ZYNYZ®
retifanlimab-dlwr
Injection 500 mg

BILLING & CODING GUIDE

- **Coverage, Coding, & Payment for ZYNYZ**
- **Best Practices for Timely Reimbursement**
- **Example Claims Forms – CMS-1500 & CMS-1450**
- **Provider Readiness – Process and Tips**
- **IncyteCARES for ZYNYZ – Patient Support Program Overview**

This Billing and Coding Guide is intended to provide an overview of coding and coverage information for ZYNYZ. Please use this guide to support the reimbursement process and as a source of information on IncyteCARES for ZYNYZ.

While this guide provides information on navigating the reimbursement process, please note all enclosed coding information is for reference purposes only and is not intended to serve as guidance for specific coding, billing, and claims submissions. Decisions on which codes best describe the services provided must be made by individual providers based on specific payer guidance and requirements.

Incyte cannot guarantee payment of any claim, and providers should contact third-party payers for specific information on their coding, coverage, and payment policies as needed.

For questions regarding ZYNYZ reimbursement and access, please call IncyteCARES at 1-855-452-5234, Monday through Friday, 8 AM – 8 PM ET.

COVERAGE & PAYMENT FOR ZYNYZ

ZYNYZ® retifanlimab-dlwr Injection 500 mg

Coverage and payment methodology for ZYNYZ will vary by payer type.

For Medicare patients, ZYNYZ will be covered under Medicare Part B when used for an FDA-approved indication and when medically reasonable and necessary.

There are no prior authorization requirements for ZYNYZ under traditional fee-for-service Medicare plans.

For patients enrolled in a commercial health plan, Medicare Advantage, or Medicaid, coverage of ZYNYZ will vary by payer. Some payers may also apply utilization restrictions for ZYNYZ. When seeking coverage, providers should be prepared for the possibility of needing to go through the prior authorization process.

PAYMENT METHODOLOGY

MEDICARE

Standard Medicare Part B reimbursement is Average Sales Price (ASP) + 6%.*

COMMERCIAL PAYERS & MEDICAID

Drug reimbursement will vary by payer but is generally the contracted reimbursement rate between the payer and provider.

Incyte cannot guarantee payment of any claim, and providers should contact third-party payers for specific information on their coding, coverage, and payment policies as needed.

*If Medicare sequestration is in effect, a statutory reduction to the payment is applied. Please visit CMS.gov for more information.

INDICATIONS AND USAGE

Squamous Cell Carcinoma of the Anal Canal

ZYNYZ, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of adult patients with inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal (SCAC).

ZYNYZ, as a single agent, is indicated for the treatment of adult patients with locally recurrent or metastatic SCAC with disease progression on or intolerance to platinum-based chemotherapy.

Merkel Cell Carcinoma

ZYNYZ is indicated for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC).

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.

CODING FOR ZYNYZ

ZYNYZ® retifanlimab-dlwr Injection 500 mg

Please refer to the coding information below to support appropriate claims processing for ZYNYZ for the treatment of Squamous Cell Carcinoma of the Anal Canal (SCAC) and Merkel Cell Carcinoma (MCC). Payer requirements for coding may vary. For the most accurate list of codes and billing requirements, please confirm with the individual payer.

NATIONAL DRUG CODES (NDCs)		
	10-Digit	11-Digit
500 mg/20 mL (25 mg/mL) Single-Dose Vial	50881-006-03	50881-**0**006-03

HCPCS CODING		HCPCS MODIFIER	
J9345	Injection, retifanlimab-dlwr, 1 mg	**JZ**	Zero drug amount discarded/not administered to any patient

SCAC ICD-10-CM DIAGNOSIS CODES			
C21.0	Malignant neoplasm of anus, unspecified	**C21.1**	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone	**C21.8**	Malignant neoplasm of overlapping sites of rectum, anus, and anal canal

MCC ICD-10-CM DIAGNOSIS CODES			
C4A0	MCC of lip	**C4A4**	MCC of scalp and neck
C4A10	MCC of unspecified eyelid, including canthus	**C4A51**	MCC of anal skin
C4A111	MCC of right upper eyelid, including canthus	**C4A52**	MCC of skin of breast
C4A112	MCC of right lower eyelid, including canthus	**C4A59**	MCC of other part of trunk
C4A121	MCC of left upper eyelid, including canthus	**C4A60**	MCC of unspecified upper limb, including shoulder
C4A122	MCC of left lower eyelid, including canthus	**C4A61**	MCC of right upper limb, including shoulder
C4A20	MCC of unspecified ear and external auricular canal	**C4A62**	MCC of left upper limb, including shoulder
C4A21	MCC of right ear and external auricular canal	**C4A70**	MCC of unspecified lower limb, including hip
C4A22	MCC of left ear and external auricular canal	**C4A71**	MCC of right lower limb, including hip
C4A30	MCC of unspecified part of face	**C4A72**	MCC of left lower limb, including hip
C4A31	MCC of nose	**C4A8**	MCC of overlapping sites
C4A39	MCC of other parts of face	**C4A9**	MCC, unspecified

REVENUE CODES			
Administration		Drug	
0335	Chemotherapy Administration - IV	**0636**	Drugs requiring detailed coding

DRUG ADMINISTRATION / CPT® CODE	
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial drug

CPT®, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IV, intravenous.

IMPORTANT SAFETY INFORMATION (CONT)

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Pneumonitis

ZYNYZ can cause immune-mediated pneumonitis. Immune-mediated pneumonitis occurred in 3.1% (14/452) of patients, including 1 (0.2%) patient with fatal pneumonitis, Grade 3 (0.9%), and Grade 2 (1.3%) reactions. Pneumonitis led to permanent discontinuation of ZYNYZ in 1 patient and withholding in 1.1%.

Systemic corticosteroids were required in 71% (10/14) of patients. Pneumonitis resolved in 11 of the 14 patients.

BEST PRACTICES FOR TIMELY CLAIMS REIMBURSEMENT

ZYNYZ® retifanlimab-dlwr Injection 500 mg

EFFECTIVE OCTOBER 1, 2023, ZYNYZ HAS A UNIQUE J-CODE

J9345
Injection, retifanlimab-dlwr, 1 mg

One single-dose vial of ZYNYZ contains 500 mg of retifanlimab-dlwr, equal to 500 billing units when using HCPCS code J9345.

Payer requirements regarding detailed claim form information may vary. It is important to check with individual payers on their specific requirements and ensure accurate documentation of services and units of measure.

For an efficient claims and reimbursement process, employ the following strategies:

- **Verify accuracy** of patient information
- **Use the ZYNYZ-specific J-code:** J9345 (Injection, retifanlimab-dlwr, 1 mg) when completing a claim
- **Ensure accurate coding** - refer to the ZYNYZ Billing & Coding Guide for appropriate codes and modifiers
  - Reference the included Example Claims Forms for guidance on accurately recording appropriate codes and supplemental information
- **Include correct number** of units administered
- **Include correct modifier** to report no product discarded – record the JZ Modifier on the same line as the HCPCS code
- **Ensure accuracy** of information needed to process the claim
  - Correct NDC Format – use 10- or 11-digit format based on payer requirements
  - Prior Authorization Number, if applicable
- **Check your payer agreements** to ensure you understand any specific reimbursement needs for ZYNYZ and follow the payer's recommendations for providing additional information (e.g., medical records)
- **Make sure** electronic claims are successfully submitted
- **Stay up to date** with payer coverage policies

HCPCS, Healthcare Common Procedure Coding System; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; NDC, National Drug Code.

For questions regarding billing, coding, or reimbursement for ZYNYZ, call IncyteCARES to be connected with a Field Access Manager

1-855-452-5234
M–F, 8 AM to 8 PM ET

The information herein is provided for educational purposes only. Insurance coverage and reimbursement are not guaranteed. Coverage and reimbursement may vary significantly by payer, plan, patient, and setting of care. It is the sole responsibility of the health care provider to select the proper codes and ensure the accuracy of all statements used in seeking coverage and reimbursement for an individual patient.

IMPORTANT SAFETY INFORMATION (CONT)

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

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.

ZYNYZ as a Single Agent: Immune-mediated colitis occurred in 2.7% (12/452) of patients, including Grade 4 (0.2%), Grade 3 (0.4%), and Grade 2 (1.1%). Colitis led to permanent discontinuation of ZYNYZ in 0.9% of patients and withholding in 1.3%. Systemic corticosteroids were required in 75% (9/12) of patients. Colitis resolved in 8/12 patients.

ZYNYZ EXAMPLE CMS-1500 CLAIM FORM
PHYSICIAN OFFICE SETTING

ZYNYZ® retifanlimab-dlwr Injection 500 mg

This example form is provided for guidance and reference only.

ZYNYZ and the associated services provided in a physician office setting are billed on the CMS-1500 Claim Form. It is always the provider's responsibility to determine the appropriate healthcare setting, and to submit true and correct claims for the products and services rendered. **Incyte cannot guarantee payment of any claim, and providers should contact third-party payers for specific information on their coding, coverage, and payment policies as needed.**

Box 19
Some payers may require additional information for proper processing. This may include*: *Drug name, strength, route of administration, dosage administered, and NDC*

Box 21
Enter the ICD-10-CM diagnosis code

Box 24 A-B
Enter the date of service and appropriate place of service code. If NDC reporting is required, include the following in the shaded portion of Box 24A*: *N4+11-Digit NDC+ML+Unit quantity administered*

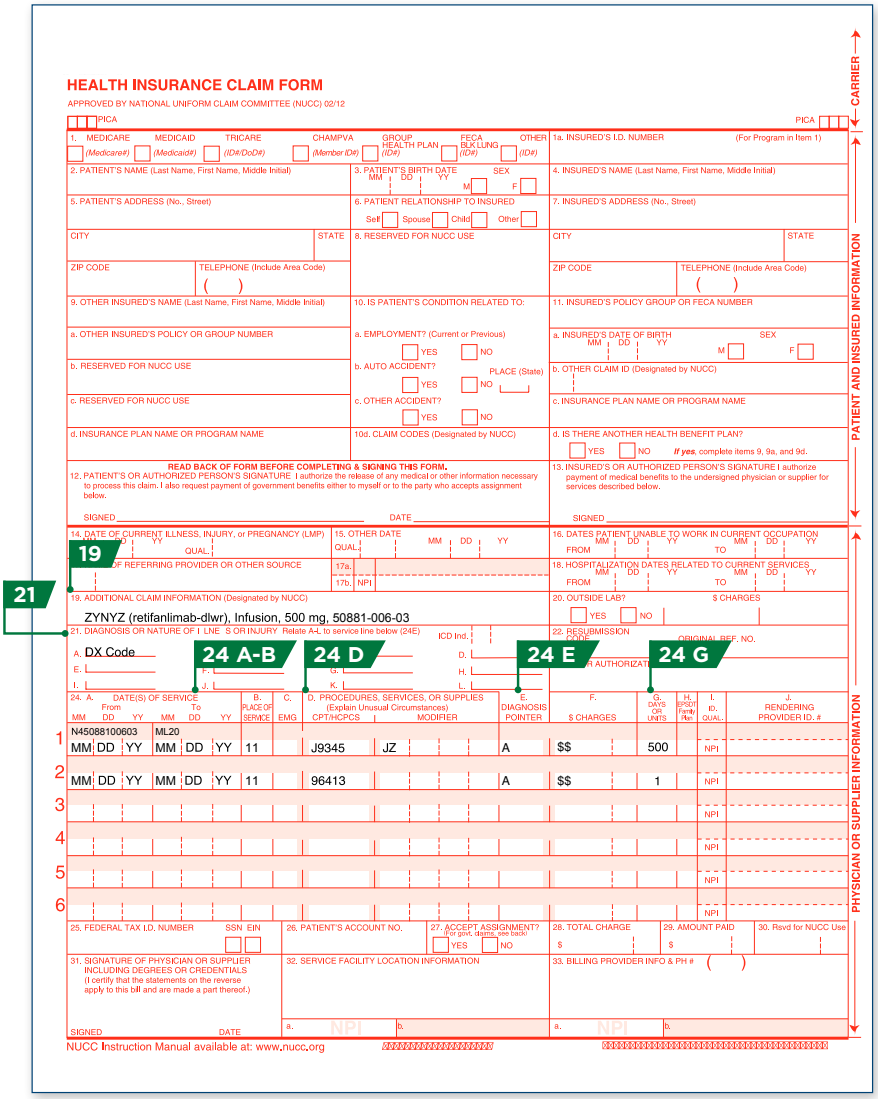
Box 24 D
Enter the appropriate HCPCS, modifier, and CPT® codes. For example:

- Drug - J9345 (Injection, retifanlimab-dlwr, 1 mg)
- Modifier – JZ (Include the JZ modifier on the same line as the HCPCS code to indicate no amount of drug was discarded)
- Administration - 96413 (Chemo infusion for 1st hour, single or initial drug)

Box 24 E
Refer to the diagnosis (Box 21) relating to the drug or procedure listed in Box 24D

Box 24 G
Enter number of units for each line item

- J9345 Billing Unit = 1 mg
- Single-Dose Vial = 500 mg
- 500 mg Vial = 500 Units



*Always refer to specific payer policies as billing requirements may vary by payer, including use of the 10- or 11-digit NDC.

CPT®, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; NDC, National Drug Code.

IMPORTANT SAFETY INFORMATION (CONT)

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Colitis (cont)

ZYNYZ in Combination with Carboplatin and Paclitaxel: Immune-mediated colitis occurred in 10% (16/154) of patients receiving ZYNYZ in combination with carboplatin and paclitaxel, including Grade 4 (0.6%), Grade 3 (2.6%), and Grade 2 (3.2%). Colitis led to permanent discontinuation of ZYNYZ in 2 patients and withholding of ZYNYZ in 2 patients. Systemic corticosteroids were required in 94% (15/16) of patients. Colitis resolved in 15 of the 16 patients.

ZYNYZ EXAMPLE CMS-1450 CLAIM FORM
HOSPITAL OUTPATIENT SETTING

ZYNYZ® retifanlimab-dlwr Injection 500 mg

This example form is provided for guidance and reference only.

ZYNYZ and the associated services provided in a hospital outpatient setting are billed on the CMS-1450 Claim Form (or UB-04). It is always the provider's responsibility to determine the appropriate healthcare setting, and to submit true and correct claims for the products and services rendered. **Incyte cannot guarantee payment of any claim, and providers should contact third-party payers for specific information on their coding, coverage, and payment policies as needed.**

Box 42
List the appropriate revenue code for each service provided. Drugs billed with HCPCS codes usually require revenue code 0636 (drugs requiring detailed coding)

Box 43
Enter a description for each revenue code.

If NDC reporting is required, include the following*: *N4+11-Digit NDC+ML+Unit quantity administered*

Box 44
Enter the appropriate HCPCS, modifier, and CPT® codes. For example:

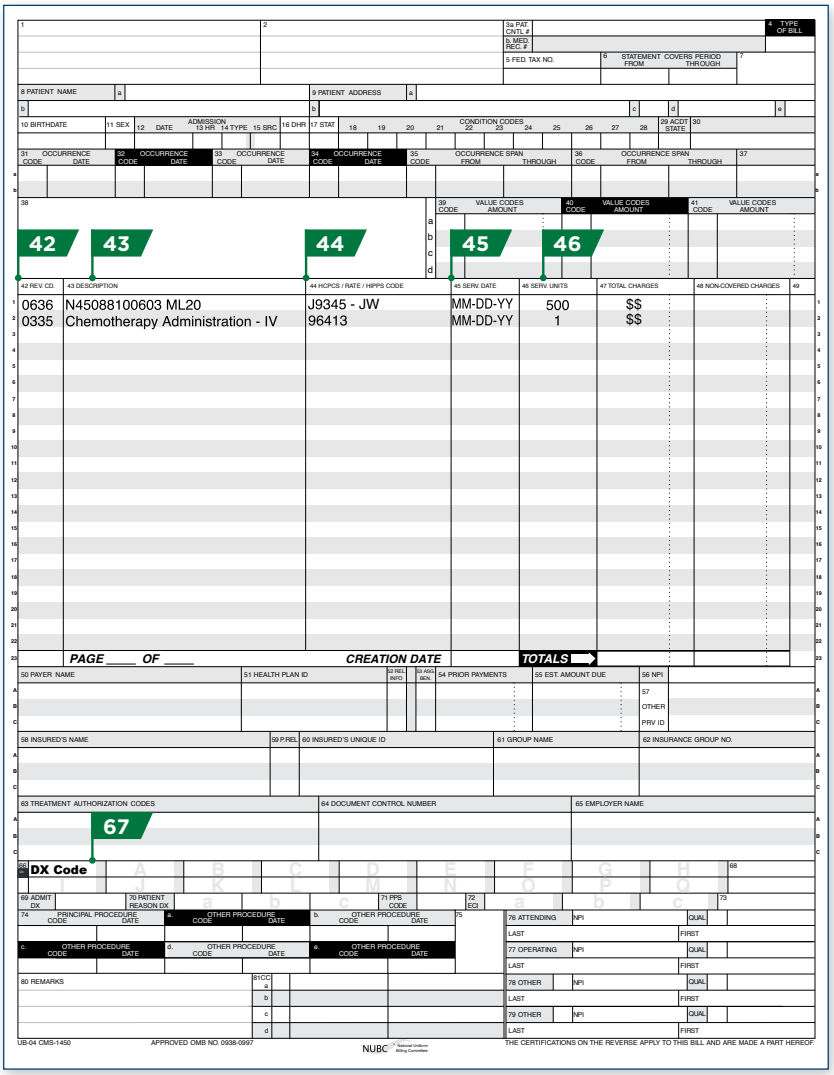
- Drug - J9345 (Injection, retifanlimab-dlwr, 1 mg)
- Modifier – JZ (Include the JZ modifier on the same line as the HCPCS code to indicate no amount of drug was discarded)
- Administration - 96413 (Chemo infusion for 1st hour, single or initial drug)

Box 45
Enter the date of service

Box 46
Enter number of units for each line item

- J9345 Billing Unit = 1 mg
- Single-Dose Vial = 500 mg
- 500 mg Vial = 500 Units

Box 67
Enter the ICD-10-CM diagnosis code



*Always refer to specific payer policies as billing requirements may vary by payer, including use of the 10- or 11-digit NDC.

CPT®, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; NDC, National Drug Code.

IMPORTANT SAFETY INFORMATION (CONT)

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Hepatitis

ZYNYZ can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 3.5% (16/452) of patients, including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (0.9%). Hepatitis led to permanent discontinuation of ZYNYZ in 1.5% of patients and withholding in 1.1%.

Systemic corticosteroids were required in 81% (13/16) of patients. Hepatitis resolved in 9/16 patients.

PROVIDER READINESS – PROCESS & TIPS

ZYNYZ® retifanlimab-dlwr Injection 500 mg

When preparing to treat a patient with ZYNYZ for Squamous Cell Carcinoma of the Anal Canal (SCAC) or Merkel Cell Carcinoma (MCC), consider the steps below to facilitate patient access, proper claims submission, and appropriate reimbursement. For questions or support on any of these steps, please reach out to IncyteCARES for ZYNYZ at **1-855-452-5234** or visit **HCP.IncyteCARES.com/ZYNYZ** to complete an Enrollment Form.

1 — **Research and understand** patient-specific benefits and coverage for ZYNYZ

2 — If there are access concerns, be sure to **enroll your patient** in IncyteCARES to understand potential financial assistance options that may be available for eligible patients

3 — **Schedule the patient** for his or her first ZYNYZ infusion

4 — **Purchase ZYNYZ** (if not already in inventory) through one of the following Specialty Distributors:

SPECIALTY DISTRIBUTORS

CardinalHealth | cencora | McKESSON

Prescribers who do not wish to use buy-and-bill should check with their preferred Specialty Pharmacy for availability. Specialty Pharmacies may obtain access to ZYNYZ through the Specialty Distributors listed above.

5 — After treatment, **complete and submit a claim** to the payer, including all necessary information. If no product was discarded, include the JZ modifier to attest to no wastage

IF YOU HAVE QUESTIONS ABOUT THIS PROCESS,
INCYTECARES AND YOUR FIELD ACCESS MANAGER MAY BE ABLE TO HELP.

Access more information online at **HCP.IncyteCARES.com/ZYNYZ**

Call **1-855-452-5234** **M–F, 8 AM to 8 PM ET**

IMPORTANT SAFETY INFORMATION (CONT)

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

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.

ZYNYZ as a Single Agent: Adrenal insufficiency occurred in 0.9% (4/452) of patients, including Grade 3 (0.4%) and Grade 2 (0.4%). 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 4 patients.

ZYNYZ in Combination with Carboplatin and Paclitaxel: Adrenal insufficiency occurred in 5.8% (9/154) of patients receiving ZYNYZ in combination with carboplatin and paclitaxel, including Grade 3 and Grade 2 (1.9% each). Adrenal insufficiency led to permanent discontinuation of ZYNYZ in 1 patient and withholding of ZYNYZ in 3 patients. All patients required systemic corticosteroids. Adrenal insufficiency resolved in 4 of the 9 patients.

INCYTECARES FOR ZYNYZ

PATIENT SUPPORT PROGRAM OVERVIEW

ZYNYZ® retifanlimab-dlwr Injection 500 mg

When You Enroll a Patient, an IncyteCARES for ZYNYZ Representative Will:

- Call your patient to welcome them and explain their insurance coverage for ZYNYZ
- Assess your patient's eligibility for savings or financial assistance programs,* and help them enroll
- Explain the additional support and resources available to them during treatment

*Terms and conditions apply. Program terms may change at any time.

IncyteCARES

IncyteCARES Supports Your Eligible Patients During Treatment With ZYNYZ

Our mission is to help patients start and stay on therapy by assisting with access and as-needed support.

For Eligible Patients With Commercial Health Insurance

IncyteCARES for ZYNYZ Savings Program

ELIGIBLE PATIENTS CAN RECEIVE ZYNYZ FOR AS LITTLE AS $15, SUBJECT TO CERTAIN LIMITS†

TO QUALIFY, PATIENTS MUST:

- Have commercial healthcare coverage. Patients insured under federal or state government healthcare programs—including Medicare Part B, Medicare Advantage, Medicaid, TRICARE, or any state medical or pharmaceutical assistance program—are not eligible. Patients without healthcare coverage are also not eligible
- Be a resident of the United States or Puerto Rico
- Have a valid prescription for ZYNYZ for an FDA-approved use

†Uninsured, cash-paying, or Alternate Funding Program (AFP) patients are not eligible. Not valid for patients insured through Medicare Part B, Medicare Advantage, Medicaid, TRICARE, or any state medical or pharmaceutical assistance program. Patient enrollment in a copay adjustment program, such as a maximizer or accumulator program, may impact the value of this offer. Annual benefit maximum applies, as may other restrictions. Program benefit applies to medication cost only and does not cover any costs to administer the medication. Valid prescription for ZYNYZ® (retifanlimab-dlwr) for an FDA-approved indication or compendia-recognized use is required. Please see the full **Patient Terms and Conditions** or call IncyteCARES for ZYNYZ at **1-855-452-5234**. Update effective as of January 1, 2024.

IMPORTANT SAFETY INFORMATION (CONT)

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Endocrinopathies (cont)

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 0.7% (3/452) of patients receiving ZYNYZ, including Grade 3 (0.2%) and Grade 2 (0.4%). Hypophysitis led to permanent discontinuation of ZYNYZ in 1 patient and withholding of ZYNYZ in 1 patient.

All patients required systemic steroids. Hypophysitis resolved in 1 of the 3 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% (3/452, all Grade 1) of patients. No patients discontinued or withheld ZYNYZ due to thyroiditis. Thyroiditis resolved in 1 of the 3 patients.

INCYTECARES FOR ZYNYZ

PATIENT SUPPORT PROGRAM OVERVIEW

ZYNYZ® retifanlimab-dlwr Injection 500 mg

Enroll Your Eligible Patients in IncyteCARES for ZYNYZ

Completing the enrollment form takes about 15 minutes.
Simply download and complete the form, then fax it to 1-855-525-7207.

Visit **HCP.IncyteCARES.com/ZYNYZ** for more information

Other Financial Assistance and Support Options

When you enroll your patient in IncyteCARES for ZYNYZ, we will also review their eligibility for the following programs:

For Eligible Patients Who Are Uninsured or Underinsured for ZYNYZ

IncyteCARES for ZYNYZ Patient Assistance Program

For All Patients

Information About Nonprofit or Other Support Organizations

The IncyteCARES Team Is Available by Phone Every Weekday

IncyteCARES

Call **1-855-452-5234**, M–F, 8 AM to 8 PM ET
Visit **HCP.IncyteCARES.com/ZYNYZ** to learn more

IMPORTANT SAFETY INFORMATION (CONT)

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Endocrinopathies (cont)

Hypothyroidism

Hypothyroidism occurred in 10% (46/452) of patients receiving ZYNYZ, including Grade 2 (4.9%). No patients discontinued due to hypothyroidism. ZYNYZ was withheld in 0.4% of patients.

Systemic corticosteroids were required for 1 patient, and 78% (36/46) of patients received endocrine therapy.

Hyperthyroidism

Hyperthyroidism occurred in 6% (26/452) of patients receiving ZYNYZ, including Grade 2 (2.7%). ZYNYZ was not discontinued in any patient and was withheld in 0.4% of patients. Systemic corticosteroids were required for 15% (4/26) of patients, and 50% (13/26) 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% (1/452) of patients, including Grade 3 (0.2%).

IMPORTANT SAFETY INFORMATION (CONT)

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Nephritis with Renal Dysfunction

ZYNYZ can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 2% (9/452) of patients receiving ZYNYZ, including Grade 4 (0.4%), Grade 3 (1.1%), and Grade 2 (0.4%). Nephritis led to permanent discontinuation of ZYNYZ in 1.1% of patients and withholding in 0.7% of patients.

Systemic corticosteroids were required in 67% (6/9) of patients. Nephritis resolved in 4/9 patients.

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 10% (43/452) of patients, including Grade 4 (0.2%), Grade 3 (1.1%), and Grade 2 (8%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation of ZYNYZ in 0.7% of patients and withholding in 2.7% of patients.

Systemic corticosteroids were required in 33% (14/43) of patients. Immune-mediated dermatologic adverse reactions resolved in 72% (31/43) of patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in 452 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, other transplant (including corneal graft) rejection.

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Infusion-Related Reactions

A severe infusion-related reaction (Grade 3) occurred in 5 (0.8%) of 606 patients receiving ZYNYZ. 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.

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

Metastatic or Recurrent Locally Advanced MCC: ZYNYZ as a Single Agent

The safety of ZYNYZ was evaluated in 107 patients with metastatic or recurrent locally advanced MCC.

Serious adverse reactions occurred in 26% 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 21% of patients. These included asthenia, colitis, demyelinating polyneuropathy, diarrhea, drug hypersensitivity, eosinophilic fasciitis, hepatitis, hypophysitis, increased transaminases, infusion-related reaction, pancreatitis, polyarthritis, radiculopathy, toxic epidermal necrolysis, and tubulointerstitial nephritis (1 patient each).

Dosage interruptions due to an adverse reaction occurred in 39% of patients. Adverse reactions or laboratory abnormalities that required dosage interruption in > 2% of patients were increased transaminases, increased lipase, increased amylase, and pyrexia.

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

IMPORTANT SAFETY INFORMATION (CONT)

Adverse Reactions (cont)

Inoperable Locally Recurrent or Metastatic SCAC: ZYNYZ in Combination with Carboplatin and Paclitaxel

The safety of ZYNYZ in patients with inoperable locally recurrent or metastatic SCAC was evaluated in 154 patients enrolled in the POD1UM-303 trial.

Serious adverse reactions occurred in 47% of patients receiving ZYNYZ in combination with carboplatin and paclitaxel. The most frequent serious adverse reactions (≥ 2% of patients) were sepsis (3.2%), pulmonary embolism (3.2%), diarrhea (2.6%), and vomiting (2.6%).

In patients receiving ZYNYZ in combination with carboplatin and paclitaxel, ZYNYZ was permanently discontinued due to an adverse reaction in 11% of patients. Adverse reactions that resulted in permanent discontinuation of ZYNYZ included immune-mediated enterocolitis (2 patients) and warm autoimmune hemolytic anemia, hepatitis, adrenal insufficiency, blood bilirubin increased, AST increased, blood alkaline phosphatase increased, arthritis, encephalopathy, peripheral sensorimotor neuropathy, hypothyroidism, immune-mediated cholangitis, pruritus, malaise, and rash (1 patient each).

Dosage interruptions due to an adverse reaction, excluding temporary interruptions due to infusion-related reactions, occurred in 55% of patients who received ZYNYZ in combination with carboplatin and paclitaxel. Adverse reactions that resulted in dosage interruptions in ≥ 2% of patients were neutropenia, anemia, thrombocytopenia, leukopenia, fatigue, COVID-19, and urinary tract infection.

The most common (≥ 20%) adverse reactions were fatigue, peripheral neuropathy, nausea, alopecia, diarrhea, musculoskeletal pain, constipation, hemorrhage, rash, vomiting, decreased appetite, pruritus, and abdominal pain.

Platinum-refractory Intolerant Locally Recurrent or Metastatic SCAC: ZYNYZ as a Single Agent

The safety of ZYNYZ in patients with platinum-refractory intolerant locally recurrent or metastatic SCAC was evaluated in 94 patients in the POD1UM-202 trial.

Serious adverse reactions occurred in 40% of patients receiving ZYNYZ. The most frequent serious adverse reactions (≥ 2% of patients) were non-urinary tract infection, perineal pain, abdominal pain, anemia, hemorrhage, diarrhea, pyrexia, urinary tract infection, musculoskeletal pain, and dyspnea.

Permanent discontinuation of ZYNYZ due to an adverse reaction occurred in 4.3% of patients. These adverse reactions included diarrhea, non-urinary tract infection, perineal pain, and rash.

Dosage interruptions due to an adverse reaction occurred in 21% of patients who received ZYNYZ. Adverse reactions that resulted in dose delay in ≥ 2% of patients who received ZYNYZ were non-urinary tract infection, rash, diarrhea, abdominal pain, hemorrhage, musculoskeletal pain, pyrexia, and urinary tract infection.

The most common (≥ 10%) adverse reactions that occurred in patients receiving ZYNYZ were fatigue, musculoskeletal pain, diarrhea, non-urinary tract infections, perineal pain, hemorrhage, urinary tract infection, rash, nausea, decreased appetite, constipation, abdominal pain, dyspnea, pyrexia, vomiting, cough, pruritus, hypothyroidism, headache, and decreased weight.

Please see the Full Prescribing Information.

ZYNYZ®
retifanlimab-dlwr
Injection 500 mg