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The *Agricultural and Veterinary Chemical Code Act 1994* (the Act) commenced on 15 March 1995. The Agricultural and Veterinary Chemicals Code (the Agvet Code) scheduled to the Act requires notices to be published in the *Gazette* containing details of the registration of agricultural and veterinary chemical products and other approvals granted by the Australian Pesticides and Veterinary Medicines Authority. The Agvet Code and related legislation also requires certain other notices to be published in the *Gazette*. A reference to Agvet Codes in this publication is a reference to the Agvet Code in each state and territory jurisdiction.

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General information

The APVMA Gazette is published fortnightly and contains details of the registration of agricultural and veterinary chemicals products and other approvals granted by the APVMA, notices as required by the Agricultural and Veterinary Chemicals Code (the Agvet Code) and related legislation and a range of regulatory material issued by the APVMA.

Pursuant to section 8J(1) of the Agvet Code, the APVMA has decided that it is unnecessary to publish details of applications made for the purpose of notifying minor variations to registration details. The APVMA will however report notifications activity in quarterly statistical reports.

Distribution and subscription

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New veterinary chemical product containing a new veterinary active constituent – UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application for the approval of a new active constituent, lipoteichoic acid (LTA) from biofilm adhesion component (BAC) of *Streptococcus uberis*, strain 5616, and an application for the registration of a new product containing the new active constituent. The product is UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle, for the active immunisation of healthy cows and heifers to reduce the incidence of clinical intramammary infections caused by *Streptococcus uberis*; to reduce the somatic cell count in *Streptococcus uberis* positive quarter milk samples; and to reduce milk production losses caused by *Streptococcus uberis* intramammary infections.

Active constituent particulars

As part of the application to register UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle, containing the new active, the APVMA has evaluated the safety of the new active constituent, lipoteichoic acid (LTA) from biofilm adhesion component (BAC) of *Streptococcus uberis*, strain 5616. The particulars of the active constituent lipoteichoic acid (LTA) from biofilm adhesion component (BAC) of *Streptococcus uberis*, strain 5616 are shown in Table 1 below.

Table 1: Particulars of the active constituent

Name of active constituent	Lipoteichoic acid (LTA) from biofilm adhesion component (BAC) of *Streptococcus uberis*, strain 5616.
Brief description of active (GMO, recombinant, live, inactivated)	BAC LTA of *Streptococcus uberis* (S. *uberis*), strain 5616 (inactivated)
Gene technology	Not applicable. The antigen organism was not derived from genetically modified starting materials.
Mode of action	Active immunisation with LTA from BAC of *Streptococcus uberis*, strain 5616.

Summary of the APVMA's evaluation of lipoteichoic acid (LTA) from biofilm adhesion component (BAC) of *Streptococcus uberis*, strain 5616 active constituent

The APVMA has evaluated the new active constituent LTA from BAC of *Streptococcus uberis*, strain 5616, under sections 5A(1)(a),(b) and (c) of the Agvet Code and proposes to be satisfied that the active constituent is not, or would not: be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues; be likely to have an effect that is harmful to human beings; or be likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

The APVMA has evaluated the chemistry and manufacturing aspects of LTA from biofilm adhesion component (BAC) of *Streptococcus uberis*, strain 5616 active constituent and has determined that the active constituent is manufactured to an acceptable standard. The assessment included the starting materials, including the master seed (origin, passage history, identity, and purity), and culture media. The assessment covered each stage of manufacture of the vaccine and, the quality control tests to monitor the in process and final product specifications for batch release. The shelf life was established by stability studies in accordance with APVMA guidance for veterinary vaccines.

LTA from BAC of *Streptococcus uberis*, strain 5616 master seed details were provided. This seed was assessed and approved by the Department of Agriculture, Fisheries and Forestry for import into Australia.

The APVMA has considered the toxicological aspects of LTA from BAC of *Streptococcus uberis*, strain 5616, and concluded that there are no toxicological concerns regarding the approval of this active constituent or for the adjuvants and the excipients in UBAC vaccine.

The APVMA proposes to be satisfied that the proposed use of LTA from BAC of *Streptococcus uberis*, strain 5616, in a veterinary chemical product would not be an undue toxicological hazard to the safety of people exposed to it during its handling and use, nor would it be likely to have an unintended effect that is harmful to human beings, animals, plants or things or to the environment.

UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle, containing lipoteichoic acid from biofilm adhesion component of *Streptococcus uberis*

In addition to the application to approve the new active constituent, the APVMA has under consideration an application to register a new product, UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle, containing lipoteichoic acid (LTA) biofilm adhesion component (BAC) of *Streptococcus uberis*, strain 5616. Particulars of the product are shown in Table 2 below.

Table 2: Particulars of the product

Proposed product name	UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle
Applicant company	Laboratorios Hipra S.A.
Name of active constituent	LTA from BAC of *Streptococcus uberis*.
Signal heading	Schedule 0
Summary of proposed use	For active immunisation of healthy cows and heifers to reduce the incidence of clinical intramammary infections caused by *Streptococcus uberis;* to reduce the somatic cell count in *Streptococcus uberis* positive quarter milk samples; and to reduce milk production losses caused by *Streptococcus uberis* intramammary infections. • Onset of immunity: approximately 36 days after the second dose. • Duration of immunity: approximately the first 5 months of lactation. UBAC is given as a course of 3 injections into the neck muscles, alternating sides of the neck. The first injection is given at about 60 days before the expected calving date followed by a second injection given at least 3 weeks before the expected calving date. The third injection is given about 15 days after calving. The whole herd should be vaccinated. The full course should be repeated with each pregnancy.
Pack sizes	20 × 2 mL, 10 mL, 50 mL, 100 mL
Withholding period	Zero (0) days

A summary of the APVMA's evaluation of UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle in accordance with the requirements of section 14(1)(C) of the Agricultural and Veterinary Chemicals Code (the 'Agvet Code'), scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994*:

1) The APVMA has evaluated the application and in its assessment in relation to whether the safety criteria have been met in accordance with the definition set out in section 5A of the Agvet Code, proposes to determine that:

i. The APVMA is satisfied that proposed use of UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle would not be an undue hazard to the safety of people exposed to it during their handling and use.

a. The APVMA conducted a risk assessment for the product, in conjunction with the estimated hazard profile, to determine whether the proposed use of the product would represent an undue health hazard to humans.

b. The applicant did not provide any toxicological studies for lipoteichoic acid (LTA) extracted from S. *uberis* and stated that the LTA from biofilm adhesion component (BAC) does not pose any infectious safety risk because the active ingredient is not capable of replication. After the extraction process of the UBAC antigen (LTA), it can be considered as non-pathogenic and, moreover, no residues of this microorganism exist in the final antigen. This reasoning was accepted.

c. Additionally, the APVMA agreed to the applicant's request to accept the European Medicines Agency (EMA) assessment of the vaccine. The safety of the adjuvants was considered from a user safety and residues perspective. In particular, the hazards associated with mineral oil-based vaccines were considered and were found to be satisfactory. Considering the product is administered by injection, exposure and risk assessments undertaken by APVMA mainly used a qualitative approach.

d. After consideration of the toxicological profile and potential accidental/incidental exposure associated with the use of UBAC vaccine, the APVMA concludes that the human health risks are acceptable according to the criteria stipulated in Section 5A of the *Agricultural and Veterinary Chemicals Code Act* (1994 as amended), for its proposed application method provided the certain recommendations are incorporated on the product label.

e. To mitigate potential risks, the following signal headings, first aid instructions, and safety directions statements are to appear on the product label:

Signal heading

FOR ANIMAL TREATMENT ONLY KEEP OUT OF REACH OF CHILDREN

First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131 126. If swallowed, do not induce vomiting. If in eyes wash out immediately with water. While this product is well tolerated by cattle, there is a risk of severe injury to humans associated with accidental self-injection. Care should be taken to avoid needle-stick injury when injecting this product.

Safety directions

Harmful if swallowed. May irritate the eyes and skin. Avoid contact with eyes and skin. When using the product, ensure use of appropriate injection equipment and wear needle-stick resistant gloves.

Additional user safety

Take care to avoid self-injection.

This product contains mineral oil and is an irritant. In the event of self-administration, it can cause significant pain and swelling at the injection site, perhaps also involving the draining lymph nodes. Medical or surgical intervention may be required. Contact a doctor immediately, even if only a very small amount is injected, and take this package leaflet/carton with you. Allow the wound to bleed freely and DO NOT squeeze or interfere with the injection site.

In case of accidental self‑injection, seek medical advice immediately. DO NOT DRIVE OR OPERATE MACHINERY as the ability to perform these tasks may be impaired.

Ancillary advice to the medical practitioner

This product contains mineral oil. Even small amounts of self-administered mineral oil can cause intense swelling and a persistent granulomatous inflammatory reaction. If injected into a finger joint or tendon sheath, the product may track along the tendon, perhaps also involving the draining lymph nodes. The swelling and

inflammation may compromise blood supply and result in necrosis that, in rare cases, may lead to the loss of a digit.

Following appropriate immediate local cleansing, corticosteroids may be considered to decrease the severity of any local reaction. Ascertain the patient's tetanus immunisation status, and provide booster or primary series, as appropriate.

In some cases of self-injection, PROMPT surgical attention may be required. The wound should be incised and irrigated to remove the vaccine, especially where there is involvement of finger pulp or tendon. Complete curettage or total excision of the lesion may be required for chronic granulomatous reactions. Meticulous technique is required to stop inadvertent spread of the product.

ii. The APVMA is satisfied that the proposed use of UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle will not be an undue hazard to the safety of people using anything containing its **residues.**

The APVMA agreed to the applicant's request to accept the EMA assessment of this vaccine. All substances included in the composition of the vaccine are listed in Table 1 of the Annex to Commission Regulation (EU) 37/2010 or are considered outside the scope of Council Regulation (EC) No 470/2009. As numerical MRLs have not been set for any of the ingredients, there was no need to perform residue studies for UBAC and a withdrawal period of zero days can be established.

iii. The APVMA is satisfied that the proposed use of UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle is not likely to have an unintended effect that is harmful to animals, plants or the environment if used according to the **product label directions**.

Neither the active constituent nor excipients are listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). As a bacterial 'component' vaccine (not a live vaccine), the active constituent does not require Scheduling.

iv. The APVMA is satisfied that the proposed use of the new product UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle containing the active constituent lipoteichoic acid (LTA) from biofilm adhesion component (BAC) of *Streptococcus uberis*, strain 5616 would not be likely to have an unintended effect that is harmful to animals, plants, or the environment.

The potential risk to the environment was considered and found to be negligible. The label will, therefore, have the minimum required disposal statement in alignment with the Veterinary Labelling Code:

- Dispose of container by wrapping with paper and putting in garbage.
- Discarded needles/sharps should immediately be placed in a designated and appropriately labelled 'sharps' container.

v. Target animal safety was demonstrated using laboratory trials and trials under field conditions:

a. Laboratory Trial: The design of this trial was according to the monograph no. 50206 of the Ph. Eur. current edition and to the VICH GL 44 Target animal safety for veterinary live and inactivated vaccines - Scientific guideline. Considering that UBAC is an inactivated and not a live vaccine, the applicant justified that overdose testing is not required according to the VICH guideline. The safety study was conducted in 14 pregnant heifers (considered the most sensitive category) with 14 non-vaccinated pregnant heifers as controls. The recommended 3 dose vaccination schedule was administered to the vaccinated group with the controls receiving a placebo (saline). The animals were observed and examined daily for signs of abnormal local and systemic reactions following each vaccination at Day 0, Day 37, and Day 73. The rectal temperature and milk production were also recorded as per protocol. The safety data regarding reproductive performance (peripartum incidences and calf viability) and milk production were also recorded. No significant general clinical signs attributable to the vaccine were observed after any of the 3

administrations and only small swellings were observed at the injection site. The label contains information on the expected local reactions and generalised reactions. Regarding reproductive performance (peripartum incidences and calf viability) and milk production during the vaccination phase, no significant differences between the groups were detected.

b. Field Trial: One multicentre randomised, double blinded, placebo-controlled field trial was conducted in 6 commercial farms located in Spain with a history of clinical mastitis caused by S. *uberis*, in which the safety and the efficacy of the vaccine was assessed. Pregnant heifers and cows were administered UBAC according to the recommended schedule of 3 doses of vaccine or phosphate-buffered saline as a control. This study design complies with the European Pharmacopoeia General text (5.2.7 Evaluation of Efficacy of Veterinary Vaccines and Immunosera) and was conducted in conformance with the VICH Guideline 9 on Good Clinical Practices (GCP).

vi. Post-vaccination rectal temperature increases were statistically significant on day 1 post-vaccination after each vaccination. The mean increases per group were below 0.5° C and, therefore, the temperature increase can be classified as not clinically relevant. The highest individual increase in one vaccinated animal was 1.8° C. Adverse events, including reproductive adverse events, were recorded at comparable incidence in both vaccinated and control groups and corresponded to levels previously reported for the included farms. Therefore, UBAC was shown not to increase the risk of reproductive adverse events if administered according to the recommended vaccination schedule.

c. The results demonstrated that vaccination with UBAC vaccine is safe when administered in dairy cows according to the recommended vaccination program.

2) The APVMA has evaluated the application and in its assessment in relation to whether the efficacy criteria have been met in accordance with the definition set out in section 5B of the Agvet Code, and proposes to determine that:

i. In relation to its assessment of efficacy the APVMA is satisfied that data from trials supporting the efficacy of the product adequately demonstrate that, if used according to the product label directions, the product is effective for its proposed uses.

a. Target Animal Efficacy was demonstrated using laboratory trials and trials under field conditions:

The applicant carried out laboratory and field studies to establish the efficacy of the product. Two laboratory studies were conducted to investigate the efficacy of the product. The first laboratory trial looked at challenge after the administration of the primary vaccination schedule and the second investigated protection by challenge following a 2-dose vaccination scheme. A multicentre field trial conducted in Spain was also conducted to establish field safety and efficacy (see target animal safety).

b. Laboratory studies:

The efficacy of the vaccine in pregnant cows after administration of the primary vaccination schedule (consisting of 3 administrations of one dose) against challenge of S. *uberis* was conducted in accordance with the requirements of Europe monograph on veterinary vaccines (0062) and the General Text on Efficacy (5.2.7). 28 pregnant heifers were divided into 2 groups of 14 animals, either vaccinated or PBS (phosphate buffered saline) controls, and administered UBAC by the recommended administration route (intramuscular) and the recommended application schedule (3 vaccinations). Animals were challenged 15 days after the third vaccination. The results supported a trend of reduced clinical mastitis, somatic cell counts (SCC), and bacterial counts in the vaccinated group.

c. A second laboratory challenge study

The study did not follow the recommend vaccination schedule but used a 2-dose schedule to establish the onset of immunity. In this study, 16 pregnant heifers received the vaccine, and an appropriate control group (16 pregnant heifers) received a placebo (PBS). 36 days after the second vaccination (about 15 days after

parturition), vaccinated and control animals were challenged by intramammary application of S. *uberis*. The results supported an onset of immunity approximately 36 days after the second dose.

d. Field study

One multisite field study to evaluate both the safety and the efficacy of vaccine UBAC under field conditions at the recommended dose and according to the recommended vaccination schedule was provided. The trial was performed according to the Good Clinical Practices (GCP) in 6 dairy farms located in Spain. The farms had historical records of *Streptococcus uberis* clinical mastitis. A total of 781 clinically healthy heifers and cows were distributed in 2 groups. They were vaccinated with UBAC (n=401) and Control (n=380) by the recommended route of administration (intramuscular) and according to the vaccination programme. All animals were observed until 21 weeks after parturition.

The results demonstrated that UBAC vaccine:

- Reduces the overall incidence of *S. uberis* clinical intramammary infections.
- Provides protection a total period of 21 weeks (5 months) of lactation.
- Reduces the Somatic Cell Counts in cows with *S. uberis* subclinical mastitis.
- Reduces milk production losses in farms with *S. uberis* mastitis.

It was concluded that UBAC is efficacious when administered according to the recommended schedule.

Scientific arguments were submitted to justify how the studies conducted overseas were applicable to the Australian dairying conditions. These were assessed and found to be acceptable.

3) The APVMA has evaluated the application and in its assessment in relation to whether the **trade criteria** have been met in accordance with the definition set out in section 5C of the Agvet Code, proposes to determine that:

The trade risk associated with the proposed use of UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle is negligible. As MRLs are not required for any of the ingredients, a withholding period, and an Export Slaughter Interval (ESI) of ‘Zero (0) days’ will be associated with the proposed use of this product.

As there are no concerns from a trade perspective relating to the registration of this product, the APVMA is satisfied that the proposed use of UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle, would not adversely affect trade between Australia and places outside Australia.

Making a submission

In accordance with section 12 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether lipoteichoic acid (LTA) from biofilm adhesion component (BAC) of *Streptococcus uberis*, strain 5616 should be approved. Submissions should relate only to matters that are considered in determining whether the safety criteria set out in section 5A of the Agvet Code have been met. Submissions should state the grounds on which they are based.

In accordance with section 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether UBAC Inactivated Subunit Vaccine against *Streptococcus uberis* for Cattle should be registered. Submissions should relate only to matters that are required by the APVMA to be taken into consideration in determining whether the safety, efficacy or trade criteria have been met. Submissions should state the grounds on which they are based.

Submissions must be received by the APVMA within 28 days of the date of this notice 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.

Please note: Submissions will be published on the APVMA's website, unless you have asked for the submission to remain confidential (see public submission coversheet).

Please lodge your submission with a public submission coversheet, which provides options for how your submission will be published.

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

Please send your written submission and coversheet by email or post to:

Email: casemanagement@apvma.gov.au

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