

Zorvec™ active

Technical Bulletin





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Zorvec™ active

A new, highly effective fungicide with a favorable environmental profile.

Zorvec is not registered for sale or use in any country. No offer for sale or use of this product is permitted prior to the issuance of the required country level registrations.



Overview

Zorvec™ active is the first member of a novel class of fungicides to control diseases caused by oomycete pathogens.

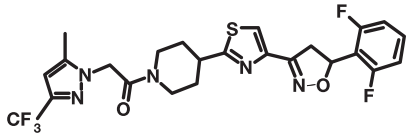
Zorvec affects a novel target site with a completely new biochemical mode of action and has no cross-resistance with existing fungicides. It produces multiple effects on the pathogen's life cycle (preventative, curative, eradicator and antispore) for better efficacy, efficiency and length of control. Zorvec protects treated leaves as they grow and expand, including leaves that are less than 20% final size at the time of application. Studies in potato and certain vegetable crops have also demonstrated that Zorvec protects new leaves as they emerge and grow.*

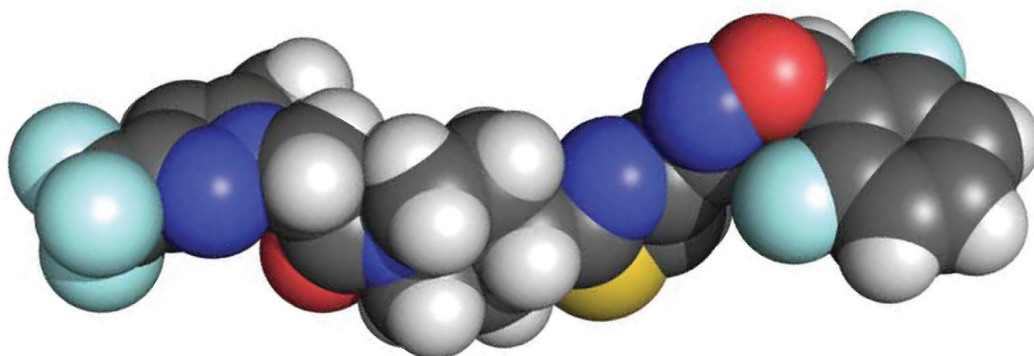
Zorvec features a favorable environmental profile, being effective on target organisms at very low use rates and having very low toxicity to non-target organisms. Mammalian oral, neurological, developmental and dermal toxicity is low, as is avian and bee toxicity. When assessed on these and other criteria, Zorvec represents a highly effective oomycete disease control technology.

* Source: DuPont Stine-Haskell Research Center - Delaware, USA 2014



Description of Chemistry

Common name	Oxathiapiprolin
Code Names Tested	DPX-QGU42
Chemical Name (IUPAC)	1-(4-{4-[(5RS)-5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}-1-piperidyl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanone
CAS-Number	1003318-67-9
Chemical Structure	
Chemical Family	Piperidiny thiazole isoxazolines
Empirical Formula	C ₂₄ H ₂₂ F ₅ N ₅ O ₂ S
Molecular Weight	539.53
Biological action	Fungicide
Mode of action	Lipid homeostasis disruption via inhibition of an oxysterol-binding protein (OSBP)
Resistance group (FRAC)	#49 (F9): oxysterol-binding protein homologue inhibition (OSBPI)
Plant translocation	Contact/residual and some plant mobility (translaminar and via xylem) providing protection of new growth
Disease spectrum	Diseases caused by oomycete pathogens



Source: DuPont Stine-Haskell Research Center - Delaware, USA, 2009-2013

Disease control spectrum

Crop	Disease caused by	Common name
Potato	<i>Phytophthora infestans</i>	Late blight
Grape	<i>Plasmopara viticola</i>	Downy mildew
Cucurbits	<i>Pseudoperonospora cubensis</i> <i>Phytophthora capsici</i>	Downy mildew Phytophthora crown rot
Tomato and related crops	<i>Phytophthora infestans</i>	Late blight
Peppers	<i>Phytophthora capsici</i>	Phytophthora crown rot
Tobacco	<i>Phytophthora nicotianae</i>	Tobacco black shank
Leafy vegetables	<i>Bremia lactucae</i> <i>Peronospora</i> spp	Downy mildew
Bulb vegetables	<i>Peronospora destructor</i>	Downy mildew
Other vegetables	<i>Phytophthora</i> species <i>Peronospora</i> species	Various blights, rots and downy mildews



Favorable toxicological profile

Acute Toxicity Studies – no acute toxicity observed

Acute Oral Rat $LD_{50} > 5000$ mg/kg
Acute Dermal Rat $LD_{50} > 5000$ mg/kg
Acute Inhalation Rat $LD_{50} > 5.1$ mg/kg
Not an irritant to the eyes or skin of rabbits
Dermal sensitization – Non-sensitizing in guinea pigs

Genetic Toxicity Studies

Not mutagenic in a battery of tests

Developmental Toxicity Studies

No developmental toxicity observed in rats or rabbits

Reproductive Toxicity Studies in Rats

No effects on reproduction
Slight delays in maturation at high doses
Decreases in body weight at extremely high doses

Neurotoxicity Studies

Acute Rat (oral gavage): no neurotoxicity observed
Repeated Dose Rat (diet): no neurotoxicity observed

Immunotoxicity Study

No immunotoxicity observed in mice

Repeated Dose Toxicity Studies

No adverse effects in rats, mice and dogs

Carcinogenicity Studies

Not carcinogenic in rats or mice

Physical Properties

Water solubility (distilled)	0.175 mg/L
Log Kow	3.67
Kfoc	8368 g/kg
Vapor pressure (20°C)	1.14×10^{-6} PA
Hydrolysis	Stable
Aqueous photolysis	$DT_{50} \sim 15$ days
Degradation in soil	$DT_{50} \sim 90$ days

Aquatic Toxicity

Exposure limited by solubility $LD_{50} >$ highest dose

Avian Toxicity

Acute Oral	$LD_{50} > 2250$ mg/kg bw
Acute Dietary	$LD_{50} > 1280$ mg/kg bw
Reproduction	NOAEC > 1200 mg/kg bw

Bee Toxicity

Oral	LD_{50} 48hr ~ 40 µg/bee
Contact	LD_{50} 48hr ~ 100 µg/bee

Non-target arthropods

48hr ER_{50} & $LR_{50} >$
highest rate tested

Earthworms

LC_{50} , 28d; EC_{50} , 28d
growth/biomass;
56d repro > 1000 mg
ai/kg soil

Mode of action/activity

Zorvec™ active

Studies show novel target site, new mode of action and diverse movement properties deliver effective disease control with no cross-resistance and a favorable environmental profile.

New chemistry, multiple advantages

- Novel target site, completely new biochemical mode of action
- Target: Oxysterol-binding protein (OSBP)
- Target function: Oxysterol-binding proteins are implicated in the movement of lipids between membranes, among other processes. Inhibiting OSBP may disrupt other processes in the fungal cell, such as signaling, maintaining cell membranes, and the formation of more complex lipids that are essential for the cell to survive
- No cross-resistance with existing fungicides
- Zorvec binds in the Oxysterol-binding protein (OSBP) domain
- FRAC #49 (group F9): OSBP homologue inhibition (OSBPI)

Improved effectiveness, favorable environmental profile

- Oomycete-specific OSBP domain
- Highly effective against *Phytophthora* and downy mildews at low rates for reduced environmental load
- Very low toxicity to non-target organisms

Multiple effects

Zorvec produces multiple effects on the pathogen's life cycle, providing unmatched consistency and control for a healthier crop.

Preventative*: inhibits zoospore and sporangia germination.

Curative: stops mycelial growth in the host plant before visible symptoms occur, providing up to three days' protection.

Eradicant Activity: stops mycelial growth; inhibits further lesion growth.

Antisporulant: inhibits spore production

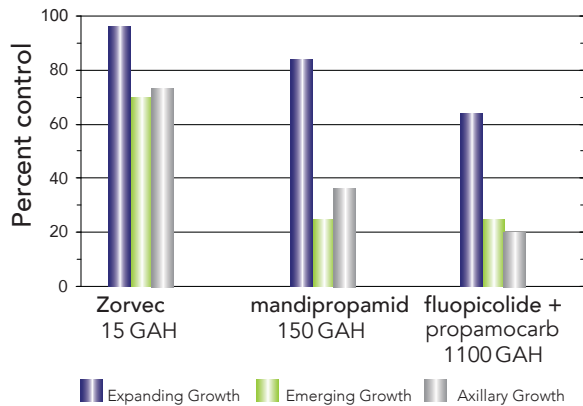
* Zorvec will be recommended in a preventative manner.

Protects new plant growth

Studies on potatoes and various vegetable crops have shown that Zorvec™ active protects plants in three distinct ways:

- protects new plant growth for better crop establishment
- protects treated leaves as they grow and expand with no spread of disease
- protects new leaves as they emerge and grow

Protection of expanding and emerging potato growth ten (10) days after a preventative treatment



Expanding growth refers to leaves that were 30-50% of final size at time of application

Emerging growth refers to leaves that were only 5-25% of final size at time of application

Axillary growth refers to new leaves emerging from stem axils NOT present at application

Excellent control on expanding and emerging new growth following Zorvec at 15 gai/ha. Superior protection of new growth compared with mandipropamid at 150 gai/ha and fluopicolide + propamocarb at 1100 gai/ha.



During treatment

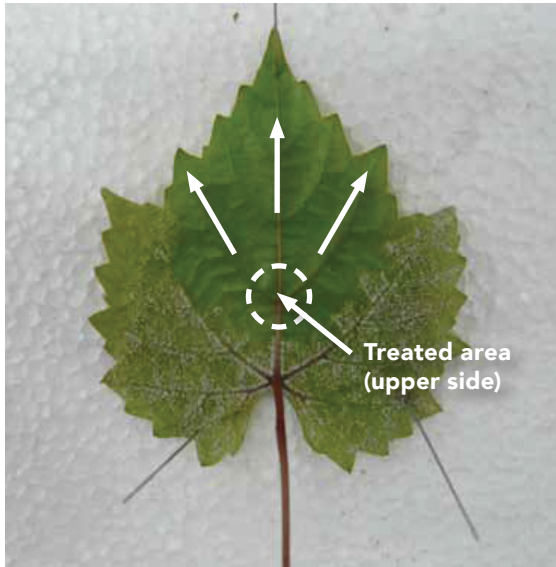
(expanding and emerging growth above tagged leaf)



10 days after treatment

(fully expanded leaves above tagged leaf)

Systemic movement



Zorvec™ active

Upper side of leaf treated
Underside of leaf inoculated



Untreated

Source: DuPont European Research and Development Center, France, 2012

Consider the impact of Zorvec as it relates to these treated and untreated leaves. For the treated leaf, the upper side was treated while the underside was inoculated with the pathogen and rated. As these photos show, the translaminar movement of Zorvec protects the underside of the plant. Its translaminar and xylem systemic movement enables uniform coverage of sprayed foliage and protection from wash-off by rain.

Notes

- Both photos are from the bottom side of the leaf
- Zorvec is only applied to the upper leaf surface, within the circled area
- Translaminar – movement is from the upper leaf surface to the lower
- Acropetal (indicated by arrows) – movement in xylem tissue out to the leaf tip
- Systemic movement in xylem tissue gives complete protection outward to the leaf tip
- No movement in the phloem, thus the presence of disease below the treated area

Grape - Europe

Zorvec™ active: Key Product Attributes and Features versus Competitive Products at Commercial Rates

Active Ingredient	Rainfastness	Multiple Effects on the Pathogen's Life Cycle		Translaminar activity	Systemic
		Preventative	Curative		
Zorvec	+++	+++	++	+++	++
fluopicolide + foseetyl-Al	NT	++	—	+	+
mandipropamid + folpet	NT	+	++	++	+
cyazofamid + disodium phosphonate	NT	++	++	—	—

+++ Excellent ++ Good + Moderate — Poor NT: not tested at this time

Source: DuPont European Research and Development Center, France, 2012

Potato

Zorvec: Key Product Attributes and Features versus Competitive Products at Commercial Rates

Fungicide	Rainfastness	Multiple Effects on the Pathogen's Life Cycle			Stem blight	Systemic
		Preventative	Curative	Anti-Sporulant		
Zorvec	+++	+++	++	+++	+++	++
fluopicolide + propamocarb	++*	+++	++	++	++	+
mandipropamid	+++	+++	—	++	++	—
cyazofamid	+++*	+++	—	—	+	—
cymoxanil + mancozeb	++*	++	++	+	+++*	+
benthiavalicarb + mancozeb	++*	+++	—	+*	+*	NT

+++ Excellent ++ Good + Moderate — Poor NT: not tested at this time

Source: DuPont European Research and Development Center, France, and Stine-Haskell Research Center - USA, 2012-2014 and Euroblight fungicide comparison, 2012. Euroblight rating indicated by *.

Ratings based on both internal data comparisons and Euroblight rating for registered actives.

Key Features

Controlled wash-off studies have demonstrated that Zorvec™ active is protected from wash-off just 20 minutes after application.

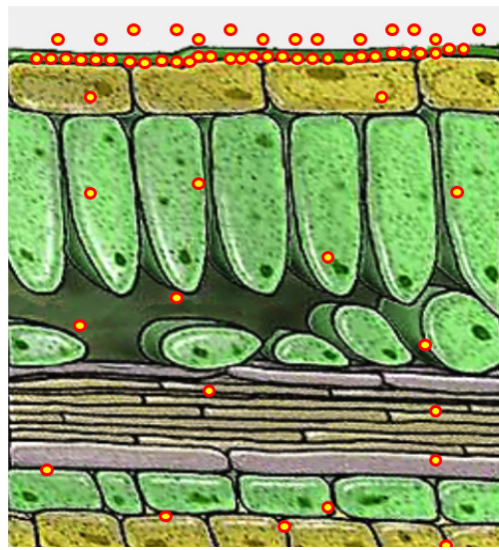


Rainfastness

Rainfastness is related to how quickly an active moves into the plant. Zorvec™ active moves quickly into the waxy epicuticular layer of plant tissue, making it extremely resistant to wash-off. In fact, controlled wash-off studies have demonstrated that Zorvec is protected from wash-off just 20 minutes after application.



Rainfastness is related to how quickly an active moves into plant tissue



Leaf cross section

Location of Zorvec 1 hour after application

12-15% on the leaf surface



Up to 80% associated with the waxy cuticle

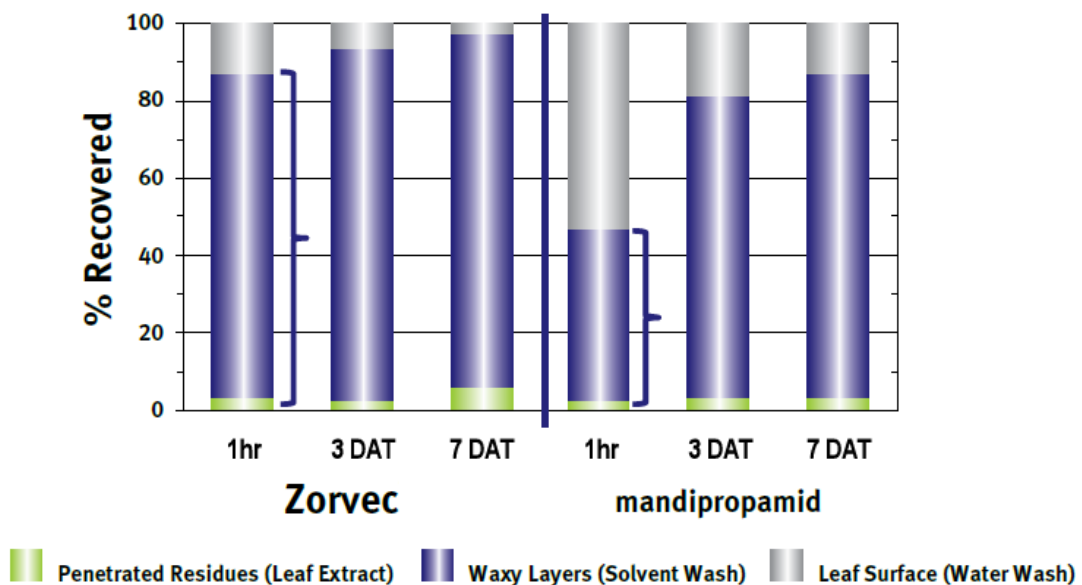


3-5% associated with the intercellular layers



Source: DuPont Stine-Haskell Research Center, USA, 2013

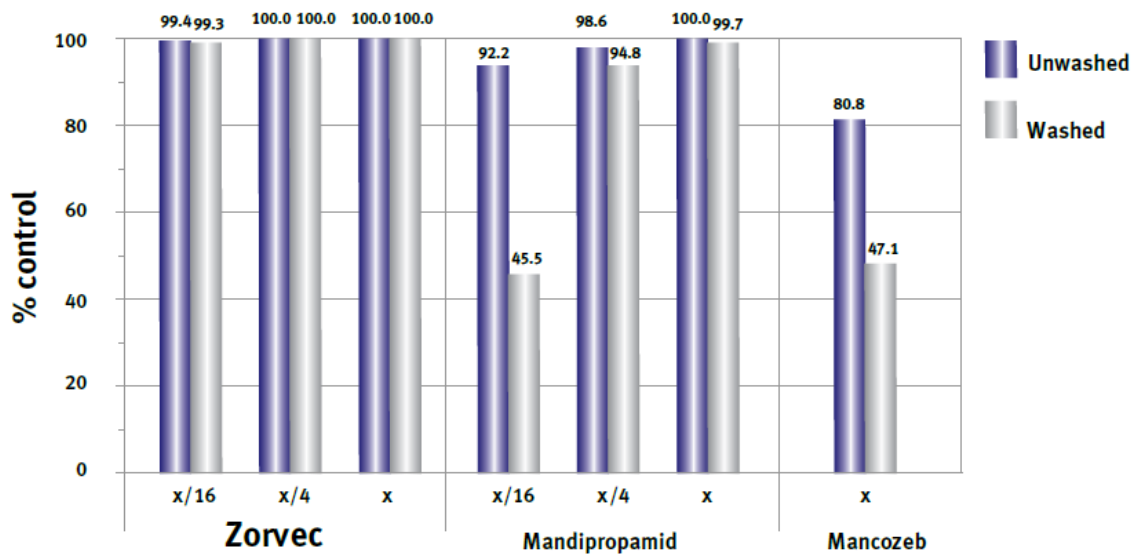
Leaf partitioning following a preventative application



Rainfastness at low rate

Zorvec™ active is effective against target diseases at low rates. Even at the low rate of 5 gai/ha, Zorvec exhibits significant rainfastness compared to competitive products. In fact, research shows that competitive fungicides' control drops off rapidly in the face of rain, even when applied at much higher rates. The rainfastness of Zorvec also mitigates the shadow effect caused by overlapping leaves, for more consistent control throughout the crop canopy.

Rainfastness of Zorvec on potato versus mandipropamid and mancozeb
(mean of two tests, % infection in untreated > 99%)



x = Commercial rate or dose rate for registration

Source: European Research Development Centre, France - 2013

Consistently robust disease control at low use rates

When plants treated with Zorvec™ active at various rates are compared with untreated plants and with the performance of competitive products, Zorvec exhibits a consistently higher level of disease control.

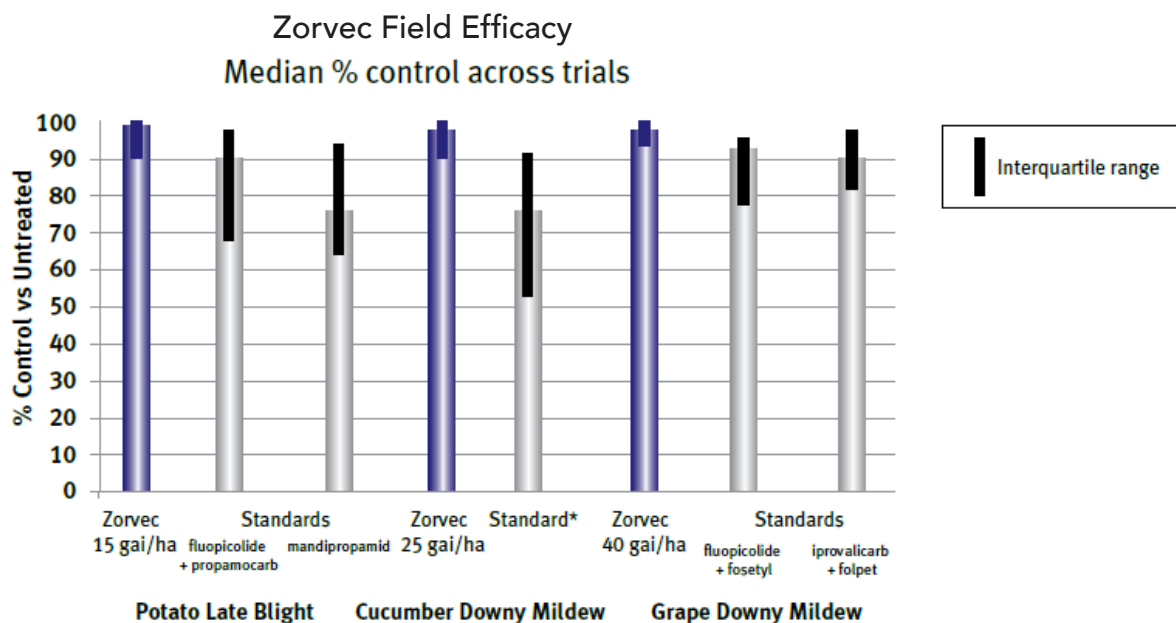
Intrinsic activity against *Phytophthora infestans*

Highly active
 Active
 Inactive

In vitro test type	Zorvec EC50 , ppm	Cyazofamid EC50 , ppm	mandipropamid EC50 , ppm
Zoospore germination	<input checked="" type="checkbox"/> < 0.00001	<input type="checkbox"/> 0.00002	<input checked="" type="checkbox"/> < 0.00001
Sporangia direct germination	<input checked="" type="checkbox"/> < 0.00001	<input type="checkbox"/> 0.0002	<input checked="" type="checkbox"/> > 0.1
Mycelial growth	<input checked="" type="checkbox"/> 0.0002	<input type="checkbox"/> 0.004	<input checked="" type="checkbox"/> > 0.1
Zoospore release	<input checked="" type="checkbox"/> < 0.01	<input type="checkbox"/> 0.03	<input checked="" type="checkbox"/> > 1.0

EC50 = concentration needed to inhibit 50% of the population
 X Inactive at concentrations used in these studies

Based on laboratory studies with *Phytophthora infestans*. Effect on zoospore release varies between species. Source: DuPont Stine-Haskell Research Center, USA, 2011- 2012



Source: DuPont sponsored trials in various countries, 2008 - 2012
 * Commercial standards varied between regions.

Summary

Zorvec™ active helps protect treated leaves as they grow and expand, so that disease does not spread, and protects new leaves as they emerge and grow. Studies show that rainfastness occurs just 20 minutes after application. Systemic movement from treated areas reaches the underside of the plant and protects new growth.

Zorvec delivers unparalleled disease control effectiveness. By expressing multiple effects on the pathogen, it provides favorable and more diverse plant protection. The product is rainfast, provides excellent disease control at low rates, has no cross-resistance to other products and offers a favorable environmental profile.

For these reasons, Zorvec is a crop protection technology with the potential to provide many benefits to growers, including lower operational costs and overall improved farm management efficiency.



Potato Late Blight (*Phytophthora infestans*)



Zorvec™ active

Cyazofamid

Source - Internal DuPont trials in the United Kingdom - 2010

Cucurbit Downy Mildew (*Pseudoperonospora cubensis*)



Farmer practice

4 applications: 1 - Dimethomorph, 2 - Dimethomorph + Azoxystrobin, 3 - Fluopicolide + propamocarb + Chlorothalonil, 4 - Cyazofamid + Metalaxyl



Zorvec

Two applications of Zorvec + mancozeb

Source: Jinan, Shandong, China - 2014

Grape Downy Mildew
(*Plasmopara viticola*)



Untreated control



Zorvec™ active

Source: Internal DuPont Trials - France - 2012

Cucurbit Downy Mildew
(*Pseudoperonospora cubensis*)



Untreated control



Zorvec

Source: Internal DuPont Trials - China - 2012

Continuous Innovation

Reliable resistance management with Zorvec™ active.

The risk of resistance development with the use of fungicides is generally known. The unparalleled efficacy, efficiency and length of control means that Zorvec will become the cornerstone of growers' control programs and therefore needs to be used responsibly.

Corteva Agriscience will integrate clear strategies of stewardship in launching Zorvec branded products to minimize the risk of resistance development.

Reduced risk status

Oxathiapiprolin has been granted reduced risk status by US/EPA for all of the food uses which were proposed.

Consistency and control

Zorvec provides an unmatched combination of consistency and control that can be used every season to help growers achieve a better crop, even under challenging environmental conditions.

Most innovative chemistry and formulation

In 2012, Zorvec (piperidinyl thiazole isoxazoline) was recognized with the global Agrow Award for most innovative chemistry.

The Zorvec chemistry received yet another Agrow Award in 2014, this time for best formulation innovation.

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