



Australian Government
Australian Pesticides and
Veterinary Medicines Authority



PUBLIC RELEASE SUMMARY

on the evaluation of the new active BLAD (Banda de Lupinus albis doce) in the product PROBLAD PLUS FUNGICIDE

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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 Environment and State Departments of Primary Industries.

The APVMA has a policy of encouraging transparency in its activities and 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 to encourage 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 Problad Plus Fungicide should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target crop or animal safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 25 July 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.

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:

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Kingston ACT 2604

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Further information

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

Further information on Public Release Summaries can be found on the APVMA website: www.apvma.gov.au

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

1 INTRODUCTION

1.1 Applicant

CEV, S.A.

1.2 Purpose of application

CEV, S.A has applied to the APVMA for registration of the new product Problad Plus Fungicide, containing 250 g/L of the new active constituent, BLAD (Banda de Lupinus albis doce), as a soluble concentrate formulation.

This publication provides a summary of the information reviewed and an outline of the regulatory considerations for the proposed registration of Problad Plus Fungicide, and approval of the new active constituent, BLAD.

1.3 Product claims and use pattern

Problad Plus Fungicide is the first product containing BLAD to be introduced into the Australian market. The active constituent, BLAD, is the naturally-occurring seed storage protein formed during the germination process in sweet lupins. It is characterized as a 20 kDa polypeptide sourced from the proteolysis of the seed protein which are considered a human food and livestock feed.

Problad Plus Fungicide is intended for use as a preventative fungicide that will be applied as a foliar spray in the suppression of brown rot and blossom blight (*Monilinia spp.*) in stone fruit. Problad Plus Fungicide is to be applied at 3.0 L/ha where spray volume is less than 1000 L/ha or 300 mL/100 L water where spray volume equals or exceeds 1000 L/ha.

Problad Plus Fungicide is intended to be applied to Stonefruit with not more than two consecutive applications and a maximum of five applications to any crop in one season.

1.4 Mode of action

BLAD polypeptide has recently been classified by the Fungicide Resistance Action Committee as FRAC Group BM 01 which is defined as having a multi-site mode of action.

BLAD strongly binds to chitin, a major component of the fungal cell wall, inhibiting any fungal growth. It also degrades chitin by catalysing and successfully removing the N-acetyl-D-glucosamine terminal chitin monomers, resulting in the destruction of the fungal cells.

1.5 Overseas registrations

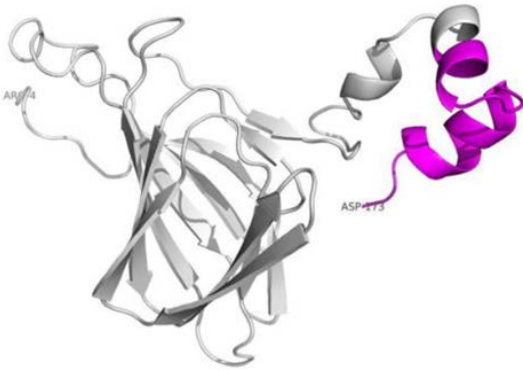
Problad Plus Fungicide is registered as Fracture Fungicide in the USA and Canada in a range of crops. In the USA it is registered for use on grapes, tomatoes and strawberries for the control of Botrytis and Powdery mildew and in almonds for the control of Brown rot and Blossom blight. In Canada it is registered for use on grapes and strawberries for the control of Botrytis and Powdery mildew, in tomato for the control of Botrytis, in Stone fruit and almonds for the control of Blossom blight and in outdoor ornamentals for the control of Powdery mildew and Botrytis. Chemistry and manufacture

1.6 Active constituent

The active constituent BLAD, or BLAD manufacturing concentrate, is a naturally occurring seed storage protein in germinated sweet lupins. BLAD is a 20 kDa polypeptide of β -conglutin which binds to chitin, a major component of the fungal cell wall, inhibiting any fungal growth. BLAD is a fungicide proposed for use in the suppression of fungal diseases of stone fruit.

The chemical active constituent BLAD has the following properties:

COMMON NAME (GENBANK):	BLAD (polypeptide, band from sweet <i>Lupinus albus</i>)
CHEMICAL NAME:	20 kDa polypeptide sourced from the proteolysis of the seed protein β -conglutin belonging to the 7S seed storage protein family being known as the 'cupin family'
SOURCE PLANT SPECIES:	<i>Lupinus albus</i>
CAS NUMBER:	1219521-95-5
MOLECULAR FORMULA:	Equivalent to 173 amino acids (see below)
MOLECULAR WEIGHT:	20,408.95 Da
PHYSICAL STATE:	Viscous liquid
COLOUR:	Dark brown
ODOUR:	Sweet-like odour
DENSITY:	1.256 g/mL at 20 °C
PH:	6.3 at 22 °C (1% aqueous solution)

SOLUBILITY:	Soluble in water
OXIDATION/REDUCTION:	Compatible with 10% mono-ammonium phosphate, iron powder and kerosene. Not compatible with 10% potassium permanganate.
FLAMMABILITY:	100°C
STRUCTURE (PREDICTED):	

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

On the basis of the chemistry and manufacture data provided and the toxicological assessment, it is proposed that the following APVMA Active Constituent Standard be established for BLAD:

APVMA ACTIVE CONSTITUENT STANDARD FOR BLAD

CONSTITUENT	SPECIFICATION	LEVEL
BLAD manufacturing concentrate	BLAD polypeptide (Banda de lupinus albus doce, a 20 kDa polypeptide of β -conglutin, which is a seed storage protein found in germinated sweet lupin seeds)	200 g/kg minimum
	Lupanine	0.1 g/kg maximum

1.7 Formulated product

The APVMA has evaluated the chemistry aspects of the product, Problad Plus Fungicide (composition and form of constituents, formulation process, stability, analytical method, validation data and specifications for containers).

The product Problad Plus Fungicide will be manufactured and formulated overseas, and packaged in 1 to 110 L high-density polyethylene (HDPE) containers. The manufacturing and quality control procedures are acceptable.

PROBLAD PLUS FUNGICIDE

DISTINGUISHING NAME	Problad Plus Fungicide
FORMULATION TYPE	Soluble concentrate
ACTIVE CONSTITUENT CONCENTRATION:	250 g/L BLAD manufacturing concentrate

PHYSICAL AND CHEMICAL PROPERTIES OF THE FORMULATED PRODUCT

COLOUR:	Dark brown
PHYSICAL FORM:	Viscous liquid
ODOUR:	Sweet-like odour
PH:	6.3 at 22 °C (1% aqueous solution)
VISCOSITY (KINEMATIC):	765.932 at 20 °C 230.181 at 40 °C
SOLUBILITY:	Soluble in water
FLAMMABILITY:	> 100oC
DENSITY AT 20°C	1.255
SURFACE TENSION AT 20°C	29.3 mN/m

1.8 Recommendations

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

2 TOXICOLOGICAL ASSESSMENT

2.1 Evaluation of toxicology

The active constituent is a polypeptide termed BLAD (from the Portuguese 'banda de *Lupinus albus* doce' or band from sweet *Lupinus albus*). BLAD is a naturally-occurring seed storage protein, which accumulates exclusively in the cotyledons of *Lupinus* species (for example, *Lupinus albus*), between days four and twelve after the onset of germination. It is a 20 kDa polypeptide of β -conglutin, or characterized as a fragment of the amino acid sequence of β -conglutin. The β -conglutin protein is classified as a 7S globulin which is part of the broader family of cupin proteins, which provides a major nitrogen source for germination of the developing plant.

Lupinus albus, commonly known as white or sweet lupine or lupin, is a member of the genus *Lupinus* in the family of Fabaceae. *Lupinus albus* contains the full range of essential amino acids and for hundreds of years has been widely cultivated worldwide, thus sweet lupines have a long history of safe use in human and livestock consumption without any adverse effects. BLAD is directly extracted from the flowering plant, sweet lupines. It has a dark brown colour with a sweet odour and is reputed to be 60% biodegradable within 14 days after application.

The toxicity profile of the active ingredient (BLAD) and the formulated product Problad Plus Fungicide are considered equivalent. Whilst the product contains additional non-reactive excipients, removal of the aqueous solvent during manufacture results in the concentration of the BLAD active constituent remaining unchanged for both the technical grade active constituent (TGAC) and the formulated product. On this basis the toxicity profile of BLAD and Problad Plus Fungicide were considered identical.

Acute toxicity

As previously noted, the active and product were considered equivalent in toxicity. Six acute toxicity tests were submitted for Problad Plus Fungicide. The acute toxicity of Problad Plus Fungicide in laboratory animals was low via the oral ($LD_{50} > 5000$ mg/kg bw, no deaths), dermal ($LD_{50} > 2000$ mg/kg bw, no deaths), and inhalation ($LD_{50} > 5340$ mg/kg bw, no deaths) routes of exposure. Problad Plus Fungicide was mildly irritating to the skin and eyes but was not a dermal sensitiser.

Subchronic toxicity

No subchronic toxicity or genotoxicity studies have been conducted using BLAD, as the active ingredient is a naturally occurring product with a history of use in food and feed (sweet lupines). Furthermore, noting its very low acute toxicity by any route and its rapid biodegradation, the absence of these studies is considered acceptable and have also been accepted by other regulatory agencies.

Reproductive, developmental and chronic toxicity and carcinogenicity

No long term toxicology or carcinogenicity studies have been conducted using BLAD. As specified previously, the active ingredient is a naturally occurring product with a history as a food and feed item (sweet lupines), it has very low acute toxicity by any route, is rapidly biodegraded and if use according to label direction will lead to negligible chronic exposure. The absence of these studies is considered acceptable and has been considered acceptable by other regulatory agencies.

Both the United States Environmental Protection Agency (USEPA) and the Canadian Pest Management Regulatory Agency (PMRA) reviewed studies pertaining to the chronic exposure of lupine products. Ballester et al (1984) reported a study of the potential reproductive and developmental toxicity of lupin protein. In that study, sweet lupine flour was fed for 9 months to two generations of rats (F1 and F2) at a level that provided 20% dietary protein. The diets were supplemented with 0.2% DL-methionine. The lupine diet had no effect on the general condition, mortality or behaviour of the animals. The growth rate of males fed sweet lupine was significantly higher than that of the controls. Haematological parameters and tests of liver function were normal in all treatment groups. At autopsy there were no significant changes in the weight of the heart, kidney, spleen, brain and gonads but the relative weight of the liver of lupine-fed rats was significantly lower than that in the controls. However, there were no histological changes in these livers. The lupin protein was reported to have no effect on either fertility or reproductive parameters in any of the generations.

Chronic life-time studies (ie 700 and 800 days) in rats fed sweet lupin seeds did not reveal any evidence of carcinogenicity in lupin-treated animals, and no signs of toxicity or decreases in body weight occurred (Grant et al, 1993 ; Grant et al 1995).

Allergenicity

Based on informatics, susceptibility to protease digestion and estimates of dietary intake, the BLAD polypeptide is expected to be of low potential to cause allergic reactions and to cross-react with known allergens from other legumes, such as peanuts and soybean. The PMRA noted that the proteins (conglutins) in lupine seed that are responsible for allergic reactions in sensitive individuals were not present in Problad Plus Fungicide.

2.2 Public health standards

ADI & ARfD

Given the minimal exposure during short-term use and the expected lack of residues on crops there was no need for these health-based guideline values.

Poisons standard

On 19 November 2015, the Delegate of the Secretary of the Department of Health published a final scheduling decision to create a new entry for BLAD (banda de *Lupinus albus* doce) in Appendix B in the Poisons Standard. An implementation date of 1 February 2016 was notified for this decision.

3 RESIDUES ASSESSMENT

An assessment of the application for Problad Plus Fungicide was undertaken by the APVMA. BLAD which is derived from sweet lupines, has a mammalian non-toxic mode of action (ie specific to fungi glycoproteins and chitin formation) and has rapid bio-degradability to simple proteins which minimises exposure. The APVMA has determined that the proposed product Problad Plus Fungicide containing the new active constituent BLAD for use on stone fruit is unlikely to present an unsafe hazard via dietary exposure. Therefore, for the proposed use pattern, a Table 5 entry for BLAD is recommended. [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].

4 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

The active constituent, BLAD, is the naturally-occurring seed storage protein formed during the germination process in sweet lupins. It is characterised as a 20 kDa polypeptide sourced from the proteolysis of the seed protein which are considered a human food and livestock feed. BLAD has rapid bio-degradability to simple proteins and has a non-toxic (mammalian) mode of action. Based on the available information, it is not expected that there will be any undue prejudice to trade with other countries with regards to residues in exported food commodities.

5 WORK HEALTH AND SAFETY ASSESSMENT

5.1 Health hazards

Problad Plus Fungicide will be used on stone fruit. Application will be by spray equipment commonly used for making ground applications (ground boom, airblast, and handheld equipment). Spray concentrations will be achieved by mixing the aqueous soluble concentrate (SL) with water at 3.0 L/ha where spray volume is less than 1000 L/ha, or 300 mL/100L where spray volume equals or exceeds 1000 L/ha. This equates to 750 g a.i./ha or 75 g a.i./100 L.

Problad Plus Fungicide has an application interval of 7 to 14 days and a maximum of 5 applications per season. According to the draft label information Problad Plus Fungicide will be available in containers of 1–110L.

Exposure to workers mixing, loading, and applying Problad Plus Fungicide is expected to be short-term in duration and to occur primarily by the dermal and inhalation routes. Dermal absorption of BLAD polypeptide is not expected to be of concern due to the large size of the polypeptide molecules (MW > 500) and its low toxicity via the dermal route. The potential for occupational exposure of workers will be minimised and the subsequent risk considered acceptable, when workers observe the precautionary statements on the label.

Likely post-application activities for the proposed crop may include irrigation, scouting, thinning, weeding of immature plants, and pruning. Given the nature of the post-application activities typically performed (for example, scouting treated areas), dermal contact with treated surfaces is possible, as well as inhalation of dislodged material that has dried on the treated crops. While the degree of exposure will be related to the time of re-entry and the duration of the activities, the potential risk due to exposure resulting from post-application work is considered acceptable based on the proposed re-entry statement.

5.2 Exposure during use

This product is intended for professional use only.

Bystander exposure of members of the public is possible where access to a spraying operation is not restricted and/or through spray drift.

Given the properties of the compound and the use pattern, the risk to workers from repeated use of the product was considered to be negligible, as long as the label instructions for the acute toxicity hazard are followed (low via the oral, dermal, and inhalation routes of exposure, mildly irritating to the skin and eyes but not a dermal sensitiser).

5.3 Recommendations for safe use

Based on the risk assessment, Problad Plus Fungicide is supported for professional use; the following First Aid Instructions, Safety Directions and Re-entry Statement are considered appropriate:

First aid

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766. If in eyes wash out immediately with water. If skin contact occurs, remove contaminated clothing and wash skin thoroughly.

Safety directions

Harmful if swallowed. May irritate the eyes and skin. Avoid contact with eyes and skin. When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist, elbow-length rubber gloves and goggles. If product in eyes, wash it out immediately with water. Wash hands after use. After each day's use wash gloves, goggles and contaminated clothing.

Re-entry

Do not enter treated areas until spray has dried unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing). Clothing must be laundered after each day's use.

No warning statements or general safety precautions are indicated for Problad Plus Fungicide.

5.4 Conclusion

The approval of the new active constituent BLAD for agricultural use, and the registration of Problad Plus Fungicide for the suppression of Brown Rot and Blossom Blight in stonefruit, is supported. Problad Plus Fungicide 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 (SDS).

6 ENVIRONMENTAL ASSESSMENT

6.1 Introduction

CEV S.A. has applied to the Australian Pesticides and Veterinary Medicines Authority (APVMA) for registration of a new product, PROBLAD PLUS FUNGICIDE containing a new active constituent (ac) BLAD (250 g ac/L) for the control of fungal diseases in stonefruit. The maximum single application rate is 2250 g ac/ha based on a conservative assumption for water rates per hectare for stonefruit (3000 L/ha). The maximum number of seasonal applications using medium quality ground spray is 5 with an interval of 7 to 14 days (minimum 7 days interval between two consecutive applications). The applicant has provided environmental fate and effects studies for the product formulation and additional supportive documents. These were considered adequate to undertake an environmental risk assessment for the proposed use.

6.2 Environmental fate

Biodegradation

The ready biodegradability test on the proposed product demonstrates that BLAD is degradable in soil and in water based on the European Union (EU) scheme which allows for the use of half-lives of 30 and 15 days for soil and water, respectively. As a storage protein, BLAD contains an extremely high proportion of the nitrogen-rich amino acids which are readily decomposed into free amino acids and inorganic nitrogen by soil microbes and become a part of microbial protein or taken up by plants. Therefore, it was concluded that DT₅₀ values of 30 and 15 days in soil and water, respectively, for BLAD are considered appropriate.

Bioaccumulation

BLAD is a polypeptide protein with large molecular size and contains an extremely high proportion of nitrogen-rich amino acids which are likely to be protonated (N⁺) in water normally at pH 6 or below 7 due to its isoelectric point of 9.6. Consequently, the charged species is likely to be partitioned to the aqueous phase.

Lupin seeds containing BLAD are used to feed fish and lupin seed meal in trout diets at levels as high as 30% of dietary protein was demonstrated. It is likely that BLAD would behave like polypeptides such as peforelin which is broken down into the individual amino acids in the animal body. The amino acids produced enter the general metabolism of the treated animal and are excreted to the environment as urea and carbon dioxide which are commonly occurring animal waste products.

Given that BLAD is expected to partition to aqueous phase, is likely to be rapidly metabolised in animals and is readily degradable in water, there is little potential for BLAD to bioaccumulate.

6.3 Environmental effects

Aquatic organisms

The applicant provided effects studies on aquatic organisms (rainbow trout, *Daphnia magna* and green algae) for the proposed product. The product was moderately toxic to algae (E_rC_{50} 14 mg ac/L). BLAD was not toxic to fish or aquatic invertebrates at the limit doses tested.

No effects study on sediment dwelling organisms was provided for BLAD or the product although as BLAD is considered to be miscible in water and readily degradable in water it is therefore likely to have limited exposure to sediment dwellers. Due to the non-toxic acute effects to *Daphnia magna* as a surrogate for sediment dwellers and the limited sediment exposure, BLAD is unlikely to cause any adverse effects on sediment dwelling organisms.

Terrestrial organisms

Effects on birds and mammals

The product is not expected to be toxic to mammals based on an acute oral toxicity endpoint of $LD_{50} > 5000$ mg product/kg bw for rats. Given the fungicidal specific mode of action of BLAD and the expected rapid metabolism of BLAD in the animal body, it is unlikely that consumption of BLAD will pose a toxic effect to birds.

Effects on bees

The results of the product formulation effects on honeybees indicate that the product is not toxic to honeybees with contact and oral toxicity endpoints of $LD_{50} > 100$ µg ac/bee. No data were provided for reproduction/brood on bees; however, no adult mortality or other adverse effects were observed at the limit dose following oral or contact exposure (NOEL 100 µg ac/bee). Given that BLAD is a naturally occurring substance in a crop that is highly attractive to bees (lupins), risk to brood was considered to be acceptable.

Effects on non-target terrestrial arthropods

Tests using a representative formulation of the product indicate that the product is not expected to be harmful to beneficial insects under the proposed conditions of use. The LR_{50} values were greater than 10 500 mL product/ha (> 2625 g ac/ha) for predatory and parasitic arthropod indicator species.

Effects on earthworms and soil micro-organisms

The results of product formulation effects study on earthworms indicate that the product is not toxic to earthworms ($LC_{50} > 200$ mg ac/kg dry soil). No adverse effects were observed in short term nitrogen and carbon transformation in soil micro-organisms.

Effects on terrestrial plants

BLAD is not considered to be phytotoxic. Tests using a representative formulation of the product indicate the ER₂₅ values for six test species are all >2000 mL product/ha (>500 g ac/ha). Furthermore, no adverse impact on plants were observed in efficacy studies.

6.4 Risk assessment

In considering the submitted data, particular attention was given to the potential risk to aquatic and terrestrial organisms in the environment arising from the proposed product use. The assessment determined that risks to the environment are acceptable with no risk mitigation measures required.

6.5 Conclusions

The APVMA is satisfied that the proposed use of this product is unlikely to have an unintended effect that is harmful to animals, plants or things or the environment.

7 EFFICACY AND SAFETY ASSESSMENT

7.1 Proposed product use pattern

The proposed use of Problad Plus Fungicide is for the suppression of Brown rot and Blossom blight (*Monilinia spp.*) in Stonefruit, which includes Apricot, Cherry, Nectarine, Peach, Plum and Prune.

More details on the proposed use are provided in Section 1—Introduction. A copy of the proposed label is included in Section 9—Labelling Requirements.

7.2 Summary of evaluation of efficacy and crop safety

Efficacy

Fifteen Australian trials and one USA trial were conducted to evaluate Problad Plus Fungicide for the suppression of Brown rot and Blossom blight (*Monilinia spp.*) in stonefruit. All of the trials were conducted using randomised complete block trial design with adequate plot sizes and replication. Detailed assessments for disease control were undertaken and statistical analysis were undertaken using an analysis of variance (ANOVA).

Of the sixteen trials submitted to support efficacy and crop safety there were 2 trials in Apricots, 4 trials in cherries, 5 trials in nectarines, 2 trials in plums and 3 trial in peaches. Studies were conducted in South Australia, New South Wales, Queensland, Victoria and one trial in California (USA). Of the 16 trials four trials did not result in any disease development due to warm and dry field conditions. Whilst there were no recorded disease development in these trials, these trials were used to further support crop safety.

Whilst several of the trials proved unfavourable for disease development in the field, fruit and flower samples were collected in several such trials and were incubated in the laboratory to encourage disease development. In one such trial, Problad Plus Fungicide gave control of a low level of blossom blight infection and control was equal to that demonstrated by industry standards. A very high level of brown rot developed in incubated fruit and whilst Problad Plus Fungicide demonstrated a reduction in disease equivalent to industry standards this was not significant when compared to the untreated control.

Some of the field trials submitted in support of Problad Plus Fungicide demonstrated good control when compared to industry standards across a range of disease pressures. For example, one small plot field trial conducted in cherries for the control of brown rot demonstrated significant control when compared to the untreated control. Treatment at labelled rates reduced disease incidence to 4% in the Problad Plus Fungicide treatments (when compared to 15% in the untreated control), treatment also reduced disease severity to 1.5% in the Problad Plus Fungicide treatments (when compared to 5.5% in the untreated control). A second trial conducted in cherries for the control of blossom blight demonstrated significant control of a low level disease situation where the mean percentage of flowers infected with blossom blight was 6% in the untreated control and 0.8% in the Problad Plus Fungicide treatment plots. A third trial conducted in plums demonstrated significant control of blossom blight (27%) when compared to the untreated control (42%) and was considered equivalent to the commercial standards (25.8% and 25.1%).

Some of the trials indicate variable efficacy when Problad Plus Fungicide is used under high infection pressure ranging from suppression to control equivalent to industry standards. The trial results are consistent with the proposed label which identifies that suppression rather than control may be observed especially under conditions of high or extreme infection pressure. Label claims advise the user to apply Problad Plus Fungicide prior to disease infection once conditions favour disease development. Users are also advised to reduce the spray interval when weather conditions favour disease development, such as following rainfall events and during high humidity.

Crop safety

All trial plots were inspected for symptoms of phytotoxicity on leaves and on fruit.

In all of the trial data, Problad Plus Fungicide demonstrated excellent crop safety when applied on different stone fruit crops (apricots, cherries, nectarines, peaches and plums). Problad Plus Fungicide was applied to different crop varieties and at different growth stages, in different geographical areas and soil conditions, at rates of up to twice the maximum label rate. There was no evidence of phytotoxicity from the use of the product to leaves, flowers or fruit in any treatment.

Integrated disease management

Problad Plus Fungicide is intended for use in integrated disease management systems. Users are advised to consult local agricultural advisors for specific IDM strategies meeting the specific crop and locations.

Resistance management

Problad Plus Fungicide contains the active constituent BLAD, which has been classified by the Fungicide Resistance Action Committee as FRAC Group BM 01 which is defined as having a multi-site mode of action.

BLAD strongly binds to chitin, a major component of fungal cell wall, inhibiting any fungal growth. It also degrades chitin by catalysing and successfully removing the N-acetyl-D-glucosamine terminal chitin monomers, resulting in the destruction of the fungal cells. For resistance management purposes, do not make more than five foliar applications of Problad Plus Fungicide per crop per season. Do not make more than two sequential applications of Problad Plus Fungicide before alternating to a labelled fungicide with a different mode of action.

7.3 Conclusions

Trial data support that Problad Plus Fungicide will provide acceptable suppression of Blossom blight and Brown rot (*Monilinia spp.*) in stonefruit when used as directed.

Acceptable crop safety is expected when the product is used as directed. The directions for use are appropriate and consistent with fungicide use in commercial agriculture in Australia.

The application for registration of Problad Plus Fungicide is supported on efficacy and crop safety grounds when used in accordance with label directions.

8 LABELLING REQUIREMENTS

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

PROBLAD PLUS Fungicide

ACTIVE INGREDIENT: 250g/L BLAD*

*BLAD is the naturally occurring seed storage protein in germinated sweet lupins; 20 kDa polypeptide of β -conglutin, or fragment of the amino acid sequence of β -conglutin.

GROUP	BM 01	FUNGICIDE
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For the suppression of Brown rot and Blossom blight in Stonefruit as per the directions for use table

IMPORTANT: READ THE ATTACHED LEAFLET BEFORE USE

CONTENTS: 1 - 110 Litres



Manufacturer:
CEV, SA
Parque Tecnológico de Cantanhede
Lote 120
3060-197 Cantanhede
Portugal



Australian distributor:
FMC Crop Protection Pty Ltd
5 Palmer Place
Murarrie QLD 4172
Phone: 1800 901 939

APVMA Approval No. 70334/63200

STORAGE AND DISPOSAL

Keep out of reach of children. Store in the closed, original container in a well ventilated area, as cool as possible. Do not store for prolonged periods in direct sunlight.

Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging for appropriate disposal 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. DO NOT use empty container for any other purpose.

Spillage - In case of spillage, confine and absorb spilled product with absorbent material such as sand, clay or cat litter. Dispose of waste as indicated in the Storage and Disposal section or according to Australian Standard 2507 - Storage and Handling of Pesticides. Do NOT allow spilled product to enter sewers, drains, creeks or any other waterways.

SAFETY DIRECTIONS

Harmful if swallowed. May irritate the eyes and skin. Avoid contact with eyes and skin. When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist, elbow-length rubber gloves and goggles. If product in eyes, wash it out immediately with water. Wash hands after use. After each day's use, wash gloves, goggles and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766. If in eyes wash out immediately with water. If skin contact occurs, remove contaminated clothing and wash skin thoroughly.

SAFETY DATA SHEET

Additional information is listed in the Safety Data Sheet. Copies of the SDS can be found at www.fmccrop.com or call FMC Customer Service on: 1800 901 939

WARRANTY

FMC makes no warranty expressed or implied, concerning the use of this product other than that indicated on the label. Except as so warranted the product is sold as is. Buyer and user assume all risk of use and/or handling and/or storage of this material when such use and/or handling and/or storage is contrary to label instructions.

In a Transport Emergency Dial 000 Police or Fire Brigade	SPECIALIST ADVICE IN EMERGENCY ONLY 1800 033 498 ALL HOURS – AUSTRALIA WIDE
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APVMA Approval No: 70334/63200

BN:

DOM:

DIRECTIONS FOR USE**RESTRAINTS:**

DO NOT apply by aircraft.
 DO NOT apply if rain is expected within 4 hours.
 DO NOT apply when slow drying conditions prevail.
 DO NOT apply to wet crops.

DO NOT make more than 5 applications to any crop in any one season.

DO NOT make more than two sequential applications of PROBLAD PLUS Fungicide before alternating to a labelled fungicide with a different mode of action.

CROPS	DISEASE	RATE	CRITICAL COMMENTS
Stonefruit (including; Apricot Cherry Nectarine Peach Plum Prune)	Brown rot, Blossom blight (<i>Monilinia spp.</i>) Suppression	3.0 L / ha where spray volume is less than 1000 L/ha <u>Or</u> 300 mL / 100 L water where spray volume equals or exceeds 1000 L/ha	GENERAL: Apply PROBLAD PLUS Fungicide in a minimum spray volume of 465 L per hectare. Apply at 7–14 day intervals depending on conditions that may favour disease development. Reduce the application interval for varieties that are highly susceptible to the indicated diseases or when severe disease conditions exist. The use of ground application after petal fall is preferred because of difficulty in penetrating the canopy and obtaining thorough coverage of the foliage and fruit. For suppression of brown rot and blossom blight, begin application at pink, white or red bud depending on the crop. Make a second application at full bloom and if conditions remain favourable for disease, make another application at petal fall. For brown rot on fruit a second set of treatments should be applied at least a month before harvest

WITHHOLDING PERIOD

HARVEST: NOT REQUIRED WHEN USED AS DIRECTED

WARNING

DO NOT apply during surface temperature inversion conditions at the application site. Except when applying with orchard airblast equipment, DO NOT apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the BCPC Guideline.
 DO NOT direct the spray above trees during airblast applications. TURN OFF outward pointing nozzles at row ends and outer rows during airblast applications.

RAINFEST PERIOD

PROBLAD PLUS Fungicide requires two to four hours drying time on plant foliage for the active ingredient to fix into the plant tissue before rain or irrigation occurs. If, during the next 12 hours it rains significantly, a new application will be needed as soon as possible during the next 4 days.

UNDER HIGH OR EXTREME INFECTION PRESSURE

Efficacy may be compromised under high or extreme infection pressure. Treatment should be made prior to disease infection once conditions favour disease development, and continue until the threat of disease passes. Repeated applications may be required to protect new growth. Reduce the spray interval when weather conditions favour disease development, such as following rainfall events and during high humidity.

APPLICATION INSTRUCTIONS

Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient product to cover the crop to the point of run-off or under dosing will occur and disease control may be inadequate. Avoid excessive run-off.

GENERAL INSTRUCTIONS

PROBLAD PLUS Fungicide is a broad spectrum, contact, preventive fungicide formulated as an aqueous concentrate containing 250 grams active ingredient per litre. PROBLAD PLUS Fungicide is used for the suppression of Brown rot and Blossom blight. Apply as a foliar spray alone, in alternating fungicide spray programs. Applications should be made once conditions favouring disease development exist and prior to any sign of disease.

Preparation of the Spray Solution: Ensure the spray tank is clean and free of residues from previous spray treatments. Fill the spray tank $\frac{3}{4}$ full with clean water. Shake the container and pour the required amount of PROBLAD PLUS Fungicide into the sprayer tank while the tank agitation system is operating. Add specified amount of PROBLAD PLUS Fungicide while filling with the appropriate amount of water into the spray tank. Maintain agitation. Do not store the mixture overnight.

Spray Volume: Apply PROBLAD PLUS Fungicide in a minimum 465L of spray solution per hectare through appropriate ground equipment. Ensure the minimum amount of product per hectare is used. Increase spray volume as crop growth increases to ensure thorough coverage of the foliage and fruit. Check equipment calibration frequently. Complete coverage and uniform application are essential for the most effective results, especially when lower spray volumes are applied.

Pre-Harvest Interval: PROBLAD PLUS Fungicide can be applied up to and during the day of harvest.

Re-Entry Interval: Do not enter treated areas until spray has dried unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing). Clothing must be laundered after each day's use.

Integrated Disease Management (IDM): Integrate PROBLAD PLUS Fungicide into a disease management strategy that follows practices known to reduce disease development and prevent fungicide resistance. Consult local agricultural advisors for specific IDM strategies meeting the specific crop and location. PROBLAD PLUS is a contact fungicide with penetration properties. For resistance management purposes:

- Do not make more than five foliar applications of PROBLAD PLUS per crop season.
- Do not make more than two sequential applications of PROBLAD PLUS before alternating to a labelled fungicide with a different mode of action.

COMPATIBILITY

DO NOT tank mix with products containing a prohibition against tank mixing. PROBLAD PLUS Fungicide may be mixed with foliar fertilizers, provided that the fertilizer is added after PROBLAD PLUS Fungicide has been diluted to the recommended field application. Follow the most restrictive labeling requirements of any tank mix product. To determine the physical compatibility of PROBLAD PLUS Fungicide with other products use a jar test. The following procedure should be followed: Pour the specified proportions of the products into a suitable container of one quart of water; mix thoroughly and allow to stand for at least 15 minutes. If the combination remains mixed or can be re-mixed readily, the mixture is considered a homogeneous solution and physically compatible. If separation occurs (eg oils float to top, clumps of solids form, etc.), the combination is incompatible and cannot be used. For further information, contact your local FMC representative.

FUNGICIDE RESISTENCE WARNING

GROUP	BM 01	FUNGICIDE
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PROBLAD PLUS Fungicide is a member of the polypeptide (from plant extract) group of fungicides. For fungicide resistance management, the product is a Group BM 01 fungicide. Some naturally occurring individual fungi resistant to the product and other Group BM 01 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi will not be controlled by this product or other Group BM 01 fungicides, thus resulting in a reduction in efficacy and possible yield loss. Since the occurrence of resistant fungi is difficult to detect prior to use, CEV S.A. accepts no liability for any losses that may result from the failure of this product to control resistant fungi.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

DO NOT contaminate wetlands or watercourses with this product or used containers.

STORAGE AND DISPOSAL

Keep out of reach of children. Store in the closed, original container in a well ventilated area, as cool as possible. Do not store for prolonged periods in direct sunlight.

Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging for appropriate disposal 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. DO NOT use empty container for any other purpose.

Spillage - In case of spillage, confine and absorb spilled product with absorbent material such as sand, clay or cat litter. Dispose of waste as indicated in the Storage and Disposal section or according to Australian Standard 2507 - Storage and Handling of Pesticides. Do NOT allow spilled product to enter sewers, drains, creeks or any other waterways.

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In a Transport Emergency Dial 000 Police or Fire Brigade	SPECIALIST ADVICE IN EMERGENCY ONLY 1800 033 498 ALL HOURS – AUSTRALIA WIDE
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APVMA Approval No: 70334/63200

BN:

DOM:

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
bw	bodyweight
°C	Degrees Celsius
CAS	Chemistry Abstracts Service
d	day
Da	Dalton
DAT	Days After Treatment
DT ₅₀	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
EC ₅₀	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
ER ₂₅	Effective residue concentration to 25% of test organisms
E _r C ₅₀	concentration at which the rate of growth of 50% of the test population is impacted
EUP	End Use Product
FRAC	Fungicides Resistance Action Committee
F ₀	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour

ha	hectare
HDPE	High Density Polyethylene
id	intra-dermal
im	intra-muscular
ip	intra-peritoneal
IPM	Integrated Pest Management
kDa	Kilodalton
kg	kilogram
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
LR ₅₀	Application rate that kills 50% of the test population of organisms
mg	milligram
mL	millilitre
mN	millinewtons
MoA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limit
ND	Not Detectable
ng	nanogram
NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OECD	Organisation of Economic Cooperation and Development
OM	Organic Matter
PMRA	Pest Management Regulatory Agency (Canada)
Pa	Pascals
po	oral

ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
s	second
sc	subcutaneous
SDS	Safety Data Sheet
SL	Soluble Concentrate
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
µg	microgram
US EPA	United States Environmental Protection Authority
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
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
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

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