ZYNYZ™
retifanlimab-dlwr
Injection 500 mg

BILLING AND CODING GUIDE

- Introduction
- Coverage, Coding, and Payment in the Physician Office Setting
- Coverage, Coding, and Payment in the Hospital Outpatient Setting
- Miscellaneous J-Code Guide
- Provider Readiness - Process and Tips
- IncyteCARES - Program Overview

Please note this information is provided for your background education 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.

Introduction

This Billing and Coding Guide is intended to provide an overview of ZYNYZ™ (retifanlimab-dlwr) coding and coverage information. Please use this guide to support the reimbursement process and as a source of information on services available through IncyteCARES for ZYNYZ.

While this guide provides information on navigating the reimbursement process, please note all enclosed coding information is for reference purposes only. 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.

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

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.

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. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1–blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1–blocking antibodies, they can also manifest after discontinuation of PD-1/PD-L1–blocking antibodies. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1–blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, 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. Upon improvement to ≤ Grade 1, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed subsequently.

Immune-Mediated Pneumonitis

ZYNYZ can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

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

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Coverage, Coding, and Payment in the Physician Office Setting

For Medicare patients, ZYNYZ™ (retifanlimab-dlwr) 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 Medicaid, a Medicare Advantage plan, or a commercial health plan, coverage of ZYNYZ will vary by payer. Some payers may also apply utilization restrictions for ZYNYZ.

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.

Please refer to the table below to support appropriate claims processing for ZYNYZ.

MCC ICD-10-CM DIAGNOSIS CODES

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

ZYNYZ DRUG AND ADMINISTRATION CODES

National Drug Code (NDC)	Drug Administration / CPT Codes	Physician Office Setting
10-digit: 50881-006-03 11-digit: 50881-**0**006-03	**96413** (Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial drug)	**J3490** (Unclassified drugs), **J3590** (Unclassified biologics), **J9999** (Not otherwise classified, antineoplastic drugs)

PAYMENT METHODOLOGY

Medicare	Commercial Payers and Medicaid
Wholesale Acquisition Cost (WAC) +3%[a]	Most non-Medicare payers will pay separately for ZYNYZ; however payment rates will vary by payer and provider contract

[a] Medicare reimbursement for a newly approved product is typically WAC +3% until Average Sales Price (ASP) is established.

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Miscellaneous Coding and Billing Reference Guide
Example CMS-1500 Claim Form – Physician Office Setting

This example form is provided for guidance and reference only.

ZYNYZ™ (retifanlimab-dlwr) and the associated services provided in the physician's office are billed on the CMS-1500 Claim Form or its electronic equivalent. An example CMS-1500 Claim Form is provided below. 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
Payers require drug name, route of administration, NDC, and total dosage

Check with your payer to verify specific requirements, including use of the 10-digit or 11-digit NDC

Box 21
Enter appropriate diagnosis code(s)

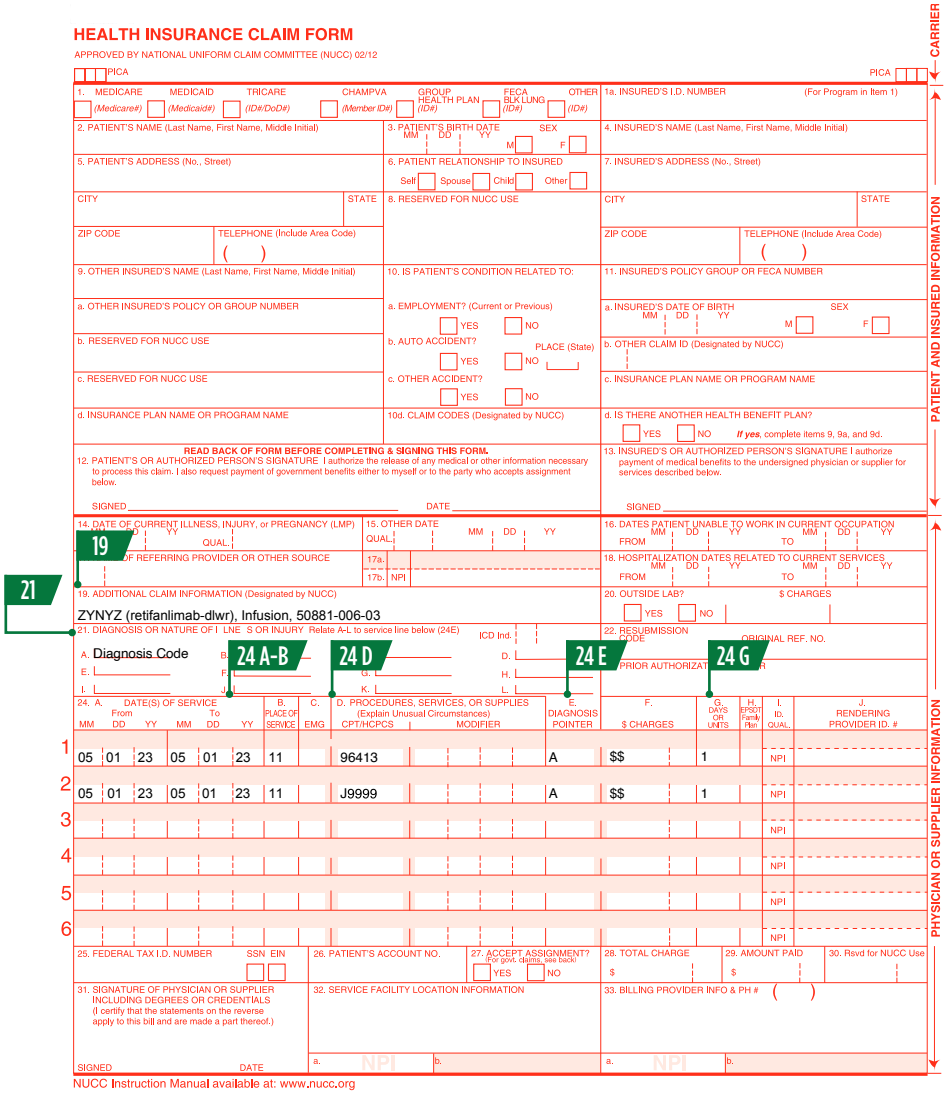
Box 24 A-B
Enter the date of service and the appropriate place of service code

Box 24 D
Enter the appropriate drug and administration codes, for example:

- Drug - J9999 (not otherwise classified, anti-neoplastic drugs)
- Administration - 96413 (chemo infusion for 1st hour, single or initial drug)

Box 24 E
Specify the diagnosis, from Box 21, that relates to the drug or procedure listed in Box 24 D

Box 24 G
Enter the number of service units for each line item



IMPORTANT SAFETY INFORMATION (CONT'D)

Systemic corticosteroids were required in 77% (10/13) of patients with pneumonitis. Pneumonitis resolved in 10 of the 13 patients. Of the 4 patients in whom ZYNYZ was withheld for pneumonitis, 3 reinitiated ZYNYZ after symptom improvement; of these, 1 had recurrence of pneumonitis.

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

Coverage, Coding, and Payment in the Hospital Outpatient Setting

For Medicare patients, ZYNYZ™ (retifanlimab-dlwr) 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 Medicaid, a Medicare Advantage plan, or a commercial health plan, coverage of ZYNYZ will vary by payer. Some payers may also apply utilization restrictions for ZYNYZ.

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.

Please refer to the table below to support appropriate claims processing for ZYNYZ.

MCC ICD-10-CM DIAGNOSIS CODES

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

ZYNYZ DRUG AND ADMINISTRATION CODES

National Drug Code (NDC)	Drug Administration / CPT Codes	Hospital Outpatient Setting
10-digit: 50881-006-03 11-digit: 50881-**0**006-03	**96413** (Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial drug)	**Non-Medicare OPPS: J3490** (Unclassified drugs), **J3590** (Unclassified biologics), **J9999** (Not otherwise classified, antineoplastic drugs) **Medicare OPPS: C9399** (Unclassified drugs or biologics)

PAYMENT METHODOLOGY

Medicare	Commercial Payers and Medicaid
Wholesale Acquisition Cost (WAC) +3%[a]	Most non-Medicare payers will pay separately for ZYNYZ; however payment rates will vary by payer and provider contract

[a] Medicare reimbursement for a newly approved product is typically WAC +3% until Average Sales Price (ASP) is established.
OPPS, Outpatient Prospective Payment System.

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Miscellaneous Coding and Billing Reference Guide
Example CMS-1450 Claim Form – Hospital Outpatient Setting

This example form is provided for guidance and reference only.

ZYNYZ™ (retifanlimab-dlwr) and the associated services provided in a hospital outpatient setting are billed on the CMS-1450 Claim Form or its electronic equivalent. An example CMS-1450 Claim Form is provided below. 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 that are billed with HCPCS codes usually require revenue code 0636 (drugs requiring detailed coding)

Box 43
For each item, enter the description of the revenue code used

Box 44
Enter the appropriate HCPCS codes, for example:

- Drug - C9399 (unclassified drugs or biologicals)
- Administration - 96413 (chemo infusion for 1st hour, single or initial drug)

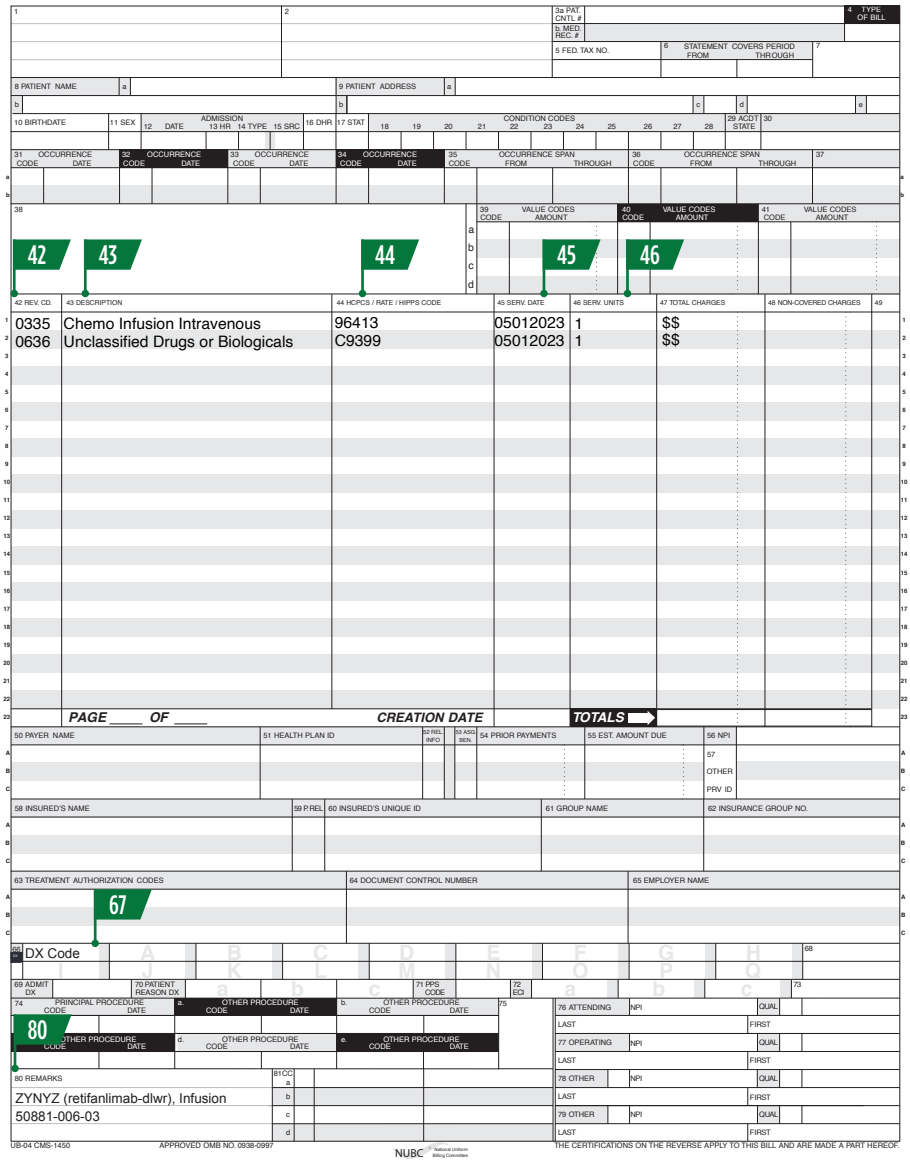
Box 45
Enter the service date

Box 46
Enter the number of service units for each line item

Box 67
Enter the primary diagnosis code

Box 80
Payers require drug name, route of administration, NDC, and total dosage

Check with your payer to verify specific requirements, including use of the 10-digit or 11-digit NDC



IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Colitis

ZYNYZ can cause immune-mediated colitis. Cytomegalovirus infection/reactivation 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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Miscellaneous Code Guide

Permanent J-codes are typically not assigned immediately upon FDA approval of a new product. To support appropriate patient access, use the following information to help navigate the reimbursement process during the miscellaneous J-code (or C-code in the hospital outpatient setting).

What is an unclassified or miscellaneous code?

A miscellaneous code is used when there is no permanent code to describe a medication or service being billed. A miscellaneous code is also used when a new, permanent J-code under the HCPCS II system has not yet been assigned.

Will I receive reimbursement if I bill using a miscellaneous code?

J-codes are typically reimbursed if aligned with payer policies. Understanding a payer's specific process and instructions is important when submitting a claim for reimbursement. Please refer to the tips below and contact the respective payer for more information.

Which unclassified or miscellaneous code should I use?

Until a permanent J-code is assigned for ZYNYZ™ (retifanlimab-dlwr), the appropriate HCPCS codes to use depend on payer preference and can include:

- **J9999** (not otherwise classified, antineoplastic drugs)
- **J3490** (unclassified drugs)
- **J3590** (unclassified biologics)
- **C9399** (unclassified drugs or biologicals)

Always consult a payer's specific policies to ensure you are using the appropriate miscellaneous codes for payer-specific reimbursement needs.

What can I do to support timely reimbursement of ZYNYZ claims?

- **Verify accuracy** of patient information
- **Check your payer agreements** to ensure you understand the reimbursement for a miscellaneous J-code or C-code, as it may differ from your traditional billing rates
- **Refer to the ZYNYZ Billing and Coding Guide** for appropriate codes (e.g., HCPCS, CPT, ICD-10-CM)
  - Special billing instructions may be required in Box 19 of the CMS-1500 Claim Form (Additional Claim Information) to ensure the payer has enough information to adjudicate the claim correctly
- **Include correct number** of units administered
- **Ensure accuracy** of the following information needed to process the claim:
  - Correct NDC Format (use 10- or 11-digit format based on payer requirements)
  - Prior Authorization Number (if applicable)
- **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

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.

For Billing and Coding or Reimbursement Questions,
or to Request Support From a Field Access Manager,
Call 1-855-452-5234, M-F 8 AM to 8 PM ET

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Provider Readiness—Process and Tips

When preparing to treat a patient with ZYNYZ™ (retifanlimab-dlwr) as prescribed, 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 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 and accounting for any unused portion of the product (wastage), if required by the payer

IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-mediated colitis occurred in 1.6% (7/440) of patients receiving ZYNYZ, 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 of ZYNYZ in 0.9% of patients.

Systemic corticosteroids were required in 71% (5/7) of patients. Colitis resolved in 4 of the 7 patients. Of the 4 patients in whom ZYNYZ was withheld for colitis, 1 reinitiated ZYNYZ after symptom improvement; this patient did not have recurrence of colitis.

Immune-Mediated Hepatitis

ZYNYZ can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 3% (13/440) of patients receiving ZYNYZ, 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 of ZYNYZ in 0.9% of patients.

Systemic corticosteroids were required in 85% (11/13) of patients. Hepatitis resolved in 6 of the 13 patients. Of the 4 patients in whom ZYNYZ was withheld for hepatitis, 2 reinitiated ZYNYZ after symptom improvement; of these, 1 had recurrence of hepatitis.

IncyteCARES

Contact IncyteCARES at
1-855-452-5234 or
HCP.IncyteCARES.com/ZYNYZ

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IncyteCARES – Program Overview

We're Here to Support Your Eligible Patients During Treatment

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

When You Enroll a Patient, an IncyteCARES Representative Will:

- Call your patient to welcome them and explain their insurance coverage for ZYNYZ™ (retifanlimab-dlwr)
- Assess patient's eligibility for 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.

For Eligible Patients With Commercial Prescription 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 prescription drug coverage. Patients insured under federal or state government healthcare programs—including Medicare Part B, Medicare Advantage, Medicaid, TRICARE or any state or medical or pharmaceutical assistance program—are not eligible. Patients without prescription drug 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

† Maximum benefits per claim and per calendar year apply. Program benefit applies to medication cost only and does not cover any costs to administer the medication. Uninsured, cash-paying patients are not eligible. Not valid for patients insured through Medicare Part B, Medicare Advantage, Medicaid, and TRICARE or any state medical or pharmaceutical assistance program. Offer valid only for an FDA-approved indication or recognized compendia use for ZYNYZ™ (retifanlimab-dlwr). Please see full criteria for eligibility at www.IncyteCARES.com or call IncyteCARES for ZYNYZ. Update effective as of January 1, 2023.

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 receiving ZYNYZ, including Grade 3 (0.5%) and Grade 2 (0.2%). Adrenal insufficiency did not lead to permanent discontinuation of ZYNYZ. ZYNYZ 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. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue ZYNYZ depending on severity.

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IncyteCARES – Program Overview

Enroll Your Eligible Patients in IncyteCARES for ZYNYZ™ (retifanlimab-dlwr)

Completing the enrollment form takes about 15 minutes. Simply download, complete, and fax it. 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

Questions?
Call IncyteCARES for ZYNYZ at 1-855-452-5234,
Monday through Friday, 8 AM - 8 PM ET

Please see HCP.IncyteCARES.com/ZYNYZ for full program terms and conditions.

IMPORTANT SAFETY INFORMATION (CONT'D)

Hypophysitis occurred in 0.5% (2/440, both Grade 2) of patients receiving ZYNYZ. 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 receiving ZYNYZ. 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 ZYNYZ due to hypothyroidism. Hypothyroidism led to withholding of ZYNYZ 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%). No patients discontinued ZYNYZ due to hyperthyroidism. Hyperthyroidism led to withholding of ZYNYZ in 1 patient. Systemic corticosteroids were required for 13% (3/24) of patients and 46% (11/24) of patients received endocrine therapy.

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IMPORTANT SAFETY INFORMATION (CONT'D)

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™ (retifanlimab-dlwr) depending on severity.

Type 1 diabetes mellitus occurred in 0.2% (1/440) of patients receiving ZYNYZ, including Grade 3 (0.2%) adverse reactions. Type 1 diabetes mellitus led to withholding of ZYNYZ in 1 patient. This event led to ZYNYZ being withheld and did not lead to permanent discontinuation of ZYNYZ. The patient received insulin.

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 of ZYNYZ in 1 patient.

Systemic corticosteroids were required in 57% (4/7) of patients. Nephritis resolved in 3 of the 7 patients. The 1 patient in whom ZYNYZ was withheld for immune-mediated nephritis had ZYNYZ reinitiated after symptom improvement and did not have recurrence of immune-mediated nephritis.

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 receiving ZYNYZ, 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 of ZYNYZ 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. Of the 10 patients in whom ZYNYZ was withheld for immune-mediated dermatologic adverse reactions, 7 reinitiated ZYNYZ after symptom improvement; of these, 1 had recurrence of immune-mediated dermatologic adverse reactions.

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 receiving ZYNYZ. Monitor patients for signs and symptoms of infusion-related reactions. 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.

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IMPORTANT SAFETY INFORMATION (CONT'D)

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). These complications 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

Based on its mechanism of action, ZYNYZ™ (retifanlimab-dlwr) 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 with ZYNYZ and for 4 months after the last dose.

Adverse Reactions

The safety of ZYNYZ was evaluated in 105 patients enrolled in the POD1UM-201 trial 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 who received ZYNYZ. Adverse reactions or laboratory abnormalities that required dosage interruption in ≥ 2% of patients who received ZYNYZ were increased transaminases, increased lipase, increased amylase, pneumonitis, and pyrexia.

The most common (≥ 10%) adverse reactions that occurred in patients receiving ZYNYZ were fatigue, musculoskeletal pain, pruritus, diarrhea, rash, pyrexia, and nausea.

Specific Populations

Based on its mechanism of action, ZYNYZ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ZYNYZ in pregnant women. Human IgG4 immunoglobulins are known to cross the placenta; therefore, retifanlimab-dlwr has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

There is no information regarding the presence of retifanlimab-dlwr in human milk, or its effects on the breastfed child or on milk production. 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 of ZYNYZ.

ZYNYZ can cause fetal harm when administered to a pregnant woman.

Verify pregnancy status in females of reproductive potential prior to initiating ZYNYZ.

Advise females of reproductive potential to use effective contraception during treatment with ZYNYZ and for 4 months after the last dose.

The safety and effectiveness of ZYNYZ have not been established in pediatric patients.

Of the 65 patients with metastatic or recurrent locally advanced MCC treated with ZYNYZ, 79% were ≥ 65 years, and 37% were ≥ 75 years. Clinical studies of ZYNYZ did not include sufficient numbers of younger adult patients to determine if patients ≥ 65 years of age respond differently than younger adult patients.

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.

ZYNYZ™
retifanlimab-dlwr
Injection 500 mg

ZYNYZ™

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Injection 500 mg