
CL	Corpus luteum
C_{max}	Maximum concentration
eCG	Equine chorionic gonadotropin
EEC	Estimated Environmental Concentration
ESI	Export Slaughter Interval
ET	Embryo transfer
FTAI	Fixed time artificial insemination
FTET	Fixed time embryo transfer
GnRH	Gonadotropin releasing hormone
IM	Intramuscular
LH	Luteinising hormone
LOEC	Lowest observable effect concentration
Log K_{OW}	Log to base 10 of octanol water partitioning co-efficient, synonym P_{OW}
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
P4	Progesterone
PID	Progesterone-releasing intravaginal device
NOAEL	No Observed Adverse Effect Level
NOEC/NOEL	No Observable Effect Concentration Level

NORG	Norgestomet ear implant
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
T_{max}	Time to reach C_{max}
VTG	Vitellogenin
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
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
Metabolism	The chemical processes that maintain living organisms
Subcutaneous	Under the skin
Toxicology	The study of the nature and effects of poisons

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