ZYNYZ®
retifanlimab-dlwr
Injection 500 mg

MEDICAL EXCEPTIONS & COVERAGE GUIDE

- **What is a Medical Exception?**
- **Securing Coverage for Eligible Patients**
- **Coverage & Appeals Letter Templates**
- **IncyteCARES for ZYNYZ – Patient Support 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.

WHAT IS A MEDICAL EXCEPTION?

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When a product is not covered by an insurance plan, it is often referred to as non-formulary or as requiring a medical exception for coverage consideration.

A medical exception refers to the process in which a healthcare professional requests that a payer consider covering a product that is not typically approved or covered for a specific patient, based on medical necessity. When a healthcare professional determines that a drug is medically necessary, they can demonstrate this by submitting the appropriate documentation and requesting payer approval for the treatment.

When a drug is newly approved, or approved for an additional indication, a medical exception is commonly sought during the period before a payer has determined coverage or established a medical policy.

Prior authorizations (PAs) are standard for many oncology therapies and require accompanying documentation. If a PA is denied, the medical exception request process can be used as a PA appeal, and the same forms and processes can typically be used.

Like the traditional PA process, the medical exception request process varies by payer. It is crucial to follow the necessary steps, provide all required documentation, and ensure that the correct forms are submitted.

WHAT INFORMATION IS REQUIRED, AND WHERE CAN I FIND IT?

COMMERCIAL

You can obtain information about the medical exception request process for a specific payer by contacting the payer's provider relations department or checking their online resources.

Additionally, IncyteCARES may be able to provider payer-specific details as needed.

MEDICARE

Medicare Part B does not require a PA. Medicare Advantage plans may utilize a PA or a medical exception process for ZYNYZ.

Specific requirements related to a given Medicare Advantage plan may be obtained by contacting the plan directly, and may also be available online.

IncyteCARES

For Assistance in Obtaining Payer-Specific Details and Forms

Contact IncyteCARES at 1-855-452-5234

INDICATIONS & 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.

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.

Please see additional Important Safety Information throughout.
Please see the Full Prescribing Information.

SECURING COVERAGE FOR ELIGIBLE PATIENTS

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A patient's health plan may request additional information before approving coverage for treatment. In your efforts to secure coverage for ZYNYZ for an individual patient, you may need to provide one or more supporting letters. Template versions of these letters are available on the following pages.

Please refer to the checklist below to help you create accurate payer correspondence to support your ZYNYZ patients.

CHECKLIST FOR PAYER CORRESPONDENCE

✔ PATIENT INFORMATION

- ☐ Patient Name
- ☐ Date of Birth
- ☐ Insurance Carrier
- ☐ Insurance ID
- ☐ Insurance Group Number
- ☐ Case ID Number (if applicable)

✔ CLINICAL RATIONALE FOR MEDICAL NECESSITY

- ☐ Patient's diagnosis for a condition ZYNYZ is FDA-approved to treat
- ☐ Severity of patient's condition, patient's performance status
- ☐ Summary of patient's previous treatments, including the duration of each treatment, response to past treatments, rationale for discontinuation, and recent symptoms / condition. Include coding information for prior treatments / services if available
- ☐ Patient's disease progression
- ☐ Clinical rationale for ZYNYZ treatment, including clinical trial data supporting FDA approval, administration, and dosage information

✔ ADDITIONAL ENCLOSURES

- ☐ ZYNYZ Full Prescribing Information **(www.ZYNYZHCP.com/SCAC)**
- ☐ Clinical Notes / Medical Records
- ☐ FDA Approval Information **(www.fda.gov/drugsatfda)**
- ☐ Relevant Peer-Reviewed Articles

IF YOU HAVE QUESTIONS ABOUT APPEALS OR MEDICAL EXCEPTIONS,
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'D)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

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.
Please see the Full Prescribing Information.

COVERAGE & APPEALS LETTER TEMPLATES

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The following template letters are included to help support the development of payer-specific communications in the event of medical policy restrictions, prior authorizations, and/or denials.

1. **Medical Exception Request**

   If ZYNYZ is not available on the payer's medical policy, you may want to submit a Medical Exception Request

2. **Letter of Medical Necessity**

   If the payer's medical policy includes a prior authorization for the patient to be treated with ZYNYZ, you can submit a Letter of Medical Necessity

3. **Letter of Appeal**

   If you have experienced a health plan's denial of coverage for ZYNYZ and would like to appeal, you can submit a Letter of Appeal

Fillable versions of these letters are available on the IncyteCARES for ZYNYZ website at **HCP.IncyteCARES.com/ZYNYZ**

Some health plans may require supporting documentation with your outreach. This documentation could include relevant patient medical history, treatment records, and chart documentation. Additionally, some payers may request further information, so it is always advisable to check directly with the payer to identify any specific requirements they may have.

To avoid delays in a coverage decision, it is recommended that you provide as much documentation as possible when submitting your requests. For additional detail, please refer to the checklist on page 3.

Note - supplying information in your request does not guarantee coverage for ZYNYZ and this information is not intended to substitute or influence a physician's independent medical judgment.

QUESTIONS ABOUT BILLING OR REIMBURSEMENT?

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

IMPORTANT SAFETY INFORMATION (CONT'D)

Severe and Fatal Immune-Mediated Adverse Reactions (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.

Please see additional Important Safety Information throughout.
Please see the Full Prescribing Information.

MEDICAL EXCEPTION REQUEST

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This template letter is not meant to be used as a form letter. You should customize this letter to reflect the unique background and diagnosis of a particular patient, as well as the special requirements of the particular payer involved. The provider is responsible for ensuring the medical necessity of the procedure.

Be sure to describe the coverage restriction in detail

In this section, include any previous treatment the patient has received so the insurer does not request a treatment that may not be appropriate for your patient

Be specific in this section so the insurer can make informed and timely decisions

A FILLABLE VERSION OF THIS LETTER IS AVAILABLE ON HCP.IncyteCARES.com/ZYNYZ

<<Date>>
<<Payer Name>>
<<Payer Street Address>>
<<Payer City, State, and ZIP Code>>

Re: Medical Exemption Request

Patient Name: <<Patient Name>>
Date of Birth: <<Patient Date of Birth>>
Member ID: <<Patient Member ID Number>>
Policy or Group Number: <<Patient Policy or Group Number>>
Case ID Number: <<Patient Case ID Number>>

To Whom It May Concern:

I understand that the <<Plan Name>> policy for <<Patient Name>> requires <<Restriction Description>> prior to approving treatment with <<Product Name(s)>>. However, I believe that <<Patient Name>> requires <<Product Name(s)>> without <<Restriction Description>> due to clinical and medical circumstances.

Please see below for details about symptoms, previous treatments, medical history, and treatment rationale that supports the claim for medical exception for <<Patient Name>>.

Patient Clinical/Medical History

ICD-10-CM diagnosis code: <<ICD-10-CM Diagnosis Code>>
Date of diagnosis: <<Date of Diagnosis>>
Date of patient's first visit: <<Date of Patient's First Visit>>
Date of referral: <<Date of Referral>>
Patient's performance status: <<Patient's Performance Status>>
Prior treatments including product name, duration, and response: <<Prior Treatments>>
Reason for discontinuation: <<Reason for Discontinuation>>
Patient's disease progression history: <<Patient's Disease Progression History>>
Other factors impacting product treatment selection: <<Other Factors Impacting Product Treatment Selection>>

Justification for Medical Exception

Clinical rationale for treatment with product name(s): <<Clinical Rationale>>
Why plan requirement is not appropriate for patient: <<Why Plan Requirement Is Not Appropriate for Patient>>
Concerns: <<Concerns>>

Treatment Plan

Product name(s): <<Product Name(s)>>
How administered (oral, IV infusion, topical): <<How Administered>>
Dosage frequency: <<Dosage Frequency>>
Duration of treatment: <<Duration of Treatments>>
Treatment schedule: <<Treatment Schedule>>

Summary

Based on the above information, I hope you agree <<Product Name(s)>> is an appropriate treatment for <<Patient Name>>. A timely approval of <<Product Name(s)>> by <<Payer Name>> without <<Restriction Description>> would be greatly appreciated by myself and my patient. If you have any questions about approving this medical exception, please do not hesitate to call me at <<Phone Number>>. Thank you for your prompt attention.

Sincerely,
<<Physician Name, Degree Initials>>
<<Provider Identification Number>>
<<Physician Address>>

Enclosures:
<<List Relevant Enclosures, Such as Prescribing Information, Patient Medical History>>

IMPORTANT SAFETY INFORMATION (CONT'D)

Severe and Fatal Immune-Mediated Adverse Reactions (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.

ZYNYZ as a Single Agent: 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.

LETTER OF MEDICAL NECESSITY

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This template letter is not meant to be used as a form letter. You should customize this letter to reflect the unique background and diagnosis of a particular patient, as well as the special requirements of the particular payer involved. A prior authorization allows the payer to review the reason for the requested therapy and to determine medical appropriateness. A patient-specific letter of medical necessity will help to explain the rationale and clinical decision making in choosing a therapy.

IMPORTANT!

You must include your patient's medical history, diagnosis, and treatment plan or the health plan cannot make a coverage determination

In order to substantiate your request for ZYNYZ coverage, you should include any supporting documents that will assist the insurer in making a decision

A FILLABLE VERSION OF THIS LETTER IS AVAILABLE ON HCP.IncyteCARES.com/ZYNYZ

<<Date>>
<<Contact Name of Medical Director or Other Payer Representative>>
<<Contact Title>>
<<Name of Health Insurance Company>>
<<Address>>
<<City, State, Zip>>

Re: Letter of Medical Necessity for <<Product>> <<Strength>>

Patient: <<Patient Name>>
Group/policy Number: <<Number>>
Date(s) of service: <<Dates>>
Diagnosis: <<Code & Description>>

Dear <<Insert Contact Name or Department>>:

I am writing on behalf of my patient, <<Patient Name>>, to <<Request Prior Authorization/Document Medical Necessity>> for treatment with <<Product>>.
<<Product>> is indicated for treatment of <<Indication Statement>>. This letter serves to document that <<Patient Name>> has a diagnosis of <<Diagnosis>> and needs treatment with <<Product>>, and that <<Product>> is medically necessary for <<Him/Her>> as prescribed. On behalf of the patient, I am requesting approval for use and subsequent payment for the treatment.

Patient Medical History and Diagnosis
<<Patient Name>> is a <<Age>>-year-old <<Male/Female>> diagnosed with <<Diagnosis>>. <<Name Of Patient>> has been in my care since <<Date>>. As a result of <<Diagnosis>>, my patient <<Enter Brief Description of Patient History>>.
Additionally, <<Patient>> has tried <<Previous Therapies>> and <<Outcomes>>. The attached medical records document <<Patient Name>>'s clinical condition and medical necessity for treatment with <<Product>>.

Based on the above facts, I am confident that you will agree that <<Product>> is indicated and medically necessary for this patient. The plan of treatment is to start the patient on <<Product>>, monitor platelet count and response to therapy and adjust dose accordingly.

Please consider coverage of <<Product>> on <<Patient Name>>'s behalf, and approve use and subsequent payment for <<Product>> as planned. Please refer to the enclosed Prescribing Information for <<Product>>. If you have any questions regarding this matter, please do not hesitate to call me at <<Physician Telephone Number>>. Thank you for your prompt attention.

Sincerely,
<<Physician Name>>, <<Degree Initials>>
<<Provider Identification Number>>

Enclosures:
Prescribing Information (PI)
<<Clinic Notes & Labs If Applicable>>

IMPORTANT SAFETY INFORMATION (CONT'D)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

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.

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.

LETTER OF APPEAL

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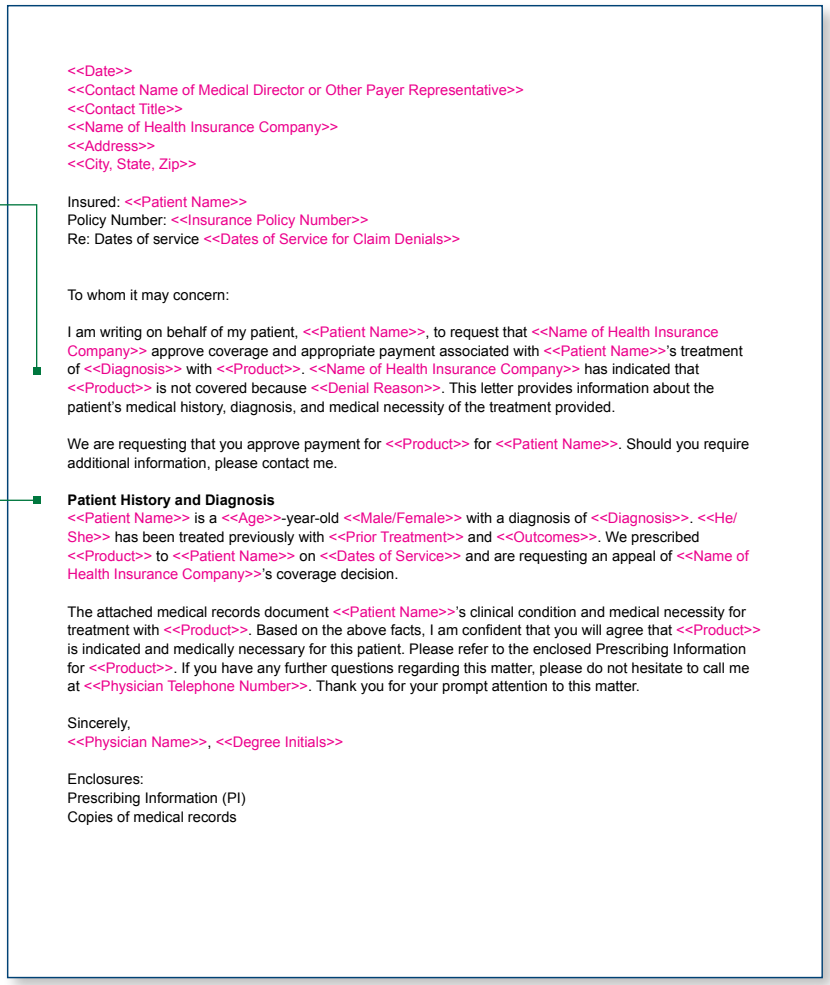
This template letter is not meant to be used as a form letter. You should customize this letter to reflect the unique background and diagnosis of a particular patient, as well as the special requirements of the particular payer involved. Responding to an insurer's denial of coverage with a detailed, patient-specific letter of appeal which includes information on the patient's history and diagnosis will help expedite the appeal process.

It is important to include a detailed description of the denial as including specific information may reduce the appeal process timeline and mitigate additional requests for information

By including the patient's detailed history, you highlight the rationale for the insurer to cover ZYNYZ. It is particularly important to emphasize the severity of your patient's condition, previous treatments, and the patient's failure on prior treatments

A FILLABLE VERSION OF THIS LETTER IS AVAILABLE ON HCP.IncyteCARES.com/ZYNYZ



<<Date>>
<<Contact Name of Medical Director or Other Payer Representative>>
<<Contact Title>>
<<Name of Health Insurance Company>>
<<Address>>
<<City, State, Zip>>

Insured: <<Patient Name>>
Policy Number: <<Insurance Policy Number>>
Re: Dates of service <<Dates of Service for Claim Denials>>

To whom it may concern:

I am writing on behalf of my patient, <<Patient Name>>, to request that <<Name of Health Insurance Company>> approve coverage and appropriate payment associated with <<Patient Name>>'s treatment of <<Diagnosis>> with <<Product>>. <<Name of Health Insurance Company>> has indicated that <<Product>> is not covered because <<Denial Reason>>. This letter provides information about the patient's medical history, diagnosis, and medical necessity of the treatment provided.

We are requesting that you approve payment for <<Product>> for <<Patient Name>>. Should you require additional information, please contact me.

Patient History and Diagnosis
<<Patient Name>> is a <<Age>>-year-old <<Male/Female>> with a diagnosis of <<Diagnosis>>. <<He/She>> has been treated previously with <<Prior Treatment>> and <<Outcomes>>. We prescribed <<Product>> to <<Patient Name>> on <<Dates of Service>> and are requesting an appeal of <<Name of Health Insurance Company>>'s coverage decision.

The attached medical records document <<Patient Name>>'s clinical condition and medical necessity for treatment with <<Product>>. Based on the above facts, I am confident that you will agree that <<Product>> is indicated and medically necessary for this patient. Please refer to the enclosed Prescribing Information for <<Product>>. If you have any further questions regarding this matter, please do not hesitate to call me at <<Physician Telephone Number>>. Thank you for your prompt attention to this matter.

Sincerely,
<<Physician Name>>, <<Degree Initials>>

Enclosures:
Prescribing Information (PI)
Copies of medical records

IMPORTANT SAFETY INFORMATION (CONT'D)

Severe and Fatal Immune-Mediated Adverse Reactions (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.

ZYNYZ as a Single Agent: 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.

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.

Please see additional Important Safety Information throughout.
Please see the Full Prescribing Information.

INCYTECARES FOR ZYNYZ

PATIENT SUPPORT PROGRAM OVERVIEW

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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.
SCAC, Squamous Cell Carcinoma of the Anal Canal.

IncyteCARES

IncyteCARES Supports Your Eligible Patients With SCAC 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'D)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

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.

Please see additional Important Safety Information throughout.
Please see the Full Prescribing Information.

INCYTECARES FOR ZYNYZ

PATIENT SUPPORT PROGRAM OVERVIEW

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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'D)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

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.

Please see additional Important Safety Information throughout.
Please see the Full Prescribing Information.

IMPORTANT SAFETY INFORMATION (CONT'D)

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Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

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.

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, other transplant (including corneal graft) rejection.

Infusion-Related Reactions

A severe infusion-related reaction (Grade 3) occurred in 1 (0.2%) of 440 patients receiving ZYNYZ as a single agent. 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

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