Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active streptomyces lydicus WYEC108 in the product Actinovate BioFungicide

MAY 2017

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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, 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 on the APVMA website.

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

About this document

This is a Public Release Summary.

It indicates that the APVMA is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety.

Comment is sought from interested stakeholders on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of Actinovate Biofungicide 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.

[The date entered below must be at least 28 days from the date on which the related Gazette Notice was published. Please confirm this date with Public Affairs and provide this document to them with the Gazette Notice to ensure they are published in unison.]

Submissions must be received by the APVMA by close of business on 13 June 2017 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

All personal information, and confidential information judged by the APVMA to be confidential commercial information (CCI)[1] contained in submissions will be treated confidentially.

[1] A full definition of ‘confidential commercial information’ is contained in 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:

Case Management and Administration Unit
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

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

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 are available from the APVMA on request.

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

1 INTRODUCTION

1.1 Applicant

Novozymes BioAg Limited.

1.2 Purpose of application

Novozymes BioAg Limited has applied to the APVMA for registration of the new product Actinovate Biofungicide containing 0.0371% (mg/Kg) of the new active constituent, Streptomyces lydicus Strain WYEC108 (1 x 10^7 cfu/mL) as a soluble powder (SP) formulation.

This publication provides a summary of the information reviewed and an outline of the regulatory considerations for the proposed registration of Actinovate Biofungicide, and approval of the new active constituent, Streptomyces lydicus WYEC108.

1.3 Product claims and use pattern

Actinovate Biofungicide is intended for use as a preventative fungicide that will be applied as a foliar or soil drench, or seed treatment in agriculture, horticulture, greenhouse, nursery and turf.

The proposed uses include foliar application at a rate of 200–850 g/ha for suppression of:

- powdery mildew and phytophthora on strawberries
- various species of powdery mildew on carrots, cucurbit vegetables, fruiting vegetables and the commercial flower crops of verbena
- rhizoctonia in ornamental grasses, and
- phytophthora and Fusarium wilt in tomato.

The product will initially be applied prior to planting followed by an application every 14–90 days depending on environmental conditions, situations and dosage level.

The proposed uses also include a soil drench application at a rate of 420 g/ha or 45 g/100L water for suppression of:

- fusarium in cyclamen, and
- cylindrocladium in peace lily.

The other use is as a seed treatment at a rate of 1 kg/100 kg seed for suppression of fusarium, rhizoctonia and pythium on vegetable seeds.

Actinovate Biofungicide also makes various biological soil amendment claims which do not require assessment as pesticidal claims and will not be considered further as part of the regulatory considerations in this Public Release Summary (PRS).

1.4 Mode of action

Streptomyces lydicus WYEC108 is a ubiquitous and naturally-occurring gram positive soil bacterium and belongs to the genus Streptomyces (largest genus of Actinobacteria), known for its complex secondary metabolite, antibiotics and drug production characteristics. Several Streptomyces species have antifungal or anti-parasitic activities. The strain WYEC108 was first isolated from an English soil sample and is deposited at the United States Department of Agriculture (USDA)-American Type Culture Collection (ATCC) with the accession number ATCC 55445.

S. lydicus demonstrates antifungal properties, which involve colonisation of the growing root tips of plants and acting as a mycoparasite of fungal root pathogens reducing their activity through a variety of mechanisms, including competitive exclusion and excretion of lytic enzymes and unidentified antibiotics. The inhibitory activity of S. lydicus WYEC108 in the soil is based on its ability to colonize the plant root rhizosphere competing with pathogens for root surface, excreting antifungal metabolites including antibiotics, and secreting fungal cell wall degrading lytic enzymes such as chitinases and β1,3 glucanases following colonization.

1.5 Overseas registrations

Actinovate Biofungicide (under different names) is registered in the USA and New Zealand as a soil amendment and plant pathogen suppressive product.

Actinovate Biofungicide is currently registered in the following countries:

- New Zealand—as Actinovate, Agricultural Chemicals & Veterinary Medicines (ACVM) Product No. 7969
- USA: The product is registered as Actinovate Soluble (US EPA Registration No. 73314–1). The product also has a number of alternate brand names: Actinovate SP,Actinovate AG and Actinovate L&G.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

The microbiological active constituent streptomyces lydicus WYEC108 is manufactured overseas, and has the following properties:

COMMON NAME:	Streptomyces lydicus WYEC108
DESCRIPTION:	A gram-positive, aerobic, filamentous soil bacteria producing grey spiralled chains of spores in an aerial mycelium.
ORDER:	Actinomycetales
FAMILY:	Streptomycetacea
GENUS AND SPECIES:	Strepyomyces lydicus
STRAIN:	WYEC108
MODE OF ACTION:	Acts as a mycoparasite of fungal pathogens and excretes antifungal metabolites into the rhizosphere after colonisation of plant root tips

The APVMA chemistry section has evaluated the chemistry aspects of streptomyces lydicus WYEC108 active constituent (methods of identification, manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable.

2.2 Formulated product

The active constituent Streptomyces lydicus WYEC108 and the product Actinovate BioFungicide will both be manufactured overseas. Actinovate Biofungicide will be available in 80 g or 500 g foil-backed ziplock plastic bags with self-adhesive labels, or 7.72 kg HDPE pails with resealable lids and adhesive labels.

DISTINGUISHING NAME:	Actinovate BioFungicide
FORMULATION TYPE:	Soluble powder (SP)
ACTIVE CONSTITUENT CONCENTRATION:	Minimum 1 × 107 colony-forming units per gram of Streptomyces lydicus WYEC108

Physical and chemical properties of product

PHYSICAL FORM:	White powder with grey speckles
PH (1% SOLUTION IN DISTILLED WATER):	6.4
DENSITY:	1.51 g/mL
WATER SOLUBILITY:	Formulation is generally soluble, with a maximum of 2% insoluble material
REACTIVITY:	Not corrosive
PACK SIZES AND MATERIALS:	56 gram and 500 gram foil-backed ziplock plastic bags with adhesive labels 7.72 kg high density polyethylene (HDPE) pails with resealable lids and adhesive labels
PRODUCT STABILITY:	Stable in real time (1 year at 5 or 25°C) in the commercial packaging material

2.3 Recommendations

Based on a review of the chemistry and manufacturing details provided by the applicant, the registration of Actinovate BioFungicide is supported from a chemistry perspective.

3 TOXICOLOGICAL ASSESSMENT

3.1 Evaluation of toxicology

The database for streptomyces lydicus WYEC108 comprised studies on acute oral and dermal toxicity, eye and skin irritation, acute intravenous injection toxicity/pathogenicity and acute pulmonary toxicity/ pathogenicity. The majority of the studies submitted complied with Good Laboratory Practice (GLP), and were undertaken according to standard test guidelines. These studies, along with other information provided by the applicant, were considered adequate for the purposes of this evaluation.

In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur.

Chemical class

The active constituent, S. lydicus WYEC108, is a ubiquitous soil bacterium belonging to Actinobacteria with antifungal properties based on competitive exclusion, antibiotic production and secretion of lytic enzymes.

Toxicokinetics and metabolism

Acute toxicity

Formulated product

Four acute toxicity studies were conducted with a surrogate formulation containing the active constituent streptomyces lydicus WYEC108 (at ≥1 x 10^7 CFU/g) and a carrier material at the same concentrations as the proposed product for Australian registration. In the surrogate product, other formulation components were also substituted at equivalent concentrations. Overall, the surrogate product is comparable to the proposed product and the studies submitted on the surrogate product are considered appropriate for the purposes of this assessment. Based on the submitted toxicological studies, the proposed product is of low acute oral and dermal toxicity. It is not an irritant to the skin or eye.

The applicant did not provide acute inhalation or skin sensitisation studies on the formulated product. The toxicity of the product was estimated for these two endpoints. The product is expected to be of low acute inhalation toxicity, and is unlikely to be a skin and respiratory sensitiser.

Active constituent

In acute toxicity studies, S. lydicus WYEC108 was of low acute oral (LD_{50} > 5050 mg/kg bw; equivalent to 2.5 x 10^9 CFU/kg bw) and low acute dermal (LD_{50} > 5050 mg/kg bw, equivalent to 9.95 x 10^9 CFU/kg bw) toxicity. It was a slight eye irritant and was not a skin irritant in rabbits.

Acute inhalation toxicity and sensitisation studies on the active constituent (S. lydicus WYEC108) were not provided. Justification was provided for an exemption of hypersensitivity/allergy study requirements for this assessment. In the absence of sensitisation study data and noting that members of the genus Streptomyces have been reported as potential skin and respiratory sensitisers, the S. lydicus strain WYEC108 is considered as a potential sensitising agent.'

Systemic toxicity

Acute pulmonary toxicity/infectivity

Adult rats were given 0.1 mL (9.1 x 10^8 CFU/rat) S. lydicus WYEC108 by intra-tracheal injection. No deaths were observed during the observation period. The test group administered S. lydicus WYEC 108 demonstrated transient weight loss. No treatment-related clinical signs of toxicity were observed. Post-mortem examination revealed no observable anomalies. The study gave strong indications that S. lydicus WYEC108 was excreted from the bodies of rats. S. lydicus WYEC108 was not considered to be a pulmonary toxicant or pathogen when administered by intra-tracheal injection to Sprague Dawley (SD) rats at 9.1 x 10^8 CFU/animal.

3.2 Public health standards

Poisons scheduling

On 23 June 2016, the Delegate of the Secretary of the Department of Health published a final scheduling decision to create a new Appendix B entry for streptomyces lydicus WYEC108 in the Standard for the Uniform Scheduling of Medicines and Poisons, with an implementation date of 1 October 2016.

No Observable Effect Level (NOEL)/Acceptable Daily Intake

The acceptable daily intake (ADI) for humans is the level of intake of an agricultural or veterinary chemical which can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall No Observable Effect Level (NOEL) for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate uncertainty (safety) factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intra-species variation, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

No repeat-dose studies were available for S. lydicus WYEC 108 and no repeat dose toxicological endpoints were available for S. lydicus in the absence of an appropriate NOEL a qualitative assessment was undertaken. It is important to note that, Streptomyces. lydicus WYEC108 is a naturally occurring soil

organism. Based on the stated use pattern of the product, the microbial pest control agent does not persist at significant levels in the environment, and residues in the food crops are unlikely to result in exposures significantly above the normal background levels. It is considered the microbial pesticide can be easily removed from foods by washing, peeling, cooking and processing, hence minimizing the potential dietary exposure.

Therefore, it is considered that an ADI is unnecessary for streptomyces. lydicus WYEC108.

Acute Reference Dose (ARfD)

The acute reference dose (ARfD) is the estimate of the amount of a substance in food or drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a short period of time, usually in one meal or during one day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

The available data indicate that S.lydicus WYEC108 has low toxicity and no infectivity/pathogenicity potential via acute oral exposure. It is considered that an ARfD is unnecessary for streptomyces. lydicus WYEC108.

4 RESIDUES ASSESSMENT

Streptomyces lydicus WYEC108 is a ubiquitous bacteria in soil that readily colonises the growing root tips of plants, providing protection to crops against fungal pathogens largely by competitive exclusion.

The proposed use patterns are expected to result in S. lydicus WYEC108 in the soil at levels (106 cfu/g) that are below natural streptomycete levels (107–8 cfu/g) with smaller, background amounts expected in air and on plant surfaces. This represents a small proportion of the naturally occurring streptomycetes in the soil and therefore is not expected to add substantially to the effects of the naturally occurring streptomycete populations.

The toxicological assessment recommended that the establishment of an ADI and/or an ARfD was not considered to be required for streptomyces lydicus WYEC108 due to its low toxicity profile and apparent non-pathogenicity/ non-infectivity to animals.

As S. lydicus WYEC108 is a ubiquitous bacteria and residues of S.lydicus WYEC108 from use of actinovate biofungicide are not likely to result in exposures significantly above background levels, and also because S. lydicus is unlikely to pose a toxicological concern, it is concluded that Maximum Residue Levels(MRLs) are not required for S. lydicus WYEC108.

It is recommended that a Table 5 entry be established for S. lydicus WYEC108 as a fungicide. [Note: Table 5 exists for situations where residues do not or should not occur in foods or animal feeds; or where the residues are identical to or indistinguishable from natural food components; or are otherwise of no toxicological significance.]

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Residues of streptomyces lydicus WYEC108 from use of actinovate biofungicide are not likely to result in exposures significantly above background levels as a result of the use of this product. Therefore, it is not expected that there will be any undue prejudice to trade with other countries with regards to residues in exported food commodities.

6 WORK HEALTH AND SAFETY ASSESSMENT

6.1 Health hazards

The active constituent streptomyces lydicus WYEC108 is not subject to hazardous chemical requirements under the current Work Health and Safety (WHS) legislation.

6.2 Formulation, packaging, transport, storage and retailing

The active constituent streptomyces lydicus WYEC108 and the product Actinovate BioFungicide will be manufactured overseas. It will be available in 80 g and 500 g foil-backed zip-lock plastic bags, or 7.72 kg HDPE plastic pails with sealable lid and self-adhesive labels.

6.3 Use pattern

Actinovate BioFungicide is intended for use for the suppression of root rot and damping off fungi, foliar fungal pathogens; and for seed treatment in vegetables.

The product is to be mixed in an appropriate amount of water and applied by soil drench or foliar application methods at a rate of up to 850 g/ha, or used as a seed treatment at a rate of 1 kg/100 kg seed.

6.4 Exposure during use

Farmers and their employees, as well as contract sprayers will be the main users of Actinovate BioFungicide. Workers may be exposed to the product when opening containers, mixing/loading and during application, cleaning up spills, maintaining equipment and re-entering treated crops. The main routes of exposure to the product spray will be dermal and inhalational with a low potential for ocular exposure.

A qualitative risk assessment for Actinovate BioFungicide was undertaken by the OCS in this case, noting that no repeat-dose studies were available for S. lydicus WYEC108 and no repeat dose toxicological endpoints were available for S. lydicus.

The potential key hazards associated with exposure to S. lydicus WYEC108 are skin and respiratory sensitisation. While the active constituent is present at only 0.0371% w/w in the proposed product, prolonged and repeated exposure may enhance the sensitisation effects.

It is concluded that repeated exposure to S. lydicus WYEC108 may result increased risk of skin and respiratory sensitisation for workers through inhalation, dermal and/or ocular routes, during handling and application of the product. First Aid Instructions and Safety Directions have been recommended to mitigate these risks.

6.5 Exposure during re-entry

Exposure of farmers and their employees to S. lydicus WYEC108 is likely during post-application activities. Workers entering treated areas may be exposed to product residues during activities like irrigation, scouting, weeding, pruning, thinning, harvest or mulching. The product use patterns may also include protected horticulture scenarios. However, exposure levels are not expected to be greater than levels expected when using the product. Therefore, additional risk management is not expected to be required, and no re-entry statements have been proposed.

6.6 Recommendations for safe use

Based on the risk assessment, the product is appropriate for professional use. Users should follow the First Aid Instructions and Safety Directions on the product label.

6.7 Conclusion

The approval of the new biological active constituent streptomyces lydicus WYEC108 for agricultural use, and the registration of Actinovate BioFungicide (containing (1×10^7 CFU/g) for the control and/or suppression of root rot and of foliar fungal pathogens in vegetables and ornamentals, for seed treatment in vegetables, is supported.

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

7 ENVIRONMENTAL ASSESSMENT

An environmental risk assessment has been conducted according to methods appropriate for a microbial product and based on the available information and the proposed use pattern. The applicant has also provided six toxicity trial reports (1 x acute birds, 2 x acute aquatic species, 1 x acute bees, 1 x acute earthworms and 1 x other non-target organisms). A summary of the endpoints are presented in Table 7–1 and were applied in the risk assessment.

The proposed use of streptomyces lydicus WYEC108 in Actinovate BioFungicide will result in treatment related soil concentrations much lower than Streptomyces spp. background concentrations in natural soils (~300 versus 105–107 colony forming units (CFU)/gram soil). Where streptomyces lydicus WYEC108 is expected to exhibit similar biological traits to Streptomyces spp. the incremental risk is considered minimal. The studies presented showed no harmful effects to non-target species at the concentrations expected from the proposed use.

Actinovate BioFungicide is applied as a soil drench, seed treatment and via foliar application. Indirect exposure via runoff or drainage are expected to be limited for a microorganism based on low mobility. Further to this streptomyces lydicus WYEC108 has little ability to survive in aquatic environments. Therefore, ground and surface water contamination through the proposed use of products containing streptomyces lydicus WYEC108 is not expected. Streptomyces lydicus WYEC108 was observed to have a physical (non-pathogenic) effect on daphnia magna at very high concentrations; therefore, a hazard statement is required on the label for aquatic organisms.

A potential concern with respect to non-target plants revolves around the possibility of horizontal gene transfer between pathogenic streptomyces species and streptomyces lydicus WYEC108 possibly resulting in a new pathogenic strain. The APVMA considers the likelihood of such an event occurring to be minimal but because this risk cannot be ruled out when pathogenic streptomyces spp. are present, the APVMA requires a restriction that product should not be applied in those circumstances.

In conclusion, based on an assessment of the environmental data, it was considered that there should be no unacceptable adverse effects on non-target organisms from the use of Actinovate Biofungicide when used in accordance with label directions. Therefore, the APVMA can be satisfied that the proposed use of this product is unlikely to have an unintended effect that is harmful to animals, plants or the environment.

7.1 Environmental effects

TOXICITY OF ACTIVE CONSTITUENT STREPTOMYCES LYDICUS WYEC108 AND THE PRODUCT ACTINOVATE® FOR VARIOUS ORGANISMS

ORGANISM		MEASURE OF TOXICITY OR EFFECT	PARAMETER (TEST PERIOD)	TOXICITY (UNIT)
TERRESTRIAL SPECIES				
Mammals	(Rattus norvegicus)	Acute oral toxicity	LD50	>2.5×109 CFU/kg bw
		Technical active	LD50	>5.0×107 CFU/kg bw
		Acute oral toxicity	LD50	>9.3×108 CFU/animal No infectivity/ pathogenicity
		Formulated product	LD50	>9.1×108 CFU/animal No infectivity/ pathogenicity
Bird	Bobwhite quail, mallard duck	5 d avian oral pathogenicity and toxicity	NOEC LD50	1.25 x 108 CFU/kg of body weight per day (no effect at highest dose) >6.25 x 108 CFU/kg bodyweight. CFU
	Honeybee (apis mellifera)	19 day dietary effect	NOEC	17,980 µg/mL of Actinovate® Soluble (no effect at highest dose tested)
Non-target arthropods	Parasitoid (aphidius rhopalosiphi)	Tier 1 dose/response	LR50	g ac/ha
	Predatory mite (typhlodromus pyri)			
	Earthworm	14 d acute toxicity	LC50 NOEC	>1000.0 mg/kg 1000.0 mg/kg (~300 CFU/g) (no effect at highest dose

ORGANISM		MEASURE OF TOXICITY OR EFFECT	PARAMETER (TEST PERIOD)	TOXICITY (UNIT)
				tested)
		56 d Reproduction	NOErC LOErC	555.6 mg/kg (~150 CFU/g soil) 1000 mg/kg (decrease in number of young produced)
	Collembola (folsomia candida)	28 d survival and reproduction	NOErC	1000.3 mg/kg (~300 CFU/g) (no effect at highest dose tested)
AQUATIC SPECIES				
Fish	Rainbow trout	96–Hour Static Acute Toxicity Test	LC50. NOEC LC50	>167 µg WYEC108/L 167 µg WYEC108/L. >9.9x104 CFU/mL (mean measured)
Aquatic invertebrate	Daphnia magna	21–day static renewal test	EC50survival EC50reproduction EC50growth EC50growth	5,044 CFU/mL 2745.17 CFU/mL 3791.80 CFU/mL 5446.28 CFU/mL (based on surviving organisms)
		21–day static renewal test	NOECsurvival LOECsurvival EC10	3125 CFU/mL 12500 CFU/mL 373 CFU/mL

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product use pattern

Actinovate Biofungicide is intended for use as a preventative fungicide that will be applied as a foliar or soil drench, or seed treatment in agriculture, horticulture, greenhouse, nursery and turf situations. A copy of the proposed label is included in Section 9 Labelling Requirements

8.2 Summary of evaluation of efficacy and crop safety

Efficacy

Fifteen trials for efficacy and crop safety were submitted including U.S. laboratory assays, U.S. and Canada field trials and 3 Australian field trials. Whilst the information on efficacy in Australian trials was limited, data from trials in the US and Canada were more comprehensive and generally supported the claims made for the product.

Three Australian studies on efficacy and safety were submitted in this application. Two of the studies were of field trials on powdery mildew, one was conducted in Western Australia on cucumbers and one on carrots in Tasmania. The third study was for control of powdery mildew on greenhouse grown cucumbers in New South Wales. In each of these studies the product was applied as a foliar spray. As these trials were conducted under a range of conditions it is expected that these results would be applicable to Australian conditions. In addition to this numerous published articles from reputable scientific researchers and publications on the use of streptomyces lydicus WYEC108 as a biological control organism for use on plant fungal pathogens were provided.

The information provided supports the label claims regarding the suppression only of the effects of various fungal diseases on certain crops if used according to the label directions. Appropriate user information is provided on the proposed label indicating that as Actinovate BioFungicide is a biological compound results may vary and use of the product alone may not give adequate control.'

The following label claims for suppression of various diseases are supported by the application:

Foliar application at a rate of 200–850 g/ha

- powdery mildew and phytophthora on strawberries
- various species of powdery mildew on carrots, cucurbit vegetables, fruiting vegetables and verbena
- rhizoctonia in ornamental grasses
- phytophthora in tomato
- fusarium wilt in tomato

Drench application at a rate of 420 g/ha or 45 g/100 L water

- fusarium oxysporum on cyclamen
- cylindrocladium spathiphylli in peace lily

Seed treatment at a rate of 1.0 kg/100 kg seed

- various species of fusarium, rhizoctonia and pythium on treated vegetables seeds

Crop safety

There was no evidence of acute phytotoxicity to any of the crops or plant species tested.

Integrated disease management

This product is intended for use in integrated disease management systems. Consult local agricultural authorities for specific IDM strategies developed for your crop(s) and locations

8.3 Conclusions

The product Actinovate BioFungicide is expected to provide acceptable suppression of specific diseases as detailed on the proposed label, when used as directed, whilst providing acceptable crop safety for the nominated crops. The product is expected to be suitable for use in integrated plant health and disease management systems.

9 LABELLING REQUIREMENTS

KEEP OUT OF REACH OF CHILDREN
'READ SAFETY DIRECTIONS BEFORE OPENING OR USING

ACTINOVATE®
BioFungicide

ACTIVE CONSTITUENT:

$1x10^7$ cfu/g Streptomyces lydicus WYEC108

A biological fungicide for use in a plant health and disease management program for the reduction of effects caused by root and foliar diseases in vegetables and other crops as specified in the Directions for Use table. Supplements activity of natural soil organisms and makes nutrients more available.

OFS Logo

NASAA Logo & Certification No. 6177M

Contents: 80 g, 500 g, 7.72 kg

Imported by:

Produced in the USA.

US Patent No. 5403584.

APVMA Approval No. 64384/48185

DIRECTIONS FOR USE:

Applications should be made before or at the very early stages of disease development. In high disease pressure situations use alternate controls before applying actinovate or in rotation with actinovate to reduce the incidence of disease organisms.

Actinovate becomes active in the soil and on plant foliage when the temperatures are above 7°C.

Restraints

DO NOT apply if a disease known to be caused by *Streptomyces* is present.

SITUATION	***DISEASES***	***RATE***	***CRITICAL COMMENTS***
All crops	Biological Soil Amendment to supplement the activity of natural soil organisms by making nutrients more available for improved plant growth	200–850 g/ha dissolved in an appropriate amount of water	Apply as a soil drench, transplant dip or through irrigation to the area immediately surrounding the roots or seeds. Apply until soil around seed or root ball of plant is saturated without creating run-off. Apply every 14–90 days depending on environmental conditions and dosage level.
Foliar Application		200–850 g/ha	For suppression of the indicated diseases, apply initial application prior to onset of disease season. Apply as part of a program alternating applications with other products. Use of Actinovate alone may not give adequate control. For best results, use with an adjuvant.
Strawberries	Powdery mildew Phytophthora species		
Carrots, Cucurbit Vegetables, Fruiting Vegetables, Verbena	Powdery mildew		
Ornamental grasses	Rhizoctonia		
Tomato	Phytophthoraspecies Fusarium wilt		
Drench Application		420 g/ha or 45 g /100 L water	Apply to the area immediately surrounding the roots or seeds until soil around seed or root ball of plant is saturated without creating run-off or as a drench to plants/growing media in sufficient water to saturate soil. Apply initially prior to planting then follow-up every 14–90 days depending on environmental conditions and dosage level.
Cyclamen	Fusarium species		
Peace Lily	Cylindricladium species		
Seed Treatment Vegetables	Fusarium, Rhizoctonia, Pythium	1.0 kg /100 kg seed	Apply this product through mist-type commercial seed treatment equipment, slurry or other comparable methods that provide complete coverage of treated seed. Apply in sufficient water to ensure even coverage of seed.

NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPROPRIATE LEGISLATION.

WITHHOLDING PERIOD: NOT REQUIRED WHEN USED AS DIRECTED.

GENERAL INSTRUCTIONS

Actinovate is a biological fungicide that helps suppress the effects of root rot and damping-off fungi and certain foliar fungal pathogens when used as part of a total crop health management program. Actinovate works with the crop, nutrients and other organisms to suppress disease organisms and their effects. When applied to the soil, Actinovate helps release minerals and micronutrients making them more available to plants resulting in increased size and vitality. Plants treated with a soil application will become hardier, more vigorous and have a robust and protected root system. The product also colonises the root system and helps protect it from harmful fungi. Actinovate can be applied to sterilised or fumigated soil (provided no fumigant remains in the soil). When applied as a foliar spray it helps suppress the establishment of disease organisms. Actinovate can be used in all types of spray equipment.

Use alternative controls in situations with high disease pressure. Once pathogen populations have been reduced to manageable levels Actinovate will help keep the pathogen populations under control.

The application of Actinovate may need to be adapted to local conditions for best results.

Mixing

Mix Actinovate in an appropriate amount of water. Actinovate dissolves readily in water and does not require constant agitation. Prepare only the required amount of spray or soil drench solution and use within 4 hours of preparation. Accurate calibration of spray equipment is essential. Best results are obtained by addition of a non-ionic spreader-sticker (adjuvant).

Application

Actinovate can be used in all types of spray equipment. For best results, use with a non-ionic spreader-sticker (adjuvant).

Compatibility

Actinovate is compatible with most chemical fungicides, insecticides and fertilisers, and can be tank mixed or dry mixed. If tank mixes are required, observe all directions, precautions and limitations on labels of all products used. Do not apply soil fumigants to areas treated with Actinovate.

Integrated Disease Management (IDM)

Actinovate should be used as part of an overall disease management strategy. Follow practices known to reduce disease development. Consult local agricultural authorities for specific IDM strategies developed for your crop(s) and location.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers.

STORAGE AND DISPOSAL:

Store in the closed, original container in a cool, well-ventilated area. Keep from overheating or freezing. Optimum storage temperature 5˚C to 30˚C. Do not store for prolonged periods in direct sunlight.

Shake and empty contents into spray tank. Do not dispose of undiluted chemicals on site. Break, crush, or puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available, bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose, clear of waterways, desirable vegetation and tree roots, in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.

SAFETY DIRECTIONS

Avoid inhaling dust. When opening the container and preparing the spray and using the prepared spray wear elbow-length chemical resistant gloves and disposable dust face mask covering mouth and nose. Wash hands after use. After each day's use, wash gloves and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26; New Zealand 0800 764 766.

SAFETY DATA SHEET

Additional information is listed in the Safety Data Sheet which is available from the supplier.

Batch No.:

Date of Manufacture:

Expiry Date:

Imported by:

Produced in the USA.

US Patent No. 5403584.

ABBREVIATIONS

ac	active constituent
ACCS	Advisory Committee on Chemicals Scheduling
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ARfD	Acute Reference Dose
bw	bodyweight
^{o}C	Degrees Celsius
CEC	Cation Exchange Capacity
CFU	Colony Forming Units
Codex	Codex Alimentarius Commission
Codex CXLs	Codex Maximum Residue Limits
COEX	Co-extruded (packaging material)
COEX E-VAL	COEX material using EVOH Ethylene vinyl alcohol) resin under trade name EVAL
COEX PA	COEX material using polyamide
CRD	United Kingdom Chemicals Regulation D .irectorate
CT	product Concentration multiplied by Time
DofE	Department of Environment
EC	Emulsifiable Concentrate
EC	European Commission
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
Eq	equivalent
ESI	Export Slaughter Interval

EUP	End Use Product
Fo	original parent generation
F_1	first generation offspring
FRAC	Fungicide Resistance Action Committee
FSANZ	Food Standards Australia and New Zealand
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GJR	Global Joint Review
GLP	Good Laboratory Practice
GPMT	Guinea Pig Maximisation Test
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hb	haemoglobin
Hct	Heamatocrit
HDPE	High Density Polyethylene
HEEG	Human Exposure Expert Group
Hg	Haemoglobin
Hg	Mercury
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HR	Highest Residue
HSIS	Hazardous Substances Information System
id	intradermal
Idf	food ingestion rate (dry weight) in grams per day
ID_{50}	dose that infects50% of the target population of organisms
im	intramuscular

ip	intraperitoneal
IPM	Integrated Pest Management
IRM	Integrated Resistance Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
JMPR	Joint Meetings on Pesticide Residues
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
K_{ow}	Octanol-water partition coefficient
Kt	kilotonne
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOAEL	Lowest Observable Adverse Effect Level
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
mN	milliNewton
MoA	Mode of Action
MoE	Margin of Exposure
mPa	milliPascal
MRL	Maximum Residue Limit
ND	Not Detectable
NDPSC	National Drugs and Poisons Schedule Committee

NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
Nm	nanonmetre
NOEC/NOEL	No Observable Effect Concentration Level
NOER	No Observable Effect Rate
OC	Organic Carbon
OCS	Office of Chemical Safety
OD	Oil Dispersion (oil-based suspension concentrate)
OECD	Organisation of Economic Cooperation and Development
OGTR	Office of the Gene Technology Regulator
OM	Organic Matter
Pa	Pascals
PCV	Pack Cell Volume
PE	PolyEthylene
PEC	Predicted Environmental Concentration
PE/EVOH	Polyethylene with ethylene vinyl alcohol
PET	Polyethylene terephthalate
PHI	Post-Harvest Interval
pKa	Dissociation constant (acid)
PMRA	Pest Management Regulatory Agency (Canada)
PNEC	Predicted No Effect Concentration
po	oral
PP	PolyPropylene
ppb	parts per billion
PPE	Personal Protective Equipment

ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
RCP	Restricted Chemical Product
RNA	Ribonucleic acid
s	second
sc	subcutaneous
SC	Suspension Concentrate
SCBA	Self-Contained Breathing Apparatus
SDS	Safety Data Sheet
SE	SuspoEmulsion
SG	Soluble granule
STMR	Supervised Trials Median Residue
STMR-P	STMR corrected for processing
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SWA	Safe Work Australia
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T_{max}	Time to achieve maximum concentration
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
$T_{1/2}$	Elimination half-life
µg	microgram
US EPA	United States Environmental Protection Agency
UV	Ultra Violet light
vmd	volume median diameter
WBC	White Blood Count

WG	Water Dispersible Granule
WHP	Withholding Period
w/v	Weight/volume

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Actinobacteria	A group of Gram-positive bacteria
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
Excretion	The process of eliminating or expelling matter
Formulation	A combination of both active and inactive constituents to form the end use product
Gram-positive bacteria	Bacteria which have a very thick cell wall made of a protein called peptidoglycan.
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 K_{OW}
Mycoparasitism	A parasitic fungus whose host is another fungus
Metabolism	The chemical processes that maintain living organisms
Ocular	Of the eye
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Siderophores	A molecule which binds and transports iron in microorganisms
Subcutaneous	Under the skin
Total Radioactive Residue (TRR)	The total amount of ^{14}C-labelled active constituent and its metabolites detected in residue studies
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

Ubiquitous	Present, appearing, or found everywhere

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