Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active constituent sometribove zinc

in the product Elanco Posilac

APVMA Product Number 70120

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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, Department of Environment and Energy, 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. Definition of terms found in this document are located on the APVMA website.

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 Elanco Posilac 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 29 November 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
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Australian Pesticides and Veterinary Medicines Authority
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Kingston ACT 2604
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Email: enquiries@apvma.gov.au

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 at www.apvma.gov.au.

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

1 INTRODUCTION

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application from Elanco Animal Health a Division of Eli Lilly Australia Pty Ltd for the approval of a new active constituent sometribove zinc. The APVMA also has before it an application from the same applicant for the registration of the new product Elanco Posilac containing the new active constituent.

Elanco Posilac contains 500 mg/syringe of the active constituent sometribove zinc. It is proposed to be registered as an injection for increased milk production in lactating dairy cows. The proposed instructions for use indicate to inject one syringe of Elanco Posilac subcutaneously every 14 days, starting treatment 57–70 days after calving and continuing until the end of lactation.

Elanco Posilac has been approved by the Food and Drug Administration (FDA) with the same use pattern as proposed for the Australian market. The FDA approval number is NADA#140–872.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Elanco Posilac, and approval of the new active constituent sometribove zinc.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent properties

The APVMA has evaluated the chemistry aspects of the active constituent sometribove zinc, including physico-chemical properties and identification, manufacturing process and quality control procedures (including specifications), batch analysis and stability results and analytical methods.

Sometribove zinc is the zinc salt of sometribove, a bovine growth hormone, one of four members of the bovine somatotropin/growth hormone family, which includes somidobove, somagrebove and somavubove. The chemical active constituent sometribove zinc has the following properties:

COMMON NAME (USAN):	Sometribove zinc
CHEMICAL NAME (IUPAC):	1-L-Methionine-127-L-leucine growth hormone (Ox), for sometribove
CAS REGISTRY NUMBER:	102744-97-8 (for sometribove)
EMPIRICAL FORMULA:	$C_{978}H_{1537}N_{265}O_{286}S_9$ (for sometribove)
MOLAR MASS:	21,872.29 g/mol (for sometribove)
PHYSICAL FORM:	Lyophilised powder
COLOUR:	White
STRUCTURAL FORMULA:	MFPAMSLSGL FANAVLRAQH LHQLAADTFK EFERTYIPEG QRYSIQNTQV AFCFSETIPA PTGKNEAQQK SDLELLRISL LLIQSWLGPL QFLSRVFTNS LVFGTSDRVY EKLKDLEEGI LALMRELEDG TPRAGQILKQ TYDKFDTNMR SDDALLKNYG LLSCFRKDLH KTETYLRVMK CRRFGEASCA F

2.2 Product

The APVMA has evaluated the chemistry and manufacturing aspects of Elanco Posilac, including composition and form of constituents, formulation process, product specifications, batch analysis and stability data, analytical methods, product containers and label. Chemical details of the product are as follows:

Dose form

Subcutaneous injection.

Formulation type

Suspension.

Level of active

500 mg/syringe sometribove zinc.

Physical properties—appearance

A white to off-white suspension.

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 sensitive to light, therefore a protection statement is proposed for inclusion on the label.

The product is for single use only therefore in-use stability was not provided and an in-use storage stability statement for the label in not necessary.

Packaging

The product will be packaged in a 1.33 g capacity prefilled polypropylene syringe with high-density polyethylene plunger and cap with thermally welded polypropylene cord extending through the pre-attached stainless steel needle. 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.

2.3 Conclusion

The quality of the new active constituent sometribove zinc in the product Elanco Posilac has been evaluated and determined to satisfy the legislative requirements. The APVMA therefore proposes to be satisfied that the active constituent and chemical product meet the safety criteria of section 5A of the Agvet Code with regards to quality.

3 TOXICOLOGICAL ASSESSMENT

Sometribove zinc is a recombinant bovine somatotropin. Somatotropins (growth hormones) are peptide hormones secreted by the anterior pituitary gland that stimulate cell growth and development in humans and animals. Bovine somatotropins bind to bovine somatotropin receptors, but do not bind to the human somatotropin receptor. Most growth-promoting effects of somatotropins are mediated through a polypeptide hormone, insulin-like growth factor-1 (IGF-1).

Other recombinant bovine somatotropins which are highly similar to sometribove are somagrebove, somavubove and somidobove. All recombinant bovine somatotropins are biologically and toxicologically similar.

Available toxicology information for sometribove zinc included toxicity tests conducted in laboratory animals and review articles by the applicant, published papers and Joint FAO/WHO Expert Committee on Food Additives (JECFA) toxicological evaluation reports. The most recent JECFA report (seventy eighth meeting) was for recombinant bovine somatotropins (Toxicological evaluation of certain veterinary drug residues in food (WHO Food Additive Series 69, 2014)), and there were two earlier JECFA reports. Toxicology data were also available for IGF-1. The APVMA considered that the available data were sufficient to assess the toxicology of the product and the new active constituent and to establish Safety Directions.

3.1 Evaluation of toxicology data

Sometribove zinc showed low acute oral toxicity in rats (LD50 > 5000 mg/kg bodyweight) and low acute subcutaneous toxicity in mice (LD50 > 500 mg/kg bodyweight). The active constituent was a mild skin irritant in rabbits, and a mild to moderate eye irritant in the same species. No animal studies were conducted to investigate skin sensitisation, but allergic reactions have been reported in a manufacturing setting.

No toxic effects were observed in rats at oral doses of up to 50 mg/kg bodyweight per day for 90 days. The related recombinant bovine somatotropin, somidobove was also without toxic effects at oral doses up to 100 mg/kg bodyweight per day for 90 days in rats and 10 mg/kg bodyweight per day for 90 days in dogs. Orally-administered IGF-1 also showed no toxic effects in rats at doses up to 2 mg/kg bodyweight per day for 14 days (albeit with no histopathological evaluation) or in hypophysectomised rats at doses up to 1 mg/kg bodyweight per day for 17 days.

Sometribove zinc was negative in an *in vitro* genotoxicity study (forward mutation at the HGPRT locus in Chinese Hamster Ovary cells), both in the presence or absence of metabolic activation, and in an *in vivo* study (mouse micronucleus test). No carcinogenicity studies were conducted on sometribove zinc, but carcinogenicity studies conducted on recombinant mouse and rat somatotropins in the corresponding species, were negative. Reproduction and developmental studies on sometribove zinc were not conducted and were not considered necessary.

The consumption of milk and tissues from cows treated with sometribove zinc is not considered to be hazardous to human health. Recombinant bovine somatotropins have little or no activity at the human somatotropin receptor, and are largely, if not completely, destroyed by pasteurisation and cooking, as well as by gastrointestinal digestive processes. Further, the concentrations of recombinant bovine somatotropins in the milk and tissues of treated cows were comparable to those in the milk of untreated cows. Concentrations

of IGF-1 in the milk of treated cows were slightly higher than those in the milk of untreated cows, but were within the normal range, while concentrations in tissues were ≤ 2–fold higher than those in the milk of untreated cows. IGF-1 is largely, but probably not completely, destroyed by gastrointestinal digestive processes. Additionally, as noted above, both recombinant bovine somatotropins and IGF-1 were of low toxicity.

3.2 Public health standards

Poisons scheduling

Sometribove zinc is not specifically listed in the current Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). However, the broader class of bovine somatotropins is listed under Appendix B, Part 3 'Substances considered not to require control by scheduling'. Given the high degree of structural similarity of the bovine somatotropins, this entry is considered adequate to cover sometribove zinc. The product will therefore be unscheduled.

Acceptable Daily Intake (ADI) and Acute Reference Dose (ARfD)

The Acceptable Daily Intake (ADI) is that quantity of an agricultural compound which can safely be consumed on a daily basis for a lifetime. An ADI has not been established for sometribove zinc as an ADI was not considered necessary, because as noted above, the consumption of milk and tissues from cows treated with sometribove zinc was not considered to be hazardous to human health. The related somatotropin, somidobove, has an 'ADI not necessary' entry in the current Department of Health's ADI list (December 2014).

The acute reference dose (ARfD) is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated event. An ARfD was not established for sometribove zinc because the consumption of milk and tissues from cows treated with sometribove zinc was not considered to be hazardous to human health.

3.3 Conclusion

It is considered that the approval and use of the new active constituent sometribove zinc in the product Elanco Posilac would not be likely to have an effect that is harmful to human beings. The APVMA therefore proposes to be satisfied that the active constituent meets the safety criteria of section 5A of the Agvet Code with regards to human health.

4 RESIDUES ASSESSMENT

The proposed use of Elanco Posilac involves one subcutaneous injection containing 500 mg sometribove zinc to the neck or tailhead per animal every 14 days starting from 57–70 days after calving and continuing until the end of lactation. The meat and milk withholding period is zero (0) days.

The Australian toxicological evaluation of sometribove-zinc and the JECFA monographs for bovine somatotropins indicate that the proposed use of sometribove-zinc as an injectable to lactating dairy cows should not pose a hazard to human health for the following reasons:

1. The concentrations of recombinant bovine somatotropin (rbST) and insulin-like growth factor-1 (IGF-1) in the milk and tissues of treated cows lie within the normal range and are comparable to those in the milk of untreated cows.
2. rbSTs and IGF-1 are largely destroyed by gastrointestinal digestive processes and are of low toxicity.
3. The establishment of an ADI and ARfD for sometribove-zinc was not considered to be necessary by the Australian and JECFA toxicological evaluations as the consumption of milk and tissues from cows treated with sometribove-zinc was not considered to be hazardous to human health.

Sometribove-zinc, when used as an injection for the improvement of milk production in lactating dairy cattle, fulfils the requirement that ‘residues are otherwise of no toxicological significance’ and is therefore, eligible for a Table 5 entry in MRL Standard (‘uses of substances where MRLs are not necessary’).

The following Table 5 entry is considered appropriate for the proposed use:

Table 1: MRL standard—Table 5 amendment

SUBSTANCE	USE
ADD:	
Sometribove-zinc	For increasing milk production in lactating dairy cows

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Cattle meat and offal in addition to dairy products are considered to be major export commodities[2].

5.2 Destination and value of exports

Beef meat and offal

The significant export markets for Australian beef meat and offal are Codex, the EU, Japan, the Republic of Korea, Russia, Taiwan, and the USA, as listed in the APVMA Regulatory Guidelines—Data Guidelines: Veterinary—Overseas trade (Part 5B).

In 2014–15, 1,349 kt of Australian beef and veal were exported in total, valued at $8.9 billion[3].

The proposed use is for lactating dairy cattle only. Export statistics for dairy cattle meat are not readily available but the applicant has indicated that beef from culled dairy cows contributes approximately three per cent of Australia's total supply of beef, primarily as low-value manufacturing meat.

Dairy

The value of Australian dairy exports in 2014–15 was $2.9 billion[4]. Asia (excluding South East Asia, $1 214 million, 42%), South East Asia ($1 022 million, 35%) and the Middle East ($303 million, 11%) are the significant regions for Australian Dairy Exports while the European Union is the least significant region ($19 million, 0.7%).

The major export markets for Australian dairy products including butter and butterfat, cheese, milk, milk powder and other dairy products in 2014/2015 are presented in the following table:

COUNTRY	GREATER CHINA*	JAPAN	SINGAPORE	INDONESIA	MALAYSIA	PHILIPPINES	THAILAND	NEW ZEALAND
Volume (tonnes)	136 400 (18%)	103 900 (14%)	86 600 (11%)	59 400 (8%)	51 100 (7%)	40 900 (5%)	31 000 (4%)	28 470 (4%)

[2] APVMA Regulatory Guidelines—Data Guidelines: Veterinary drug residues in food commodities and overseas trade

[3] ABARES (2015), Agricultural commodity statistics 2015.

[4] Dairy Australia and ABS (2015), Australian Dairy Industry in Focus 2015, www.dairyaustralia.com.au/Industry-information/About-Dairy-Australia/~/media/Documents/Stats%20and%20markets/Australian%20Dairy%20Industry%20In%20Focus/Australian%20Dairy%20Industry%20In%20Focus%202015.pdf

COUNTRY	GREATER CHINA*	JAPAN	SINGAPORE	INDONESIA	MALAYSIA	PHILIPPINES	THAILAND	NEW ZEALAND
Value (A$ million)	424 (15%)	483 (17%)	243 (8%)	256 (9%)	201 (7%)	124 (4%)	127 (4%)	129 (4%)

*Includes China, Hong Kong, and Macau

Australia is currently the fourth largest global exporter of dairy products (6% share of world dairy trade in 2014), behind NZ (38%), the EU (32%) and the USA (14%).

5.3 Proposed Australian use-pattern

Elanco Posilac (500 mg sometribove-zinc)

ANIMAL	CLAIM	DOSAGE AND ADMINISTRATION:
Lactating dairy cattle	For increased milk production in lactating dairy cows	Inject one syringe of Posilac (500 mg/syringe) every 14 days. Start treatment 57–70 days after calving and continue until the end of lactation. Allow syringes to warm to room temperature before use. Inject Posilac subcutaneously (under the skin). Recommended injection sites are the neck area or in the depression on either side of the tailhead. Alternate between the cow's left and right hand side on consecutive injections. Inject entire contents of the syringe subcutaneously. Do not reuse syringes. Inject directly into the deepest depressions on either side of the tailhead. Avoid the bones, muscles, tendons and ligaments of the tail and the rectal and anal muscles. Do NOT inject into the caudal fold because this may invalidate tuberculosis testing. Locate the caudal fold by raising the tail.

Withholding periods:

Meat: Zero (0) days

Milk: Zero (0) days

Restraints: Use in lactating dairy cattle only.

General Information:

High-producing cows are at an increased risk for mastitis (visibly abnormal milk) and may have higher somatic cell counts. Have a comprehensive management program and a comprehensive and ongoing herd reproductive health program in place on your dairy before using Posilac.

Milk production response during each 14–day injection period is cyclic and will be greatest during the middle of each period.

Caution: avoid carcass damage

1. Keep needles capped until immediately before use.
2. Maintain cleanliness at all times.

3. Needle is intended for single use only.
4. As far as possible avoid injection of animals during wet weather or under dusty conditions.
5. This product should be injected only under the skin.
6. If possible, inject high on the neck behind the ear or in the depression on either side of the tailhead.

Cows injected with Posilac increase voluntary feed intake over several weeks following the start of supplementation. The increased feed intake continues during supplementation and may continue through the dry period and the following early lactation.

Feed diets formulated to meet or exceed the nutritional requirements recommended by the National Research Council. Consider milk yield, stage of lactation and body condition when making dietary changes. Manage the feeding program to optimise milk yield and to have cows in appropriate body condition, particularly during late lactation and the dry period. Avoid sudden dietary changes.

Trade Advice: Export Slaughter Interval (ESI): Zero (0) days. Before using this product, confirm the current ESI from Elanco Animal Health on 1800 226 324 or the APVMA website (www.apvma.gov.au/residues).

5.4 Overseas registration and approved label instructions

The applicant indicated that Posilac is currently registered for use on lactating dairy cows in Brazil, Chile, Columbia, Costa Rica, Ecuador, Mexico, El Salvador, Guatemala, Honduras, Jamaica, Lebanon, Pakistan, Panama, Paraguay, Peru, South Africa, South Korea, USA, Uruguay and Venezuela. The presentation, claims and proposed use pattern of Elanco Posilac in Australia is the same as that currently registered in overseas markets.

The European Union banned the use of rbST within the European Union on 1 January 2000 due to animal welfare concerns following a moratorium introduced in 1990. At the time an EC press release noted that the ban had no impact on imports of dairy or meat products from third countries[5].

In New Zealand, rbST is not permitted to be registered due to a specific clause in New Zealand's mutual recognition arrangement with the EU[6].

5.5 Comparison of Australian MRLs with Codex and overseas MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits for pesticides and veterinary medicines. Codex MRLs are primarily intended to facilitate international trade, and accommodate differences in Good Veterinary Practice (GVP) employed by various countries. Some countries may accept Codex MRLs when importing foods. Codex MRLs for sometribove have been

[5] European Commission press release 26 October 1999: http://europa.eu/rapid/press-release_IP-99-798_en.htm

[6] Registration of Somatotropins, ACVM Operational Interpretation No 162, August 2010: http://www.foodsafety.govt.nz/elibrary/industry/somatotropins.htm

proposed by JECFA as ‘not specified’, but have been held at Step 8 of the Codex process since 1995. There are no MRLs for sometribove-zinc in any overseas jurisdiction.

From 2003, India has required a veterinary certificate for import of dairy products which specifies that source animals must not have been treated with rbST. This makes India the only country known to place a restriction on import of dairy products from rbST-treated cows. India is not a significant export market for Australian dairy or cattle meat products.

Whilst the European Union and NZ do not have approved rbST products, these markets are not known to restrict the import of dairy products from rbST-treated cows.

The European Union, China and the Russian Federation are among the countries that do not permit the import of beef from cattle administered substances with hormonal activity for the purposes of meat production. The requirements for these countries list either the specific hormones, or types of androgenic activity that are banned. These requirements are not known to preclude the use of rbST on imported product.

5.6 Potential risk to trade

Export of treated produce containing finite (measurable) residues of sometribove-zinc 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 concentrations of recombinant bovine somatotropin (rbST) in the milk and tissues of treated cows are comparable to those in the milk of untreated cows. A Table 5 entry is considered appropriate for sometribove-zinc with a use ‘for increasing milk production in lactating dairy cows’. The use of recombinant bovine somatotropin (rbST) does not present a dietary intake concern to consumers, however its use in dairy cows is not permitted within some overseas jurisdictions.

There are no MRLs for rbST or other bovine growth hormones in any overseas jurisdiction, including the US and South Korea which currently have the use of sometribove-zinc approved in dairy cattle. Codex MRLs for sometribove have been proposed by JECFA as ‘not specified’, but are not currently established.

While the use of rbST within the European Union and New Zealand is not currently approved, no regulatory restrictions have been identified in those markets, and they are not known to restrict the import of dairy products from rbST-treated cows. No major export market is known to currently restrict the import of dairy product and meat from dairy cows supplemented with rbST. The use of rbST in dairy cows is currently approved in the United States which like Australia is a significant global exporter of dairy products and beef.

Stakeholders are invited to provide comment on the potential of the proposed use to result in an unacceptable trade risk in exported animal products and the ability of industry systems to effectively manage any identified risk.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Occupational health and safety summary

Sometribove zinc is currently not listed on the Safe Work Australia Hazardous Substances Information System (HSIS) Database (SWA, 2014).

With the available toxicology information, sometribove zinc is classified as a non-hazardous substance according to the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) or the Globally Harmonised System (GHS) of classification (Revision 3; OECD, 2009).

Formulation, packaging, transport, storage and retailing

The active constituent sometribove zinc and the product Elanco Posilac will be manufactured overseas. The applicant proposes using 1.33 g (25 or 100 syringes) sterile syringes.

6.2 Use Pattern

Elanco Posilac will be supplied in single-dose syringes. One entire syringe (500 mg sometribove) will be administered subcutaneously to an individual animal every 14 days. Recommended injection sites are the neck area and the depression on either side of the tailhead.

No exposure studies were submitted with this application, but the occurrence of repeated exposure during use is highly unlikely because the product is presented in a single dose, ready-to-use syringe.

While the use of gloves is normally recommended for the handling of products which are slight skin irritants, given that Elanco Posilac is presented in a single-dose, ready-to-use syringe and is of low acute toxicity and low skin irritancy, and that gloves are not typically used for animal injections in the general veterinary or farming scenarios unless handling highly toxic products, it is considered appropriate to waive the safety direction requirement for gloves when injecting Elanco Posilac.

Recommendations for safe use

Users should follow the First Aid Instructions and Safety Directions on the product label. The following First Aid Instructions and Safety Directions are proposed to be included on the label:

First Aid: If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26.

Safety Directions: May irritate the eyes. May irritate the skin. Avoid contact with eyes and skin. Wash hands after use.

NOTE: As the label requires safety directions, the signal heading to read the safety directions will be included on the label.

Exposure and risk during re-entry

There was no exposure or risk associated with re-entry with Elanco Posilac.

6.3 Conclusion

It is considered that the approval and use of the new active constituent sometribove zinc in the product Elanco Posilac would not be likely to have an effect that is harmful to human beings. The APVMA therefore proposes to be satisfied that the active constituent meets the safety criteria of section 5A of the Agvet Code with regards to human health.

7 ENVIRONMENTAL ASSESSMENT

No environmental data was provided with the application. Sometribove zinc is a natural substance (protein) that will be rapidly degraded upon entry into the environment and consequently not alter the concentration of distribution of the substance in the environment. Material entering the environment from either the urine or faeces from treated cattle is likely to be fully metabolised and indistinguishable from metabolites of the naturally occurring bovine somatotropin. The product therefore meets the VICH Phase 1 criteria and no further environmental assessment is required.

7.1 Disposal

The label will contain the following disposal statement:

Dispose of empty containers by wrapping in paper and putting in garbage. Discarded needles/sharps should immediately be placed in a designated and appropriately labelled ‘sharps’ container.

7.2 Conclusion

It is considered that the approval and use of the new active constituent sometribove zinc in the product Elanco Posilac would not be likely to have an effect that is harmful to the environment. The APVMA therefore proposes to be satisfied that the active constituent meets the safety criteria of section 5A of the Agvet Code with regards to environmental safety.

8 EFFICACY AND SAFETY ASSESSMENT

Elanco Posilac, based on a new active ingredient, sometribove zinc, is intended to be registered to increase milk production in lactating dairy cows. One syringe of product is to be injected subcutaneously into the neck or tailhead every 14 days, starting from 57–70 days after calving and continuing until the end of lactation. The studies presented broadly fall into five categories:

1. published literature describing independently conducted studies
2. overseas dose determination studies
3. overseas dose confirmation studies
4. overseas confirmatory clinical studies for efficacy and safety plus target animal safety studies
5. one Australian based clinical efficacy and safety confirmatory study.

8.1 Evaluation of efficacy data

Dose determination and confirmation studies

Both the intramuscular and subcutaneous routes of administration were evaluated in dose determination studies. A dose range of zero and then 30 through to 750 mg per dose in a variety of formulations, repeated after a 7 or 14 day intervals, were tested in a number of studies. These studies collectively identified that a range of doses up to 750 mg every 14 days modified milk production.

Administration of 500 mg sometribove zinc every 14 days, via intramuscular or subcutaneous injection, was evaluated in a number of dose confirmation studies. Subcutaneous and intramuscular routes of administration were evaluated with the subcutaneous method demonstrated to be the most suitable route of administration. In determining dose and dose interval, one study compared doses of 500 mg sometribove zinc for 14 days or 625 mg sometribove zinc for 12 days. The higher daily dose of sometribove zinc did not result in a higher milk production per cow, therefore 500 mg sometribove-zinc every 14 days was determined to be the optimal treatment regimen. Suitability of injection sites areas was also evaluated. The data generated demonstrated that subcutaneous injection in either the neck area or in the depression on either side of the tailhead are suitable sites of administration.

Clinical efficacy trials

A series of pivotal and post marketing overseas studies have evaluated the efficacy of Elanco Posilac when administered to lactating dairy cows. The substantial body of evidence provided demonstrates that the product is effective at increasing milk production. In addition to the clinical studies carried out overseas, Australian clinical efficacy data was provided.

The Australian study was a blinded, randomised, placebo-controlled, three period clinical trial. All cows were healthy and of similar body condition score. Cows were enrolled from between 35 to 49 days post-partum if their milk yield was greater than 20 L per day. Cows were fed pasture by grazing plus supplementary feeds including feeding out when pasture was inadequate, and pelleted feed at each milking. The amount of

pelleted feed was adjusted according to milk production. The primary study outcome considered for determination of efficacy was milk yield, which was measured using automatic milk meters, with the individual cow as the experimental unit.

Appropriateness of trial design and experimental conditions

The study design was appropriate. The feeding practices used in the study are common practices of Australian pasture-based dairy farms. The chosen primary efficacy outcome was uncorrected milk yield (L) and was not corrected for milk fat (per cent).

Validation

This study is likely to be externally valid for pasture-based dairy cattle in Australia that are located in warm-temperate and subtropical regions. The pasture species and supplemental feeding patterns in those regions do not, however, necessarily coincide with the pasture species and supplemental feeding patterns for the irrigated pasture, and/or the wet and temperate pasture grazing systems.

The data package supplied contained several publications which describe studies that compared feeding regimens and their effect on the efficacy of sometribove zinc. It is clear from these publications that the efficacy response to sometribove zinc depends upon a complex interaction of cow-genetic potential, baseline milk production, parity, body condition score and nutrition. With such a matrix of influencing factors, it is reasonable to anticipate that the extent of the drug's efficacy will vary from occasion to occasion.

Conclusions on efficacy

The Australian clinical efficacy study demonstrated that administration of Elanco Posilac to healthy Holstein-Friesian cows in Australian dry pasture-based dairy at subcutaneous doses of 500 mg each 14 days, starting at day 57–70 of lactation for approximately 17 treatments gives rise to greater milk production than control cows and has no significantly detrimental health effects. The overseas dose confirmation and clinical studies also support the proposed dosage regimen and claim that the product will effectively increase milk production in lactating dairy cows.

8.2 Evaluation of target animal safety data

An extensive data package was submitted to demonstrate the safety profile of the product. The data was primarily reviewed through two meta-analyses and the Australian clinical trial.

Meta-analysis 1

This analysis included the evaluation of the literature with regard to target animal safety up until 1999. A total of 546 outcome parameter estimates from 94 groups of cows were extracted and included in the database of production and health effects. The review focussed on measures of incidence or prevalence of health outcomes. Notably, the adverse effect outcomes from this study included a small increase in risk of clinical mastitis, an increased risk of non-pregnancy, an increased risk of lameness and an increased risk of treated animals being culled.

Meta-analysis 2

A more recent meta-analysis with studies of more robust and relevant design was also submitted in the data package. This study included only trials where the product was used as indicated on the label. While the findings of this more recent meta-analysis place emphasis on the use of final product at labelled doses, the number of studies that included safety outcome information (such as incidence of lameness and culling) was lower than for meta-analysis 1. While the more recent meta-analysis failed to demonstrate statistically significant effects of the product on safety outcomes, this does not allow the conclusion that the safety outcomes are not altered.

Target animal safety studies

In addition to the clinical efficacy and safety studies, the applicant has provided reports of a drug tolerance study, target animal safety studies including 0, 1.2, 3.6 and 6 times the labelled dose, and a further study in heifers. These studies were appropriately designed and conducted. At high doses, sometribove zinc was shown to induce lameness and clinical mastitis in the 6x group and to increase early removal from the herd and to decrease reproductive performance for all dose groups. These findings are proposed to be included on the product labelling.

Safety evaluation of Australian based clinical efficacy study

The Australian clinical efficacy study (described above) evaluated safety parameters at the proposed label dose. The outcome measures for safety assessment included; body condition, body weight, mastitis, lameness, metabolic disorders and adverse events. The safety outcomes of body weight, body condition score and lameness were not affected by treatment in this study.

The safety outcomes of injection site score, incidence of clinical mastitis and somatic cell counts were increased by treatment, albeit without establishment of a cause-effect relationship. The change in the incidence of mastitis in the treatment group was associated with a spike in cases at about day 110 of the study, and corresponded to hot weather and a *Streptococcus uberis* outbreak in the herd. These factors decrease the probability that the differences between treatment and control groups were drug-associated, especially in the light of extensive evaluation of the incidence of mastitis in other studies, and the determination that sometribove zinc at the current labelled dose is not associated with increased incidence of mastitis, other than as is associated with increased milk production.

While other studies have indicated that use of the product may result in decreased reproductive performance, this outcome was not evaluated in the Australian study. Decreased reproductive performance can, however, be managed by using timed artificial insemination and not relying on detection of oestrus. This instruction is proposed for inclusion on the product labelling.

Conclusions on safety

The extensive target animal safety data package submitted with the application provided evidence that the product would be safe for use as proposed on the draft label. However the data provided also indicated that adverse events, such as increased incidence of clinical mastitis, lameness, increased non-pregnancy rates, and increased culling rates, may occur under some management conditions. Warnings to this effect are proposed for inclusion on the product labelling as outlined in section 9.

8.3 Overall conclusions regarding efficacy and animal safety

It is considered that the proposed product Elanco Posilac would meet the efficacy criteria if used in accordance with instructions proposed for its use and would be effective according to the draft Relevant Label Particulars (RLPs) in section 9. The APVMA therefore proposes to be satisfied that the product meets the efficacy criteria of section 5B of the Agvet Code.

It is considered that the approval and use of the new active constituent sometribove zinc in the product Elanco Posilac would not be likely to have an effect that is harmful to the target animals when used according to the draft Relevant Label Particulars (RLPs) in section 9. The APVMA therefore proposes to be satisfied that the active constituent and chemical product meet the safety criteria of section 5A of the Agvet Code with regards to target animal safety.

9 LABELLING REQUIREMENTS

Proposed relevant label particulars (RLPs).

SIGNAL HEADING:	READ SAFETY DIRECTIONS BEFORE OPENING OR USING FOR ANIMAL TREATMENT ONLY
PRODUCT NAME:	ELANCO POSILAC®
ACTIVE CONSTITUENT/S:	500 mg/syringe Sometribove zinc
STATEMENT OF CLAIMS:	For increased milk production in lactating dairy cows
NET CONTENTS:	25 x 1.33 g, 100 x 1.33 g
DIRECTIONS FOR USE HEADING:	DIRECTIONS FOR USE
RESTRAINTS:	Use in lactating dairy cattle only
CONTRAINDICATIONS:	-
PRECAUTIONS:	High-producing cows are at an increased risk for mastitis (visibly abnormal milk) and may have higher somatic cell counts. Have a comprehensive mastitis management program and a comprehensive and ongoing herd reproductive health program in place on your dairy before using POSILAC®. Decreased reproductive performance may occur, but this can be managed by using timed artificial insemination and not relying on detection of oestrus. A mild temporary swelling of 3–5 cm in diameter may occur at the injection site beginning about 3 days after injection and may persist up to 6 weeks following injection. Swellings are more likely to occur with injections in the neck area compared to the depression on either side of the tailhead. Stop using POSILAC® in cows with injection site swellings that repeatedly open and drain.
SIDE EFFECTS:	Use of this product may result in an increased risk of non-pregnancy, lameness and culling.
DOSAGE & ADMINISTRATION:	Inject one syringe of POSILAC® every 14 days. Start treatment 57–70 days after calving and continue until the end of lactation. Allow syringes to warm to room temperature before use. Inject POSILAC subcutaneously (under the skin). Recommended injection sites are the *neck area* or in *the depression on either side of the tailhead* (see diagrams below). Alternate between the cow's left and right hand side on consecutive injections. Inject entire contents of the syringe subcutaneously. Do not reuse syringes. Inject directly into the deepest depressions on either side of the tailhead (marked "Yes"). Avoid the bones, muscles, tendons and ligaments of the tail and the rectal and anal muscles. Do NOT inject into the caudal fold (marked "No") because this may invalidate tuberculosis testing. Locate the caudal fold by raising the tail. Injection Sites: [Diagram of correct injection sites]
GENERAL DIRECTIONS:	Milk production response during each 14–day injection period is cyclic and will be greatest during the middle of each period. Caution: avoid carcass damage

	1. Keep needles capped until immediately before use. 2. Maintain cleanliness at all times. 3. Needle is intended for single use only. 4. As far as possible avoid injection of animals during wet weather or under dusty conditions. 5. This product should be injected only under the skin. 6. If possible, inject high on the neck behind the ear or in the depression on either side of the tailhead. Cows injected with POSILAC® increase voluntary feed intake over several weeks following the start of supplementation. The increased feed intake continues during supplementation and may continue through the dry period and the following early lactation. Feed diets formulated to meet or exceed the nutritional requirements recommended by the National Research Council. Consider milk yield, stage of lactation and body condition when making dietary changes. Manage the feeding program to optimise milk yield and to have cows in appropriate body condition, particularly during late lactation and the dry period. Avoid sudden dietary changes.
WITHHOLDING PERIOD/S:	Meat: Zero (0) days Milk: Zero (0) days
TRADE ADVICE:	EXPORT SLAUGHTER INTERVAL (ESI): Zero (0) days. Before using this product, confirm the current ESI from Elanco Animal Health on 1800 226 324 or the APVMA website (www.apvma.gov.au/residues).
SAFETY DIRECTIONS:	May irritate the eyes. May irritate the skin. Avoid contact with eyes and skin. Wash hands after use.
FIRST AID:	If poisoning occurs, contact a doctor or the Poisons Information Centre: Phone 13 11 26.
ADDITIONAL USER SAFETY:	-
ENVIRONMENTAL STATEMENTS:	-
DISPOSAL:	Dispose of empty containers by wrapping with paper and putting in garbage. Discarded needles/sharps should immediately be placed in a designated and appropriately labelled “sharps” container.
STORAGE:	Store between 2°C and 8°C (Refrigerate. DO NOT FREEZE). Allow syringes to warm to room temperature (15°C to 30°C) before use. Avoid prolonged exposure to excessively high temperature and sunlight.

ABBREVIATIONS

ADI	Acceptable Daily Intake (for humans)
ARfD	Acute Reference Dose
bw	bodyweight
CAS	Chemical Abstracts Service
C	Celsius
Cm	centimetre
CODEX	Codex Alimentarius Commission
d	day
ESI	Export Slaughter Interval
g	gram
IGF-1	insulin-like growth factor (1)
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	kilogram
L	Litre
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
rBST	Recombinant bovine somatotropin
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
USAN	United States Adopted Name
WHP	Withholding Period
WHO	World Health Organization