HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use UNLOXCYT safely and effectively. See full prescribing information for UNLOXCYT.

UNLOXCYT (cosibelimab-ipdl) injection, for intravenous use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------
UNLOXCYT is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of adults with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation. (1.1)

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage of UNLOXCYT is 1,200 mg as an intravenous infusion over 60 minutes every 3 weeks. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 300 mg/5 mL (60 mg/mL) solution in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Immune-Mediated Adverse Reactions (5.1)
  - Immune-mediated adverse reactions can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue UNLOXCYT based on the severity of reaction. (2.2)
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue based on severity of reaction. (2.2, 5.2)
- Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT): Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥10%) were fatigue, musculoskeletal pain, rash, diarrhea, hypothyroidism, constipation, nausea, headache, pruritus, edema, localized infection, and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised date: 11/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

1

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

UNLOXCYT is indicated for the treatment of adults with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.

2. DOSAGE AND ADMINISTRATION

2.1. Recommended Dosage

The recommended dosage of UNLOXCYT is 1,200 mg administered as an intravenous infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity.

2.2. Dose Modifications for Adverse Reactions

No dose reductions of UNLOXCYT are recommended. In general, withhold UNLOXCYT for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue UNLOXCYT for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to a prednisone equivalent of 10 mg or less per day within 12 weeks of initiating steroids.

Dosage modifications for UNLOXCYT for adverse reactions that require management different from these general guidelines are summarized in Table 1.

Table 1: Recommended Dose Modifications for Adverse Reactions

Adverse Reaction	**Severity[a]**	**UNLOXCYT Dosage Modifications**
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[b]
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to	Withhold[b]

Adverse Reaction	Severity[a]	UNLOXCYT Dosage Modifications
	more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies[d]	Grade 3 or 4	Withhold until clinically stable or permanently discontinue, depending on severity[b]
Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[b]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold[b]
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[b]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

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

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 5.

[b] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce corticosteroid to a prednisone equivalent of 10 mg/day or less within 12 weeks of initiating steroids.

[c] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue UNLOXCYT based on recommendations for hepatitis with no tumor involvement of the liver.

[d] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

2.3. Preparation and Administration

Visually inspect the vial for particulate matter and discoloration. UNLOXCYT is clear to opalescent, colorless to yellow or slightly brown. Discard the vial if visible particles are observed.

Do not shake the vial.

Preparation for Intravenous Infusion:

- Add 20 mL (1,200 mg) of UNLOXCYT to a 250 mL intravenous infusion bag containing 0.9% Sodium Chloride Injection. UNLOXCYT is compatible with an infusion bag made of polyolefin or polyvinyl chloride.
- Mix diluted solution by gentle inversion. **Do not shake**.
- Discard any unused portion left in the vial.

Storage of Infusion Solution:

The prepared infusion solution may be stored either:

- At room temperature up to 25°C (77°F) for no more than 24 hours from the time of preparation until the end of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation until end of infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration.
- Discard after 24 hours.
- Do not freeze.

Administration:

- Visually inspect the infusion bag for particulate matter and discoloration prior to administration. Discard if the solution is discolored or contains particulate matter.
- Administer by intravenous infusion over 60 minutes through an intravenous line containing a sterile, in-line or add-on of 0.2-micron to 0.22-micron filter.
- Do not administer UNLOXCYT as an intravenous push or bolus injection.
- Do not co-administer other drugs through the same infusion line.

3. DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/5 mL (60 mg/mL), clear to opalescent, colorless to yellow or slightly brown solution in a single-dose vial.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1. Severe and Fatal Immune-Mediated Adverse Reactions

UNLOXCYT is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed in WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting 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 closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function tests 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 UNLOXCYT depending on severity *[see Dosage and Administration (2.2)]*. In general, if UNLOXCYT requires interruption or discontinuation, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids.

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

Immune-Mediated Pneumonitis

UNLOXCYT 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 1% (3/223, Grade 2) of patients receiving UNLOXCYT. Pneumonitis led to withholding of UNLOXCYT in 0.4% (1/223) of patients. All 3 patients required systemic corticosteroids and pneumonitis did not resolve. One patient in whom UNLOXCYT was withheld for pneumonitis, had UNLOXCYT reinitiated after symptom improvement and had recurrence of pneumonitis.

Immune-Mediated Colitis

UNLOXCYT can cause immune-mediated colitis, which may present with diarrhea, abdominal pain, and lower gastrointestinal (GI) bleeding. Cytomegalovirus infection/reactivation has

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.

Immune-mediated colitis occurred in 0.4% (1/223, Grade 1) of patients receiving UNLOXCYT. Systemic corticosteroids were required in the patient experiencing colitis. The event of colitis did not resolve, and UNLOXCYT was not reinitiated.

Immune-Mediated Hepatitis

UNLOXCYT can cause immune-mediated hepatitis, defined as requiring the use of systemic corticosteroids and the absence of a clear alternate etiology.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

UNLOXCYT can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue UNLOXCYT depending on severity *[see Dosage and Administration (2.2)]*.

Adrenal insufficiency occurred in 0.9% (2/223) of patients receiving UNLOXCYT, including Grade 2 in 0.4% (1/223) of patients. UNLOXCYT was withheld for adrenal insufficiency in one of these patients and was reinitiated after symptom improvement. Systemic corticosteroids were required in both patients with adrenal insufficiency.

Hypophysitis

UNLOXCYT 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 UNLOXCYT depending on severity *[see Dosage and Administration (2.3)]*.

Thyroid Disorders

UNLOXCYT 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 UNLOXCYT depending on severity *[see Dosage and Administration (2.2)]*.

Hypothyroidism: Hypothyroidism occurred in 10% (22/223) of patients receiving UNLOXCYT, including Grade 2 in 5% (10/223) of patients. Hypothyroidism resolved in 7 of the 22 patients.

Hyperthyroidism: Hyperthyroidism occurred in 5% (12/223) of patients receiving UNLOXCYT, including Grade 2 in 0.4% (1/223) of patients. Hyperthyroidism resolved in 10 of the 12 patients.

Type 1 Diabetes Mellitus, *which can present with diabetic ketoacidosis*

UNLOXCYT can cause 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 or permanently discontinue UNLOXCYT depending on severity *[see Dosage and Administration (2.2)]*.

Immune-Mediated Nephritis with Renal Dysfunction

UNLOXCYT can cause immune-mediated nephritis, defined as the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

Immune-Mediated Dermatologic Adverse Reactions

UNLOXCYT can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue UNLOXCYT depending on severity *[see Dosage and Administration (2.2)]*.

Immune-mediated dermatologic adverse reactions occurred in 7% (15/223) of patients receiving UNLOXCYT, including Grade 3 in 0.9% (2/223) of patients and Grade 2 in 4% (9/223) of patients. Dermatologic adverse reactions led to permanent discontinuation of UNLOXCYT in 0.4% (1/223) of patients and withholding of UNLOXCYT in 0.9% (2/223) of patients. Systemic corticosteroids were required in 33% (5/15) of patients with dermatologic adverse reactions. Dermatologic adverse reactions resolved in 7 of the 15 patients. Of the 2 patients in whom UNLOXCYT was withheld for dermatologic adverse reactions, 1 patient reinitiated UNLOXCYT after symptom improvement and had recurrence of the dermatologic adverse reaction, which resolved after UNLOXCYT was withheld a second time.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred in <1% of the 223 patients who received UNLOXCYT *[see Adverse Reactions (6.1)]* or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy.

Ocular: Uveitis, iritis, 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.

Gastrointestinal: Pancreatitis, including increases in serum amylase and lipase levels, gastritis, duodenitis.

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica.

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Autoimmune hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing

lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection, other transplant (including corneal graft) rejection.

5.2. Infusion-Related Reactions

UNLOXCYT can cause severe or life-threatening infusion-related reactions. Infusion-related infusion reactions were reported in 11% (24/223) of patients, including Grade 2 in 5.8% (13/223) of patients receiving UNLOXCYT.

Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue UNLOXCYT based on severity of reaction *[see Dosage and Administration (2.2)]*. Consider premedication with an antipyretic and/or an antihistamine for patients who have had previous systemic reactions to infusions of therapeutic proteins.

5.3. 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.

5.4. Embryo-Fetal Toxicity

Based on its mechanism of action, UNLOXCYT 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 pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with UNLOXCYT and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*
- Infusion-related reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (**Error! Reference source not found.**)]*

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to UNLOXCYT as a single agent in 223 patients in two open-label, single-arm, multicohort studies, including 141 patients with advanced CSCC and 82 patients with other solid tumors and hematologic malignancies. UNLOXCYT was administered intravenously at doses of 800 mg every 2 weeks (n=174), 1,200 mg every 3 weeks (n=35), or other doses (n=14). Among the 223 patients, 54% were exposed for ≥24 weeks and 17% were exposed for ≥72 weeks.

The safety of UNLOXCYT was evaluated in Study CK-301-101 in 141 patients with metastatic or locally advanced disease CSCC *[see Clinical Studies (14)]*. Patients received UNLOXCYT 800 mg every 2 weeks (n=115) or 1,200 mg every 3 weeks (n=26) as an intravenous infusion until disease progression or unacceptable toxicity. The median duration of exposure was 36 weeks (2 weeks to 3.7 years).

Serious adverse reactions occurred in 31% of advanced patients with CSCC who received UNLOXCYT. The most frequent serious adverse reactions (≥ 2% of patients) were sepsis (2.8%), pneumonia (2.8%) and pyrexia (2.1%).

Permanent discontinuation of UNLOXCYT due to an adverse reaction occurred in 8% of patients. Adverse reactions resulting in permanent discontinuation of UNLOXCYT were COVID-19, COVID-19 pneumonia, sepsis, ulcerative keratitis, tumor thrombosis, axillary pain, paresthesia, cholestasis, hepatic cytolysis, wound hemorrhage, neck pain, pemphigoid, and eye pain (1 patient each).

Dosage interruptions due to an adverse reaction occurred in 36% of patients who received UNLOXCYT. The adverse reaction that required dosage interruption in ≥ 2% of patients who received UNLOXCYT was COVID-19 (2%).

The most common (≥ 10%) adverse reactions were fatigue, musculoskeletal pain, rash, diarrhea, hypothyroidism, constipation, nausea, headache, pruritus, edema, localized infection, and urinary tract infection.

Table 2 and Table 3 summarize adverse reactions and laboratory abnormalities, respectively in CK-301-101.

Table 2: Adverse Reactions in ≥ 10% of Patients with Metastatic or Locally Advanced CSCC Receiving UNLOXCYT in Study CK-301-101

	UNLOXCYT N = 141 %	
System Organ Class Preferred Term	**All Grades %**	**Grade 3 or 4 %**
General disorders and administrative site conditions		
Fatigue*	33	3
Edema*	11	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	25	3
Skin and subcutaneous tissue disorders		
Rash*	23	1
Pruritus*	12	0
Endocrine disorder		
Hypothyroidism*	14	0
Gastrointestinal disorders		
Diarrhea	14	0
Nausea	13	0
Constipation	13	0
Nervous system disorders		
Headache*	12	0
Infections and infestations		
Localized infection	10	0.7
Urinary tract infection*	10	0

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03 (or later version)

* Represents a composite of multiple related terms

Table 3: Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥ 1% of Patients with Metastatic or Locally Advanced CSCC Receiving UNLOXCYT in Study CK-301-101

Laboratory Abnormality	UNLOXCYT (N = 141)	
	All Grades %[a]	Grade 3 or 4 %[a]
Hematology		
Hemoglobin decreased	45	4
Lymphocytes decreased	41	6
Platelets decreased	14	1
Leukocytes decreased	10	1
Chemistry		
Sodium decreased	38	5
Alkaline phosphatase increased	26	1
Alanine transferase increased	25	4
Lipase increased	25	3
Aspartate transaminase increased	24	3
Potassium increased	23	3
Calcium increased	14	2

Toxicity graded per NCI CTCAE v5

[a] The denominator used to calculate the rate varied from 122-140 based on the number of patients with a baseline value and at least one post-treatment value.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Based on its mechanism of action, UNLOXCYT can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of UNLOXCYT in pregnant women. 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 *(see Data)*. Human IgG1 immunoglobulins (IgG1) are known to cross the placental barrier; therefore, cosibelimab-ipdl has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: Animal reproduction studies have not been conducted with cosibelimab-ipdl to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering UNLOXCYT during pregnancy include increased rates of abortion or stillbirth. As reported in the

literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to UNLOXCYT may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2. Lactation

Risk Summary

There is no information regarding the presence of cosibelimab-ipdl in human milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 4 months after the last dose of UNLOXCYT.

8.3. Females and Males of Reproductive Potential

UNLOXCYT can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating UNLOXCYT *[see Use in Specific Populations (8.1)]*.

Contraception

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

8.4. Pediatric Use

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

8.5. Geriatric Use

Of the 141 patients treated with UNLOXCYT as a single agent, 21% (29) were younger than 65 years, 31% (44) were aged 65 through 75 years, and 48% (68) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

11. DESCRIPTION

Cosibelimab-ipdl is a human programmed death ligand-1 (PD-L1) blocking antibody. Cosibelimab-ipdl is a human IgG1 lambda monoclonal antibody. Cosibelimab-ipdl is produced in Chinese hamster ovary (CHO) cells and has a calculated molecular weight of approximately 147 kDa.

UNLOXCYT (cosibelimab-ipdl) injection for intravenous use is a sterile, preservative-free, clear to opalescent, colorless to yellow or slightly brown solution. It is supplied in single-dose vials.

Each vial contains 300 mg of UNLOXCYT in 5 mL of solution with a pH of 5.3. Each mL of solution contains 60 mg of cosibelimab-ipdl, acetic acid (0.24 mg), mannitol (37.35 mg), polysorbate 80 (1.1 mg), sodium acetate (1.31 mg), sodium chloride (4.09 mg), and Water for Injection, USP.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

PD-L1 may be expressed on tumor cells and tumor-infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation, and cytokine production. Cosibelimab-ipdl binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This interaction releases the inhibitory effects of PD-L1 on the anti-tumor immune response. Cosibelimab-ipdl has also been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.

12.2. Pharmacodynamics

Cosibelimab-ipdl exposure-response relationships and the time course of pharmacodynamic responses have not been fully characterized.

12.3. Pharmacokinetics

Cosibelimab-ipdl pharmacokinetic parameters are presented as geometric mean (coefficient of variation) unless otherwise stated. At the recommended dosage, the cosibelimab-ipdl steady-state maximum plasma concentration (C_{max}) is 492 µg/mL (24.3%) and area under curve (AUC) is 112000 µg*h/mL (39.6%). Cosibelimab-ipdl C_{max} and AUC increased proportionally over the dose range of 800 mg to 1,200 mg following single dosing. Steady-state concentrations of cosibelimab-ipdl are reached by 12 weeks.

At 1,200 mg every 3 weeks, the mean cosibelimab-ipdl concentrations (coefficient of variation, CV%) at steady-state ranged between a minimum concentration of 120 µg/L (46.3%) and a maximum concentration of 453 µg/L (22.2%). Steady-state exposure was achieved after 84 days of treatment.

In patients with CSCC, cosibelimab-ipdl steady-state exposure at 1,200 mg every 3 weeks (the recommended dosage) was comparable to the exposure at 800 mg every 2 weeks.

Distribution

Cosibelimab-ipdl steady state volume of distribution is approximately 5.67 L (19.7%).

Elimination

Cosibelimab-ipdl steady state elimination half-life is 17.8 days (43.8%), and the clearance is 0.256 L/day (41%).

Specific Populations

No clinically significant differences in the pharmacokinetics of cosibelimab-ipdl were observed based on age (24.8 to 95.0 years), sex, race (79.6% White, 10.7% Asian, 0.5% African American, and 1.5% other), ethnicity (76.9% Not Hispanic/Latino and 4.9% Hispanic/Latino), ADA and nAb status, albumin (22 to 51 g/L), tumor type, tumor diameter, and renal impairment (CLcr 15 mL/min and higher). The effect of severe hepatic impairment (bilirubin > 3 x ULN and any AST) on cosibelimab-ipdl pharmacokinetics is unknown.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of UNLOXCYT or of other cosibelimab products.

Anti-drug antibody (ADA) and neutralizing antibody (nAb) responses were monitored throughout the treatment period where the benefit to risk ratio was assessed. ADAs were detected in 65/133 (49%) of patients treated with UNLOXCYT and nAbs were detected in 2/65 (3.0%) of the patients. UNLOXCYT-treated patients who developed anti-cosibelimab antibodies had reduced UNLOXCYT concentrations (20% lower compared to UNLOXCYT-treated subjects who did not develop anti-cosibelimab-ipdl antibodies).

There was no clinically significant effect of anti-cosibelimab-ipdl antibodies on the efficacy or safety of cosibelimab-ipdl.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of cosibelimab-ipdl for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with cosibelimab-ipdl in animals. In 1- and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs up to the highest dose tested of 100 mg/kg/dose; however, many animals in these studies were not sexually mature.

13.2. Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1–blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14. CLINICAL STUDIES

14.1. Cutaneous Squamous Cell Carcinoma (CSCC)

The efficacy of UNLOXCYT was evaluated in Study CK-301-101 (NCT03212404), a multicenter, multicohort, open-label study in patients with metastatic CSCC (mCSCC) or locally advanced CSCC (laCSCC) who were not candidates for curative surgery or curative radiation. Patients were excluded if they had the following: active or suspected autoimmune disease, allogeneic transplant within 6 months prior to treatment, prior treatment with anti–PD-1/PD-L1 blocking antibodies or other immune checkpoint inhibitor therapy, uncontrolled or significant cardiovascular disease, ECOG PS $\geq$ 2, or infection with HIV, hepatitis B or hepatitis C.

Patients received UNLOXCYT 800 mg every 2 weeks until disease progression or unacceptable toxicity. Tumor response assessments were performed every 8 weeks for the first 8 months and

every 12 weeks thereafter.

The major efficacy outcomes were objective response rate (ORR) and duration of response (DOR) as assessed by an independent central review committee (ICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. For patients with laCSCC with externally visible target lesions not assessable by radiologic imaging, ORR was determined by ICR assessments of digital photography (WHO criteria).

The efficacy population consisted of 109 patients. The median age was 75 years (range 37-95); 78% were ≥ 65 years; 72% were male; 85% were White; 6% were Asian; 1% were Black or African American; 7% were race unknown or missing; 34% had ECOG performance status of 0, and 66% had ECOG performance score of 1. Seven percent of patients received at least one prior anti-cancer systemic therapy, 66% of patients had prior surgery, and 69% of patients had prior radiotherapy. Efficacy results are summarized in Table 4.

Table 4: Efficacy Results for Study CK-301-101

Efficacy Endpoints	**mCSCC N = 78**	**laCSCC N = 31**
Objective Response Rate (ORR)		
ORR, n (%) (95% CI)	39 (50) (38, 62)	17 (55) (36, 73)
Complete response, n (%)	10 (13)	8 (26)
Partial response, n (%)	29 (37)	9 (29)
Duration of Response (DOR)[a]		
Number of responders	N=39	N=17
Median DOR in months[b] (Range)	NR (1.4+, 45.3+)	NR (8.3, 31.3+)
Responders with observed DOR ≥ 6 months, n (%)[c]	33 (85)	17 (100)
Responders with observed DOR ≥ 12 months, n (%)[c]	26 (67)	15 (88)

CI: confidence interval; NR: not reached; +: Denotes ongoing at last assessment.

[a] Median follow up time: mCSCC: 29.3 months; laCSCC: 24.1 months.

[b] Based on Kaplan-Meier estimate.

[c] The numerator includes the number of patients whose observed DOR reached at least the specified times of 6 or 12 months. Patients who did not have the opportunity to reach the specified timepoint were included in the denominator only.

16. HOW SUPPLIED/STORAGE AND HANDLING

UNLOXCYT (cosibelimab-ipdl) injection is a clear to opalescent, colorless to yellow or slightly brown solution supplied in a carton containing one 300 mg/5 mL (60 mg/mL), single-dose vial (NDC 70095-130-01).

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.

Do not freeze or shake.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Advise patients that UNLOXCYT can cause immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of UNLOXCYT including the following [*see Warnings and Precautions (5.1)*]:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of pneumonitis, including new or worsening symptoms of cough, chest pain, or shortness of breath.
- Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of colitis, including diarrhea, blood or mucus in stools, or severe abdominal pain.
- Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.
- Other Immune-Mediated Adverse Reactions:
    - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms *[see Warnings and Precautions (5.1)]*.
    - Advise patients of the risk of solid organ transplant rejection and other transplant (including corneal graft) rejection. Advise patients to contact their healthcare provider immediately for signs or symptoms of organ transplant (including corneal graft) rejection *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [*see Warnings and Precautions (5.2)*].

Complications of Allogeneic HSCT or Solid Organ Transplant Rejection

Advise patients to contact their healthcare provider immediately if they develop signs or symptoms of post-allogeneic HSCT complications or of solid organ transplant rejection [*see Warnings and Precautions (5.1, 5.3)*].

Embryo-Fetal Toxicity

- Advise females of reproductive potential that UNLOXCYT can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.4)* and *Use in Specific Populations (8.1, 8.3)*].
- Advise females of reproductive potential to use effective contraception during treatment with UNLOXCYT and for 4 months after the last dose [*see Use in Specific Populations (8.3)*].

Lactation

- Advise female patients not to breastfeed during treatment with UNLOXCYT and for 4 months after the last dose [*see Use in Specific Populations (8.2)*].

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