For the use only of registered medical practitioners or a hospital or a laboratory

WARNING: To be sold by retail on the prescription of Oncologist only

Bristol Myers Squibb®

RELOPDUO™

FDC of nivolumab and relatlimab 240mg/80 mg in 20 ml concentrate for solution for infusion

1. GENERIC NAME

FDC of nivolumab and relatlimab 240mg /80 mg in 20 ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fixed dose combination of 240 mg of nivolumab and 80 mg of relatlimab in 20 mL- concentrate for solution for infusion.

Nivolumab and relatlimab is a fixed-dose combination of two IgG4 kappa monoclonal antibodies (mAbs). Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody that has a calculated molecular mass of 146 kDa and is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line. Relatlimab is a lymphocyte activation gene-3 (LAG-3) blocking antibody that has a calculated molecular mass of 148 kDa and is expressed in a recombinant CHO cell line.
RELOPDUO (nivolumab and relatlimab) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution that may contain few translucent-to-white particles. RELOPDUO is supplied as 240 mg of nivolumab and 80 mg of relatlimab in a 20 mL single-dose vial for intravenous use. Each mL of RELOPDUO solution contains 12 mg of nivolumab, 4 mg of relatlimab.

For the full list of excipients, see *7 Description*.

3. DOSAGE FORM AND STRENGTH

Concentrate for solution for infusion.
For intravenous use.
Injection: 240 mg nivolumab and 80 mg relatlimab per 20 mL (12 mg and 4 mg per mL) as a clear to opalescent, colorless to slightly yellow solution in a single-dose vial.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RELOPDUO™ is indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

4.2.1 Recommended dosage

The recommended dosage of RELOPDUO for adult patients and pediatric patients 12 years of age or older who weigh at least 40 kg is 480 mg nivolumab and 160 mg relatlimab administered intravenously every 4 weeks until disease progression or unacceptable toxicity occurs.

The recommended dosage for pediatric patients 12 years of age or older who weigh less than 40 kg has not been established *[see 4.6 Use in Special Populations]*.

Dosage Modifications

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

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

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
Immune-Mediated Adverse Reactions *[see 4.4 Special warnings and precautions for use, sub-section 4.4.1]*		
Pneumonitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[a]
	Grade 4	Permanently discontinue
Hepatitis	AST/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[a]

Adverse Reaction	Severity*	Dose Modification
Immune-Mediated Adverse Reactions *[see 4.4 Special warnings and precautions for use, sub-section 4.4.1]*		
	AST or ALT increases to more than 8 times ULN regardless of baseline. or Total bilirubin increases to more than 3 times ULN.	Permanently discontinue
Endocrinopathies[b]	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[see 4.4 Special warnings and precautions for use, sub-section 4.4.2]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

*Based on National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

[a] 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 last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

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

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 normal

4.2.2 Method of Administration

RELOPDUO is a fixed-dose combination of nivolumab and relatlimab. Visually inspect the solution in the drug product vial for particulate matter and discoloration prior to administration. RELOPDUO is a clear to opalescent, colorless to slightly yellow solution.

Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white particles.

Preparation

- During preparation of the infusion solution, use aseptic technique to assure sterility, as the product does not contain a preservative.
- RELOPDUO can be administered diluted or undiluted and administered at a final concentration as specified in Table 2 below.
- Withdraw the required volume of RELOPDUO and transfer into an intravenous container. RELOPDUO is compatible with di(2-ethylhexyl)phthalate (DEHP)-plasticized polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), and polyolefin (PO) intravenous bags.
- If diluting RELOPDUO prior to administration:
  - Dilute RELOPDUO solution with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion meeting the final concentration and maximum infusion volume parameters as specified in Table 2 below.
  - Then mix the diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials following infusion preparation.

Table 2: Maximum Infusion Volumes and Concentration Ranges by Patient Group

Patient Group	Maximum Infusion Volume (mL or mL/kg)	Concentration Range (mg/mL)*
Adult patients who weigh at least 40 kg and pediatric patients 12 years of age or older who weigh at least 40 kg	160 mL	Nivolumab: 3 mg/mL to 12 mg/mL Relatlimab: 1 mg/mL to 4 mg/mL
Adult patients who weigh less than 40 kg	4 mL/kg	Nivolumab: 3 mg/mL to 12 mg/mL Relatlimab: 1 mg/mL to 4 mg/mL

* The concentration range in each group includes 12 mg/mL nivolumab and 4 mg/mL relatlimab as the upper limit, which represents a scenario in which the drug product is infused without dilution.

Storage of Prepared Solution

Store the prepared solution either:

- at room temperature and room light for no more than 8 hours from the time of preparation to the end of the infusion. Discard the prepared solution if not used within 8 hours from the time of preparation;

  -or-

- under refrigeration at 2°C to 8°C (36°F to 46°F) with protection from light for no more than 24 hours from the time of preparation, which includes the time allowed for equilibration of the infusion bag to room temperature and the duration of the infusion. Discard the prepared solution if not used within 24 hours from the time of preparation.

Do not freeze.

Administration

- Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line polyethersulfone (PES), nylon, or polyvinylidene fluoride (PVDF) filter (pore size of 0.2 micrometer to 1.2 micrometer).
- Flush the intravenous line at the end of the infusion.
- Do not co-administer other drugs through the same intravenous line.

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

4.4.1 Severe and Fatal Immune-Mediated Adverse Reactions

RELOPDUO potentially breaks peripheral tolerance and induces immune-mediated adverse reactions (IMARs) *[see 5. Pharmacological properties, sub-section 5.1]*. Important IMARs listed under Warnings and Precautions may not include all possible severe and fatal IMARs.

IMARs, which may be severe or fatal, can occur in any organ system or tissue. IMARs can occur at any time after starting treatment with a LAG-3 and PD-1/PD-L1 blocking antibodies. While IMARs usually manifest during treatment, IMARs can also manifest after discontinuation.

Early identification and management of IMARs are essential to ensure safe use. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying IMARs. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected IMARs, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate. Withhold or permanently discontinue RELOPDUO depending on severity *[see 4.2 Posology and method of administration]*. In general, if RELOPDUO requires interruption or discontinuation, administer systemic corticosteroid therapy (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 IMARs are not controlled with corticosteroid therapy.

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

Immune-Mediated Pneumonitis

RELOPDUO can cause immune-mediated pneumonitis, which may be fatal. 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 3.7% (13/355) of patients receiving RELOPDUO, including Grade 3 (0.6%), and Grade 2 (2.3%) adverse reactions. Pneumonitis led to permanent discontinuation of RELOPDUO in 0.8% and withholding of RELOPDUO in 1.4% of patients.

Systemic corticosteroids were required in 100% (13/13) of patients with pneumonitis. Pneumonitis resolved in 85% of the 13 patients. Of the 5 patients in whom RELOPDUO was withheld for pneumonitis, 5 reinitiated RELOPDUO after symptom improvement; of these, none had recurrence of pneumonitis.

Immune-Mediated Colitis

RELOPDUO can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated diarrhea or colitis occurred in 7% (24/355) of patients receiving RELOPDUO, including Grade 3 (1.1%) and Grade 2 (4.5%) adverse reactions. Colitis led to permanent discontinuation of RELOPDUO in 2% and withholding of RELOPDUO in 2.8% of patients.

Systemic corticosteroids were required in 100% (24/24) of patients with diarrhea or colitis. Colitis resolved in 83% of the 24 patients. Of the 10 patients in whom RELOPDUO was withheld for colitis, 9 reinitiated RELOPDUO after symptom improvement; of these, 67% had recurrence of colitis.

Immune-Mediated Hepatitis

RELOPDUO can cause immune-mediated hepatitis, defined as requiring the use of corticosteroids and no clear alternate etiology.

Immune-mediated hepatitis occurred in 6% (20/355) of patients receiving RELOPDUO, including Grade 4 (0.6%), Grade 3 (3.4%), and Grade 2 (1.4%) adverse reactions. Hepatitis led to permanent discontinuation of RELOPDUO in 1.7% and withholding of RELOPDUO in 2.3% of patients.

Systemic corticosteroids were required in 100% (20/20) of patients with hepatitis. Hepatitis resolved in 70% of the 20 patients. Of the 8 patients in whom RELOPDUO was withheld for hepatitis, 6 reinitiated RELOPDUO after symptom improvement; of these, 50% had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

RELOPDUO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold RELOPDUO depending on severity *[see 4.2 Posology and method of administration]*.

Adrenal insufficiency occurred in 4.2% (15/355) of patients receiving RELOPDUO, including Grade 3 (1.4%) and Grade 2 (2.5%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of RELOPDUO in 1.1% and withholding of RELOPDUO in 0.8% of patients.

Approximately 87% (13/15) of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 87% (13/15) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 33% of the 15 patients. Of the 3 patients in whom RELOPDUO was withheld for adrenal insufficiency, all 3 reinitiated RELOPDUO after symptom improvement.

Hypophysitis

RELOPDUO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue RELOPDUO depending on severity *[see 4.2 Posology and method of administration]*.

Hypophysitis occurred in 2.5% (9/355) of patients receiving RELOPDUO, including Grade 3 (0.3%) and Grade 2 (1.4%) adverse reactions. Hypophysitis led to permanent discontinuation of RELOPDUO in 0.3% and withholding of RELOPDUO in 0.6% of patients.

All (9/9) of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 100% (9/9) of patients with hypophysitis. Hypophysitis resolved in 22% of the 9 patients. Of the 2 patients in whom RELOPDUO was withheld for hypophysitis, none reinitiated RELOPDUO after symptom improvement.

Thyroid Disorders

RELOPDUO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management as clinically indicated. Withhold or permanently discontinue RELOPDUO depending on severity *[see 4.2 Posology and method of administration]*.

Thyroiditis

Thyroiditis occurred in 2.8% (10/355) of patients receiving RELOPDUO, including Grade 2 (1.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of RELOPDUO. Thyroiditis led withholding of RELOPDUO in 0.3% of patients.

Systemic corticosteroids were required in 20% (2/10) of patients with thyroiditis. Thyroiditis resolved in 90% of the 10 patients. For the 1 patient in whom RELOPDUO was withheld for thyroiditis, RELOPDUO was reinitiated after symptom improvement without recurrence of thyroiditis.

Hyperthyroidism

Hyperthyroidism occurred in 6% (22/355) of patients receiving RELOPDUO, including Grade 2 (1.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of RELOPDUO. Hyperthyroidism led to withholding of RELOPDUO in 0.3% of patients.

Systemic corticosteroids were required in 23% (5/22) of patients. Hyperthyroidism resolved in 82% of the 22 patients. For the 1 patient in whom RELOPDUO was withheld for hyperthyroidism, RELOPDUO was reinitiated after symptom improvement without recurrence of hyperthyroidism.

Hypothyroidism

Hypothyroidism occurred in 17% (59/355) of patients receiving RELOPDUO, including Grade 2 (11%) adverse reactions. Hypothyroidism led to the permanent discontinuation of RELOPDUO in 0.3% and withholding of RELOPDUO in 2.5% of patients.

None of the patients with hypothyroidism required systemic corticosteroids. Hypothyroidism resolved in 12% of the 59 patients. Of the 9 patients in whom RELOPDUO was withheld for hypothyroidism, 6 reinitiated RELOPDUO after symptom improvement; of these, 33% had recurrence of hypothyroidism.

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 RELOPDUO depending on severity *[see 4.2 Posology and method of administration]*.

Diabetes occurred in 0.3% (1/355) of patients receiving RELOPDUO, a Grade 3 (0.3%) adverse reaction, and no cases of diabetic ketoacidosis. Diabetes did not lead to the permanent discontinuation or withholding of RELOPDUO in any patient.

Immune-Mediated Nephritis with Renal Dysfunction

RELOPDUO can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear alternate etiology. Withhold or permanently discontinue RELOPDUO depending on severity *[see 4.2 Posology and method of administration]*.

Immune-mediated nephritis and renal dysfunction occurred in 2% (7/355) of patients receiving RELOPDUO, including Grade 3 (1.1%) and Grade 2 (0.8%) adverse reactions. Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of RELOPDUO in 0.8% and withholding of RELOPDUO in 0.6% of patients.

Systemic corticosteroids were required in 100% (7/7) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 71% of the 7 patients. Of the 2 patients

in whom RELOPDUO was withheld for nephritis or renal dysfunction, 1 reinitiated RELOPDUO after symptom improvement without recurrence of nephritis or renal dysfunction.

Immune-Mediated Dermatologic Adverse Reactions

RELOPDUO can cause immune-mediated rash or dermatitis, defined as requiring use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms has occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue RELOPDUO depending on severity *[see 4.2 Posology and method of administration]*.

Immune-mediated rash occurred in 9% (33/355) of patients receiving RELOPDUO, including Grade 3 (0.6%) and Grade 2 (3.4%) adverse reactions. Immune-mediated rash did not lead to permanent discontinuation of RELOPDUO. Immune-mediated rash led to withholding of RELOPDUO in 1.4% of patients.

Systemic corticosteroids were required in 88% (29/33) of patients with immune-mediated rash. Rash resolved in 70% of the 33 patients. Of the 5 patients in whom RELOPDUO was withheld for immune-mediated rash, 4 reinitiated RELOPDUO after symptom improvement; of these, 25% had recurrence of immune-mediated rash.

Immune-Mediated Myocarditis

RELOPDUO can cause immune-mediated myocarditis, which is defined as requiring use of steroids and no clear alternate etiology. The diagnosis of immune-mediated myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, withhold dose, promptly initiate high dose steroids (prednisone or methylprednisolone 1 to 2 mg/kg/day) and promptly arrange cardiology consultation with diagnostic workup. If clinically confirmed, permanently discontinue RELOPDUO for Grade 2-4 myocarditis *[see 4.2 Posology and method of administration]*.

Myocarditis occurred in 1.7% (6/355) of patients receiving RELOPDUO, including Grade 3 (0.6%), and Grade 2 (1.1%) adverse reactions. Myocarditis led to permanent discontinuation of RELOPDUO in 1.7% of patients.

Systemic corticosteroids were required in 100% (6/6) of patients with myocarditis. Myocarditis resolved in 100% of the 6 patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant IMARs occurred at an incidence of <1% (unless otherwise noted) in patients who received RELOPDUO 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: Pericarditis, vasculitis.

Nervous System: 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 can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other IMARs, 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): 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.

4.4.2 Infusion-Related Reactions

RELOPDUO can cause severe infusion-related reactions. Discontinue RELOPDUO in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions *[see 4.2 Posology and method of administration)]*.

In patients who received RELOPDUO as a 60-minute intravenous infusion, infusion-related reactions occurred in 7% (23/355) of patients.

4.4.3 Complications of Allogeneic Hematopoietic Stem Cell Transplantation

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 receptor 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) *[see 4.8 Undesirable effects, sub section 4.8.1.1)]*. 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 receptor blocking antibody prior to or after an allogeneic HSCT.

4.4.4 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, RELOPDUO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in

increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RELOPDUO for at least 5 months after the last dose of RELOPDUO *[see* 4.*6 Use in special populations, sub-sections 4.6.1, 4.6.3]*.

4.5 DRUG INTERACTIONS

Not specified.

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

4.6.1 Pregnancy

Risk Summary

Based on findings in animals and mechanism of action, RELOPDUO can cause fetal harm when administered to a pregnant woman. Administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death (*see Data*). Human IgG4 is known to cross the placenta; therefore, nivolumab and relatlimab have the potential to be transmitted from the mother to the developing fetus. The effects of RELOPDUO are likely to be greater during the second and third trimesters of pregnancy. There are no available data on RELOPDUO in pregnant women to evaluate a drug-associated risk. Advise the patient 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

RELOPDUO injection for intravenous use contains nivolumab and relatlimab *[see 7 Description]*.

Nivolumab:

One function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining immune tolerance to the fetus. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

Relatlimab:

There are no available animal data on relatlimab. The effects of a murine surrogate anti-LAG-3 antibody was evaluated in mice using syngeneic and allogeneic breeding models. When anti-LAG-3 antibodies were administered beginning on gestation day 6, there were no maternal or developmental effects in either syngeneic or allogeneic breedings.

4.6.2 Lactation

Risk Summary
There are no data on the presence of nivolumab and relatlimab in human milk, the effects on the breastfed child, or the effects on milk production. Because nivolumab and relatlimab may be excreted in human milk and because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with RELOPDUO and for at least 5 months after the last dose *[see 5 Pharmacological properties, sub-section 5.3]*.

4.6.3 Females and Males of Reproductive *Potential*

RELOPDUO can cause fetal harm when administered to a pregnant woman *[see 4.6 Use in special population, sub-section 4.6.1]*.
Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating RELOPDUO *[see 4.6 Use in special population, sub-section 4.6.1]*.
Contraception
Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months following the last dose of RELOPDUO *[see 5 Pharmacological properties, sub-section 5.3]*.

4.6.4 Pediatric Use

The safety and effectiveness of RELOPDUO for the treatment of unresectable or metastatic melanoma have been established in pediatric patients 12 years of age or older who weigh at least 40 kg. Use of RELOPDUO for this indication is supported by evidence from an adequate and well-controlled study in adults and additional data analyses that suggest that nivolumab and relatlimab exposures in pediatric patients 12 years of age who weigh at least 40 kg are expected to result in similar safety and efficacy to that of adults. The pharmacokinetics of monoclonal antibodies and the course of unresectable or metastatic melanoma are sufficiently similar in adults and pediatric patients 12 years of age or older to allow extrapolation of data from adult patients to pediatric patients 12 years of age or older (who weigh at least 40 kg). A recommended dosage for pediatric patients 12 years of age or older who weigh less than 40 kg has not been established *[see 4.8. Undesirable effects sub section 4.8.1.1, 5 Pharmacological properties, sub-section 5.2.1 and 5.3]*.

The safety and effectiveness of RELOPDUO have not been established in pediatric patients 12 years of age or older who weigh less than 40 kg, and pediatric patients younger than 12 years of age.

4.6.5 Geriatric use

Of the 355 patients treated with RELOPDUO in RELATIVITY-047, 47% of patients were 65 years or older, 29% were 65 to 74 years, 17% were 75 to 84 years, and 1.7% were 85 years and older. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

4.7 EFFECTS ON ABILITY TO DRIVE AND TO USE MACHINES

Not specified

4.8 UNDESIRABLE EFFECTS

4.8.1 Adverse Reactions

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling.

- Severe and Fatal IMARs [*see 4.4 Special warnings and precautions for use*]
- Infusion-Related Reactions [*see 4.4 Special warnings and precautions for use*]
- Complications of Allogeneic HSCT [see *4.4 Special warnings and precautions for use*]

4.8.1.1 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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of RELOPDUO was evaluated in RELATIVITY-047, a randomized (1:1), double-blinded trial in 714 patients with previously untreated metastatic or unresectable melanoma *[see* 5. *Pharmacological Properties*, *sub-section 5.2.1]*. Patients received intravenous RELOPDUO (nivolumab 480 mg and relatlimab 160 mg) every 4 weeks (n=355) or nivolumab 480 mg by intravenous infusion every 4 weeks (n=359). Patients were treated with RELOPDUO or nivolumab until disease progression or unacceptable toxicity. The median duration of exposure was 6 months (range: 0 to 31 months) in RELOPDUO-treated patients and 5 months (range: 0 to 32 months) in nivolumab-treated patients.

Serious adverse reactions occurred in 36% of patients treated with RELOPDUO. The most frequent serious adverse reactions reported in ≥1% of patients treated with RELOPDUO were adrenal insufficiency (1.4%), anemia (1.4%), colitis (1.4%), pneumonia (1.4%), acute myocardial infarction (1.1%), back pain (1.1%), diarrhea (1.1%), myocarditis (1.1%), and pneumonitis (1.1%). Fatal adverse reaction occurred in 3 (0.8%) patients who were treated with RELOPDUO; these included hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis.

RELOPDUO was permanently discontinued due to adverse reactions in 18% of patients. Adverse reactions which resulted in permanent discontinuation of RELOPDUO in ≥1% of patients included myocarditis (1.7%) and pneumonitis (1.4%).

Dosage interruptions due to an adverse reaction occurred in 43% of patients who received RELOPDUO. Adverse reactions that required dosage interruption in ≥2% of patients who received RELOPDUO were diarrhea (3.9%), troponin increased (3.9%), AST increased (2.8%), troponin T increased (2.8%), ALT increased (2.3%), arthralgia (2.3%), hypothyroidism (2.3%), anemia (2%), fatigue (2%), pneumonitis (2%), and rash (2%).

The most common (≥20%) adverse reactions that occurred in patients treated with RELOPDUO were musculoskeletal pain (45%), fatigue (39%), rash (28%), pruritus (25%), and diarrhea (24%).

The most common (≥20%) laboratory abnormalities that occurred in patients treated with RELOPDUO were decreased hemoglobin (37%), decreased lymphocytes (32%), increased AST (30%), increased ALT (26%), and decreased sodium (24%).

Tables 3 and 4 summarize both the adverse reactions and laboratory abnormalities, respectively, in RELATIVITY-047.

Table 3: Adverse Reactions in ≥15% of Patients - RELATIVITY-047

Adverse Reaction	RELOPDUO (n=355)		Nivolumab (n=359)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[a]	45	4.2	31	1.7
General				
Fatigue[a]	39	2	29	0.6
Skin and Subcutaneous Tissue				
Rash[a]	28	1.4	21	1.9
Pruritus	25	0	17	0.6
Gastrointestinal				
Diarrhea[a]	24	2	17	1.4
Nausea	17	0.6	14	0
Nervous System				
Headache[a]	18	0.3	12	0.3
Endocrine				
Hypothyroidism[a]	17	0	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	15	0.6	7	0.3
Respiratory, Thoracic and Mediastinal Disorders				
Cough[a]	15	0.3	11	0

Toxicity was graded per NCI CTCAE v5.

[a] Includes multiple terms.

Clinically relevant adverse reactions in <15% of patients who received RELOPDUO included vitiligo, adrenal insufficiency, myocarditis, and hepatitis.

Table 4: Laboratory Abnormalities (≥15%) That Worsened from Baseline[a] in Patients Who Received RELOPDUO in RELATIVITY-047

Laboratory Abnormality	RELOPDUO[a]		Nivolumab[a]	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased AST	30	2.3	22	1.4
Increased ALT	26	3.2	25	2
Decreased sodium	24	1.2	21	0.6
Increased alkaline phosphatase	19	0.6	17	0.9
Increased creatinine	19	0	16	0
Hematology				
Decreased hemoglobin	37	2.7	31	3.5
Decreased lymphocytes	32	2.5	24	2.9

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: RELOPDUO group (range: 280 to 342 patients) and nivolumab group (range: 276 to 345 patients).

4.9 OVERDOSE

Not specified

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Relatlimab is a human IgG4 monoclonal antibody that binds to the LAG-3 receptor, blocks interaction with its ligands, including MHC II, and reduces LAG-3 pathway-mediated inhibition of the immune response. Antagonism of this pathway promotes T cell proliferation and cytokine secretion.

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor, blocks interaction with its ligands PD-L1 and PD-L2, and reduces PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

The combination of nivolumab (anti-PD-1) and relatlimab (anti-LAG-3) results in increased T-cell activation compared to the activity of either antibody alone. In murine syngeneic tumor models, LAG-3 blockade potentiates the anti-tumor activity of PD-1 blockage, inhibiting tumor growth and promoting tumor regression.

5.2 Pharmacodynamics properties

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of RELOPDUO have not been fully characterized.

5.2.1 Clinical Studies

The efficacy of RELOPDUO was investigated in RELATIVITY-047 (NCT03470922), a randomized (1:1), double-blinded trial in 714 patients with previously untreated metastatic or unresectable Stage III or IV melanoma. Patients were allowed to have received prior adjuvant or neoadjuvant melanoma therapy: anti-PD-1, anti-CTLA-4, or BRAF-MEK inhibitors were allowed if received at least 6 months between the last dose of therapy and date of recurrence; interferon therapy was allowed if the last dose was at least 6 weeks prior to randomization. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic treatment with moderate or high dose corticosteroids or immunosuppressive medications, uveal melanoma, and active or untreated brain or leptomeningeal metastases. Patients were randomized to receive RELOPDUO (nivolumab 480 mg and relatlimab 160 mg) by intravenous infusion every 4 weeks (n=355) or nivolumab 480 mg by intravenous infusion every 4 weeks (n=359) until disease progression or unacceptable toxicity. Randomization was stratified by tumor PD-L1 expression (≥1% vs. <1%) using PD-L1 IHC 28-8 pharmDx test, LAG-3 expression (≥1% vs. <1%) using a clinical trial assay, BRAF V600 mutation status (V600 mutation positive vs. wild type), and M stage per the American Joint Committee on Cancer (AJCC) version 8 staging system (M0/M1any[0] vs. M1any[1]).

The major efficacy outcome measure was progression-free survival (PFS) determined by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Additional efficacy outcome measures were overall survival (OS) and overall response rate (ORR) determined by BICR using RECIST v1.1. Tumor assessments were conducted 12 weeks after randomization and continued every 8 weeks up to week 52 and then every 12 weeks.

The trial population characteristics were: median age 63 years (range: 20 to 94); 58% male; 97% White 0.7% African American, and American Indian/Alaskan Native 0.1%; Hispanic 7%; and ECOG performance score was 0 (67%) or 1 (33%). Disease characteristics were: PD-L1 expression ≥1% (41%), LAG-3 expression ≥1% (75%), AJCC Stage IV disease (92%), M1c disease (39%); M1d disease (2.4%), elevated LDH (36%), and BRAF V600 mutation-positive melanoma (39%).

The trial demonstrated a statistically significant improvement in PFS for patients randomized to the RELOPDUO arm compared with the nivolumab arm. The final analysis of OS was not statistically significant. Efficacy results are shown in Table 5 and Figure 1.

Table 5: Efficacy Results in RELATIVITY-047

	RELOPDUO N=355	**Nivolumab N=359**
Progression-free Survival[a,b]		
Disease progression or death (%)	180 (51)	211 (59)
Median (months)[c] (95% CI)	10.1 (6.4, 15.7)	4.6 (3.4, 5.6)
Hazard ratio[d] (95% CI)	0.75 (0.62, 0.92)	
p-value[e]	0.0055	
Overall Survival[f]		
Deaths (%)	137 (39)	160 (45)
Median in months (95% CI)	NR (34.2, NR)	34.10 (25.2, NR)
Hazard ratio[d] (95% CI)	0.80 (0.64, 1.01)	
p-value[e]	NS[g]	
Overall Response Rate[a,f, h]**, n (%)**	153 (43)	117 (33)
(95% CI)	(38, 48)	(28, 38)
Complete response rate (%)	58 (16)	51 (14)
Partial response rate (%)	95 (27)	66 (18)

[a] Assessed by BICR.

[b] Final PFS analysis.

[c] Kaplan-Meier estimate.

[d] Based on stratified Cox proportional hazard model.

[e] Based on stratified log-rank test.

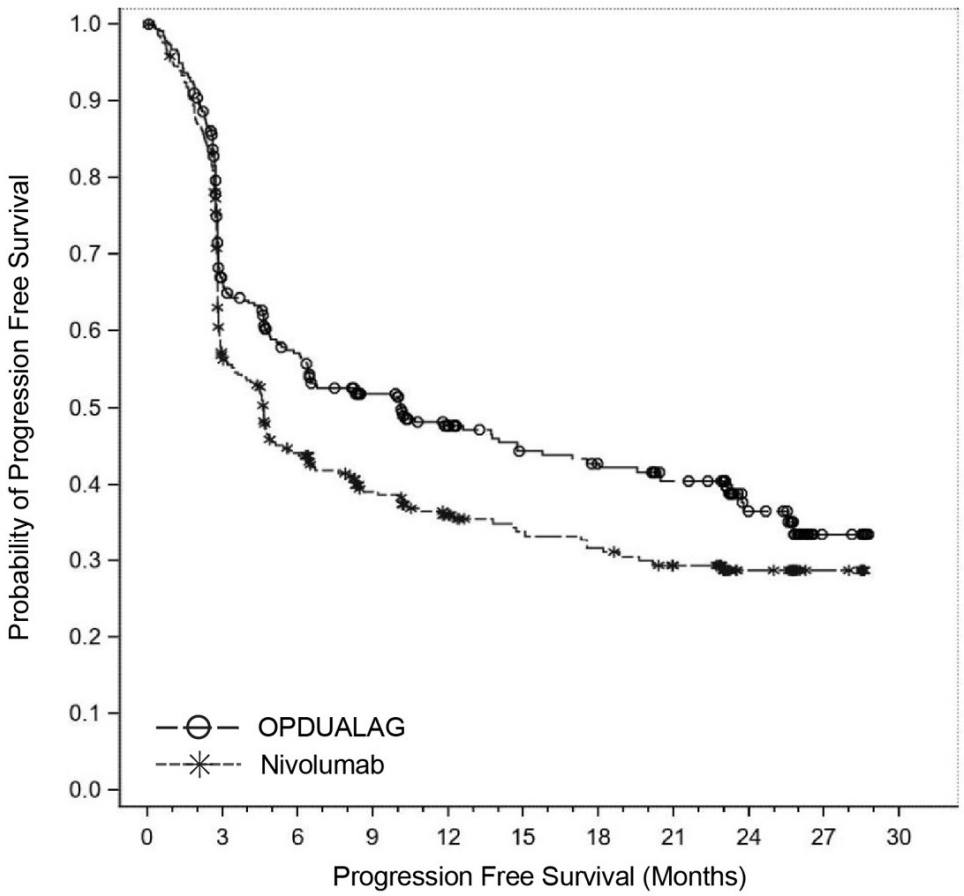
[f] At the time of the final OS analysis, which was event-driven and occurred after the final PFS analysis.

[g] Not Significant at alpha level 0.04302.

[h] Not formally tested based on the testing hierarchy.

NR = Not reached.

Figure 1:Progression-free Survival - RELATIVITY-047



Number of Subjects at Risk

OPDUALAG	355	201	163	132	99	81	75	67	30	6
Nivolumab	359	174	124	94	72	61	57	49	27	6

Note: The global brand name of this product is OPDUALAG, brand name in India is RELOPDUO

5.3 Pharmacokinetic properties

The pharmacokinetics (PK) of relatlimab following the administration of RELOPDUO were characterized in patients with cancer who received relatlimab 20 to 800 mg every 2 weeks (0.25 to 10 times the approved recommended dosage) or 160 to 1440 mg every 4 weeks (1 to 9 times the approved recommended dosage) either as a monotherapy or in combination with nivolumab dosages of 80 or 240 mg every 2 weeks or 480 mg every 4 weeks.

Steady-state concentrations of relatlimab were reached by 16 weeks with an every 4-week regimen and the systemic accumulation was 1.9-fold. The average concentration (Cavg) of relatlimab after the first dose increased dose proportionally at doses ≥160 mg every 4 weeks.

Following the recommended dosage, the geometric mean [coefficient of variation (CV%)] maximum and average concentrations (Cmax and Cavg) of relatlimab at steady state were 62.2 (30%), and 28.8 (45%) µg/mL, respectively; and the mean Cmax and Cavg of nivolumab at steady state were 187 (33%) and 94.4 (43%) µg/mL, respectively.
In RELATIVITY-047, the nivolumab geometric mean minimum concentration (Cmin) at steady state in the RELOPDUO arm was comparable to the nivolumab arm.

Distribution
The geometric mean (CV%) volume of distribution at steady state of relatlimab is 6.6 L (20%) and 6.6 L (19%) of nivolumab.

Elimination
The geometric mean (CV%) clearance of relatlimab is 5.5 mL/h (41%) at steady state, 10% lower than after the first dose [6 mL/h (39%)]. Following RELOPDUO (nivolumab 480 mg and relatlimab 160 mg administered every 4 weeks) administration, the geometric mean (CV%) effective half-life (t1/2) of relatlimab is 26.2 days (37%).

The geometric mean (CV%) clearance of nivolumab is 7.6 mL/h (40%) at steady state, 21% lower than after the first dose [9.6 mL/h (40%)] and the terminal t1/2 is 26.5 days (36%).

Specific Populations
The following factors had no clinically important effect on the clearance of nivolumab and relatlimab: age (17 to 92 years), sex, race (White, Asian, and Black/African American), mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m2), mild hepatic impairment (total bilirubin [TB] less than or equal to upper limit of normal [ULN] and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). The effects of severe renal impairment, or severe hepatic impairment on the pharmacokinetics of nivolumab and relatlimab are unknown.

Pediatric patients:
The exposures of nivolumab and relatlimab in pediatric patients 12 years of age or older who weigh at least 40 kg are expected to be in the range of exposures in adult patients at the recommended dosage.

5.4 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 studies of nivolumab and relatlimab products, or nivolumab products.
During the initial 24-month treatment period in RELATIVITY-047, the incidence of:
• anti-nivolumab antibodies and neutralizing antibodies in the RELOPDUO group was 3.8% (11/288) and 0.3% (1/288), respectively, which was similar to that observed in the nivolumab group: 5.9% (16/272) and 0.4% (1/272), respectively.

• anti-relatlimab antibodies and neutralizing antibodies in the RELOPDUO group was 5.6% (16/286) and 0.3% (1/286), respectively.

Because of the low incidence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, or effectiveness of RELOPDUO is unknown.

6 NON CLINICALPROPERTIES

6.1 Animal Toxicology or Pharmacology

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium tuberculosis*–infected PD-1 knockout mice exhibited markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockade using a primate anti-PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-1 and PD-L1 knockout mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.
Inhibition of PD-1 and LAG-3 results in autoimmunity in preclinical models. Mice deficient in both PD-1 and LAG-3 develop lethal systemic autoimmunity that includes myocarditis.
In a 1-month study in monkeys dosed with nivolumab and relatlimab, inflammation within the central nervous system (choroid plexus, vasculature, meninges, spinal cord) and the reproductive tract (epididymis, seminal vesicles, and testes) was observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

RELOPDUO contains nivolumab and relatlimab.
No studies have been performed to assess the potential of nivolumab or relatlimab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab or relatlimab.

7. DESCRIPTION

Nivolumab and relatlimab is a fixed-dose combination of two IgG4 kappa monoclonal antibodies (mAbs). Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody that has a calculated molecular mass of 146 kDa and is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line. Relatlimab is a lymphocyte activation gene-3 (LAG-3) blocking antibody that has a calculated molecular mass of 148 kDa and is expressed in a recombinant CHO cell line.
RELOPDUO (nivolumab and relatlimab) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution that may contain few translucent-to-white particles. RELOPDUO is supplied as 240 mg of nivolumab and 80 mg of relatlimab in a 20 mL single-dose vial for intravenous use. Each mL of RELOPDUO solution contains 12 mg of nivolumab, 4 mg of relatlimab, and histidine (1.1 mg), Histidine hydrochloride monohydrate (2.7 mg), pentetic acid (0.008 mg), polysorbate 80 (0.5 mg), sucrose (85.6 mg), and Water for Injection, USP. The pH is 5.8.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not specified

8.2 Shelf life

Unopened vial: Refer to the outer carton, for the expiry date.

For details on storage of prepared solution see section 4.2 posology and method of administration, sub-section 4.2.2.

8.3 Packaging Information

RELOPDUO (nivolumab and relatlimab) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for intravenous use supplied in a single-dose vial containing 240 mg of nivolumab and 80 mg of relatlimab per 20 mL (12 mg and 4 mg per mL) per carton.

Pack of 1 Vial.

8.4 Storage and handling instructions

Store in a refrigerator (2°C-8°C).

Do not freeze.

Do not shake.

Store in the original package in order to protect from light.

For details on preparation and storage of prepared solution see section 4.2 posology and method of administration, sub-section 4.2.2.

9. PATIENT COUSELLING INFORMATION

Immune-Mediated Adverse Reactions (IMAR)
Inform patients of the risk of IMARs that may require corticosteroid treatment and withholding or discontinuation of RELOPDUO, including:

• Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see 4.4 Special warnings and precautions for use]*.

• Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see 4.4 Special warnings and precautions for use]*.

• Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see 4.4 Special warnings and precautions for use]*.

• Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, thyroiditis, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see 4.4 Special warnings and precautions for use]*.

• Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis, including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see 4.4 Special warnings and precautions for use]*.

• Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see 4.4 Special warnings and precautions for use]*.

• Myocarditis: Advise patients to contact their healthcare provider immediately for signs or symptoms of new or worsening chest pain, palpitations, shortness of breath, fatigue, or swelling in ankles *[see 4.4 Special warnings and precautions for use]*.

Infusion-Related Reactions

• Advise patients of the potential risk of infusion-related reactions [*see 4.4 Special warnings and precautions for use]*.

Complications of Allogeneic HSCT

• Advise patients of potential risk of post-transplant complications *[see 4.4 Special warnings and precautions for use].*

Embryo-Fetal Toxicity

• Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see 4.4 Special warnings and precautions for use, see* 4.*6 Use in special populations, sub-sections 4.6.1, 4.6.3]*.

• Advise females of reproductive potential to use effective contraception during treatment with RELOPDUO and for at least 5 months following the last dose *[see* 4.*6 Use in special populations, sub-section 4.6.3].*

Lactation

• Advise women not to breastfeed during treatment with RELOPDUO and for 5 months after the last dose *[see* 4.*6 Use in special populations, sub-section 4.6.2]*.

10. DETAILS OF MANUFACTURER

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11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

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