Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the registration of a product containing the new active constituent bupivacaine in the Product TRI-SOLFEN Topical Anaesthetic and Antiseptic Solution for Pain Relief in Lambs containing:

40.6 g/L lignocaine (as hydrochloride)

4.2 g/L bupivacaine (as hydrochloride)

5.0 g/L cetrimide

0.0248 g/L adrenaline (as acid tartrate)

APVMA Product Number 60099

OCTOBER 2011

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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's Office of Chemical Safety (OCS), Department of Sustainability, Environment, Water, Population and Communities (DSEWPaC), and the 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 publications Ag MORAG: Manual of Requirements and Guidelines and Vet MORAG: Manual of Requirements and 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 Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application for registration of a veterinary chemical product containing a new active constituent. 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 Agricultural and Veterinary Chemicals Code (the Agvet Code), the APVMA invites any person to submit a relevant written submission as to whether the application for registration of TRI-SOLFEN Anaesthetic and Antiseptic Solution for Pain Relief in Lambs, which includes an application for approval of the new active constituent bupivacaine, should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target animal safety. Submissions should state the grounds on which they are based.

Submissions must be received by the APVMA by close of business on Tuesday, 25 October 2011 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.

[1] A full definition of "confidential commercial information" is contained in section 3 of the Agvet Code.

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:

Veterinary Medicines Program
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

Phone: (02) 6210 4789
Fax: (02) 6210 4741
Email: vetmedicines@apvma.gov.au

Further information

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

Copies of full technical evaluation reports covering toxicology, occupational health and safety aspects, residues in food and environmental aspects may be requested from the APVMA.

Further information on public release summaries can be found on the APVMA website: www.apvma.gov.au.

1 INTRODUCTION

Animal Ethics Pty Ltd has submitted an application for the registration of a new veterinary medicine, which includes an application for approval of the new active constituent bupivacaine, for use in lambs called TRI-SOLFEN Topical Anaesthetic and Antiseptic Solution for Pain Relief in Lambs (called TRI-SOLFEN throughout this report).

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of TRI-SOLFEN for use as a topical anaesthetic and antiseptic for pain relief in lambs. The product contains two local anaesthetic agents, 40.6 g/L lignocaine (as hydrochloride) and 4.2 g /L bupivacaine (as hydrochloride), an antiseptic agent 5.0 g/L cetrimide, and 0.0248 g/L adrenaline (as acid tartrate) which is a vasoconstrictor to increase the duration of the local anaesthetic effect, reduce bleeding, and reduce systemic absorption of the other active constituents in the formulation. The product will be used to provide pain relief for lambs following mulesing.

The active constituents in TRI-SOLFEN are currently used in Australia and overseas in animals and humans by topical and/or parenteral routes. Lignocaine, adrenaline and cetrimide are currently approved for use in APVMA registered products, and registered veterinarians may use bupivacaine, which is registered for human use, to treat individual animals under their care.

TRI-SOLFEN is intended to treat lambs that are to be kept for wool producing purposes, to relieve pain associated with mulesing. Mulesing is used as one strategy to manage fly-strike (cutaneous myiasis), a debilitating infestation to which high-producing wrinkled merino sheep, are susceptible. It involves the removal of strips of wool-bearing skin from the crutch (breech) area, leaving a wound, which heals over the ensuing 4-6 weeks. Mulesing is usually carried out by contractors or sheep producers who have been accredited or by registered veterinary practitioners.

TRI-SOLFEN is intended for use only as a one-off (that is, once in a lifetime) treatment for lambs that are to be kept for wool producing purposes, for the relief of pain associated with mulesing. It is proposed for use by or under the direction of a registered veterinary practitioner, as a topical gel spray applied using a pour-on applicator as a single application to wounds immediately following mulesing of lambs. The entire wound area is evenly covered, particularly the wound edges.

The proposed claim is: '*A local anaesthetic and antiseptic gel spray for use on lambs to provide pain relief following mulesing'*.

The proposed use of the product is only on lambs that are to be kept for wool production. The product must not be used on lambs intended for slaughter, other than for slaughter as adult sheep.

Since September 2005 this product has been available for use on lambs to provide pain relief following mulesing, under APVMA Permit number 8660[2]. The permit contained a number of conditions relating to the traceability of product and its use. The permit conditions were that:

- The product may only be supplied to a registered veterinary surgeon upon presentation of a written request.
- A record of all veterinary surgeons supplied with this product will be maintained, to be made available to the APVMA on request.
- Registered veterinarians who supply this product must maintain a record of all clients supplied with the product.

Once it is registered the traceability of product will be achieved by an existing legislative suite that governs the supply of Schedule 4 drugs.[3] That legislation covers the storage, distribution and prescription of Schedule 4 drugs and places record-keeping obligations on all persons in the distribution chain who handle them. In light of these legislative obligations there is no need for the conditions that were attached to the permit to be imposed on the registration.

One of the four active constituents, adrenaline, is already listed in Table 5[4] of the MRL Standard. Based on the fact that TRI-SOLFEN is only approved for use as a one-off treatment for lambs that are to be kept for wool producing purposes, and wool producing sheep are normally kept for 5-6 years before being culled for slaughter, it is proposed to enter the remaining three active constituents, as contained in the formulated product, into Table 5, when used as components in a post-mulesing treatment in lambs that are to be kept for wool production. Inclusion in Table 5 is considered appropriate because, when used only as a one-off (once in a lifetime) treatment for lambs that are to be kept for wool producing purposes, residues should not occur in foods or animal feeds.

The proposal to include these active constituents in Table 5 recognises that lambs that are to be kept for wool production are unlikely to enter the human food chain until years after they are mulesed, that the 90-day WHP is likely to be observed, and that residues therefore should not occur in foods or animal feeds. It recognises that farmers are unlikely to mules lambs that are not intended for wool production, and that in the event that they decide to send for slaughter lambs that have been mulesed, they are unlikely to do so within the WHP. The proposal to regard lambs that are to be kept for wool production differently from other sheep is consistent with previous APVMA decisions which have recognised the differential residues risks associated with sub-groups of a species, for example chickens reared for meat vs. those intended for use as

[2] The most recent version of the permit is accessible from http://permits.apvma.gov.au/PER8660.PDF.

[3] In New South Wales that legislation is *Veterinary Practice Act 2003; Poisons and Therapeutic Goods Act 1966; and Stock Medicines Act 1989. There is parallel legislation in each State and Territory*

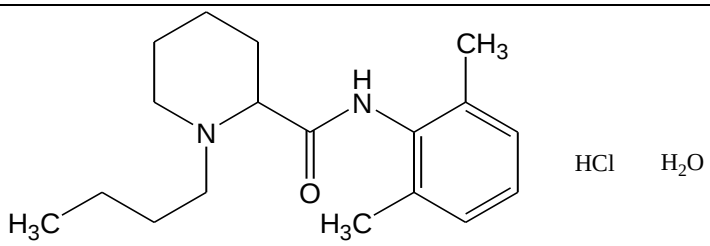
[4] Table 5 (www.apvma.gov.au/residues/standard.php) lists uses of substances where maximum residue limits are not necessary.

egg layers or breeders, and breeder turkeys vs. turkeys intended for meat production. This proposal is discussed in greater detail in Section 4, Residues Assessment.

2 CHEMISTRY AND MANUFACTURE

2.1 ACTIVE CONSTITUENT

Bupivacaine hydrochloride is a new active constituent and there are British, European and United States Pharmacopoeia compendia specifications available. The applicant has nominated the European Pharmacopoeia as the quality standard for bupivacaine hydrochloride. The active constituent bupivacaine hydrochloride has the following properties:

COMMON NAME (ISO):	Bupivacaine hydrochloride
IUPAC NAME:	(2RS)-1-Butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide, monohydrochloride, monohydrate
CA NAME:	(±)-1-Butyl-2',6'-pipercoloxylidide monohydrochloride, monohydrate
PRODUCT NAME:	Tri-Solfen Topical Anaesthetic and Antiseptic Solution for Pain Relief in Lambs
CAS REGISTRY NUMBER:	14252-80-3
MOLECULAR FORMULA:	C18H28N2O•HCl•H2O
MOLECULAR WEIGHT:	342.90
PHYSICAL FORM:	Crystalline powder
COLOUR:	White or colourless
ODOUR:	-
MELTING POINT:	255-256 °C decomp.
DENSITY:	-
OLEYL ALCOHOL/WATER PARTITION COEFFICIENT:	1565 (free base)
POLYMORPHISM:	Several polymorphs of bupivacaine hydrochloride are known but none are relevant since the substance is fully soluble in the solvent of the proposed finished product
SOLUBILITY:	Soluble in water; Freely soluble in ethanol
STRUCTURAL FORMULA:	 HCl H_2O

The applicant has submitted a Certificate of Analysis that asserts compliance with EP6.0.

2.2 PRODUCT

Dose form: Topical spray

Formulation type: Liquid (viscous)

Level of active: 24.8 mg/L adrenaline (as acid tartrate); 4.2 g/L bupivacaine (as hydrochloride); 5.0 g/L cetrimide; 40.6 g/L lignocaine (as hydrochloride)

Each batch of TRI-SOLFEN will be manufactured with active constituents that conform fully with the following monographs:

ACTIVE CONSTITUENT	Monograph
ADRENALINE ACID TARTRATE	USP 34 monograph for epinephrine bitartrate[5]
CETRIMIDE	Ph. Eur. 7.0 monograph for cetrimide (0378)
LIGNOCAINE HYDROCHLORIDE	BP 2011 monograph for lidocaine hydrochloride[6]

Physical properties – Appearance: Blue semi-viscous liquid with no visible particles

Storage and stability: The current shelf life and storage conditions for the product supplied under permit number 8660 are 15 months and store below 30 °C (Room Temperature).

The product has been available under Permit 8660 since September 2005. The product was initially given a default shelf life of 12 months. In 2008 the APVMA granted an application to extend the shelf life of the product to 15 months for supply in HDPE containers.

A condition will be imposed that samples of product must be placed on storage stability trial, consistent with normal requirements of Good Manufacturing Practice.

[5] The name given in the USP to adrenaline acid tartrate.

[6] The name given in the BP to lignocaine hydrochloride.

Packaging: TRI-SOLFEN will be packaged in 1, 2.5 and 5 L HDPE backpacks and 10, 15, 20 and 22 L HDPE drums, as has been the case for product supplied under Permit 8660. The standard condition of registration which applies to the containers for all registered chemical products, specified in regulation 18(2) of the *Agricultural and Veterinary Chemicals Code Regulations 1995*, will apply.

2.3 SUMMARY

The APVMA has evaluated the chemistry and manufacturing aspects of bupivacaine hydrochloride and is satisfied, that the data requirements of 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 the new active constituent bupivacaine have been met.

The APVMA has evaluated the chemistry and manufacturing aspects of TRI-SOLFEN and is satisfied that the data requirements of composition and form of constituents, formulation composition, manufacturing and quality control aspects, product specification, batch analysis, stability, analytical methods, packaging and label necessary for the approval of this new veterinary chemical product have been met. The condition imposed in relation to stability testing is to provide added confirmation for the APVMA's satisfaction.

In proposing to register this product the APVMA must be satisfied that the criteria set out in section 14 of the Agvet Code are met. In regard to chemistry and manufacture, the APVMA proposes to be satisfied that the chemistry requirements of Section 14(5) have been met.

3 TOXICOLOGICAL ASSESSMENT

The applicant provided information from published studies which the APVMA considered was sufficient to assess the toxicology of the product and the new active constituent and to establish Safety Directions.

As discussed elsewhere in this document, the APVMA proposes to enter the active constituents lignocaine, bupivacaine, and cetrimide into Table 5 of the MRL Standard, when used as components in a post-mulesing treatment in lambs that are to be kept for wool production, because residues should not occur in foods or animal feeds. In this circumstance, it is not essential that acceptable daily intakes (ADIs) be established. However, ADIs were established for lignocaine, bupivacaine, and cetrimide at 0.009 mg/kg bw/d, 0.001 mg/kg bw/d and 0.01 mg/kg bw/d, respectively when the permit was granted as temporary MRLs were set. An ADI was not established for adrenaline because it would not be possible to distinguish residues arising from the proposed use of the product from background concentrations of adrenaline; adrenaline is already listed in Table 5 for this reason.

Lignocaine, bupivacaine and adrenaline are listed in Schedule 4 of the SUSMP, and are therefore available by prescription only. TRI-SOLFEN is therefore a prescription-only product. Veterinarians play an important role in educating the users on safe and proper use of the product. Cetrimide is not individually listed in the SUSMP, however as a quaternary ammonium compound, it is exempt from Scheduling because the concentration in the product is less than 5%. Based on the findings of published toxicology studies, the product is expected to have low acute oral and dermal toxicity, to be a slight skin and eye irritant, and potentially to be a skin sensitiser.

The toxicology data, and other information on the product provided, were considered in this assessment and are the basis for the First Aid Instructions and Safety Directions established in the present evaluation.

In proposing to register this product, the APVMA must be satisfied that the criteria set out in section 14 of the Agvet Code are met. In regard to toxicology and occupational health, the APVMA considers that, when used according to label directions as a one-off treatment for lambs that are to be kept for wool production, the use of TRI-SOLFEN, and the presence of the new active constituent bupivacaine, would not be an undue hazard to the safety of people exposed to it during its handling, and would not be likely to have an effect that is harmful to human beings.

PUBLIC HEALTH STANDARDS

From a human health perspective the registration of TRI-SOLFEN is supported, when the product is used on lambs that are to be kept for wool production. As mentioned above, ADIs are not essential in the circumstance where residues should not occur, as is the case with this product, when it is used as a post-mulesing treatment in lambs that are to be kept for wool production.

The existing scheduling (Schedule 4: Prescription Animal Remedy) of lignocaine, bupivacaine and adrenaline is considered appropriate. There was no data available to re-consider the Poisons Scheduling of these three actives.

The existing scheduling of cetrimide, as a quaternary ammonium compound (QAC), is considered appropriate. QACs are not scheduled poisons in preparations that contain 5 per cent or less of such QACs.

4 RESIDUES ASSESSMENT

Based on the fact that TRI-SOLFEN is only approved for use as a one-off treatment for lambs that are to be kept for wool producing purposes, and wool producing sheep are normally kept for 5-6 years before being culled for slaughter, it is proposed to enter the three active constituents not yet in Table 5 into Table 5 of the MRL Standard, when used as components in a post-mulesing treatment in lambs that are to be kept for wool production. Inclusion in Table 5 is considered appropriate because, when used only as a one-off (once in a lifetime) treatment for lambs that are to be kept for wool producing purposes, residues should not occur in foods or animal feeds. A number of safeguards are proposed to support this approach.

TRI-SOLFEN is intended for use only as a one-off treatment for merino lambs that are to be kept for wool producing purposes, for the relief of pain following mulesing.

TRI-SOLFEN is a prescription-only product because three of its four active constituents are in Schedule 4 of the SUSMP . It will only be available to sheep producers and/or mulesing contractors on prescription from their veterinarian, to provide pain relief following the mulesing of merino lambs. Veterinarians play an important role in educating the users on safe and proper use of the product.

It is used by or under the direction of a registered veterinary practitioner, as a topical gel spray applied using a pour-on applicator for a single application to wounds immediately following mulesing of lambs. The entire wound area is evenly covered, particularly the wound edges.

TRI-SOLFEN contains two local anaesthetic agents: 40.6 g/L lignocaine (as hydrochloride) and 4.2 g/L bupivacaine (as hydrochloride). It also contains 5.0 g/L cetrimide as an antiseptic agent, and 0.0248 g/L adrenaline (as acid tartrate) as a vasoconstrictor to increase the duration of the local anaesthetic effect, reduce bleeding, and reduce systemic adsorption of the other active constituents present in the formulation.

The active constituents in TRI-SOLFEN are already used in Australia and overseas in animals and humans by topical and/or parenteral routes. Lignocaine, adrenaline and cetrimide are already approved for use in APVMA-registered products, and registered veterinarians may use bupivacaine, registered overseas or for human use, to treat individual animals under their care.

The proposed claim is: *'A local anaesthetic and antiseptic gel spray for use on lambs to provide pain relief following mulesing'*.

To restrict the use of the product to the intended purpose, and so that residues in edible tissue or produce should not occur, the following restraint, re-treatment, and withholding period statements will be included on the product label.

RESTRAINTS:

DO NOT USE this product except as a one-off post-mulesing treatment of lambs that are to be kept for wool production.

DO NOT USE on lambs that may in the future produce milk or milk products for human consumption.

DOSAGE AND ADMINISTRATION:

Critical Comment: Single dose only (i.e. once-in-a-lifetime treatment).

WITHHOLDING PERIODS:

This product is only approved for use as a one-off post-mulesing treatment of lambs that are to be kept for their wool production.

MEAT: Treated sheep must not be supplied or sold for slaughter for human consumption for at least 90 days following treatment with this product.

MILK: This product **MUST NOT BE USED** in lambs that will in the future produce milk or milk products for human consumption.

To ensure good agricultural practice in the use of this product, the applicant has agreed to deliver an on-going extension program to ensure that veterinarians who stock and supply TRI-SOLFEN are aware of the 90-day withholding period and of the importance of users adhering to this withholding period. Veterinarians will be provided with an information handout to be provided to woolgrowers at the time of purchase.

Farmers are unlikely to mules lambs that may be sent for slaughter as lambs, because this would constitute an unnecessary cost and an unnecessary impact on the animal. In the unusual event that mulesed sheep were sold for slaughter earlier than ‘cull for age’, (typically around 5 years) it is unlikely that this would be within 90 days of treatment with TRI-SOLFEN because: a) the mulesing wound takes 4-6 weeks to heal and, because of their age and weight at the time of mulesing, treated sheep would usually need to be fattened for a further period of 6 weeks before slaughter; and b) the producer is required to complete a legally binding

National Vendor Declaration[7], declaring that the lambs are within the 90-day withholding period, and meatworks do not accept lambs for slaughter within the withholding period after a chemical treatment[8].

The mulesing of lambs is regulated under the *Model Code of Practice for the Welfare of Animals: The Sheep*[9]. Animal welfare codes of practice provide minimum standards and can be used in legal proceedings relating to cruelty to animals[10]. Amongst other things, this code requires –

- industry commitment to making available a mandatory, comprehensive, audited training and accreditation process for anyone who performs the mulesing procedure; the "Better Choices" program[11] is an example of meeting this commitment;
- industry commitment to adopting new technology, including analgesic treatment, promptly after approval, to minimise pain;
- the recommended age for mulesing is 2-12 weeks; if over 6 months old anaesthesia must be used; sheep must not be mulesed after 12 months of age.

APVMA-commissioned independent advice from an external consultant with specific, internationally recognised expertise in residues of veterinary drugs in food, on the residue requirements for TRI-SOLFEN supported the inclusion of the active constituents in Table 5, with the qualifier "when used as a post-mulesing treatment in sheep intended for wool production". This advice also noted that –

- "mulesing is only carried out on young sheep that are destined for wool production… the three actives would have disappeared long before the sheep ever entered the human food chain";
- treated animals should be identified in the National Livestock Identification Scheme, and there is a requirement that, when animals are sold, the vendor makes a declaration related to treatment; therefore treated animals will be traceable;
- mulesing should be carried out according to the model code of practice.

The proposal to include the active constituents of this product in Table 5 is also supported by the Department of Health and Ageing's Office of Chemical Safety (OCS). Advice from OCS is that "it would be appropriate for the APVMA to set controls to limit [the product's] use to fibre or non-food producing animals. If there is

[7] www.mla.com.au/Meat-safety-and-traceability/Livestock-identification.

[8] www.publish.csiro.au/Books/download.cfm?ID=5553.

[9] www.publish.csiro.au/nid/22/pid/5389.htm.

[10] www.daff.gov.au/animal-plant-health/welfare/aaws/online/framework/cop.

[11] www.betterchoices.com.au/answers/consumer

no risk of human exposure through the food chain, the APVMA may wish to consider including cetrimide, bupivacaine hydrochloride and lignocaine hydrochloride in Table 5 of the MRL standard".

For the reasons outlined above, the APVMA proposes to enter the 3 active constituents that are not yet in Table 5, into that Table, with the qualifier "when used as a one-off post-mulesing treatment in lambs that are to be kept for wool production".

In proposing to register this product the APVMA must be satisfied that the criteria set out in section 14 of the Agvet Code are met. In regard to residues, the APVMA considers that, when used according to label directions as a one-off treatment for lambs that are to be kept for wool production, the use of TRI-SOLFEN, and the presence of the new active constituent bupivacaine, will not be an undue hazard to the safety of people using anything containing its residues.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

The active constituents in TRI-SOLFEN are used in Australia and overseas in animals and/or humans by topical and/or parenteral routes. Lignocaine, adrenaline and cetrimide are currently approved for use in APVMA registered products.

Under veterinary prescribing legislation, as administered by the States, the use of lignocaine and adrenaline by registered veterinarians is permitted in individual animals under their care. In addition, under the veterinary prescribing legislation, registered veterinarians may use bupivacaine, that is registered for human use, to treat individual animals under their care.

As outlined in the previous section, residues of the active constituents of this product should not occur when TRI-SOLFEN is used according to label directions as a one-off treatment for lambs that are to be kept for wool production.

In proposing to register this product the APVMA must be satisfied that the criteria set out in section 14 of the Agvet Code are met. In regard to the risk to overseas trade, the APVMA considers that, when used according to label directions as a one-off treatment for lambs that are to be kept for wool production, the use of TRI-SOLFEN, and the presence of the new active constituent bupivacaine, would not unduly prejudice trade or commerce between Australia and places outside Australia.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

The active constituents in TRI-SOLFEN are used in Australia and overseas in humans by topical and/or parenteral routes. Lignocaine, adrenaline and cetrimide are currently approved for use in APVMA registered products.

Under veterinary prescribing legislation, as administered by the States, the use of lignocaine, adrenaline and cetrimide by registered veterinarians is permitted in individual animals under their care. In addition, under the veterinary prescribing legislation, registered veterinarians may use bupivacaine to treat individual animals under their care. Based on the findings of published toxicology studies, the product is expected to have low acute oral and dermal toxicity, to be a slight skin and eye irritant, and potentially to be a skin sensitiser. Given the formulation type (gel), the low concentration of the active constituents present in the formulation, the application method (pour-on applicator) and the protective equipment recommended for use, the inhalational toxicity is likely to be low and the toxicological and occupational risks are considered to have been appropriately mitigated.

Five respondents reported possible adverse reactions in humans. Following investigation, none of the adverse experiences was attributed to the use of the product. Mandated reporting of potentially adverse events for the period of use of the product under APVMA Permit PER8660 over five years supports the safety of the product when used according to label directions under practical field conditions.

In proposing to register this product the APVMA must be satisfied that the criteria set out in section 14 of the Agvet Code are met. In regard to occupational health and safety, the APVMA considers that the following label statements should be included on the product label, and that, when used according to label directions as a one-off treatment for lambs that are to be kept for wool production, the use of TRI-SOLFEN, and the presence of the new active constituent bupivacaine, would not be an undue hazard to people exposed to it during its handling and would not be likely to have an effect that is harmful to human beings.

LABEL STATEMENTS

Taking into consideration the potential toxicological hazard, use pattern and the likelihood of handler exposure the following First Aid Instructions and Safety Directions should be included on the product label:

Safety Directions

New entry

Lignocaine	LD 50 g/L or less with bupivacaine 5 g/L or less	Safety Directions 160 162 164 180 210 211 279 280 283 290 292b 294 342 351 360 361 366

The statement codes above translate into the following Safety Directions:

> May irritate the eyes and skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin immediately wash area with soap and water. When opening the container and using the product, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves. Wash hands after use. After each day's use, wash gloves and contaminated clothing.

First Aid Instructions

New entries	Lignocaine	a
	Bupivacaine	a
	Cetrimide	a

These statement codes refer to the following First Aid Instructions:

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

Re-handling Statement

The risk of re-handling exposure is expected to be low. However the following re-handling statement is recommended for the product label:

> Do not re-handle sheep until after the product has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves.

No warning or precautionary statements were required.

7 ENVIRONMENTAL ASSESSMENT

The active constituents in TRI-SOLFEN are used in Australia and overseas in humans by topical and/or parenteral routes. Lignocaine, adrenaline and cetrimide are currently approved for use in APVMA registered products.

Under veterinary prescribing legislation, as administered by the States, the use of lignocaine and adrenaline by registered veterinarians is permitted in individual animals under their care. In addition, under the veterinary prescribing legislation, registered veterinarians may use bupivacaine to treat individual animals under their care.

In assessing the environmental impact of this product, including the presence of the new active constituent bupivacaine, the APVMA has taken into account the use of the product as a one-off treatment for lambs, the nature of the product including its formulation and viscosity, the likely absorption of the bupivacaine, the projected maximum quantity of active constituent used, and label instructions on disposal of containers and unused product. Advice from DSEWPaC is that the proposed use of this product will pose an acceptable environmental risk, provided that the label contains a statement of “Do not spray to run-off”.

In proposing to register this product the APVMA must be satisfied that the criteria set out in section 14 of the Agvet Code are met. In regard to the environment, the APVMA considers that, when used according to label directions as a one-off treatment for lambs that are to be kept for wool production, and with the inclusion of the label statement mentioned above, the use of TRI-SOLFEN, and the presence of the new active constituent bupivacaine, would not be likely to have an unintended effect that is harmful to animals, plants, or things or to the environment.

8 EFFICACY AND SAFETY ASSESSMENT

Mulesing is the removal of large strips of wool-bearing, full thickness skin from the crutch (breech) area of sheep (typically lambs at marking time), leaving wounds which heal slowly over the ensuing 4-6 weeks. When mulesing wounds heal, the naturally bare area around the vulva and anus is stretched and enlarged. This reduces the moisture/dampness caused by sweating, urine and faecal staining and so reduces the animal's susceptibility to flystrike (cutaneous myiasis) in the breech area. Mulesing is carried out by contractors or sheep producers who have been accredited or by registered veterinary practitioners.

TRI-SOLFEN is intended for use only as a one-off (once in a lifetime) treatment for merino lambs that are to be kept for wool producing purposes, for the relief of pain associated with mulesing. It may only be used by or under the direction of a registered veterinary practitioner, as a topical gel spray applied using a pour-on applicator for a single application to wounds immediately following mulesing of lambs. The entire wound area is evenly covered, particularly the wound edges.

TRI-SOLFEN contains two local anaesthetic agents 40.6 g/L lignocaine (as hydrochloride) and 4.2 g/L bupivacaine (as hydrochloride). It also contains 5.0 g/L cetrimide as an antiseptic agent, and 0.0248 g/L adrenaline (as acid tartrate) as a vasoconstrictor to increase the duration of the local anaesthetic effect, reduce bleeding and reduce systemic adsorption of the other active constituents present in the formulation.

The proposed claim is: *'A local anaesthetic and antiseptic gel spray for use on lambs to provide pain relief following mulesing*'.

The pivotal published study was Lomax S, Sheil M and Windsor PA. *Impact of topical anaesthesia on pain alleviation and wound healing in lambs after mulesing*. Australian Veterinary Journal; 2008; 86:159-168. The results showed rapid (approximately 3 minutes) and prolonged wound analgesia (up to 8 hours) as shown by pain response scores ($P \leq 0.01$), with absent or significantly diminished primary and secondary hyperalgesia ($P \leq 0.01$) and significant reduction in pain-related behaviour ($P < 0.001$) in treated versus untreated lambs. In addition there was improved wound healing in the treated lambs ($P \leq 0.05$). The study used validated direct pain measurement techniques in three well-designed trials conducted according to the principles of Good Clinical Practice, on adequate numbers of animals, and provided definitive scientific support for the efficacy of the product in providing for the relief of pain following mulesing procedures.

Unpublished data was presented on the field use of the product under APVMA Permit PER8660. These consist of 100% of the mandated reports by users and prescribing veterinarians of their experiences when using the initial 576,000 doses under permit. A total of 474 reports were received. A number of respondents chose not to comment on some questions. Of those who did comment, 350 said pain relief was seen and 6 did not; 314 said wound healing was better and one said it was worse; 231said the lamb's behaviour had improved, 14 said it had not and 3 said it was worse. These are the contemporaneous assessments by persons directly involved and provide support for the efficacy of the product when used under practical field conditions.

No adverse experiences relating to animal safety that were considered to be likely to the use of the product were reported. No adverse experiences involving lack of efficacy were reported. Mandated reporting of potentially adverse events for the period of use of the product under APVMA Permit PER8660 over five years supports the safety of the product when used according to label directions under practical field conditions.

Other data presented included three unpublished studies including a pilot dose determination, a pivotal dose confirmation, and a pivotal target animal margin of safety. These trials were conducted according to the principles of Good Clinical Practice and the laboratory analyses were completed in accredited laboratories according to the principles of Good Laboratory Practice. All tests used were validated appropriately. Individual animal data and a study log were provided for each of these studies. The statistical analyses were acceptable and findings were consistent within and between trials. Acceptable direct and indirect measures of pain were used. The results show that the product is safe and effective when used according to the label directions. These data support the label claim.

Support for the product's safety comes from a margin of safety study where groups of lambs were treated at 1x and 2x label dose rates and from the absence of confirmed adverse experiences following the extensive field use of the product under APVMA Permit PER8660.

In summary, scientific support for the safety and efficacy of the product comes from pivotal dose confirmation studies, published scientific literature and mandatory reporting of field use of the product under APVMA Permit PER8660. Published and unpublished studies demonstrate the product is safe and efficacious when used according to the label.

In proposing to register this product the APVMA must be satisfied that the criteria set out in section 14 of the Agvet Code are met. In regard to efficacy and safety, the APVMA considers that, when used according to label directions as a one-off treatment for lambs that are to be kept for wool production, the use of TRI-SOLFEN, and the presence of the new active constituent bupivacaine, would not be likely to have an unintended effect that is harmful to animals, and the product would be effective to the satisfaction of the APVMA.

9 LABELLING REQUIREMENTS

[Immediate Container – main front panel]

PRESCRIPTION ANIMAL REMEDY

READ SAFETY DIRECTIONS BEFORE USING

KEEP OUT OF REACH OF CHILDREN

FOR ANIMAL TREATMENT ONLY

TRI-SOLFEN

Topical Anaesthetic & Antiseptic Solution for Pain Relief in Lambs

ACTIVE CONSTITUENTS: 40.6 g/L Lignocaine (as hydrochloride), 4.2 g/L bupivacaine (as hydrochloride), 24.8 mg/L Adrenaline (as acid tartrate), 5.0 g/L Cetrimide

IL, 2.5L, 5L, 10L, 15L, 20L, 22L

[Ancillary panel]

TRI-SOLFEN is a local anaesthetic and antiseptic gel spray for use on lambs to provide pain relief following mulesing

DIRECTIONS FOR USE

FOR TOPICAL USE ONLY

RESTRAINTS:

DO NOT USE this product except as a one-off post-mulesing treatment of lambs that are to be kept for wool production.

DO NOT USE on lambs that may in the future produce milk or milk products for human consumption.

DOSAGE AND ADMINISTRATION:

Critical Comment: Single dose only (once-in-a-lifetime treatment). Re-treatment is not permitted.

Apply TRI-SOLFEN spray to wound immediately after mulesing. Ensure that the entire wound area is evenly covered with spray, particularly wound edges. Do not spray to run-off.

Application rate:	lambs (5-10 kg)	6 mL
	lambs (11-15 kg)	8 mL
	lambs (16-20 kg)	10 mL
	lambs (20-40 kg)	12 mL

The special TRI-SOLFEN applicator applies 2mL per application. Insecticidal preparations can be applied to the wound after application of TRI-SOLFEN to prevent fly strike.

WITHHOLDING PERIODS:

This product is only approved for use as a one-off post-mulesing treatment of lambs that are to be kept for their wool production.

MEAT: Treated sheep must not be supplied or sold for slaughter for human consumption for at least 90 days following treatment with this product.

MILK: This product MUST NOT BE USED in lambs that will in the future produce milk or milk products for human consumption.

SAFETY DIRECTIONS

May irritate eyes and skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin immediately wash area with soap and water. When opening and using the product wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves. Wash hands after use. After each day's use, wash gloves and contaminated clothing.

Do not re-handle sheep until the product has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 1311126

Bayer Australia Ltd
875 Pacific Highway
Pymble NSW 2073

Phone: 1800 678 368

DISPOSAL

Do not dispose of undiluted chemicals on-site. Puncture or shred and bury empty containers in a local authority landfill. If no landfill is available, bury containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, vegetation and roots. Empty containers and product should not be burnt.

Store below 30^{o}C (Room Temperature). Do not store at low temperature. Protect from light.

[B] Expiry

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ARfD	Acute Reference Dose
bw	bodyweight
d	day
DAT	Days After Treatment
DSEWPaC	Department of Sustainability, Environment, Water, Population and Communities
DT50	Time taken for 50% of the concentration to dissipate
EA	DSEWPAC
EbC50	concentration at which the biomass of 50% of the test population is impacted
EC50	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
ErC50	concentration at which the rate of growth of 50% of the test population is impacted
ESI	Export Slaughter Interval
EUP	End Use Product
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin

HPLC	High Pressure Liquid Chromatography or High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
Koc	Organic carbon partitioning coefficient
L	Litre
LC50	concentration that kills 50% of the test population of organisms
LD50	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOEL	Lowest Observable Effect Level
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NVD	National Vendor Declaration
NDPSC	National Drugs and Poisons Schedule Committee
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OCS	Department of Health and Ageing's Office of Chemical Safety
OM	Organic Matter

po	per os (oral)
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

Australian Pesticides and Veterinary Medicines Authority 2008, *Vet MORAG: Manual of Requirements and Guidelines*, APVMA, Canberra.

Lee C, and Fisher AD (2007). *Welfare consequences of mulesing of sheep*. Australian Veterinary Journal Volume 85: 89-93

Rothwell J, Hynd P, Brownlee A, and Williams S (2007). *Research into alternatives into mulesing*. Australian Veterinary Journal Volume 85: 94-97

Chapman RE, Fell LR, and Shutt DA (1994). *A comparison of stress in surgically and non-surgically mulesed sheep*. Australian Veterinary Journal Volume 71: 243-247

Paull DR, Lee C, Colditz IG, Atkinson SJ and Fisher AD (2007). *The effect of a topical anaesthetic formulation, systemic flunixin and carprofen, singly or in combination, on cortisol and behaviour responses of merino lambs to mulesing*. Australian Veterinary Journal Volume 85: 98-106

Paull DR, Lee C, Colditz IG and Fisher AD (2009*). The effect of a topical anaesthetic formulation, systemic carprofen, given singly or in combination, on cortisol and behaviour responses of merino lambs to castration*. Australian Veterinary Journal Volume 87: 230-237

Lomax S, Sheil M and Windsor PA. (2008). *Impact of topical anaesthesia on pain alleviation and wound healing* in *lambs after mulesing.* Australian Veterinary Journal; Volume 86: 159-168.APVMA

Lomax S, Sheil M and Windsor PA. (2010). *Topical anaesthesia alleviated short term pain of castration and tail docking in lambs.* Australian Veterinary Journal; Volume 88: 67-74.