Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active constituent peforelin in the product Maprelin

APVMA Product Number 65595

AUGUST 2016

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This publication is available from the APVMA website: www.apvma.gov.au.

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PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Ageing, Office of Chemical Safety (OCS), Department of Sustainability, Environment, Water, Population and Communities (DSEWPaC), and State Departments of Primary Industries.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents.

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined in the APVMA's application requirements and data guidelines.

This Public Release Summary is intended as a brief overview of the assessment that has been conducted by the APVMA and the specialist advice received from its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

About this document

This is a Public Release Summary.

It 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 Maprelin 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 September 2016 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 information judged by the APVMA to be confidential commercial information (CCI)[1] contained in submissions will be treated confidentially.

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:

Enquiries
Registration Management and Evaluation
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

Phone: +61 2 6210 4701
Fax: +61 2 6210 4721
Email: enquiries@apvma.gov.au

[1] A full definition of 'confidential commercial information' is contained in the Agvet Code.

Further information

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

Further information on public release summaries can be found on the APVMA website.

INTRODUCTION

The APVMA has before it an application from Veyx-Pharma GmbH for registration of a new product, Maprelin, containing the new active constituent, peforelin.

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

Peforelin is a synthetic decapeptide analogue of gonadotrophin releasing hormone (GnRH). Maprelin is a solution for intramuscular injection containing 75 µg/mL of peforelin. The proposed use is for induction of the oestrous cycle in sows after weaning and for induction of oestrus in sexually mature gilts following therapy to inhibit the oestrus cycle with progestogens.

Maprelin will be packaged in 10 mL, 6 x 10 mL, 50 mL and 100 mL multi-dose containers.

Maprelin is registered in the United Kingdom and several European countries.

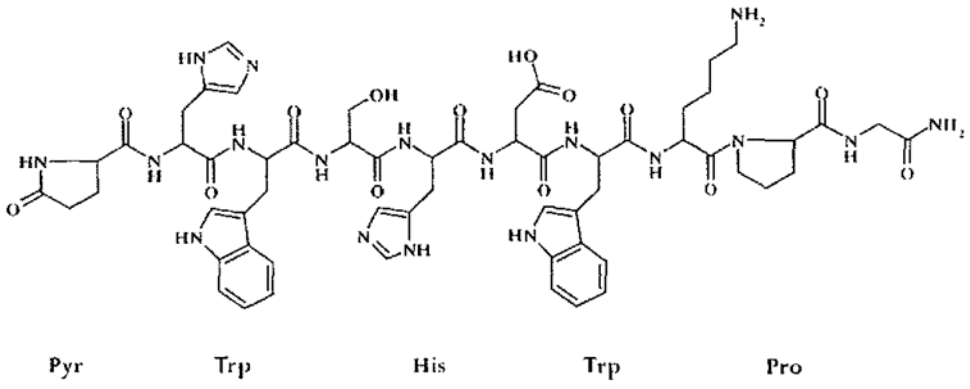
The APVMA seeks public comment on the product outlined in this document prior to the product being registered for use in Australia. The APVMA will consider all responses received during the public consultation period in deciding whether the product should be registered and in determining conditions of registration and product labelling.

CHEMISTRY AND MANUFACTURE

Active constituent properties

Peforelin is a synthetic decapeptide analogue of GnRH. Positions of 5–8 of the amino acid sequence in GnRH are replaced with histidine, asparagine, tryptophan and lysine in peforelin.

The chemical active constituent peforelin has the following properties:

COMMON NAME (ISO):	Peforelin
CHEMICAL ABSTRACTS NAME:	5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-histidyl-L-α-aspartyl-L-tryptophyl-L-lysyl-L-prolyl-glycinamide
IUPAC NAME:	5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-histidyl-L-α-aspartyl-L-tryptophyl-L-lysyl-L-prolyl-glycinamide
CAS REGISTRY NUMBER:	147859-97-0
MOLECULAR FORMULA:	C59H74N18O14
MOLECULAR WEIGHT:	1259.33
PHYSICAL STATE:	Amorphous substance
COLOUR:	White to yellowish-white
PH (FREE BASE):	5.5-7.0
OPTICAL ROTATION [ALPHA]20D:	-45° to -55°
SOLUBILITY IN:	Water, diluted acetic acid, methanol, DMSO and DMF
STRUCTURAL FORMULA:	

The chemistry section of the APVMA has evaluated the chemistry aspects of peforelin active constituent (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable.

Based on a review of the data provided by the applicant, the APVMA is satisfied that the chemistry and manufacturing details of peforelin are acceptable.

Product

Dose form

Intramuscular injection.

Formulation type

Parenteral solution.

Level of active

75 µg/mL peforelin.

Physical properties—appearance

A clear solution.

Storage and stability

The applicant provided the results of real time and accelerated stability testing conducted using samples stored in the proposed commercial containers. The results indicated that the formulated product is expected to be stable for the duration of the proposed shelf life when stored between 2°C and 8°C (refrigerate, do not freeze) in the proposed commercial packaging.

The data indicate that the active constituent is extremely sensitive to light, therefore a statement is proposed for inclusion on the label as follows: ‘Protect from light during storage and use. The product is extremely sensitive to light’.

The applicant provided the results of an in use stability study which demonstrated that the product should remain stable for the proposed duration after broaching. The label will include an in use stability statement as follows: ‘Discard unused portion within 28 days of first broaching. Store upright and protect from light after broaching.’

Packaging

The product will be packaged in 10 mL, 6 x 10 mL, 50 mL and 100 mL multi-dose glass containers with stopper and seal. Based on the storage stability results, the product is not expected to have an adverse effect on the packaging and the packaging is not expected to have an adverse effect on the product.

Recommendation

The chemistry and manufacturing section of the APVMA evaluated the chemistry and manufacturing aspects of peforelin. All the information (including the physico-chemical properties, spectral identification, manufacturing and quality control aspects, impurity formation, active constituent specification, stability, batch analysis data, analytical methods and packaging information) necessary for the approval of this new active

constituent has been provided. The chemistry and manufacturing section is satisfied that the application requirement is met.

The chemistry and manufacturing section of the APVMA evaluated the chemistry and manufacturing aspects of Maprelin**.** All the information (including formulation process, composition and form of constituents, product specifications, stability data, analytical methods, product containers and label) necessary for registration of the product has been provided. The chemistry and manufacturing section is satisfied that the application requirement is met.

TOXICOLOGICAL ASSESSMENT

Public health aspects and toxicology summary

Peforelin, or Lamprey-GnRH-III/Gonadorelin [5-His, 6-Asp, 7-Trp, 8-Lys], is a synthetic decapeptide analogue of the GnRH. Compared to natural GnRH, peforelin has chemical modifications in the amino acid composition at positions 5 through 8; the natural tyrosine-glycine-leucine-arginine sequence at these positions has been changed to histidine-asparagine-tryptophan-lysine. GnRH analogues control the release of pituitary gonadotrophins such as luteinising hormone (LH) and follicle stimulating hormone (FSH). In turn, LH and FSH stimulate gonadal production of sex steroids and gametogenesis, respectively.

Veyx-Pharma GmbH have submitted a data package seeking approval of the new active constituent peforelin, and registration of the new product Maprelin, containing peforelin at 0.075 mg/mL in an aqueous concentrate for intramuscular injection into sows and gilts. The proposed product is intended for the synchronisation of ovulation in sows and gilts. The intended use is a single injection of either 0.5 or 2.0 mL depending on the use pattern as described on the draft product label. The product will be available in pack sizes of 10 mL, 50 mL or 100 mL glass vial enclosed with a rubber stopper, as well as 6 x 10 mL glass vials.

The data package provided in the present submission comprised pharmacology and toxicology studies using peforelin and publicly available information on peforelin and related synthetic hormone analogues. Noting that the data package did not consist of standard toxicology studies, the OCS considered that there was sufficient information presented in the submission for the assessment of the toxicology profile of peforelin and the product in this instance.

The product Maprelin is expected to have low acute oral toxicity along with very low oral bioavailability. While no data on acute dermal, inhalational, irritancy or sensitisation were available it is recognised that the product is for injection only. Acute dermal, inhalational and ocular exposures are not considered to be likely under normal conditions of product use.

Peforelin is a selective inducer of FSH but has no, or minimal effect on serum LH. Other GnRH analogues have previously been classified as presenting a strong inducing effect for LH. Peforelin was readily broken down in a synthetic gastric juice mixture containing peptidases, indicating that there would be very limited oral bioavailability for the active constituent in mammals. A series of studies on other GnRH analogues indicated good tolerance of the compounds when used clinically, although the expected side effects of oestrogen deprivation were frequently noted. Genotoxicity studies have been submitted for other GnRH analogues which show a lack of genotoxicity. It would be expected a small, chemically non-reactive peptide such as the GnRH analogues (including peforelin) would not be genotoxic.

There is some data suggesting that GnRH analogues may affect pre-natal development (in the form of decreased foetal weights and skeletal variations/malformations) in mice. A conservative interpretation of the available data suggests that peforelin, as a GnRH analogue, would share a similar developmental toxicity profile.

Evaluation of toxicology

A summary of the toxicity data on peforelin and related GnRH analogues submitted as part of this application is presented below, followed by a general discussion of the toxicity of peforelin and the GnRH analogues (including publicly available information).

Chemical class

Peforelin, or Lamprey-GnRH-III/Gonadorelin [5-His, 6-Asp, 7-Trp, 8-Lys], is a synthetic decapeptide analogue of the GnRH. Compared to natural GnRH, peforelin has chemical modifications in the amino acid composition at positions 5 through 8; the natural tyrosine-glycine-leucine-arginine sequence at these positions has been changed to histidine-asparagine-tryptophan-lysine. GnRH analogues control the release of pituitary gonadotrophins such as LH and FSH. In turn LH and FSH stimulate gonadal production of sex steroids and gametogenesis, respectively.

Endogenous GnRH is a decapeptide formed in the hypothalamus which binds to receptors in the pituitary. Pulsatile administration of GnRH stimulates secretion of LH and FSH whereas continuous administration inhibits the release of these hormones.

Toxicokinetics and metabolism

Following i.m. application, 150 µg peforelin as Maprelin (the highest suggested therapeutic dose in pigs) increased FSH release in castrated male pigs from 0.5 hours until 12 hours post application at which time FSH returned to basal levels. There was no, or minimal effect on serum LH. Following oral application of the same dose (150 µg) and 100 times this dose (15 mg), no increase in serum FSH or LH was detectable.

In a similar study peforelin (150 µg) significantly increased FSH levels in male castrated pigs shortly (0.5 hrs) after intramuscular injection. The maximum increase occurred at 1 hour (≈ 2.2x baseline) with FSH gradually returning to baseline at 12 hours. LH levels were marginally affected. With a lower intramuscular dose (37.5 µg), serum FSH was elevated from 0.5 to 6 hours after injection. Again LH was only marginally affected.

In vivo metabolism data for peforelin was not submitted. However general biochemistry knowledge indicates the metabolism of peforelin is very likely to be similar to GnRH and other peptides, and be metabolised by non-specific proteases.

In an *in vitro* simulated digestion model, peforelin was incubated for 120 minutes in artificial gastric juice. After 120 minutes, artificial intestinal juice was added and exposure continued for another 120 minutes. Approximately 50% of the peforelin was hydrolysed by the artificial gastric juice within 30 minutes, 75% by 60 min and 95% at 120 min. The remainder was completely broken down by intestinal juice shortly after its addition.

Percutaneous absorption

There were no data available for dermal absorption.

Acute toxicity

In a non-guideline compliant study, gilts were dosed once intramuscularly with formulated peforelin at the intended dose (150 µg), or with 450 µg, and observed for 35 days. General and clinical signs (health, feed intake, application site, urine and dung excretions, mucous membranes including vulva) were monitored daily by a veterinarian. During this time blood was obtained at 1, 3, 10, 25 and 35 days for standard haematology and clinical chemistry measurements. At sacrifice (35d) gross pathology was undertaken and selected tissues processed for histopathology. At some sampling times there were sporadic differences in a few clinical chemistry parameters compared to the control group values. However the changes were within the normal physiological range for the species and not considered compound related. At sacrifice occasional gross pathology was observed but assigned to bacterial infection or inherited nuances. Similarly isolated incidences of hepatitis and interstitial nephritis were considered the result of parasite and bacterial infection. Overall no compound related adverse effects were observed. The dosing regime was well tolerated by the pigs.

Several references were supplied which indicate other GnRH analogues are biologically well tolerated in humans even at high dose rates and multiple treatments.

In a GLP-compliant acute toxicity study, Wistar rats were administered a single intramuscular injection of D- Phe6-GnRH (15, 30, or 60 mg/kg bw) or the vehicle water control into the right thigh and were monitored daily for 14 days after dosing. These doses are at least 10,000× higher than the highest therapeutic dose suggested for use in gilts. There were no mortalities during the entire course of the study, and animals in the control group did not show any clinical abnormalities. Both males and females in the treated groups showed local clinical signs at the site of repeated injection; including strong lameness accompanied by plantar inflection, swelling and dark blue-red discolouration of the surrounding tissue, and local pain to the touch. Discolouration was fully reversible within 24 hours after application, and severity of other symptoms decreased over time. The authors concluded lameness was most likely due to irritation of the sciatic nerve due to method of dosing.

Systemic toxicity

A non-GLP compliant 28 day toxicity study with daily subcutaneous injections of D-Phe6-GnRH to wistar rats at 0, 2, 10 or 50 µg/kg bw/d reported no mortality, clinical, or pathomorphological changes in the animals treated with D-Phe6-GnRH compared to controls. No treatment-related differences in serum analytical parameters occurred throughout the study. Dosing with D-Phe6-GnRH resulted in a slight transient decrease in body weight gain in males of the high dose group (50 µg/kg bw/d). In females, all treated groups exhibited significant increased body weight gain in comparison to controls which according to the study authors was not dose-related and unlikely to be due to treatment. According to the study authors, there was an almost identical occurrence of small inflammatory organ lesions in controls and treated animals (specifically in the lung and liver). They therefore concluded the minimal findings could not be attributed to treatment with D- Phe6-GnRH and may have been due to presumed viral and/or bacterial infection.

Genotoxicity and carcinogenicity

No studies specific to peforelin were provided. Data were provided on GnRH analogues.

The clastogenicity of D-Phe6-GnRH was investigated in a mammalian bone marrow chromosome aberration test in male mice. The mitosis frequency and chromosome aberration incidence (at 6, 24, 48 or 72 hours post injection) were not influenced by intravenous treatment with 0.45 or 1.14 mg/kg D-Phe6-GnRH. However, the lack of a positive control in the study renders it uncertain whether the test was working as intended.

An Ames test (plate incorporation and pre-incubation) was carried out using S. typhimurium TA 1535, TA 1537, TA 1538, TA 97, TA 98, and TA 100. No increase in revertant colony counts were observed in plates in any of the strains used, with or without metabolic activation. Appropriate positive controls gave expected responses. Under the test conditions, GnRH analogues were not mutagenic in the strains tested.

Reproductive and developmental toxicity

No peforelin-specific studies were provided; however, three studies on GnRH analogues were provided. In these studies, D-Phe6-GnRH was administered to female mice, immediately before mating, as a single subcutaneous does at 6.3, 18.9, or 37.8 µg/kg bw. It is noted that in all these studies control animals were not sham treated.

In a multigenerational fertility study, litter size for all three generations was used as the indicator of fertility. No compound related effect on this index was observed.

In a prenatal teratology study, no significant difference was found between the control and treated groups for gestation rate, number of implantations, post-implantation losses in dams, or sex ratio, external malformations, organ malformations, or skeletal or weight retardations in foetuses. However, for the low dose group a statistically significant reduction in weight gain, higher number of yellow bodies, and higher pre-implantation loss were observed. Foetal weights were significantly lower at all three doses compared to controls, and there was a significant increase in skeletal variations and/or number of finger appendages in the two highest dose groups, with an increase in skeletal malformations at the highest dose of 37.8 µg/kg bw/d. In discussing the observed findings, the study authors concluded the increase in pre-implantation losses should not be considered relevant due to the lack of dose response, and that the reduced foetal weight in all treated groups may be compound related. Additionally, the study authors concluded D- Phe6- GnRH only influences pre-natal development at the higher dose levels. It is noted, however, skeletal variation and malformation rates were also slightly elevated (although not statistically significantly so) in the low dose group.

In a post-natal developmental toxicity study, several developmental indices were measured at various time points post-partum. There was a tendency for higher foetal weight gain in offspring from treated dams but this only reached statistical significance on some days. There was also a trend for earlier development of offspring from treated dams. This was manifested as statistically significant improvements over control offspring for ear plication (two highest dose groups), eye opening (all groups), grasping reflex (low and high dose group), and learning ability (high dose group). Slight but statistically significant differences in absolute and relative organ weights in offspring at PPD25 were not dose-related and inconsistent. The authors considered these were not compound related. The study authors concluded that overall D-Phe6-GnRH produced a small increase in the rate of development and a tendency towards increased litter size.

Other toxicology information

The immunotoxicity of D-Phe6-GnRH was investigated in a host-defence assay in mice. Mice were immunised against *Escherichia coli* and *Erysipelothrix insidiosa* but to determine the effect of D-Phe6-GnRH on the efficiency of the vaccination, mice were also treated with four repeat subcutaneous injections (0.1 µg/animal) before or after immunisation. Approximately 2–2.5 weeks after vaccination mice were challenged (route not specified - likely to be intraperitoneal) with pathogenic versions of the organisms and lethality measured over the next 10 days. Vaccinated mice had excellent survival which was not affected by dosing with D-Phe6-GnRH. The authors cautiously concluded no immunosuppressive effect is to be expected in farmed animals with the use of D-Phe6-GnRH in veterinary practice. These results with D- Phe6- GnRH are consistent with the 28 day repeat dosing of rats with D-Phe6-GnRH, where significant macro- or microscopic changes in lymphoid tissue were not observed.

In addition, no treatment-related effects were observed on immunoglobulin levels after a single intramuscular injection of the therapeutic dose or 3x the therapeutic dose of peforelin.

Public health standards

Poisons scheduling

Peforelin is not currently listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). There is a schedule 4 entry for gonadotrophic hormones which would capture synthetic analogues of naturally occurring hormones such as peforelin. Since the product, Maprelin, contains a gonadotrophic hormone analogue, it therefore is classified as a schedule 4 compound and should be available by veterinary prescription only.

NOEL/ADI

The acceptable daily intake for humans is the level of intake of an agricultural or veterinary chemical which can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall NOEL for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intra-species variation, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

Since exposure to the compound is not expected to occur under normal conditions of use, and the compound also has negligible oral bioavailability, is likely degraded in a similar manner to the endogenous molecule and has a short elimination half-life, it is considered unlikely that peforelin would be contained in tissues available for human consumption and therefore an ADI is considered unnecessary in this instance.

ARfD

The acute reference dose is the estimate of the amount of a substance in food or drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a short period of time, usually in

one meal or during one day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

An ARfD was not established, since oral exposure to the compound is not expected to occur under normal conditions of use, and the compound also has negligible oral bioavailability, is likely degraded in a similar manner to the endogenous molecule and has a short elimination half-life. It is considered unlikely that peforelin would be contained in tissues available for human consumption and therefore an ARfD is considered unnecessary in this instance.

Conclusion

Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the use of Maprelin when used in accordance with the label directions.

RESIDUES ASSESSMENT

The APVMA has before it an application for the registration of the product Maprelin, which contains 75 µg/mL peforelin. The product is intended for induction of the oestrous cycle in sows after weaning and for induction of oestrus in sexually mature gilts following therapy to inhibit the oestrous cycle with progestogens.

The applicant has proposed that the use of peforelin for inducing ovulation in sows is eligible for a Table 5 entry in the MRL Standard under the existing entry for 'Gonadotrophin Releasing Hormone (GnRH) and analogues'.

Requirements for a Table 5 entry

Compounds are eligible for inclusion in Table 5 when one or more of the following are met:

- residues do not or should not occur in foods or animal feeds
- residues are identical to or indistinguishable from natural food components
- residues are otherwise of no toxicological significance.

The requirements for a table 5 entry for the use of peforelin in pigs are considered below.

Residues do not or should not occur in foods or animal feeds

Only very small quantities of peforelin (0.15 mg) are used to induce oestrus in pigs, and when peforelin is administered parenterally, it is quickly absorbed and metabolised. Additionally, Maprelin is for the treatment of pigs for breeding purposes and it is unlikely that treated animals will be made available for human consumption in the short term.

Therefore, when used according to the proposed relevant label particulars, peforelin residues should not occur in pig commodities.

Residues are identical to or indistinguishable from natural food components

Peforelin is a hormone found in the hypothalamus of the lamprey and is present in mammals as an endogenous substance.

Therefore, peforelin will not be distinguishable from natural food components.

Residues are otherwise of no toxicological significance

Peforelin is absorbed rapidly following intramuscular administration, and quickly metabolised in the liver and kidneys into small peptides that have negligible biological activity. Further, if commodities from treated animals are consumed, gastro-intestinal enzymes rapidly inactivate peforelin. Oral bioavailability in humans was estimated to be less than 1%. In humans, a closely chemically related peptide given orally at 2 mg/person) did not increase plasma LH and FSH. Only at a dose of 10 mg/person was the LH/FSH response measurably increased. [EMA, 2006]

Therefore, if commodities from treated animals are consumed, peforelin residues in these commodities will be of no toxicological significance. This is supported by the conclusions of the toxicological assessment that determined it was not necessary to set an ADI or ARfD for peforelin, since exposure to the compound is not expected to occur under normal conditions of use. The compound has negligible oral bioavailability, is likely degraded in a similar manner to the endogenous molecule and has a short elimination half-life.

Conclusion

The use of peforelin to induce oestrus in pigs fulfils the requirements that ‘residues do not or should not occur in foods or animal feeds’, ‘residues are identical to or indistinguishable from natural food components’ and that ‘residues are otherwise of no toxicological significance’. Therefore, the use of peforelin to induce oestrus in pigs is eligible for a table 5 entry in MRL standard.

RECOMMENDATIONS

MRL amendments

The following amendment to table 5 of the MRL standard is recommended to cover the use of Maprelin in pigs.

SUBSTANCE	USE
DELETE:	
Gonadotrophin Releasing Hormone (GnRH) and synthetic analogues [including buserelin, deslorelin, gonadorelin, triptorelin acetate and salmon GnRH analogue:	Cattle: treatment of cystic ovaries; prevention of delayed ovulation; improvement of fertility rate Horses: induction of ovulation; treatment of anoestrus Finfish: induction of spawning in finfish broodstock Pigs: induction and synchronisation of oestrus Rabbits: induction of ovulation; improvement of conception rate
ADD:	
Gonadotrophin Releasing Hormone (GnRH) and analogues [including buserelin, deslorelin, gonadorelin, triptorelin acetate, peforelin and salmon GnRH analogue:	Cattle: treatment of cystic ovaries; prevention of delayed ovulation; improvement of fertility rate Horses: induction of ovulation; treatment of anoestrus Finfish: induction of spawning in finfish broodstock Pigs: induction and synchronisation of oestrus Rabbits: induction of ovulation; improvement of conception rate

Restraints

None required.

Withholding periods

Meat: Zero (0) days

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Peforelin residues should not occur in foods and is of no toxicological significance if humans consume treated animals. Therefore, there are no residues related risks to Australia's export trade in pork.

The APVMA proposes to be satisfied that use of Maprelin, in accordance with the recommended relevant label particulars, meets the trade criteria, provided the following trade advice statement is included on the relevant label particulars:

Trade advice

Export Slaughter Interval (ESI): Zero (0) days

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Occupational health and safety summary

Maprelin will be used by veterinary surgeons or animal handlers (on veterinary prescription following veterinary instruction on how to administer the product) as an intramuscular injection to synchronise ovulation in sows and gilts. As the product is only available for use as an injection by individuals trained in how to administer the product, under the instructions of a veterinary surgeon, user exposure is expected to be minimal when observing normal workplace precautions to avoid self-injection. Therefore, a full quantitative exposure assessment was not required in this instance.

Based on the submitted data the active constituent and the product were identified as possible hazards to reproduction and development and a warning statement is recommended for inclusion on the product label. Based on the risk assessment, First Aid Instructions and Safety Directions have been recommended for the product label.

Formulation, packaging, transport, storage and retailing

The active constituent peforelin and the product Maprelin will be manufactured overseas. Maprelin will be available as a 10 mL, 6 x 10 mL, 50 mL or 100 mL glass vial enclosed with a rubber stopper.

Use pattern

The product will be used by veterinary surgeons or animal handlers (on veterinary prescription following veterinary instruction on how to administer the product) as an intramuscular injection to synchronise ovulation in sows and gilts. The intended use is a single injection of either 0.5 or 2.0 mL depending on the use pattern as described on the draft product label.

Exposure during use

Animal handlers and veterinary surgeons will be the main users of the product. Potential exposure routes include needle stick injury and accidental self-injection. The product will be used by individuals that have been trained in the handling and use of veterinary medicines and be aware of the risks and mitigation measures required for injectable drugs.

There is a possibility that users may be exposed to the product when cleaning up spills of the product. If workplace practices to avoid self-injection are followed, it is expected that exposure via that route is likely to be minimal. No exposure estimate is considered necessary since exposure will be minimal during normal conditions of product use.

The product is expected to be capable of causing reproductive/developmental toxicity following systemic exposure based on the toxicity information supplied. A warning statement for this endpoint has been recommended:

Caution: Accidental self-injection may affect fertility in both men and women and pregnancy. Care should be taken to avoid accidental self-injection and needle stick injury when administering this product. In the event of accidental self-injection, seek medical advice immediately. Not to be used by pregnant women.

Recommendations for safe use

Users should follow the First Aid Instructions, Safety Directions and note the warning statement recommended on the product label.

The following First Aid Instructions are recommended:

FIRST AID: If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766.

The following Safety Directions are recommended:

SAFETY DIRECTIONS: Avoid contact with eyes and skin. Wash hands after use.

Conclusion

The registration of Maprelin, containing 0.075 mg/mL peforelin, for induction of the oestrous cycle in sows after weaning and for induction of oestrus in sexually mature gilts following therapy to inhibit the oestrus cycle with progestogens, is supported.

Maprelin can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product material safety data sheet.

ENVIRONMENTAL ASSESSMENT

Maprelin containing the new active constituent peforelin is proposed for induction of the oestrous cycle in sows after weaning and for induction of oestrus in sexually mature gilts following therapy to inhibit the oestrus cycle with progestogens. It is proposed to be administered at the maximum rate of 150 µg per animal for single application by intramuscular injection.

The applicant has provided limited information on pharmacokinetic studies and an environmental risk assessment for the proposed product. The active constituent is expected to metabolise extensively. It is known from studies with native GnRH as well as its analogues that all the degradation products are biologically inactive. The biological half-life of the native GnRH and most of its analogues are very short. Accumulation of GnRH or its analogues in organs or tissues does not occur.

The environment assessment considered the peforelin concentration in soils following subsequent application of treated effluent to cropland for pigs under the proposed use patterns. The results on worst case conservative assumptions indicate that levels of peforelin are so low they are unlikely to pose an environmental risk when treated effluent is applied to cropland and when a subsequent run-off from cropland is considered.

No ecotoxicity and bioaccumulation data were provided for assessment. The available information indicates that peforelin is rapidly metabolised into smaller inactive peptides and amino acids in animals.

The label will contain a disposal statement as follows: *Dispose of empty container by wrapping with paper and putting in garbage.*

Conclusion

It is considered that the approval and use of the new active constituent peforelin is unlikely to have an unintended effect that is harmful to animals, plants, things or the environment.

Disposal

Dispose of empty container by wrapping with paper and putting in garbage.

The APVMA proposes to be satisfied that the use of Maprelin meets the safety criteria with regards to environment safety.

EFFICACY AND SAFETY ASSESSMENT

The APVMA has before it an application to register the product Maprelin containing 75 µg/mL of the new active constituent peforelin. The product is a solution for intramuscular injection for use in induction of the oestrous cycle in sows after weaning, and for induction of oestrus in sexually mature gilts following therapy to inhibit the oestrous cycle with progestogens.

Peforelin is a synthetic analogue of GnRH. It has not been previously assessed by the APVMA but other GnRH analogues are approved for use in swine in Australia.

Evaluation of efficacy data

In support of the application, the applicant has submitted one dose determination study, five clinical efficacy trials, a margin of safety study and published supporting information. An external reviewer assessed the information submitted by the applicant in support of the efficacy and target animal safety of the proposed product. The trials were conducted overseas but since the reproductive management and husbandry of intensively farmed pigs is similar overseas and in Australia, it is considered that the data is relevant to the Australian situation.

A series of pivotal and non-pivotal studies supported that 150 µg (pluriparous sows or gilts) or 37.5 µg (primiparous sows) peforelin administered by intramuscular injection 24 hours after weaning (pluriparous or primiparous sows) or 48 hours after termination of the medication for oestrus inhibition (gilts) is effective in induction of the oestrous cycle after weaning or induction of oestrus in sexually mature gilts following therapy to inhibit the oestrus cycle with progestagens.

The series of studies demonstrated:

1. A dose of 150 µg peforelin achieved oestrus rates after weaning equivalent to 800 IU Pregnant Mare Serum Gonadotrophin (used in established reproductive management protocols).
2. A dose of 150 µg peforelin was equally as effective as PMSG in inducing oestrus in weaned pluriparous sows when given 24 hours after weaning.
3. Treatment with peforelin in a high-producing herd resulting in decreasing the mean time from weaning to first oestrus by 0.8 half days (9.6 hours) and concentrated the inseminations to 3–6 days after weaning.
4. A dose of 150 µg peforelin did not improve percentage of sows in oestrus by 7 days, pregnancy rate or piglet index when used in primiparous weaned sows.
5. A dose of 37.5 µg peforelin given 24 hours after weaning in primiparous sows increased the number of sows coming into oestrus in 7 days compared to controls.
6. A dose of 150 µg peforelin was not less effective than PMSG in inducing oestrus and enhancing synchronisation in gilts in the first 5–8 days after cessation of 18 days of treatment with altrenogest to synchronise oestrus.

Evaluation of target animal safety data

The tolerance of the proposed product was tested in a target animal safety study in pigs, with single intramuscular administration of either saline, or the test product at 1X and 3X the recommended dose rate. The animals were observed clinically for 35–36 days, with multiple blood collections for haematology and biochemistry. The animals were slaughtered and autopsied on days 36–37.

No adverse injection site reactions were observed in the study. There were no adverse effects on weight gain or general health, and no changes in haematological or biochemical parameters. No gross or histopathological changes were observed at any dose rate.

Since no adverse effects were observed at any point in this study, it is likely that the margin of safety is greater than 3X. The toxicological information assessed for this application suggests that common side effects of this type of product (reproductive hormone) would be related to long term use and oestrogen deficiency, which is not relevant to the proposed veterinary use.

Contraindication statements will be included on the label as follows: *This product is contraindicated for use in prepubertal gilts, in case of infertility or general health disorders. This product is contraindicated for use in case of hypersensitivity to the active substance.*

Precautions statements will be included on the label as follows: *The safety of the product has not been established in sows and gilts during pregnancy and lactation. Laboratory studies in mice produced evidence of teratogenic effects. Do not use Maprelin in animals during pregnancy and lactation.*

Conclusions

The APVMA proposes to be satisfied that Maprelin, when used according to the instructions on the approved label for its use, meets the efficacy criteria and the safety criteria with regards to target animal safety.

LABELLING REQUIREMENTS

Signal heading:	PRESCRIPTION ANIMAL REMEDY KEEP OUT OF REACH OF CHILDREN READ SAFETY DIRECTIONS BEFORE OPENING OR USING FOR ANIMAL TREATMENT ONLY
Product name:	Maprelin
Active constituent/s:	75 µg/mL Peforelin
Statement of claims:	For zootechnical use and intended for group or herd treatment under the advice and supervision of the herd's consultant veterinarian. • To hasten the onset and improve the synchronisation of oestrus in sows after weaning, particularly in swine production units using batch farrowing management. • To induce oestrus and improve its synchronisation in sexually mature gilts following therapy to inhibit the oestrous cycle with progestagens
Net contents:	10 mL 6 x 10 mL 50 mL 100 mL
Directions for use heading:	Directions for use
Restraints:	-
Contraindications:	This product is contraindicated for use in prepubertal gilts, in case of infertility or general health disorders. Do not use in case of hypersensitivity to the active constituent.
Precautions:	The safety of the product has not been established in sows and gilts during pregnancy and lactation. Laboratory studies in mice produced evidence of teratogenic effects. Do not use the product in animals during pregnancy and lactation. The simultaneous use of the product with PMSG or hCG can possibly lead to an over-reaction of the ovaries. No interactions were reported following administration of the product 48 hours after the end of prior altrenogest therapy. *Incompatibilities* In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.
Side effects:	*Overdose* No adverse reactions were ascertained in pigs following treatment with up to three times the highest recommended dosage.
Dosage and administration:	Discard unused portion 28 days after first broaching. Store upright, protected from light, between 2°C and 8°C (refrigerate, do not freeze) after broaching. For intramuscular use only. Sows or sexually mature gilts should be injected in the neck muscles behind the base of the ear usually at the caudal limit of the virtually hairless region behind the ear.

	Dosage in µg peforelin and mL product (MAPRELIN) per animal. The dosage is dependent on the parity. Primiparous sows 24 hours after weaning off the piglets: 37.5 µg peforelin (0.5 mL MAPRELIN) per sow. Pluriparous sows 24 hours after weaning off the piglets: 150 µg peforelin (2.0 mL MAPRELIN) per sow. Gilts 48 hours after the termination of the medication for the inhibition of the cycle: 150 µg peforelin (2.0 mL MAPRELIN) per gilt. For single application. Use automatic syringe equipment for the 50 mL and 100 mL vials.
General directions:	-
Withholding period/s:	WITHHOLDING PERIOD: Zero (0) days
Trade advice:	EXPORT SLAUGHTER INTERVAL (ESI): Zero (0) days
Safety directions:	Avoid contact with eyes and skin. Wash hands after use.
First aid:	FIRST AID: If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766.
Additional user safety:	CAUTION: Accidental self-injection may affect fertility in both men and women and pregnancy. Care should be taken to avoid accidental self-injection and needle-stick injury when administering the product. In the event of accidental self-injection, seek medical advice immediately. Not to be used by pregnant women. In case of accidental contact with the skin, the corresponding area should be thoroughly cleaned with soap and water, as GnRH analogues may be absorbed through the intact skin. In case of contact with the eyes, they should be thoroughly rinsed with water. The product might induce irritation and sensitization. People with known hypersensitivity to GnRH analogues should avoid contact with the veterinary medicinal product. The veterinary medicinal product should not be administered by pregnant women, as an accidental self-injection by the user cannot be excluded and because GnRH analogues have been shown to be foetotoxic in laboratory animals. Women of childbearing age should administer the product with special caution.
Environmental statements:	-
Disposal:	Dispose of empty packaging by wrapping with paper and putting in garbage.
Storage:	Store between 2 °C and 8 °C (refrigerate, do not freeze). Protect from light during storage and use. The product is extremely sensitive to light. Keep the vial in the outer carton.
APVMA approval no.	APVMA No: 65595/51387

ABBREVIATIONS

ADI	Acceptable Daily Intake (for humans)
ARfD	Acute Reference Dose
bw	bodyweight
d	day
ESI	Export Slaughter Interval
FSH	Follicle stimulating hormone
g	gram
GLP	Good Laboratory Practice
GnRH	Gonadotrophin Releasing Hormone
hrs	hours
im	intramuscular
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
L	Litre
LH	Luteinising hormone
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
NOEL	No Observable Effect Level
s	second
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
µg	microgram
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
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
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons