ZYNYZ® (retifanlimab-dlwr) is a programmed death receptor-1 (PD-1)–blocking antibody indicated for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC).[1]

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[1]

DOSING AND ADMINISTRATION GUIDE

ZYNYZ®
retifanlimab-dlwr
Injection 500 mg

IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

Important immune-mediated adverse reactions listed may not be inclusive of all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, can occur at any time after starting or discontinuing treatment with a PD-1/PD-L1–blocking antibody, and can affect more than one body system simultaneously.

Monitor patients closely for symptoms and signs that may be clinical manifestations of such reactions. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1–blocking antibodies. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. If suspected, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue ZYNYZ depending on severity. In general, if ZYNYZ requires interruption or discontinuation, administer systemic corticosteroid therapy (1-2 mg/kg/day prednisone or equivalent) until improvement to ≤ Grade 1. Then, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroids.

Please see additional Important Safety Information throughout and click here for Full Prescribing Information for ZYNYZ.

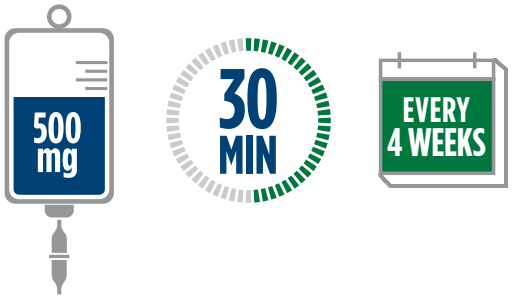
Incyte

IV dosing every 4 weeks may align with routine office visits[1]

Recommended dosage

- 500 mg IV infusion over 30 minutes every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months
- Administer ZYNYZ as an IV infusion after dilution
- Routine prophylaxis for infusion-related reactions is not required
- Consider premedication with an antipyretic and/or an antihistamine for patients who have had previous systemic reactions to infusions of therapeutic proteins

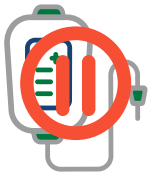
QUICK INFUSION THAT DELIVERS:



IV, intravenous.

Dosage modifications for adverse reactions

No dose reduction of ZYNYZ for adverse reactions is recommended.



In general, withhold ZYNYZ for severe (Grade 3) immune-mediated adverse reactions.

Permanently discontinue ZYNYZ for:

- life-threatening (Grade 4) immune-mediated adverse reactions,
- recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or
- an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids

Dosage modifications for ZYNYZ for adverse reactions that require management different from these general guidelines can be found on the next page.

IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Pneumonitis

ZYNYZ can cause immune-mediated pneumonitis. Immune-mediated pneumonitis occurred in 3% (13/440) of patients, including fatal (0.2%), Grade 3 (0.9%), and Grade 2 (1.4%) reactions. Pneumonitis led to permanent discontinuation of ZYNYZ in 1 patient and withholding in 0.9%.

Systemic corticosteroids were required in 77% (10/13) of patients. Pneumonitis resolved in 10 of the 13 patients.

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Recommended dosage modifications for adverse reactions[1]

ADVERSE REACTION	SEVERITY[a]	ZYNYZ DOSAGE MODIFICATIONS
IMMUNE-MEDIATED ADVERSE REACTIONS		
Pneumonitis	Grade 2	Withhold[b]
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT greater than 3 but no more than 8 times ULN OR Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]
	AST or ALT increases to more than 8 times ULN OR Total bilirubin greater than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases more than 5 and up to 10 times ULN OR Baseline AST or ALT is more than 3 and up to 5 times ULN and increases more than 8 and up to 10 times ULN	Withhold[b]
	AST or ALT increases to more than 10 times ULN OR Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies[d]	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[b]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative dermatologic conditions	Grade 3 or suspected SJS, TEN, or DRESS	Withhold[b]
	Grade 4 or confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[b]
	Grade 3 or 4	Permanently discontinue
OTHER ADVERSE REACTIONS		
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

Please see Warnings and Precautions in the Full Prescribing Information.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DRESS, drug rash with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; ULN, upper limit of normal.

[a]Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
[b]Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 12 weeks of initiating steroids.
[c]If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue ZYNYZ based on recommendations for hepatitis with no liver involvement.
[d]Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Colitis

ZYNYZ can cause immune-mediated colitis. Cytomegalovirus infections/reactivations have occurred in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

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ZYNYZ preparation and storage[1]

ZYNYZ is supplied in a carton containing one single-dose vial of 500 mg/20 mL (25 mg/mL) (NDC 50881-006-03).

Storing and handling ZYNYZ

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.

Preparing ZYNYZ

Do not administer ZYNYZ using a polyurethane infusion set. Visually inspect the vial for particulate matter and discoloration prior to administration. ZYNYZ is a clear to slightly opalescent, colorless to pale yellow solution and is free of particles. Discard the vial if the solution is cloudy, discolored, or contains particulate matter. Do not shake the vial.

01 Withdraw 20 mL (500 mg) of ZYNYZ from one vial and discard vial with any unused portion.

02 Dilute ZYNYZ with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 1.4 mg/mL to 10 mg/mL. Use polyvinylchloride (PVC) and di-2-ethylhexyl phthalate (DEHP), polyolefin copolymer, polyolefin with polyamide, or ethylene vinyl acetate infusion bags.

03 Mix diluted solution by gentle inversion. Do not shake.

04 Visually inspect the infusion bag for particulate matter and discoloration prior to administration. Discard if the solution is discolored or contains particulate matter.

Storing diluted ZYNYZ solution

Protect the diluted ZYNYZ solution from light during storage. Do not freeze or shake diluted solution.

Store diluted solution at room temperature, up to 25°C (77°F), for no more than 8 hours from the time of preparation to the end of the infusion.

OR

Store diluted solution under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to the end of the infusion. Allow the diluted solution to come to room temperature prior to administration.

Diluted solution must be administered within 4 hours, including infusion time, once it is removed from the refrigerator.

Please see Complete Preparation and Administration Instructions in the Full Prescribing Information.

IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Colitis (cont'd)

Immune-mediated colitis occurred in 1.6% (7/440) of patients, including Grade 4 (0.2%), Grade 3 (0.2%), and Grade 2 (0.7%). Colitis led to permanent discontinuation of ZYNYZ in 1 patient and withholding in 0.9%.

Systemic corticosteroids were required in 71% (5/7) of patients. Colitis resolved in 4/7 patients.

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ZYNYZ administration[1]

When administering ZYNYZ:

Administer diluted ZYNYZ solution by IV infusion over 30 minutes.

Use a polyethylene or PVC with DEHP intravenous line containing a sterile, non-pyrogenic, low-protein binding polyethersulfone, polyvinylidene fluoride, or cellulose acetate 0.2 micron to 5 micron in-line or add-on filter or 15 micron mesh in-line or add-on filter.

DEHP, di-2-ethylhexyl-phthalate; PVC, polyvinyl chloride.

When administering ZYNYZ, DO NOT:

Do not administer ZYNYZ as an intravenous push or bolus injection.

Do not co-administer other drugs through the same infusion line.

Please see Complete Preparation and Administration Instructions in the Full Prescribing Information.

IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Hepatitis

ZYNYZ can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 3% (13/440) of patients, including Grade 4 (0.2%), Grade 3 (2.3%), and Grade 2 (0.5%). Hepatitis led to permanent discontinuation of ZYNYZ in 1.4% of patients and withholding in 0.9%.

Systemic corticosteroids were required in 85% (11/13) of patients. Hepatitis resolved in 6/13 patients.

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IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

ZYNYZ can cause primary or secondary adrenal insufficiency. For ≥ Grade 2 adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue ZYNYZ depending on severity.

Adrenal insufficiency occurred in 0.7% (3/440) of patients, including Grade 3 (0.5%) and Grade 2 (0.2%). ZYNYZ was permanently discontinued in no patients and was withheld for 1 patient with adrenal insufficiency.

All patients required systemic corticosteroids. Adrenal insufficiency resolved in 1 of the 3 patients.

Hypophysitis

ZYNYZ can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts, and can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue ZYNYZ depending on severity.

Hypophysitis occurred in 0.5% (2/440, both Grade 2) of patients. No patients discontinued or withheld ZYNYZ due to hypophysitis.

All patients required systemic steroids. Hypophysitis resolved in 1 of the 2 patients.

Thyroid Disorders

ZYNYZ can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue ZYNYZ depending on severity.

Thyroiditis occurred in 0.7% (3/440, all Grade 1) of patients. No patients discontinued or withheld ZYNYZ due to thyroiditis. Thyroiditis resolved in 1 of the 3 patients.

Hypothyroidism

Hypothyroidism occurred in 10% (42/440) of patients receiving ZYNYZ, including Grade 2 (4.8%). No patients discontinued due to hypothyroidism. ZYNYZ was withheld in 0.5% of patients.

Systemic corticosteroids were required for 1 patient, and 79% (33/42) of patients received endocrine therapy.

Hyperthyroidism

Hyperthyroidism occurred in 6% (24/440) of patients receiving ZYNYZ, including Grade 2 (2.5%). ZYNYZ was not discontinued in any patient and was withheld in 1 patient. Systemic corticosteroids were required for 13% (3/24) of patients, and 46% (11/24) of patients received endocrine therapy.

Type 1 Diabetes Mellitus, Which Can Present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold ZYNYZ depending on severity.

Type 1 diabetes mellitus occurred in 0.2% (1/440) of patients, including Grade 3 (0.2%) adverse reactions.

Immune-Mediated Nephritis with Renal Dysfunction

ZYNYZ can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 1.6% (7/440) of patients receiving ZYNYZ, including Grade 4 (0.5%), Grade 3 (0.7%), and Grade 2 (0.5%). Nephritis led to permanent discontinuation of ZYNYZ in 0.9% of patients and withholding in 1 patient.

Systemic corticosteroids were required in 57% (4/7) of patients. Nephritis resolved in 3/7 patients.

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IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Dermatologic Adverse Reactions

ZYNYZ can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, has occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue ZYNYZ depending on severity.

Immune-mediated skin reactions occurred in 8% (36/440) of patients, including Grade 3 (1.1%) and Grade 2 (7%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation of ZYNYZ in 1 patient and withholding in 2.3% of patients.

Systemic corticosteroids were required in 25% (9/36) of patients. Immune-mediated dermatologic adverse reactions resolved in 75% (27/36) of patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in 440 patients who received ZYNYZ or were reported with the use of other PD-1/PD-L1–blocking antibodies, including severe or fatal cases.

Cardiac/vascular: myocarditis, pericarditis, vasculitis

Gastrointestinal: pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal: myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis, polymyalgia rheumatica

Neurological: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy

Ocular: uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Endocrine: hypoparathyroidism

Other (Hematologic/Immune): hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

Infusion-Related Reactions

A severe infusion-related reaction (Grade 3) occurred in 1 (0.2%) of 440 patients. Monitor patients for signs and symptoms; interrupt or slow the rate of infusion or permanently discontinue ZYNYZ based on severity of reaction. Consider premedication with an antipyretic and/or an antihistamine for patients who have had previous systemic reactions to infusions of therapeutic proteins.

Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1–blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause), which may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT.

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IMPORTANT SAFETY INFORMATION (CONT'D)

Embryo-Fetal Toxicity

ZYNYZ can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus, resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

Lactation

Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the last dose.

Adverse Reactions

The safety of ZYNYZ was evaluated in 105 patients with metastatic or recurrent locally advanced MCC.

Serious adverse reactions occurred in 22% of patients receiving ZYNYZ. The most frequent serious adverse reactions (≥ 2% of patients) were fatigue, arrhythmia, and pneumonitis.

Permanent discontinuation of ZYNYZ due to an adverse reaction occurred in 11% of patients. These included asthenia, atrial fibrillation, concomitant disease progression of chronic lymphocytic leukemia, demyelinating polyneuropathy, eosinophilic fasciitis, increased transaminases, infusion-related reaction, lung disorder, pancreatitis, polyarthritis, and radiculopathy (1 patient each).

Dosage interruptions due to an adverse reaction occurred in 25% of patients. Adverse reactions or laboratory abnormalities that required dosage interruption in ≥ 2% of patients were increased transaminases, increased lipase, increased amylase, pneumonitis, and pyrexia.

The most common (≥ 10%) adverse reactions were fatigue, musculoskeletal pain, pruritus, diarrhea, rash, pyrexia, and nausea.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Incyte Corporation at 1-855-463-3463.

Please see the Full Prescribing Information for ZYNYZ for additional Important Safety Information.

Reference: 1. ZYNYZ Prescribing Information. Wilmington, DE: Incyte Corporation.

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