Australian Government

Australian Pesticides and Veterinary Medicines Authority

Public Release Summary

On the evaluation of the new active zilpaterol hydrochloride in the product Zilmax Medicated Premix

APVMA product number 67405

May 2020

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 and full licence terms are available from Creative Commons.

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.

Photographic credits
Cover image: iStockphoto (www.istockphoto.com)
iStockphoto images are not covered by this Creative Commons licence.

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
GPO Box 3262
Sydney NSW 2001 Australia

Telephone: +61 2 6770 2300

Email: communications@apvma.gov.au.

This publication is available from the APVMA website.

CONTENTS

LIST OF TABLES

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 approval of the active constituent zilpaterol hydrochloride and registration of the product Zilmax Medicated Premix 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 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 June 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 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)[1] 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

GPO Box 3262

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] A full definition of "confidential commercial information" is contained in the Agvet Code.

1 INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed approval of the new active constituent, zilpaterol hydrochloride and registration of the product Zilmax Medicated Premix.

1.1 Applicant

Intervet Australia Pty Ltd.

1.2 Purpose of application

Intervet Australia Pty Ltd has applied to the APVMA for registration of the new product Zilmax Medicated Premix, as an oral medicated premix formulation containing 48 g/kg of the new active constituent zilpaterol hydrochloride.

1.3 Proposed claims and use pattern

Zilmax Medicated Premix is indicated for increased carcass leanness, increased dressing percent, improved rate of body weight gain and improved feed efficiency in cattle fed in confinement for slaughter during the last 20 days on feed. Zilmax Medicated Premix will be administered to manufactured feeds at 8.3 g zilpaterol hydrochloride per tonne (8.3 mg/kg in the feed) on a 100 per cent dry matter basis to derive a daily dose of 43–128 mg, depending on body weight and consumption rates. Zilmax Medicated Premix can also be added to liquid feeds intended for addition to dry feeds and consumed at the same daily dose of 43–128 mg, depending on body weight and consumption rates.

1.4 Mode of action

Zilpaterol is a beta II- adrenergic receptor agonist. It improves growth rate, increases skeletal muscle content and reduces body fat content. Beta II- adrenergic agonists enhance animal growth by binding to beta II-adrenergic receptors on skeletal muscle cells and adipocytes. When bound to receptors, the biochemical processes of tissue growth are modified by increasing lipolysis, decreasing lipogenesis, decreasing protein degradation, and increasing protein synthesis.

1.5 Overseas registrations

The product is currently registered in the USA and Canada as Zilmax® (48 g/kg zilpaterol hydrochloride), for increased rate of weight gain, improved feed efficiency, and increased carcass leanness in cattle fed in confinement for slaughter during the last 20 to 40 days on feed. It is also registered in Brazil, Colombia, Costa Rica, Dominican Republic, Guatemala, Honduras, Kazakhstan, Mexico, Nicaragua, Panama, Peru, South Africa and South Korea.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

The active constituent zilpaterol hydrochloride is a beta II- adrenergic agonist intended for use as a medicated premix for administration to cattle fed in confinement for slaughter. Zilpaterol hydrochloride is not described in any pharmacopeia monographs. Details of the chemical name, structure, and physicochemical properties of zilpaterol hydrochloride are listed below (Tables 1–2).

Table 1: Nomenclature and structural formula of the active constituent zilpaterol hydrochloride

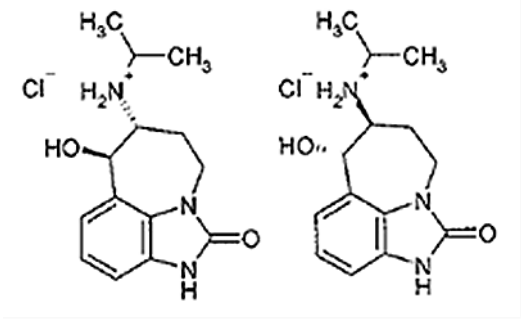
Common name (ISO):	Zilpaterol hydrochloride
IUPAC name:	IUPAC: (6*RS*,7*RS*)-7-Hydroxy-6-(isopropylamino)-4,5,6,7-tetrahydro-imidazo[4,5,1-jk]-[1]benzazepin-2(1H)-one hydrochloride (1:1) Chemical Abstracts: Trans-(±)-4,5,6,7-tetrahydro-7-hydroxy-6-[(1-methylethyl)amino]-imidazo[4,5,1-jk][1]benzazepin- 2(1H)-one, monohydrochloride
CAS registry number:	119520-06-8
Molecular formula:	$C_{14}H_{19}N_3O_2.HCl$
Molecular weight:	297.78
Structural formula:	

Table 2: Key physicochemical properties of the active constituent zilpaterol hydrochloride

Physical form:	A white to slightly yellow anhydrous powder
Melting point:	>200°C
Solubility in water:	Soluble in water: 150 g/l
Organic solvent solubility:	Slightly soluble in methanol Insoluble in chloroform, ethanol, acetone and toluene
Dissociation constant (PK_a):	pKa 8.09 at 26°C
Octanol/water partition coefficient (Log K_{ow}/K_{OW}):	Log Kow < 1 at pH 5,7,9 and at 25°C
Vapour pressure:	8×10^{-6} Pa at 25°C
Particle size distribution:	NMT 5% for fraction less than or equal to 15 µm, NMT 10% for fraction not smaller than 200 µm, NMT 0.5% for fraction not smaller than 300 µm

The chemistry aspects of zilpaterol hydrochloride active constituent (manufacturing process, quality control procedures, batch analysis results and analytical methods) have been considered and found to be acceptable.

2.2 Formulated product

Zilmax Medicated Premix is a granular formulation that will be administered in feed. The product will be formulated overseas, and packaged in 10 kg multiwall bags (three outer paper layers with an inner layer of low density polyethylene (LDPE) in direct contact with the product). Suitable details of the product formulation, specifications for the ingredients, formulation process and quality control, product specifications, stability data, analytical methods for the active constituent in the product, and details of the packaging were evaluated.

Tables 3 and 4 outline some key aspects of the formulation and physicochemical properties of the product.

Table 3: Key aspects of the formulated product Zilmax Medicated Premix

Distinguishing name:	Zilmax Medicated Premix
Formulation type:	Feed premix (granular)
Active constituent concentration/s:	Zilpaterol hydrochloride (48 g/kg)

Table 4: Physicochemical properties of the product Zilmax Medicated Premix

Physical form:	Cream to brown grains
Particle size:	Not less than 99% of the product passes through a 2 mm sieve Not more than 2% retention on a 0.5 mm sieve
Storage stability:	To be stored below 30°C (room temperature)

2.3 Recommendations

The APVMA has evaluated the chemistry of the active constituent zilpaterol hydrochloride and associated product Zilmax Medicated Premix, 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, approval of the active constituent zilpaterol hydrochloride and registration of the product Zilmax Medicated Premix, are supported from a chemistry perspective.

Repeat-dose toxicity

Short-term and sub chronic toxicity was investigated in rats, dogs and microswine. Primary effects were consistent with that expected for a beta II- adrenergic agonist, with observed changes in heart rate, heart weight, peripheral vasodilation, blood pressure and haematology parameters.

In rats given zilpaterol hydrochloride orally via gavage at doses up to 50 mg/kg bw/d for 10 days or up to 100 mg/kg bw/d for 29 days, body weight gain was observed in treated animals. Changes in clinical chemistry (reduced serum glucose and triglycerides) and haematological parameters (increased WBC and reduced prothrombin time) were also noted, but there were no treatment related gross or microscopic lesions identified at necropsy.

Rats were administered zilpaterol hydrochloride at doses up to 100 mg/kg bw/d for three months with a one month recovery period for some animals. Food consumption and body weight gain were increased in all treatment groups, although this was reversed during the recovery period. All treatment groups showed a reduction in heart rate and increased cardiac conduction times. Serum urea and triglycerides, and heart weights were increased in females at 1 mg/kg bw/d and in both sexes at 10 mg/kg bw/d. The change in heart weights was still apparent at the end of the treatment period. A NOAEL was not established in this study.

In a further three-month oral gavage study, rats were administered zilpaterol hydrochloride at doses from 0.05 to 1 mg/kg bw/d. Food consumption and body weight gain were increased at 0.5 and 1.0 mg/kg bw/d. A decrease in heart rate was noted in all treated female groups and males receiving 1 mg/kg bw/d. All treated groups showed a higher mean PQ interval. Increased heart weights were observed in males and 1 mg/kg bw/d and females at 0.5 and 1 mg/kg bw/d. Minimal to slight cardiomyopathy was seen in both treated and control animals, however there was an increase in both incidence and severity in treated male groups. An increased incidence of arteritis of large hepatic arteries was noted in 0.5 and 1 mg/kg bw/d males. A NOAEL was not established in this study.

Two dogs administered 100 mg/kg bw/d zilpaterol hydrochloride in capsules for seven days demonstrated significant treatment-related effects including frequent emesis, inactivity, apathy, lacrimation, vasodilatation of ears and abdomen, and diarrhoea. Changes in haematological parameters (increased erythrocyte counts, haematocrit and packed cell volume) and clinical chemistry (reduced total protein; increased cholesterol, phospholipids, inorganic phosphorous, and liver enzymes (ALT, AST and ALP)) were noted. The livers of treated animals were noted as being ‘putty-coloured’ with clear lobular structure. Histopathological examination identified excess glycogen and lipids in the perilobular hepatocytes, and hypertrophy and vacuolation of centrilobular hepatocytes.

When dogs were administered up to 50 mg/kg bw/d zilpaterol in capsules for 30 days, similar clinical signs were observed as in the seven day study. In addition, peripheral vasodilatation was observed within 30 minutes of administration in all treated animals. Blood pressure was reduced and heart rate increased in all treated animals. Gross necropsy findings were unremarkable.

In a 13-week oral gavage study in microswine administered zilpaterol hydrochloride at doses up to 10 mg/kg bw/d, increased body weight gain was observed at the highest dose tested in males. In females, increased erythrocytes, serum haemoglobin, haematocrit, potassium glucose, total protein and albumin levels were observed. A NOAEL was established at 1 mg/kg bw/d.

Chronic toxicity and carcinogenicity

Chronic dietary toxicity studies were conducted in female mice and in rats (both sexes).

In mice, no effects were seen at up to and including the highest dose tested of 0.25 mg/kg bw/d (0.250 mg/kg bw/d) in an 18-month oral gavage carcinogenicity study.

In a two-year carcinogenicity study in rats, changes in food consumption and decreased bodyweight gain were seen at 0.25 mg/kg bw/d. In females, an increased incidence of leiomyoma (benign uterine smooth muscle cell tumour) in the ovary suspensory ligament of 2/63 (three per cent, $p<0.05$) and 5/64 (eight per cent, $p<0.05$) was seen at 0.125 and 0.250 mg/kg bw/d, respectively, whereas the finding was absent at the lower two dosing groups and in concurrent controls. This finding has also been seen in rats exposed to other beta II- adrenergic receptor agonists, for example salbutamol, indacaterol and ractopamine. This neoplasm of smooth muscle tissue is considered to be a rat-specific response as there is a clear NOAEL for these effects, a single site of occurrence, and absence of genotoxicity findings. The NOAEL was 0.125 mg/kg bw/d, based on decreased body weight gain and increased mortality at 0.25 mg/kg bw/d.

Reproductive and developmental toxicity

A preliminary (one generation) reproduction study and a full two-generation reproduction study in rats both examined effects on reproduction at doses up to and including 14.4 ppm zilpaterol. The parental NOAEL was 0.9 ppm (0.11 mg/kg bw/d in F0 females; 0.08/0.12 mg/kg bw/d in F1 males and females), and lowest-observed-effect level (LOEL) was 3.6 ppm. Observed effects included changes in bodyweight (and bodyweight gain) and cardiomegaly/cardiotoxicity. There was no evidence of reproductive toxicity potential.

In three developmental toxicity studies in rats at up to 750 mg/kg bw/d over gestation day (GD) six to 15, the NOAEL for maternal toxicity was 0.2 mg/kg bw/d, and the NOAEL for developmental and foetal toxicity was 2 mg/kg bw/d. Observed effects included maternotoxicity (as hypersalivation, bodyweight gain), and foetoxicity as evident as skeletal variations and visceral malformations. Similar effects were observed in a rabbit model, consisting of increased maternal bodyweight gain and increased incidences of foetal abnormalities but not constituting teratogenesis at the lowest dose tested of 20 mg/kg bw/d and above.

Genotoxicity

Zilpaterol was not mutagenic in the *Salmonella typhimurium* bacterial assay at up to 5000 µg/plate with or without metabolic activation, did not induce unscheduled DNA synthesis in rat hepatocytes at up to 250 µg/mL or forward mutation in Chinese Hamster Ovary (CHO) cells at up to 5000 µg/plate, and was not clastogenic in a micronucleus test in mouse bone marrow cells at oral doses of up to 400 mg/kg.

Neurotoxicity

There was no evidence of a potential for irreversible neurotoxicity of direct nerve tissue damage.

Minimal neurological effects were seen in mice at oral doses up to 30 mg/kg, with reduced staying time in the ‘turning rod test’ was observed at doses of 20 to 50 mg/kg bw. Zilpaterol did not show anticonvulsive activity

in mice. It potentiated the neurobehavioural effect of 5-hydroxytryptophan in mice at 5 mg/kg bw and above, and potentiated dexamphetamine-induced stereotypy in rats at 5 mg/kg bw.

Mode of action (toxicology)

Pharmacological effects of zilpaterol include agonist activity to beta II- adrenergic receptors. This is associated with the cardiac effects seen in repeat dose studies.

Toxicity of metabolites and/or impurities

RU 62435 (deisopropyl zilpaterol) is the major metabolite of zilpaterol in rats and target species. It was found to have low oral toxicity in mice (LD50 = 1030 mg/kg bw), was not mutagenic in bacteria at up to 5000 µg/plate or mouse lymphoma mutation assays at up to 800 µg/mL, and it did not induce unscheduled DNA synthesis in rat hepatocytes in vitro or micronuclei in mouse bone marrow in vivo at oral doses of up to 400 mg/kg bw. The low acute oral toxicity is consistent the pharmacological agonist activity of deisopropyl zilpaterol on beta II- adrenergic receptors being one-tenth of the parent compound.

Reports related to human toxicity

A double-blind randomised four way-crossover placebo controlled multicentre randomised study was performed in 11 adult asthmatic out-patients at single oral doses of 0.05, 0.1 and 0.25 mg. Forced Expired Volume (FEV1) was increased at 0.1 or 0.25 mg up to four hours after dosing and compared to the placebo values, the actual-to-predicted FEV1 ratio was significantly higher. An increase in heart rate was recorded at the dose of 0.25 mg up to six hours after dosing, with a slight, non-significant decrease in diastolic blood pressure. A mild, short-lasting tremor occurred in eight patients at 0.25 mg and in two patients at 0.1 mg and 0.05 mg (equal to 0.76 µg/kg bw; none in placebo). The blood glucose level was increased one hour after the 0.25 mg dose. A NOAEL was not established.

3.2 Health-based guidance values and poisons scheduling

Poisons standard

In 1999, zilpaterol was listed In Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) without a concentration cut-off.

Health-based guidance values

Acceptable Daily Intake

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 ADI of 0.04 µg/kg bw/d will be established for zilpaterol hydrochloride, based on the observation of tremors at the lowest dose tested of 0.05 mg/person (equal to 0.76 µg/kg bw) in clinical examination of 11

asthmatic volunteers, together with an uncertainty factor of 20, which is comprised of an intra-human variability factor and a LOAEL to NOAEL extrapolation factor.

Acute Reference Dose

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.

As the proposed ADI is based on an acute pharmacological effect, establishment of an ARfD is appropriate. The ARfD will be established equivalent to the ADI of 0.04 µg/kg bw, based on a LOAEL for tremors of 0.05 mg/person (equal to 0.76 µg/kg bw), and a 20-fold uncertainty factor based on the same rationale for the proposed ADI.

3.3 Recommendations

The product, Zilmax Premedicated Premix, containing 48 g/kg zilpaterol hydrochloride, was found to have a low oral toxicity in mice (LD50 > 2000 mg/kg bw in both sexes, no deaths) and rats (LD50 > 2000 mg/kg bw in both sexes, no deaths).

The APVMA has considered the toxicological profile and likely exposure associated with the use of formulated product Zilmax Medicated Premix and the active constituent zilpaterol hydrochloride. The APVMA has concluded that the human health risk posed by the active and the product is acceptable according to the criteria stipulated in Section 5A of the *Agricultural and Veterinary Chemicals Code Act (1994)*.

There are no objections on human health grounds to the approval of the new active ingredient, zilpaterol hydrochloride and registration of the product Zilmax Medicated Premix.

4 RESIDUES ASSESSMENT

A similar residues dossier to that considered by Joint FAO/WHO Expert Committee on Food Additives (JECFA)[2] in 2013 (78th meeting) and 2015 (81st meeting) was submitted for evaluation.

4.1 Metabolism

Studies conducted in cattle, swine and rats demonstrated the metabolism of zilpaterol as qualitatively and quantitatively comparable in these three species and is readily absorbed after oral administration. Zilpaterol and its metabolites are readily eliminated, primarily in the urine (80 per cent in cattle, 85 per cent in swine and 50 per cent in rats) with the remainder in the faeces. Unchanged zilpaterol was the main compound excreted in the urine of these three species.

Radiolabelled residue depletion studies conducted in cattle after treatment at the recommended dose of 0.15 mg/kg bw/day demonstrated that a steady state is achieved by 12 days on treatment. Residues were detected in liver and kidney until 96 hours post-dose in this study. No residues were detected in fat after 12 hours, and no residues were detected in muscle after 48 hours. At 12 hours post-dose, the radioactive concentrations were observed in the following order:

- liver=kidney>reticulum>omasum>abomasum>rumen >muscle >fat.

Zilpaterol represents a significant part of the extractable residue in liver, kidney and muscle. The ratio of zilpaterol hydrochloride to extracted residue decreased with time for liver, kidney and muscle. Deisopropyl zilpaterol was identified as a minor fraction of the extractable residue. The ratios of zilpaterol free base to total pharmacologically active residue decreased from mean values of 94 per cent, 99 per cent and 92 per cent at 12 hours to 74 per cent, 50 per cent, and 72 per cent at 96 hours for liver, kidney and muscle respectively. Fat was not considered relevant for residue monitoring purposes due to the low potential for residues in fat.

4.2 Analytical methods

A validated analytical procedure for the determination of zilpaterol in edible bovine tissues (liver, kidney, muscle) is available. Samples of homogenized bovine tissue were fortified with a stable label internal standard (d7-zilpaterol free base) and extracted with methanol. A sub-sample of the extract was purified by cation exchange and then analysed by a validated liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method using electrospray ionization in the positive ion mode. Quantification was performed using a solvent calibration curve with a range of 0.25 to 30 µg/kg tissue equivalents for all tissues. The limit of quantitation (LOQ) was 0.250 µg/kg for liver, kidney and muscle, and the recovery of zilpaterol was acceptable in these tissues.

Prior to the development of the aforementioned analytical method, a validated high performance liquid chromatography fluorescence (HPLC/FL) methods was available. That method involves the extraction of unchanged zilpaterol from liver, kidney and muscle homogenate with a basic mixture of acetonitrile and

[2] apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=6191

methanol. The chemically stable fluorescent zilpaterol derivative is separated from other co-extractives and non-fluorescent compounds by HPLC and detected with fluorescence detection. The LOQ was 3 µg/kg for liver and 1 µg/kg for kidney and muscle.

4.3 Residue definition

Based on the available metabolism data, analytical methodology and residue depletion data, zilpaterol is considered to be the appropriate marker residue for the proposed use of zilpaterol hydrochloride in beef cattle.

4.4 Residues in food and animal feeds

The proposed use of Zilmax Medicated Premix in beef cattle involves its inclusion in manufactured feed at 8.3 g zilpaterol hydrochloride per tonne (8.3 mg/kg in the feed) on a 100 per cent dry matter basis to derive a daily dose of 43–128 mg, depending on body weight. The proposed feeding duration is for the last 20 days in the lead up to slaughter and the meat withholding period is ‘REMOVE ALL MEDICATED FEED four days before slaughter for human consumption'.

The consideration of appropriate Maximum Residue Limits (MRLs) was based on the upper 95/95 tolerance level associated with the concentration of the marker residue (zilpaterol). This was observed in a critical residue depletion study which involved analysis with the LC/MS/MS analytical method with the LOQ of 0.25 µg/kg. Beef cattle were treated at 90 mg ai/head/day and animals (n=6) were sacrificed at 12, 24, 48, 72, 120 and 240 days after the last dose. The proposed directions for use specify that 87 mg zilpaterol hydrochloride/animal should be applied for a 550 kg animal. Given the study animals weighed 503–525 kg at study commencement and 541–614 kg at study completion, the 90 mg zilpaterol hydrochloride/animal treatment is therefore equivalent to the proposed use.

The critical residues depletion study did not sample tissues at the proposed meat withholding period of four days after the last dose, therefore the residue observations at three days after the last dose have been considered. At three days after the last dose, residue observations were 1.2±0.34 µg/kg in liver, 1.0±0.02 µg/kg in kidney and 0.31±0.04 µg/kg in muscle. These levels had declined from a peak at the first sampling interval of 12 hours of 36±12 µg/kg in liver, 28±0.89 µg/kg in kidney and 4.9±1.4 µg/kg in muscle. At the sampling interval of 5 days, residues were 0.27±0.02 µg/kg in liver, 0.36±0.03 µg/kg in kidney and were below LOQ (<0.25 µg/kg, n=6) in muscle. At the last time interval of 10 days, finite residues were present in liver (0.59±0.14 µg/kg) and kidney (0.47±0.03 µg/kg) but were below LOQ (<0.25 µg/kg, n=6) in muscle. Fat was not considered relevant for residue monitoring purposes due to the low potential for residues in fat demonstrated in the radiolabelled studies.

Zilpaterol MRLs at 3.5 µg/kg for cattle liver, 0.5 µg/kg for cattle muscle and 3.3 µg/kg for cattle kidney are considered to be appropriate for the proposed use in conjunction with a four day meat withholding period. These MRLs are consistent with the MRLs recommended as part of the JECFA evaluation from the 81st meeting in 2015. As detectable residues should not occur in fat as a result of the proposed use pattern, it is also considered appropriate to recommend a zilpaterol MRL for cattle fat at the method LOQ of 0.25 µg/kg.

The restraints ‘DO NOT USE in cows which are producing or may in the future produce milk or milk products for human consumption’ and ‘DO NOT USE in calves to be processed for veal’ are required as data addressing the residue potential in milk or the tissues of pre-ruminant calves is not available.

The median and upper 95/95 tolerance limits for pharmacologically active residue as calculated by JECFA for a 72 hour withdrawal period will be considered for the purposes of the dietary exposure calculations. The median level of pharmacologically active residue after 72 hours of withdrawal were 2.4, 3.3 and 0.4 µg/kg in liver, kidney, and muscle respectively. The upper 95/95 tolerance limits of pharmacologically active residue after 72 hours of withdrawal were 6.2, 7.4 and 0.9 µg/kg in liver, kidney, and muscle respectively.

In the critical residue study, residue levels in liver and kidney at the 120 and 240 hour time-points were similar indicating a plateau at low levels just above the LOQ of 0.25 µg/kg. In three other relevant residues studies considered by JECFA at the 78th meeting in 2013, the LOQs were 3 µg/kg for liver and 1 µg/kg for kidney and muscle and residues above those LOQ’s were not observed at or beyond 96 hours post-treatment.

4.5 Estimated dietary intake

The ‘estimated daily intake’ for chronic dietary exposure based on the conservative JECFA food basket and the median residue associated with the proposed use of zilpaterol in cattle after four days of withdrawal is acceptable (<25 per cent ADI).

The chronic dietary exposure to zilpaterol hydrochloride is estimated by the National Estimated Daily Intake (NEDI). This calculation encompasses all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the 2011–12 National Nutritional and Physical Activity Survey. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for zilpaterol hydrochloride is equivalent to <five per cent of the ADI. It is concluded that the chronic dietary exposure to zilpaterol hydrochloride is acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived primarily from the 2011–12 National Nutritional and Physical Activity Survey. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. The highest acute dietary intake was estimated at <30 per cent of the ARfD. It is concluded that the acute dietary exposure is acceptable.

4.6 Recommended Maximum Residue Limits

The following amendments will be made to the APVMA MRL standard should the use pattern be approved (Table 5).

Table 5: Amendments to the APVMA MRL Standard

Amendments to Table 1: MRLs for food commodities			
Compound		**Food**	**MRL (mg/kg)**
ADD:			
Zilpaterol			
MF	0812	Cattle fat	*0.00025
MO	1280	Cattle kidney	0.0033
MO	1281	Cattle liver	0.0035
		Cattle muscle	0.0005
Amendments to Table 3: Residue definition			
Compound		**Residue**	
ADD:			
Zilpaterol		Zilpaterol	

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Cattle meat and offal are considered to be major export commodities[3]. Residues of zilpaterol hydrochloride in these commodities resulting from the use of Zilmax Medicated Premix have the potential to unduly prejudice trade.

5.2 Destination and value of exports

The significant export markets for Australian beef meat and offals are listed in the *APVMA Regulatory Guidelines—Data Guidelines: Veterinary—Overseas trade (Part 5B)*. Codex, the European Union (EU), Japan, the Republic of Korea, Taiwan and the United States are currently considered to be significant markets for cattle.

In 2017–18[4], Australian beef and veal exports were valued at $7.96 billion with the major export destinations being Japan, the United States, China and the Republic of Korea.

In 2018–19[5], the major export destinations of Australian beef offal include Indonesia, Japan, the Republic of Korea, Hong Kong and South Africa.

5.3 Comparison of Australian MRLs with Codex and international MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits for pesticides and veterinary medicines. Some countries may accept Codex CXLs when importing foods. Codex MRLs are not established for zilpaterol.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA, 81st meeting, 2015) recommended Codex MRLs for zilpaterol (free base) at 3.5 µg/kg for cattle liver, 0.5 µg/kg for cattle muscle and 3.3 µg/kg for cattle kidney. The 23rd Codex Committee for Residues of Veterinary Drugs in Food (CCRVDF 23[6]) in October 2016 agreed to hold the proposed zilpaterol MRLs at Step 4, and therefore Codex MRLs were not

[3] APVMA Regulatory Guidelines—Data Guidelines: Veterinary—Overseas trade (Part 5B)

[4] ABARES Agricultural commodity statistics: agriculture.gov.au/abares/research-topics/agricultural-commodities/agricultural-commodities-trade-data#2018

[5] MLA Australian offal Exports June 2019: mla.com.au/globalassets/mla-corporate/prices--markets/documents/os-markets/export-statistics/june-2019/1906---australian-offal-exports---global-summary.pdf

[6] Report of CCRVDF 23: fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-730-23%252FReport%252FFinal%252FREP17_RVDFe.pdf

established for zilpaterol. The EU, supported by some delegations, stated that they were opposed to the advancement of zilpaterol in the Step procedure and to the establishment of Codex MRLs for zilpaterol. At the next meeting (CCRVDF 24[7] in April 2018) it was emphasized that there were no public health or scientific concerns regarding the proposed draft MRLs recommended by JECFA for zilpaterol. However the proposed zilpaterol MRLs were again held at Step 4 as no consensus on the advancement of zilpaterol MRLs could be reached due to the opposition from some delegations. Therefore Codex MRLs have not been established.

Zilmax is registered for use in beef cattle in various countries as outlined in Section 1.5 of this document with a comparable use pattern to that proposed for Australia. Import tolerances have been established in Japan and the applicant has noted that there is an ongoing procedure to establish import tolerance MRLs in Taiwan. The EU and China have not established MRLs for zilpaterol.

The following relevant international MRLs have been established for zilpaterol (Table 6).

Table 6: Proposed Australian and current international MRLs for zilpaterol

Country	MRLs/tolerances (µg/kg)			
	Liver	Muscle	Kidney	Fat
Australia (proposed)	3.5	0.5	3.3	*0.25
Brazil	35	4	55	-
Canada	5	2	5	-
Colombia	12	10	15	-
Costa Rica	12	10	15	-
Dominican Republic	12	10	15	-
Guatemala	12	10	15	-
Honduras	12	10	15	-
Japan	10	10	10	10
Mexico	12	10	-	
Nicaragua	12	10	15	-
Panama	12	10	15	-
Peru	12	10	15	-

[7] Report of CCRVDF 24: fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-730-24%252FREPORT%252FREP18_RVDFe.pdf

Country	MRLs/tolerances (µg/kg)			
	Liver	Muscle	Kidney	Fat
Republic of Korea	5	1	10	-
South Africa	12	10	15	-
USA	12	-	-	-

5.4 Potential risk to trade

Export of treated produce containing finite (measurable) residues of zilpaterol may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

The zilpaterol MRLs established in Japan, the Republic of Korea and the United States are higher than that proposed for Australia and the potential risk to trade to these markets is considered to be low and acceptable. An Export Slaughter Interval equal to the proposed four day meat withholding period is considered to be appropriate for these three major export markets.

MRLs are not established in the EU, China or Taiwan. Codex MRLs are not established which means that many countries that may adopt Codex MRLs do not have appropriate MRLs. An Export Slaughter Interval for these markets cannot be established as residues did not decline below the LOQ of 0.25 µg/kg in liver or kidney at the last time point of 10 days. Residues above LOQ (0.25 µg/kg) were however not observed in muscle or fat at five and 10 days after the last treatment. Therefore finite residues are not expected to occur in meat following five days of withdrawal.

There is a risk to the international trade for cattle meat and offal associated with the proposed use with a four day withdrawal time for the markets that have not established zilpaterol MRLs including the EU, China, Taiwan, and countries that adopt Codex MRLs.

To assist in the mitigation of trade risk, the applicant has proposed a Zilpaterol Management Plan. This plan is presented in Section 9.

The following Trade Advice statements are proposed for the product label

> TRADE ADVICE: Exporters need to comply with the regulations/standards of importing countries with regard to the use of animal health products in livestock. Producers are advised to contact their export slaughter facility or Intervet Australia Pty Ltd for information before giving cattle feed to which this product has been added.
>
> EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than four days before slaughter for export to markets for which zilpaterol MRLs are established. Before using this product confirm the current export status for certain markets with Intervet Australia Pty Ltd on 1 800 033 461.

For the APVMA to be satisfied that the registration of Zilmax Medicated Premix should not result in an undue risk to the international trade of cattle meat and offal, it needs to be confident that the industry can manage the potential risk to international trade.

Comment is therefore requested from industry stakeholders on the potential risk to trade associated with the proposed use of Zilmax Medicated Premix. In particular industry feedback is being sought on aspects relating to industry practices, proposed label statements and the proposed Zilpaterol Management Plan (refer to Section 9) to prevent tissues from beef cattle exposed to zilpaterol being exported to countries that do not currently have zilpaterol MRLs established such as China, the EU, Taiwan and countries that adopt Codex MRLs.

6 WORK HEALTH AND SAFETY ASSESSMENT

6.1 Health hazards

The formulation is supplied as a ready-to-use granular formulation with low-dust generation potential.

6.2 Occupational exposure

Exposure during use

Workers in livestock feed mills, livestock farmers and their employees will be the main users of the product. Workers will be exposed to the product predominately by inhalation and eye contact during the preparation of stock feed.

Exposure scenarios include: opening bags, weighing portions, mixing into carrier feed, storing treated carrier feed, transferring treated carrier feed into feedlot pens, cleaning around feeding areas and disposing of containers. Of these activities, mixing the product into carrier feed incurs the highest potential exposures to zilpaterol.

Based on information indicating that workers may spend up to two hours per day preparing the premix and feed mixture together with feedlot maintenance, the risk associated with inhalation exposure to zilpaterol was considered acceptable (margin of exposure (MOE) >20) at both the 50th and 95th exposure percentile.

Exposure during re-entry or rehandling

The risk associated with re-entry/re-handling are considered minimal. Considering the limited re-handling of treated feed, the toxicity profile of the active and product, and the concentration of active in the final feed, a re-entry or re-handling statement is not required.

6.3 Public exposure

As Zilmax Medicated Premix is intended for commercial farming of beef cattle, and is not intended for domestic use, the public are unlikely to use the product. The risk to the public from accidental exposure is likely to be minimal. The most likely route of public exposure is through consumption of zilpaterol residues in food derived from treated livestock.

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; New Zealand 0800 764 766.

Safety directions

Harmful if swallowed. Harmful if inhaled especially the dust. May irritate the eye. Do not touch or rub eyes, nose or mouth with hand when handling granules. When using the product wear goggles and a disposable dust mask. Wash hands after use.

7 ENVIRONMENTAL ASSESSMENT

The environmental assessment applied the standard VICH GL6 guidance for a Phase 1 assessment which considers the primary route of entry of the active constituent into the environment is through excretion by treated cattle.

7.1 Fate and behaviour in the environment

Soil

On the basis of metabolism and excretion data, it was assumed a total dose of 95 per cent was eliminated (86 per cent in urine and 8.7 per cent in faeces), consisting mainly of zilpaterol as free base and numerous metabolites. Approximately 13 per cent of the administered dose was deisopropyl zilpaterol which retains the imidazole ring and is expected to exhibit similar activity.

Based on metabolism and excretion data and the worst-case parameters, a soil concentration of 81 µg ac/kg was predicted. The predicted soil concentration was 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 Zilmax Medicated Premix were determined to be acceptable.

7.2 Recommendations

In considering the environmental safety of the use of Zilmax Medicated Premix, the APVMA had regard to the toxicity of the active constituent and its residues, including metabolites and degradation products, in relation to relevant organisms and ecosystems. Based on the outcome of the risk assessment, the APVMA proposes to be satisfied under s 14 of the *Agricultural and Veterinary Chemicals Code Act 1994* that the use of the product meets the safety and labelling criteria.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product use pattern

Zilpaterol hydrochloride is a new β-agonist to the Australia market and is currently not approved for use as a veterinary chemical product. The product, Zilmax Medicated Premix, contains 48 g/kg zilpaterol hydrochloride as the active ingredient. Beta II- adrenergic agonists enhance animal growth by binding on to beta II- adrenergic receptors on skeletal muscle cell and adipocytes. This binding modifies biochemical processes of tissue growth by increasing lipolysis, decreasing lipogenesis, decreasing protein degradation, and increasing protein synthesis.

The proposed claims are for increased carcass leanness, increased dressing percent, improved rate of body weight gain and improved feed efficiency in cattle fed in confinement for slaughter during the last 20 days on feed.

Zilmax Medicated Premix will be administered at 8.3 g zilpaterol hydrochloride per ton of feed to provide between 43 mg to 128 mg zilpaterol hydrochloride per head per day on a 100 per cent dry matter basis. The product is prohibited from administration to breeding cattle, horses or other equines.

8.2 Efficacy and target animal safety

Efficacy

The efficacy data provided included results from dose determination, dose confirmation and field studies.

The trial designs, treatment group sizes, ages and types of animals used, trial conditions, administration of the test product, sample collection and analysis of data were generally appropriate for establishing efficacy of the test product for the proposed use in cattle.

13 dose determination and confirmation studies were conducted on Charolais, Normandy, Sussex, Sussex X Hereford, Bonsmara, and Angus cattle in France, Mexico and South Africa with dosing periods ranging from 15 to 118 days. The dose determination studies results supported the selection of an appropriate dose level of 8.3 grams zilpaterol hydrochloride/tonne on a 100 per cent dry matter basis. The dose confirmation studies demonstrated efficacy at approximately 1X and 2X the proposed use dose with dosing periods ranging from 15 days to 118 days.

In five field studies conducted in USA and Canada on Angus, Angus cross, Red Angus, Red Angus cross, Hereford, Hereford cross, Charolais, or Limousin cattle administered at the proposed dose for 20 to 40 days, the product was effective in increasing carcass leanness, dressing percent, rate of body weight gain and feed efficiency in cattle fed in confinement for slaughter. No Australian studies were conducted based on an argument of strong similarities between cattle production in USA and Australian feedlots, cattle breeds, feedlot management systems, nutrition and carcass characteristics.

No adverse effects were observed in any of the dose determination, dose confirmation and field studies.

Claims for the increasing weight gain, improved feed efficiency and increased carcass leanness in cattle fed in confinement for slaughter during the last 20 days on feed, when the product is used at the proposed dose rate of 8.3 grams Zilpaterol hydrochloride/tonne on a 100 per cent dry matter basis are supported.

Animal safety

In one target animal safety study in cross-bred fattening beef cattle, administered doses of 1X and 10X the average recommended dose of 68 mg zilpaterol hydrochloride/day/head of the test product for 28 days (ad lib feed intake) resulted in reduced feed intake resulting in mean dose levels of 44 mg/day (0.64X) and 302 mg/day (4X), respectively. Clinical signs included increased heart rates at the 10X dose. There were no toxicological changes associated with the test product in any of the clinical parameters measured in terms of clinical biochemistry, haematology and urinalysis, and gross and histopathology.

In a second target animal safety study in cross-bred fattening beef cattle, administered doses of 1X, 1.5X and 10X the average recommended dose of 68 mg zilpaterol hydrochloride/day/head of the test product for at least 40 days (ad lib feed intake) resulted in reduced feed intake resulting in mean dose levels 94 mg/day (1.4X) and 520 mg/day (8X). There were no toxicological changes associated with the test product in any of the clinical parameters measured in terms of clinical biochemistry, haematology and urinalysis.

In three target animal safety studies in steers, bullocks or Normandy heifers, administered doses of 1X and 2X the maximum recommended dose of 68 mg zilpaterol hydrochloride/day of the test product for 50 or 61 days (ad lib feed intake) resulted in increased heart rates.

Based on the evidence and literature provided by the applicant for registration as a new veterinary product, the contraindications, side effects and other label statements proposed relating to target animal safety are considered appropriate.

Contraindications

1. Not for use in cattle intended for breeding.
2. Horses and other equines must NOT be allowed access to feeds containing zilpaterol.

Side effects

Animals receiving Zilmax may exhibit an increased respiratory rate as well as elevated levels of creatine phosphokinase (CPK) and creatinine.

Dosage and administration label statements

3. Do not feed undiluted.
4. Zilmax must be thoroughly mixed into feeds before use.

8.3 Recommendations

The APVMA has evaluated the efficacy and target animal safety data of the proposed product Zilmax Medicated Premix, and found it to be acceptable. Based on a review of the data submitted, Zilmax Medicated Premix 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 PROPOSED ZILPATEROL TRADE MANAGEMENT PLAN

The applicant has proposed the following Zilpaterol Management Plan to assist in the management of trade risk:

9.1 Zilpaterol Management Plan

To manage the use of zilpaterol efficiently without posing undue risk to efficacy, safety, residue, trade and environment, working effectively and collaboratively with existing industry systems will be important. These systems include:

- feedlots: National Feedlot Accreditation Scheme (NFAS)
- processing plants: approved arrangements
- property and livestock identification: National Livestock Identification Scheme (NLIS)
- livestock movement advice: National Vendor Declaration (NVD) and NFAS delivery dockets.

It is proposed that the registered product label would include the following supply for use requirement: '**Restraints**: USE ONLY by authorised NFAS accredited feedlots.'

This restraint restricts the use of zilpaterol to NFAS accredited and authorised feedlots.

Feedlots

The National Feedlot Accreditation Scheme has agreed to develop a β-agonist management plan and individual NFAS Accredited Feedlots will be required to develop feedlot specific QA policies and procedures to ensure the correct use of zilpaterol. Individual feedlot QA policies and procedures will be audited by NFAS prior to them gaining access to zilpaterol through accredited veterinarians. Feedlots will then continue to be audited by NFAS to maintain zilpaterol approved use status.

- Feedlots will adopt procedures to ensure full traceability of all animals through the NLIS and link individual animal identification to the central NLIS database.
- Quality processes and procedures will be adopted for all identified 'Critical Control Points' including but not limited to:
  - storage and handling infrastructure
  - product purchase and receival
  - ration formulation
  - terminal drafting
  - pen identification and feed bunk isolation
  - feed batching
  - feed delivery

  - feed truck sanitisation
  - withholding periods
  - movements out of pens being fed zilpaterol
  - responses to accidental (known or possible) zilpaterol consumption
  - dispatch for slaughter
  - feed testing
  - record keeping.
- Systems will be adopted to ensure that individual animals, from which meat and offal may be destined for zilpaterol sensitive markets, do not have access to rations treated with zilpaterol.
- Systems will be put in place to ensure that zilpaterol concentrate is stored securely, and that legislative withholding periods and export slaughter intervals have been complied with prior to dispatch for slaughter.
- Systems will be put in place to ensure that the supply and use of zilpaterol is controlled and recorded for audit. The records will include, but not limited to:
  - the receipt and storage of each delivery of zilpaterol
  - feed ration formulation
  - feed ration mixing instructions
  - each batch of zilpaterol ration prepared (batch record)
  - each load of zilpaterol ration delivered to pens
  - feed truck cleaning validation and record
  - daily reconciliation of zilpaterol use
  - waste and disposal
  - compliance of withholding periods and export slaughter intervals
  - ration sampling program and testing results
  - action taken in the event of suspected accidental consumption of zilpaterol rations
  - written procedures for labelling to indicate status of containers, bunks, pens, trucks, rations, roughage bays that may come into contact with zilpaterol.
- Systems will be put in place to manage the risk of cross-contamination and actions to be taken in the event of accidental access to zilpaterol treated feed.
  - There will be dedicated and physically identified pens for zilpaterol treated cattle.
  - Any cattle involved in accidental access to zilpaterol ration will be allocated to zilpaterol pens with a newly assigned ‘beta-agonist-fed’ status on the NLIS database.
  - Frequent and regular sampling and testing to monitor the zilpaterol levels in treated feeds and confirm the zilpaterol-free status of non-treated feeds.
  - Staff are properly trained before handling Zilpaterol concentrate.

National livestock identification scheme and national vendor declaration

- Each feedlot will be required to identify its Property Identification Code (PIC) on the NLIS database, prior to the commencement of feeding zilpaterol.
- Once the feedlot has determined the specific livestock to be fed zilpaterol, each animal's NLIS device will be allocated a device base status on the NLIS database indicating that it has been fed zilpaterol.
- Should any livestock be transferred from a non-zilpaterol program to a zilpaterol program due to accidental access to feed that contains zilpaterol, the NLIS tag of each such animal will be allocated a device base status on the NLIS database indicating that the cattle have been fed zilpaterol.
- All NLIS devices will be scanned at feedlot exit confirming that the devices are operational, ESI's and WHP's have been complied with and that there are no zilpaterol fed cattle included in dispatches of cattle that are declared as zilpaterol free.
- NVD's and NFAS delivery dockets for zilpaterol treated cattle need to be completed with Question 9 on the NVD indicating that the cattle have been fed zilpaterol. Alternatively, these documents will be used to identify cattle that **have not** been treated with zilpaterol.
- Systems will be implemented to comply with the NLIS identification requirements for properties and individual animals treated with zilpaterol and ensure that individual animals are segregated and identified at dispatch in line with processor agreement.

Meat processing plants

- Processing plants will follow existing Approved Arrangements procedures that are in place to protect the integrity of products going to sensitive markets using unique carcass destination and product code numbers.
- Feedlots will follow documented segregation and identification procedures for zilpaterol treated livestock as agreed with processor partners prior to dispatch.

10 LABELLING REQUIREMENTS

Company Name: INTERVET AUSTRALIA PTY LTD
Product Name: ZILMAX MEDICATED PREMIX
APVMA Approval No: 67405/55972
Date: 4 FEB 2020

Label Name:	Zilmax Medicated Premix

Signal Headings:	PRESCRIPTION ANIMAL REMEDY KEEP OUT OF REACH OF CHILDREN READ SAFETY DIRECTIONS BEFORE OPENING OR USING FOR ANIMAL TREATMENT ONLY

Constituent Statements:	Zilpaterol hydrochloride 48 g/kg.

Claims:	The active ingredient is zilpaterol hydrochloride, a beta II adrenergic agonist for increased carcass leanness, increased dressing percent, improved rate of body weight gain and improved feed efficiency in cattle fed in confinement for slaughter during the last 20 days on feed.

Net Contents:	10 kg

Directions for Use:	

Restraints:	USE ONLY by authorised NFAS accredited feedlots. DO NOT USE in cows which are producing or may in the future produce milk that may be used or processed for human consumption. DO NOT USE in calves to be processed for veal.

Contraindications:	Not for use in cattle intended for breeding. Horses and other equines must NOT be allowed access to feeds containing zilpaterol.

Precautions:	

Side Effects:	Animals receiving Zilmax may exhibit an increased respiratory rate as well as elevated levels of creatine phosphokinase (CPK) and creatinine.

Dosage and Administration:

FOR USE IN MANUFACTURED FEEDS ONLY.
DO NOT FEED UNDILUTED.
ZILMAX MUST BE THOROUGHLY MIXED INTO FEEDS BEFORE USE.
GENERAL MIXING INSTRUCTIONS:
IMPORTANT: Thoroughly mixing ZILMAX into an intermediate premix and mixing the intermediate into the finished feed is recommended to ensure homogeneity. A dilution of 1 part ZILMAX and 9 parts carrier is the suggested working premix.
Complete Feeds: Medicated feeds should be manufactured to 8.3 grams zilpaterol hydrochloride/tonne on a 100% dry matter basis. ZILMAX and working premix addition rates for complete feeds of varying dry matter are in the following table.

Complete Feed % Dry Matter	Zilpaterol hydrochloride Level (g/tonne)	Kg to Be Added Per Tonne of Feed	
		ZILMAX	1-9 Working Premix
60	5.0	0.104	1.04
70	5.8	0.121	1.21
80	6.7	0.140	1.40
90	7.5	0.156	1.56
100	8.3	0.173	1.73

Thoroughly mix both working premix and finished feed to ensure complete and uniform distribution of the ZILMAX. Do not pellet medicated feeds containing ZILMAX.
Feeding Directions: Complete feed for cattle fed in confinement for slaughter must

be fed continuously at a rate of 8.3 g zilpaterol hydrochloride/tonne on a 100% dry matter basis for a period of 20 consecutive days at the end of the feeding period. The recommended inclusion rate in complete feed for cattle fed in confinement is 8.3 g zilpaterol hydrochloride per tonne (8.3 ppm) on a 100% dry matter basis. The amount of zilpaterol hydrochloride consumed daily by cattle fed in confinement for slaughter will depend upon the consumption rate of the medicated feed. Zilpaterol hydrochloride consumption will range between 43 and 128 mg per head per day based on the consumption rates in the following table.

Cattle Weight (kg)	Average Feed Consumption[1]/Head/Day 100% Dry Matter (kg)	Zilpaterol hydrochloride Consumed Daily by each Animal (mg)
350	5.25	43.58
400	6.40	53.12
450	7.65	63.50
500	9.00	74.70
550	10.45	86.74
600	12.00	99.60
650	13.65	113.30
700	15.50	128.65

1. Assumes ad libitum intake.

Liquid Feeds: ZILMAX may be added to Liquid feeds intended for addition to dry feeds for cattle in confinement.

Liquid feeds should be in a pH range of 3.8 to 7.5.

Liquid feeds should be recirculated or agitated daily and prior to use for 10 to 20 minutes.

Liquid feeds can be manufactured containing 83 to 830 g zilpaterol hydrochloride/tonne.

Before feeding, the medicated Liquid feed must be thoroughly mixed with other feed materials to make a complete feed. Examples of addition rates to complete feeds are shown in the following table.

Zilpaterol hydrochloride in Liquid Feed (g/tonne)	Addition Rate of Liquid Feed to Complete Feed, 100% Dry Matter (kg/tonne)	Zilpaterol hydrochloride in Final Complete Feed, 100% Dry Matter (g/tonne)
83	100	8.3
415	20	8.3
830	10	8.3

General Directions:

Carcass Effects	Effect of Zilpaterol[a]
Dressing Percentage, %	↑
Hot Carcass Weight, kg	↑
Ribeye Area, sq.cm.	↑
Yield Grade	↓[b]
12th Rib Fat Thickness, cm	NC
Marbling Score	NC
Carcass Colour Score	↑[c]
Carcass Percent Protein, %	↑

a. The effect of zilpaterol on parameters listed in this table is supported by data generated at the dose tested in the clinical efficacy trials. NC = No Change, ↑ = increased, ↓ = decreased.

b. Reduction indicates an improvement in Yield Grade.

c. Increase indicates an improvement in Colour Score.

Withholding Periods:

MEAT: REMOVE ALL MEDICATED FEED 4 days before slaughter for human consumption

MILK: DO NOT USE in cows which are producing or may in the future produce milk that may be used or processed for human consumption.

DO NOT USE in calves to be processed for veal

Trade Advice:

Exporters need to comply with the regulations/standards of importing countries with regard to the use of animal health products in livestock. Producers are advised to contact their export slaughter facility or Intervet Australia Pty Ltd for information before giving cattle feed to which this product has been added.

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 4 days before slaughter for export to markets for which zilpaterol MRLs are established. Before using this product confirm the current export status for certain markets with the Intervet Australia Pty Ltd on 1 800 033 461.

Safety Directions:

Harmful if swallowed. Harmful if inhaled especially the dust. May irritate the eyes. Do not touch or rub eyes, nose or mouth with hand when handling granules. When using the product wear goggles and a disposable dust mask. Wash hands after

	use.
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:	Use only in cattle feedlots that are compliant with the National Beef Cattle Feedlot Environmental Code of Practice (2000) with respect to drainage management to collect feedlot effluent.
Disposal:	Shake container into medicated feed. Do not dispose of undiluted chemicals on-site. Puncture bag and deliver to an approved waste management facility. If an approved waste management facility is not available, bury the container 500 mm below the surface in a disposal pit specifically marked and set up for this purpose clear of waterways, vegetation and tree roots, in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.
Storage:	Store below 30oC (Room Temperature). Protect from light.
APVMA approval no:	67405/55972

ABBREVIATIONS

ACCS/ACMS	Advisory Committee for Chemicals Scheduling/Advisory Committee for Medicines Scheduling
ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ARfD	Acute Reference Dose
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ESI	Export Slaughter Interval
EUP	End Use Product
F_0	original parent generation
g	gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
Hct	Heamatocrit
Hb	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography

in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	kilogram
K_{OC}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LC-MS/MS	Liquid chromatography/ mass spectrometry /mass spectrometry
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection—level at which residues can be detected
Log K_{OW}	Log to base 10 of octanol water partitioning co-efficient, synonym P_{OW}
LOQ	Limit of Quantitation—level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
NOEC/NOEL	No Observable Effect Concentration Level
NOAEL	No Observed Adverse Effect Level
OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value

RBC	Red Blood Cell Count
s	second
SC	Suspension Concentrate
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
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
Leaching	Removal of a compound by use of a solvent
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

APVMA 2015, *Data Guidelines,* Australian Pesticides and Veterinary Medicines Authority, Canberra, available at apvma.gov.au/registrations-and-permits/data-guidelines.

CVMP (Committee for Medicinal Products for Veterinary Use), 2008, *Revised guideline on environmental impact assessments for veterinary medicinal products in support of the VICH Guidelines GL6 and GL38.* European Medicines Agency, Document Reference EMEA/CVMP/ERA/418282/2006-Rev.1.

VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products), 2000, *Environmental impact assessment (EIAs) for veterinary medicinal products (VMPs)–Phase 1,* VICH GL6 (Ecotoxicity Phase 1).