Adavelt™ active

Technical Bulletin

CORTEVA™
agriscience

Finding Freedom To Grow Through Innovation

Dedication to farming is a life-long commitment to innovation. Through building deep knowledge and experience, farmers have forged a legacy of innovation that ensures the world's essential needs are met, generation after generation.

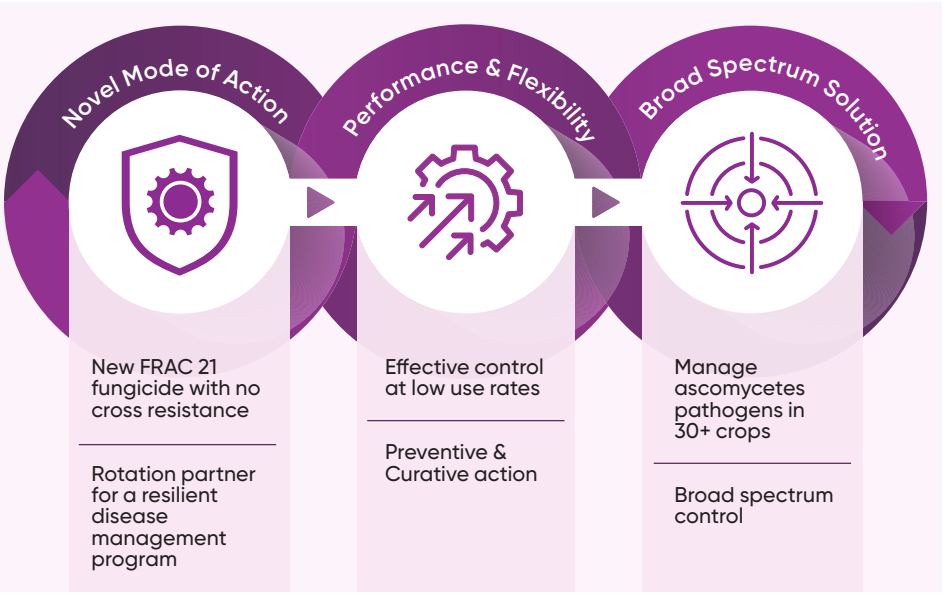
Inspired by that commitment, we seek to build together agricultural solutions that propel growth on the farm and in our communities. Innovation also provides the opportunity to create renewed strategies that meet emerging challenges and save precious time.

On every farm, ensuring exceptional yield and harvest quality is the goal of a complete disease management program. When tenacious plant pathogens are a barrier to successfully harvests, *breakthrough innovations* help achieve the greatest protection.

Corteva Agriscience introduces Adavelt™ active, a naturally inspired solution for managing challenging ascomycetes pathogens worldwide. Through a novel mode-of-action, Adavelt active delivers a new foundational tool for fungicide programs that focus on optimizing productivity while providing flexibility.

Key Features of Adavelt™ Active

- Broad spectrum of activity against difficult-to-control diseases in a wide range of crops
- Novel target site in many crops with no cross-resistance to other modes of action for Ascomycete pathogens
- A core solution that replaces products losing efficacy or under phaseout
- Outstanding performance with unsurpassed protectant efficacy
- Maintains maximum crop health where conditions favor high disease pressure
- Offers outstanding disease management to protect & enhance harvest yield and quality
- Translaminar movement provides uniform protection
- Innovative resistance management tool that fits into Integrated Pest Management programs
- Flexible tool that gives growers more time to manage their disease control programs throughout the growing season and across multiple growth stages
- Highly compatible in tank mixtures to enable customized programs and applications
- Excellent crop safety and high efficacy at lower use rates
- Favorable toxicology and environmental profile – low impact on beneficial organisms



Adavelt™ active is the first-ever picolinamide fungicide that offers a novel solution for managing key diseases over a wide range of crops. The unique structure of Adavelt enables picolinamide activity across a broad spectrum of diseases, including Septoria, Powdery Mildews, Botrytis, Anthracnose, Alternaria, Monilinia and more.

Adavelt builds upon a family of chemistry first established by Corteva Agriscience with the discovery of Inatreq™ active for use in cereal crops and banana. In seeking broader utility for farmers adopting picolinamide solutions, a breakthrough design was created in the structure of Adavelt. The result is a major expansion of value for farms producing fruits and vegetables, tree nuts, oilseed and field row crops, turf and ornamentals and more.

Adavelt delivers as a market-leading protectant and curative solution, and provides a critical new tool to manage fungicide resistance. Adavelt products will also offer growers a flexible solution for managing diseases throughout the season, and will be offered as a straight formulation and in pre-mixes to further enable custom programs.

Farmers inspire us to innovate with purpose. We share this journey and explore together the features of a breakthrough solution designed to meet growers' needs – the freedom to grow.

Navigating Together

Dedication to the land and producing crops that help our communities thrive is a personal commitment lived one season at a time. Every farm and every season is unique – and the careful selection of each input contributes to success come harvesttime. To navigate the complexity of the farm landscape introduced by plant disease, we focused our teams to find a solution for tough ascomycetes pathogens that can undermine well-designed crop management plans. To succeed together, we need more flexible tools that simplify crop management and support stewardship of the land. Through a 20-year journey dedicated to unlocking the value of naturally inspired fungicides for farms across the world, we embraced the importance of stewardship to preserve innovative tools.

To reduce the likelihood of fungicide resistance and to mitigate the effects of emerging or established resistance across the fungicide tool-box, the family of Adavelt™ active products offers a welcomed cornerstone upon which disease management programs can be strengthened. For production systems that have relied on the same program for multiple seasons, introducing alternative mode-of-action products within a rotation and/or mixture strategy can increase resiliency of the overall program. This is achieved through preserving the efficacy of each product which is carefully selected as part of the farm's tailored program.

Preserving an Innovative Tool

Adavelt™ active must be **integrated into a robust spray program with other modes of action** providing effective control of the target disease

In order to manage resistance risk, Adavelt should be **used under protectant conditions** (preventive application)

Use Adavelt as **part of an Integrated Pest Management (IPM) strategy** incorporating other methods of control

Always follow product **specific label recommendations** for resistance management

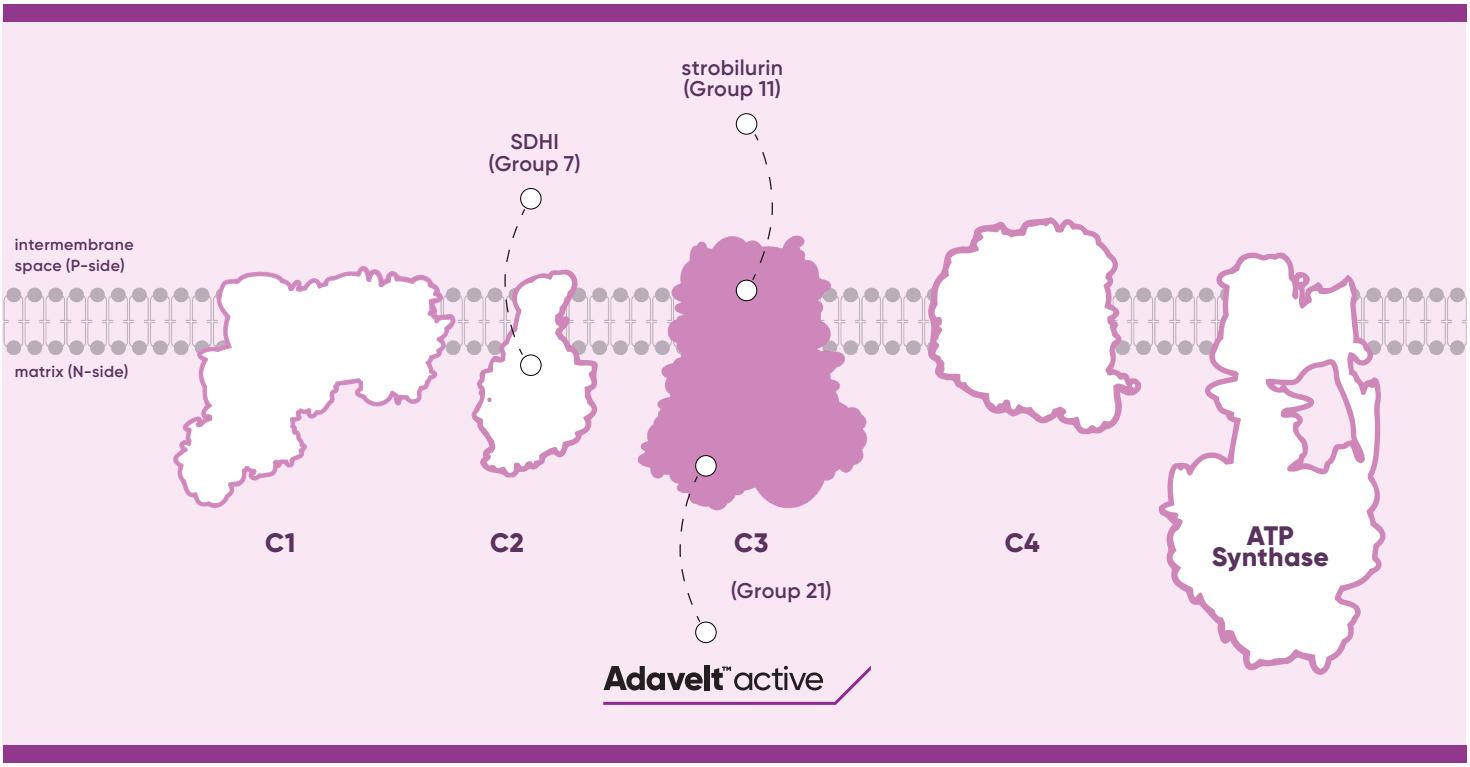
Mode of Action

The molecular structure of Adavelt™ active is based on the naturally-occurring compound UK-2A, found in soil bacteria. UK-2A is also the basis for the foundational cereals crop fungicide Inatreq™ active (fenpicoxamid) that established the picolinamide family. Adavelt active is the next-generation picolinamide fungicide that offers a new mode-of-action and/or new site-of-action across a wide range of crops. Adavelt and Inatreq are the only FRAC group 21 Qil fungicides active against ascomycetes, providing a complement to existing disease management programs that rely on previous technologies.

Group 21 fungicides act to inhibit fungal mitochondrial respiration, resulting in a reduction in the amount of ATP (adenosine triphosphate) produced, which disrupts necessary bioprocesses in the pathogen. As a Quinone Inside Inhibitor (Qil), Adavelt inhibits mitochondrial respiration in fungi by blocking electron transfer in the respiratory chain, and binds to complex III (the bc1 complex) at the Qi site (the inner mitochondrial membrane).

Unique MoA & SoA

- Adavelt is the first picolinamide fungicide developed for multi-crop use, providing programs with a novel mode-of-action or site-of-action.
- Where pathogen resistance to SDHIs, strobilurins and triazoles is a concern, Adavelt offers a powerful solution.
- Classified in FRAC Group 21, Adavelt binds to a different site (Qi) than common Group 11 strobilurins (Qo), Group 7 SDHIs and Group 3 DMI fungicides.



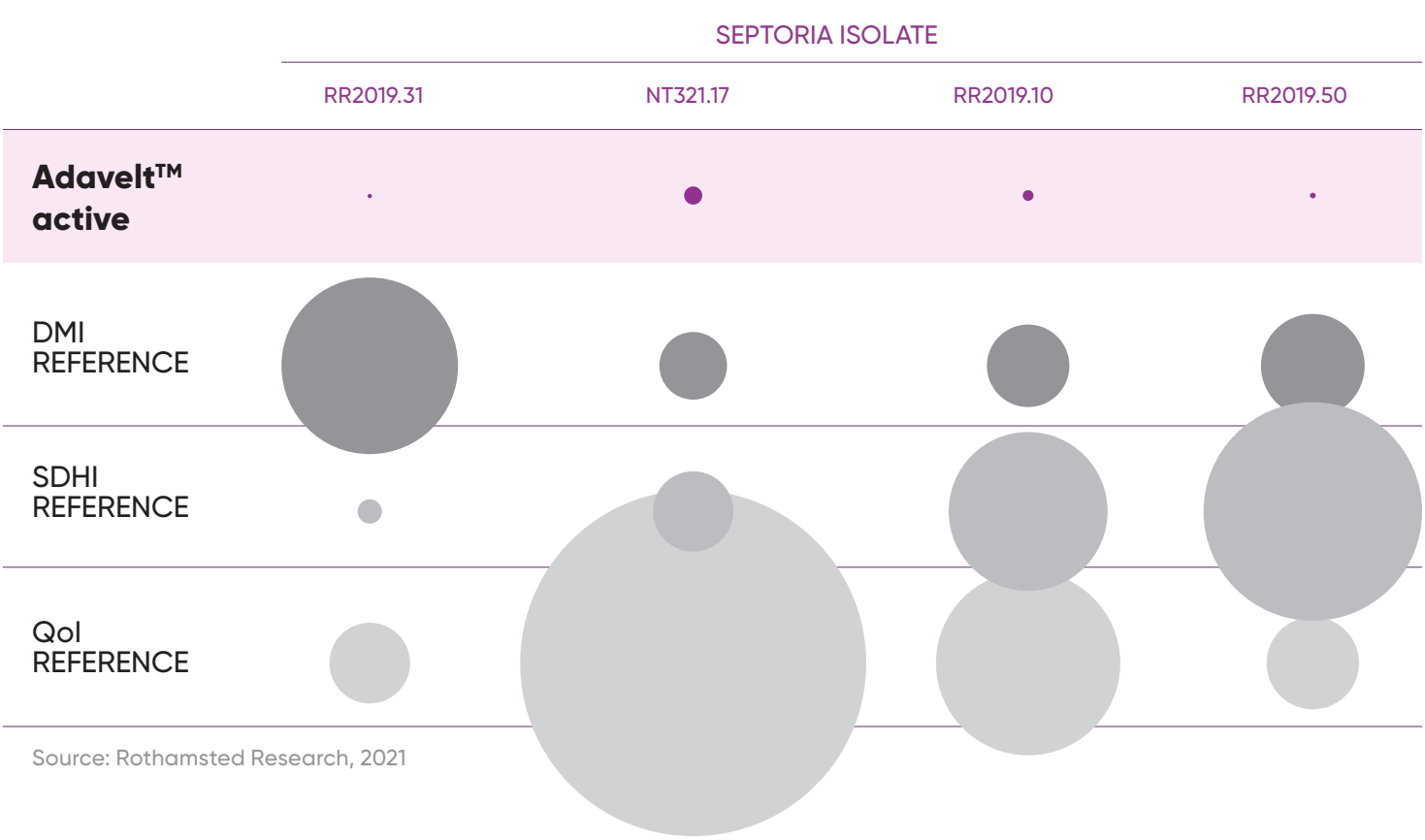
The FRAC group 21 Qil target site for Adavelt, distinguished from target sites for SDHI and strobilurin (QoI) actives in the mitochondria.

No Cross Resistance

In European field monitoring studies examining wheat Septoria, no cross-resistance was observed between Adavelt™ active and the widely used strobilurin and azole fungicide groups. Use of cereals fungicides over long periods has resulted in populations of Septoria exhibiting significant tolerance to representative products belonging to FRAC group 3 (DMIs/azoles), group 7 (SDHIs), and group 11 (QoIs/strobilurins). Large resistance factors associated with these previous technologies are presented in the below bubble plot, with calculated resistance factors for select Septoria isolates that are consistently 100 to 1000+ times more tolerant to these chemistries than wildtype strains. When tested against the same tolerant Septoria isolates, Adavelt demonstrated outstanding control, confirming no detection of pre-existing resistance and no cross-resistance for Adavelt compared with the reference fungicide products. Field monitoring studies support Adavelt as a highly anticipated replacement especially where resistance to existing products is likely, emerging, or established.

Adavelt controls Septoria strains with established resistance

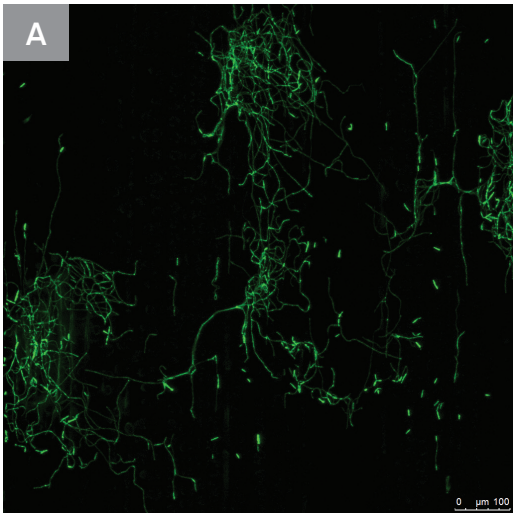
Bubble size is equal to the estimated resistance factor (RF) value for each isolate tested



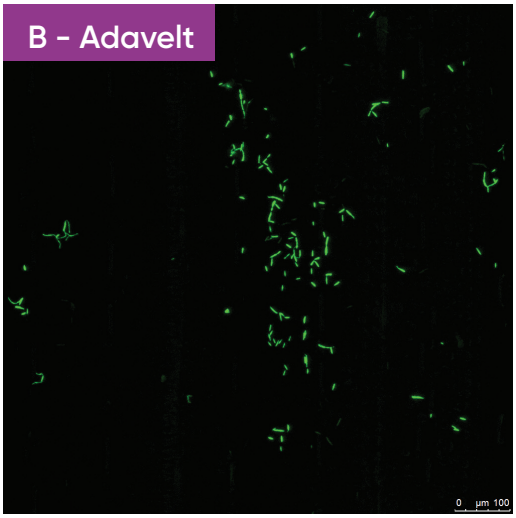
Source: Rothamsted Research, 2021

Preventive Partner

Adavelt is best used as a protectant treatment or in the earliest stages of disease development.



Non-treated wheat leaf surface showing germinated spores of *Zymoseptoria tritici* and extensive mycelial growth



Spore germination highly reduced with little to no hyphal elongation following a 1-day preventive application with Adavelt™ active

Efficacy

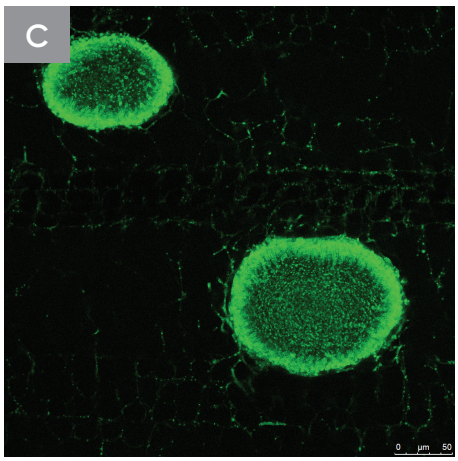
Adavelt™ active delivers powerful performance by acting upon each life stage of invading pathogens. Adavelt exerts its preventive effect by stopping spore germination on leaf surfaces, precluding plant disease. Should pathogens establish prior to fungicide application, Adavelt delivers curative activity by arresting mycelial growth and fruiting body development. Strong preventive and curative action ensure consistent product efficacy and further offer flexible timing of application.

Preventive Activity

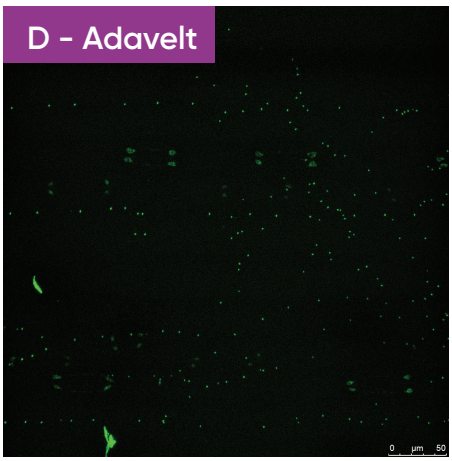
In-vitro studies show that Adavelt is a potent inhibitor of spore germination and growth when applied pre-infection. Confocal microscopy images of leaf Septoria on non-treated wheat leaves show that spores of *Zymoseptoria tritici* germinate normally and establish extensive mycelia (Panel A, 3 days after inoculation). When leaves were treated one day pre-infection (Panel B), Adavelt significantly reduced germination and hyphal elongation, leaving the pathogen nowhere to develop. For spores that germinate prior to application, Adavelt also inhibits mycelial growth thus explaining the outstanding protectant and strong curative properties observed when applied pre- or post-infection.

Curative Activity

Studies demonstrating the impact of Adavelt™ active on advanced disease confirm its ability to arrest mycelial expansion inside the leaf and interrupt the disease cycle. In Panel C , we see large, green fluorescent spore-filled pycnidia developing inside a non-treated wheat leaf, 14 days after inoculation with *Z. tritici*. Around the pycnidia are extensive networks of mycelia reflecting the disease left unchecked. Panel D shows the impressive curative reachback activity of Adavelt, applied on day seven post-inoculation and imaged on day 14. All that remains of the pathogen are the inviable fungal hyphae from the growth phase, represented by the fungal cell septa (green dots) found along the length of each hypha. This application of Adavelt ceased disease progression and prevented development of spores that lead to successive infections.



Inside a non-treated wheat leaf are *Zymoseptoria tritici* pycnidia surrounded by fungal mycelial during the sporulation phase (14 days after inoculation)



Adavelt™ active halts mycelial growth and precludes formation of pycnidia (inside a wheat leaf at day 14, after a day 7 application)

Formulation

New formulation chemistry was specifically designed to maximize the biological efficacy of Adavelt™ active during its development. Adavelt will be offered in a range of formulation concepts to meet farmer needs. The Adavelt family of products will include straight formulations and several mixtures to enable flexibility, resistance management and to enhance performance across a broad spectrum of pathogens.

Initial markets

Adavelt™ active has been developed for use on a wide range of crop groups including fruits and nuts, fruiting vegetables, cucurbits, root and tuber vegetables, cereals, oilseed and field row crops, small fruits and berries, and more. Crop registrations in many geographies are being sought to serve market needs. Approved country registration labels will provide detailed guidance on application methods, rates and labelled crops.

Spectrum of Activity and Use Rates

Adavelt™ active demonstrates a broad spectrum of activity against key ascomycetes pathogens. Based on global field trials demonstrating Adavelt performance, label use rates up to 150 g ai/ha are anticipated.

Berry & Small Fruit
- Grey mold (Botrytis)
- Mummy berry / Monilinia blight
- Powdery mildew

Cucurbits
- Anthracnose
- Powdery mildew
- Gummy stem blight
- Septoria leaf spot
- Cercospora
- Grey mold (Botrytis)
- Sclerotinia blight / White mold / Stem rot

Grapes
- Powdery mildew
- Grey mold (Botrytis)
- Anthracnose / Ripe rot

Fruiting Vegetables
- Early blight
- Anthracnose / Foot rot / Ripe rot
- Powdery mildew
- Sclerotinia blight / White mold / Stem rot
- Grey mold (Botrytis)
- Septoria leaf spot

Leafy Vegetables
- Sclerotinia / White mold
- Powdery mildew

Brassica
- Powdery mildew
- White mold

Legumes (fresh)
- White mold
- Grey mold (Botrytis)

Stone Fruit

Brown rot / Blossom blight

Powdery mildew

Grey mold (Botrytis)

Tree Nuts

Brown rot/ Blossom blight

Hull rot

Tropical Fruits

Anthracnose

Banana

Black sigatoka

Cereals

Septoria leaf blotch

Net blotch

Oil Seed Rape / Canola

Black leg

Sclerotinia blight / Stem rot

Alternaria

Potato

Early blight

Sugar Beet

Cercospora leaf spot

Cotton

Ramularia

Pulses

Mycosphaerella blight

Anthracnose

Ascochyta blight

Turf

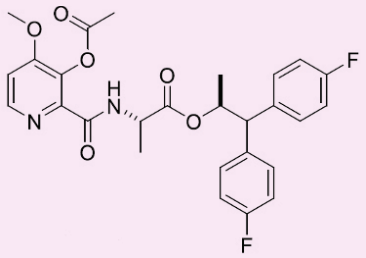
Dollar Spot

Ornamental

Grey mold (Botrytis)

Powdery mildew

Physical and Chemical Properties

Common Name	florylpicoxamid
Trade Name	Adavelt™ active
Biological Action	fungicide
Code Names Tested	XDE-659, XR-659
Chemical Family	picolinamides
Chemical Name (IUPAC)	(2S)-1,1-bis(4-fluorophenyl)propan-2-yl N-{[3-(acetyloxy)-4-methoxypyridin-2-yl]carbonyl}-L-alaninate
Chemical Name (CAS)	L-Alanine, N-[[3-(acetyloxy)-4-methoxy-2 pyridinyl]carbonyl]-, (1S)-2,2-bis(4-fluorophenyl)-1-methylethyl ester
CAS Number	1961312-55-9
Mode of Action	respiration inhibitor at MET III (cyt. bc1 complex) - QiI
Resistance Group	C4 #21
Plant Translocation	contact and local plant mobility (translaminar and acropetal)
Dissociation Constant	does not dissociate at environmentally significant pH values
Water Solubility	3.1 mg/L @ pH 7
Partition Coefficient (log10 POW)	4.2 @ pH 7
Chemical Structure	
Empirical Formula	$C_{27}H_{26}F_2N_2O_6$
Molecular Weight	512.509 g/mol
Relative Density	1.28 @ 20°C
Melting Point	91.0 to 95.5°C
Boiling Point	decomposes before boiling
Flammability	not highly flammable
Explosive Properties	not explosive
Vapor Pressure	< 5 x 10-6 Pa (3.5 x 10-8 mm Hg) @ 20°C < 9 x 10-6 Pa (6.8 x 10-8 mm Hg) @ 25°C
Odor	none discernible
Appearance	light tan solid (coarse powder) at 20°C

Mammalian and Environmental Safety

Adavelt™ active has favorable toxicological and environmental fate profiles, ensuring minimal impact to non-target organisms and the environment. Application rates of Adavelt are also relatively low compared with other active ingredients, which further minimizes potential impact and positions Adavelt as an optimal choice for renewed disease management programs. Detailed best practices and guidance will be provided on product labels and supplementary materials for all types of applications. The safety profile for Adavelt fully supports broad use and enables application programs tailored for reduced post-harvest intervals. A summary of characterization and assessment study results are presented.

In ecotoxicology studies, Adavelt exhibited very low acute toxicity to terrestrial species: mammals, birds, honeybees and earthworms. Adavelt exhibits high acute toxicity to fish and aquatic invertebrates and moderate to high toxicity to algae and aquatic plants depending upon species. No harm is expected when applied according to label guidelines.

Key points for the favorable mammalian toxicological profile of Adavelt™ active:

- Low acute toxicity
- Not carcinogenic
- Not genotoxic
- Not immunotoxic
- Not neurotoxic
- No indication of reproductive or developmental toxicity
- No evidence of endocrine toxicity

Adavelt has a favorable eco-toxicological profile including:

- Very low toxicity to birds
- Very low toxicity to honeybees and other non-target arthropods
- Very low toxicity to soil organisms including earthworms, collembola and soil mites
- High toxicity to fish and aquatic invertebrates*
- Moderate to high toxicity to algae and aquatic plants*
- Does not bioaccumulate

**Note: Use according to the approved label does not result in risk to aquatic organisms. See label for local guidance and requirements.*

Songbird

Honey bee

Collembola

Field mouse

Environmental Fate

The degradation rates observed in the soil and aquatic systems conducted in a variety of guideline studies for Adavelt™ active present a very favorable environmental profile and a low risk for groundwater. Adavelt degrades rapidly in the environment and hydrolyzes to non-active compounds. Dissipation of Adavelt occurs primarily through microbial degradation in the soil, and through hydrolysis and photolysis in water. In field studies, no lateral movement in soil was observed for Adavelt, and simulation studies demonstrate a very low potential for groundwater contamination.

Hydrolysis	Lab half-life @ pH 7: 16.7 days
Photolysis in Water	Lab half-life @ pH 7: 0.21 days
Soil	Aerobic lab half-life: 0.40 days
Water/Sediment System	Aerobic half-life (total system): 0.30 days

Worker Safety

Refer to country-specific labels for information about application and handling, including personal protective equipment (PPE), product mixers, loaders and applicators, and re-entry intervals (REI).

Regulatory Information

Regulatory registrations are pursued to serve the agricultural needs for environmentally responsible plant disease management. Consult your local Corteva Agriscience representative for current information on Adavelt registration status for your country or territory and for additional regulatory information on Maximum Residue Levels (MRLs), Import Tolerances and product Stewardship Plans.

Recommended References

Meyer, K.G., Yao, C., Lu, Y., Bravo-Altamirano, K., Buchan, Z., Daeuble, J.F., DeKorver, K., DeLorbe, J., Heemstra, R., Herrick, J., Jones, D., Loy, B.A., Rigoli, J., Wang, N.X., Wilmot, J., and Young, D. (2021). Chapter 28 – The discovery of florylpicoxamid, a new picolinamide for disease control. In P. Maienfisch and S. Mangelinckx (Eds.), Recent highlights in the discovery and optimization of crop protection products (pp. 433-442). Academic Press, https://doi.org/10.1016/B978-0-12-821035-2.00030-9

Yao, C., Meyer, K.G., Gallup, C., Hufnagl, A., and Young, D. (2020, August 10). Discovery and biological characterization of florylpicoxamid, a new broad spectrum fungicide. In S. Zhang, J. M. Crane (Moderators), Special session: New products and services [Conference presentation session] Plant Health 2020 Online: American Phytopathological Society (APS) Annual Meeting, Virtual. https://apsnet.confex.com/apsnet/2020/meetingapp.cgi/Paper/17518

Yao, C., Meyer, K.G., Gallup, C., Bowling, A.J., Hufnagl, A., Myung, K., Lutz, J., Slanec, T., Pence, H.E., Delgado, J. and Wang, N.X. (2021). Florylpicoxamid, a new picolinamide fungicide with broad spectrum activity. Pest Manag Sci. https://doi.org/10.1002/ps.6483

Meyer, K.G., Bravo-Altamirano, K., Herrick, J., Loy, B.A., Yao, C., Nugent, B., Buchan, Z., Daeuble, J.F., Heemstra, R., Jones, D.M., Wilmot, J., Lu, Y., DeKorver, K., Delorbe, J. and Rigoli, J. (2021). Discovery of florylpicoxamid: a mimic of a macrocyclic natural product. Bioorg Med Chem. 50, 116455; https://doi.org/10.1016/j.bmc.2021.116455

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