

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use UNITUXIN safely and effectively. See Full Prescribing Information for UNITUXIN.

UNITUXIN™ (dinutuximab) injection, for intravenous use
Initial U.S. Approval: 2015

WARNING: SERIOUS INFUSION REACTIONS AND NEUROPATHY
See full prescribing information for complete boxed warning.

- **Infusion Reactions:** Life-threatening infusion adverse reactions occur with Unituxin. Administer required prehydration and premedication. Immediately interrupt for severe infusion reactions and permanently discontinue for anaphylaxis [see *Dosage and Administration* (2.2, 2.3) and *Warnings and Precautions* (5.1)].
- **Neuropathy:** Unituxin causes severe neuropathic pain. Administer intravenous opioid prior to, during, and for 2 hours following completion of the Unituxin infusion. Severe peripheral sensory neuropathy ranged from 2% to 9% in patients with neuroblastoma. Severe motor neuropathy was observed in adults. Discontinue for severe unresponsive pain, severe sensory neuropathy, or moderate to severe peripheral motor neuropathy [see *Dosage and Administration* (2.2, 2.3) and *Warnings and Precautions* (5.2)].

INDICATIONS AND USAGE

Unituxin is a GD2-binding monoclonal antibody indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy. (1)

DOSAGE AND ADMINISTRATION

- 17.5 mg/m²/day as a diluted intravenous infusion over 10 to 20 hours for 4 consecutive days for up to 5 cycles. (2.1, 2.4)

DOSAGE FORMS AND STRENGTHS

- Injection: 17.5 mg/5 mL (3.5 mg/mL) in a single-use vial. (3)

CONTRAINDICATIONS

- History of anaphylaxis to dinutuximab. (4)

WARNINGS AND PRECAUTIONS

- **Capillary leak syndrome and hypotension:** Administer required prehydration and monitor patients closely during treatment. Depending upon severity, manage by interruption, infusion rate reduction, or permanent discontinuation. (5.3, 5.4)
- **Infection:** Interrupt until resolution of systemic infection. (5.5)
- **Neurological Disorders of the Eye:** Interrupt for dilated pupil with sluggish light reflex or other visual disturbances and permanently discontinue for recurrent eye disorders or loss of vision. (5.6)
- **Bone marrow suppression:** Monitor peripheral blood counts during Unituxin therapy. (5.7)
- **Electrolyte abnormalities:** Monitor serum electrolytes closely. (5.8)
- **Atypical hemolytic uremic syndrome:** Permanently discontinue Unituxin and institute supportive management. (5.9)
- **Embryo-Fetal toxicity:** May cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception. (5.10, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse drug reactions (≥ 25%) are pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatremia, increased alanine aminotransferase, anemia, vomiting, diarrhea, hypokalemia, capillary leak syndrome, neutropenia, urticaria, hypoalbuminemia, increased aspartate aminotransferase, and hypocalcemia. (5, 6.1)

The most common serious adverse reactions (≥ 5%) are infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome. (5, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

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WARNING: SERIOUS INFUSION REACTIONS AND NEUROPATHY

Infusion Reactions

- **Serious and potentially life-threatening infusion reactions occurred in 26% of patients treated with Unituxin. Administer required prehydration and premedication including antihistamines prior to each Unituxin infusion. Monitor patients closely for signs and symptoms of an infusion reaction during and for at least four hours following completion of each Unituxin infusion. Immediately interrupt Unituxin for severe infusion reactions and permanently discontinue Unituxin for anaphylaxis (2.2, 2.3, 5.1).**

Neuropathy

- **Unituxin causes severe neuropathic pain in the majority of patients. Administer intravenous opioid prior to, during, and for 2 hours following completion of the Unituxin infusion. In clinical studies of patients with high-risk neuroblastoma, Grade 3 peripheral sensory neuropathy occurred in 2% to 9% of patients. In clinical studies of Unituxin and related GD2-binding antibodies, severe motor neuropathy was observed in adults. Resolution of motor neuropathy was not documented in all cases. Discontinue Unituxin for severe unresponsive pain, severe sensory neuropathy, or moderate to severe peripheral motor neuropathy (2.2, 2.3, 5.2).**

1 INDICATIONS AND USAGE

Unituxin (dinutuximab) is indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

- Verify that patients have adequate hematologic, respiratory, hepatic, and renal function prior to initiating each course of Unituxin [see *Clinical Studies (14)*].
- Administer required premedication and hydration prior to initiation of each Unituxin infusion [see *Dosage and Administration (2.2)*].

2.1 Recommended Dose

- The recommended dose of Unituxin is 17.5 mg/m²/day administered as an intravenous infusion over 10 to 20 hours for 4 consecutive days for a maximum of 5 cycles (Tables 1 and 2) [see *Dosage and Administration (2.4)*, *Clinical Studies (14)*].
- Initiate at an infusion rate of 0.875 mg/m²/hour for 30 minutes. The infusion rate can be gradually increased as tolerated to a maximum rate of 1.75 mg/m²/hour. Follow dose modification instructions for adverse reactions [see *Dosage and Administration (2.3)*].

Table 1: Schedule of Unituxin Administration for Cycles 1, 3, and 5

Cycle Day	1 through 3	4	5	6	7	8 through 24*
Unituxin		X	X	X	X	

*Cycles 1, 3, and 5 are 24 days in duration.

Table 2: Schedule of Unituxin Administration for Cycles 2 and 4

Cycle Day	1 through 7	8	9	10	11	12 through 32*
Unituxin		X	X	X	X	

*Cycles 2 and 4 are 32 days in duration.

2.2 Required Pre-treatment and Guidelines for Pain Management

Intravenous Hydration

- Administer 0.9% Sodium Chloride Injection, USP 10 mL/kg as an intravenous infusion over one hour just prior to initiating each Unituxin infusion.

Analgesics

- Administer morphine sulfate (50 mcg/kg) intravenously immediately prior to initiation of Unituxin and then continue as a morphine sulfate drip at an infusion rate of 20 to 50 mcg/kg/hour during and for two hours following completion of Unituxin.
- Administer additional 25 mcg/kg to 50 mcg/kg intravenous doses of morphine sulfate as needed for pain up to once every 2 hours followed by an increase in the morphine sulfate infusion rate in clinically stable patients.
- Consider using fentanyl or hydromorphone if morphine sulfate is not tolerated.
- If pain is inadequately managed with opioids, consider use of gabapentin or lidocaine in conjunction with intravenous morphine.

Antihistamines and Antipyretics

- Administer an antihistamine such as diphenhydramine (0.5 to 1 mg/kg; maximum dose 50 mg) intravenously over 10 to 15 minutes starting 20 minutes prior to initiation of Unituxin and as tolerated every 4 to 6 hours during the Unituxin infusion.
- Administer acetaminophen (10 to 15 mg/kg; maximum dose 650 mg) 20 minutes prior to each Unituxin infusion and every 4 to 6 hours as needed for fever or pain. Administer ibuprofen (5 to 10 mg/kg) every 6 hours as needed for control of persistent fever or pain.

2.3 Dosage Modifications

Manage adverse reactions by infusion interruption, infusion rate reduction, dose reduction, or permanent discontinuation of Unituxin (Table 3 and Table 4) [see *Warnings and Precautions (5)*, *Adverse Reactions (6)*, *Clinical Studies (14)*].

Table 3: Adverse Reactions Requiring Permanent Discontinuation of Unituxin

Grade 3 or 4 anaphylaxis
Grade 3 or 4 serum sickness
Grade 3 pain unresponsive to maximum supportive measures
Grade 4 sensory neuropathy or Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks
Grade 2 peripheral motor neuropathy
Subtotal or total vision loss
Grade 4 hyponatremia despite appropriate fluid management

Table 4: Dose Modification for Selected Unituxin Adverse Reactions

Infusion-related reactions [see <i>Warnings and Precautions</i> (5.1)]	
Mild to moderate adverse reactions such as transient rash, fever, rigors, and localized urticaria that respond promptly to symptomatic treatment	
<i>Onset of reaction:</i>	Reduce Unituxin infusion rate to 50% of the previous rate and monitor closely.
<i>After resolution:</i>	Gradually increase infusion rate up to a maximum rate of 1.75 mg/m ² /hour.
Prolonged or severe adverse reactions such as mild bronchospasm without other symptoms, angioedema that does not affect the airway	
<i>Onset of reaction:</i>	Immediately interrupt Unituxin.
<i>After resolution:</i>	If signs and symptoms resolve rapidly, resume Unituxin at 50% of the previous rate and observe closely.
<i>First recurrence:</i>	Discontinue Unituxin until the following day. If symptoms resolve and continued treatment is warranted, premedicate with hydrocortisone 1 mg/kg (maximum dose 50 mg) intravenously and administer Unituxin at a rate of 0.875 mg/m ² /hour in an intensive care unit.
<i>Second recurrence:</i>	Permanently discontinue Unituxin.

Capillary leak syndrome [see <i>Warnings and Precautions</i> (5.3)]	
Moderate to severe but not life-threatening capillary leak syndrome	
<i>Onset of reaction:</i>	Immediately interrupt Unituxin.
<i>After resolution:</i>	Resume Unituxin infusion at 50% of the previous rate.
Life-threatening capillary leak syndrome	
<i>Onset of reaction:</i>	Discontinue Unituxin for the current cycle.
<i>After resolution:</i>	In subsequent cycles, administer Unituxin at 50% of the previous rate.
<i>First recurrence:</i>	Permanently discontinue Unituxin.
Hypotension* requiring medical intervention [see <i>Warnings and Precautions</i> (5.4)]	
<i>Onset of reaction:</i>	Interrupt Unituxin infusion.
<i>After resolution:</i>	Resume Unituxin infusion at 50% of the previous rate. If blood pressure remains stable for at least 2 hours, increase the infusion rate as tolerated up to a maximum rate of 1.75 mg/m ² /hour.
Severe systemic infection or sepsis [see <i>Warnings and Precautions</i> (5.5)]	
<i>Onset of reaction:</i>	Discontinue Unituxin until resolution of infection, and then proceed with subsequent cycles of therapy.
Neurological Disorders of the Eye [see <i>Warnings and Precautions</i> (5.6)]	
<i>Onset of reaction:</i>	Discontinue Unituxin infusion until resolution.
<i>After resolution:</i>	Reduce the Unituxin dose by 50%.
<i>First recurrence or if accompanied by visual impairment:</i>	Permanently discontinue Unituxin.

*Symptomatic hypotension, systolic blood pressure (SBP) less than lower limit of normal for age, or SBP decreased by more than 15% compared to baseline.

2.4 Instructions for Preparation and Administration

Preparation

- Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the outer carton. **DO NOT FREEZE OR SHAKE** vials.
- Inspect visually for particulate matter and discoloration prior to administration. Do not administer Unituxin and discard the single-use vial if the solution is cloudy, has pronounced discoloration, or contains particulate matter.
- Aseptically withdraw the required volume of Unituxin from the single-use vial and inject into a 100 mL bag of 0.9% Sodium Chloride Injection, USP. Mix by gentle inversion. Do not shake. Discard unused contents of the vial.

- Store the diluted Unituxin solution under refrigeration (2°C to 8° C). Initiate infusion within 4 hours of preparation.
- Discard diluted Unituxin solution 24 hours after preparation.

Administration

- Administer Unituxin as a diluted intravenous infusion only [see *Dosage and Administration* (2.1)]. **Do not administer Unituxin as an intravenous push or bolus.**

3 DOSAGE FORMS AND STRENGTHS

Injection: 17.5 mg/5 mL (3.5 mg/mL) solution in a single-use vial.

4 CONTRAINDICATIONS

Unituxin is contraindicated in patients with a history of anaphylaxis to dinutuximab.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infusion Reactions

Serious infusion reactions requiring urgent intervention including blood pressure support, bronchodilator therapy, corticosteroids, infusion rate reduction, infusion interruption, or permanent discontinuation of Unituxin included facial and upper airway edema, dyspnea, bronchospasm, stridor, urticaria, and hypotension. Infusion reactions generally occurred during or within 24 hours of completing the Unituxin infusion. Due to overlapping signs and symptoms, it was not possible to distinguish between infusion reactions and hypersensitivity reactions in some cases.

In Study 1, Severe (Grade 3 or 4) infusion reactions occurred in 35 (26%) patients in the Unituxin/13-cis-retinoic acid (RA) group compared to 1 (1%) patient receiving RA alone. Severe urticaria occurred in 17 (13%) patients in the Unituxin/RA group but did not occur in the RA group. Serious adverse reactions consistent with anaphylaxis and resulting in permanent discontinuation of Unituxin occurred in 2 (1%) patients in the Unituxin/RA group. Additionally, 1 (0.1%) patient had multiple cardiac arrests and died within 24 hours after having received Unituxin in Study 2.

Prior to each Unituxin dose, administer required intravenous hydration and premedication with antihistamines, analgesics, and antipyretics [see *Dosage and Administration* (2.2)]. Monitor patients closely for signs and symptoms of infusion reactions during and for at least 4 hours following completion of each Unituxin infusion in a setting where cardiopulmonary resuscitation medication and equipment are available.

For mild to moderate infusion reactions such as transient rash, fever, rigors, and localized urticaria that respond promptly to antihistamines or antipyretics, decrease the Unituxin infusion rate and monitor closely. Immediately interrupt or permanently discontinue Unituxin and institute supportive management for severe or prolonged infusion reactions. Permanently discontinue Unituxin and institute supportive management for life-threatening infusion reactions [see *Dosage and Administration* (2.3)].

5.2 Pain and Peripheral Neuropathy

Pain

In Study 1, 114 (85%) patients treated in the Unituxin/RA group experienced pain despite pre-treatment with analgesics including morphine sulfate infusion. Severe (Grade 3) pain occurred in 68 (51%) patients in the Unituxin/RA group compared to 5 (5%) patients in the RA group. Pain typically occurred during the Unituxin infusion and was most commonly reported as abdominal pain, generalized pain, extremity pain, back pain, neuralgia, musculoskeletal chest pain, and arthralgia.

Premedicate with analgesics including intravenous opioids prior to each dose of Unituxin and continue analgesics until two hours following completion of Unituxin. For severe pain, decrease the Unituxin infusion rate to 0.875 mg/m²/hour. Discontinue Unituxin if pain is not adequately controlled despite infusion rate reduction and institution of maximum supportive measures [see *Dosage and Administration* (2.3)].

Peripheral Neuropathy

In Study 1, severe (Grade 3) peripheral sensory neuropathy occurred in 2 (1%) patients and severe peripheral motor neuropathy occurred in 2 (1%) patients in the Unituxin/RA group. No patients treated with RA alone experienced severe peripheral neuropathy. The duration and reversibility of peripheral neuropathy occurring in Study 1 was not documented. In Study 3, no patients experienced peripheral motor neuropathy. Among the 9 (9%) patients who experienced peripheral sensory neuropathy of any severity, the median (min, max) duration of peripheral sensory neuropathy was 9 (3, 163) days.

The neuropathic effects of anti-GD2 antibody therapy appear more severe in adult patients compared to pediatric patients. In a study of a related anti-GD2 antibody conducted in 12 adult patients with metastatic melanoma, 2 (13%) patients developed severe motor neuropathy. One patient developed lower extremity weakness and inability to ambulate that persisted for approximately 6 weeks. Another patient developed severe lower extremity weakness resulting in an inability to ambulate without assistance that lasted for approximately 16 weeks and neurogenic bladder that lasted for approximately 3 weeks. Complete resolution of motor neuropathy was not documented in this case.

Permanently discontinue Unituxin in patients with Grade 2 peripheral motor neuropathy, Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks, or Grade 4 sensory neuropathy.

5.3 Capillary Leak Syndrome

In Study 1, severe (Grade 3 to 5) capillary leak syndrome occurred in 31 (23%) patients in the Unituxin/RA group and in no patients treated with RA alone. Additionally, capillary leak syndrome was reported as a serious adverse reaction in 9 (6%) patients in the Unituxin/RA group and in no patients treated with RA alone. Immediately interrupt or discontinue Unituxin and institute supportive management in patients with symptomatic or severe capillary leak syndrome [see *Dosage and Administration* (2.3)].

5.4 Hypotension

In Study 1, severe (Grade 3 or 4) hypotension occurred in 22 (16%) patients in the Unituxin/RA group compared to no patients in the RA group.

Prior to each Unituxin infusion, administer required intravenous hydration. Closely monitor blood pressure during Unituxin treatment. Immediately interrupt or discontinue Unituxin and institute supportive management in patients with symptomatic hypotension, systolic blood pressure (SBP) less than lower limit of normal for age, or SBP that is decreased by more than 15% compared to baseline [see *Dosage and Administration* (2.2, 2.3)].

5.5 Infection

In Study 1, severe (Grade 3 or 4) bacteremia requiring intravenous antibiotics or other urgent intervention occurred in 17 (13%) patients in the Unituxin/RA group compared to 5 (5%) patients treated with RA alone. Sepsis occurred in 24 (18%) patients in the Unituxin/RA group and in 10 (9%) patients in the RA group.

Monitor patients closely for signs and symptoms of systemic infection and temporarily discontinue Unituxin in patients who develop systemic infection until resolution of the infection [see *Dosage and Administration* (2.3)].

5.6 Neurological Disorders of the Eye

Neurological disorders of the eye experienced by two or more patients treated with Unituxin in Studies 1, 2, or 3 included blurred vision, photophobia, mydriasis, fixed or unequal pupils, optic nerve disorder, eyelid ptosis, and papilledema.

In Study 1, 3 (2%) patients in the Unituxin/RA group experienced blurred vision, compared to no patients in the RA group. Diplopia, mydriasis, and unequal pupillary size occurred in 1 patient each in the Unituxin/RA group, compared to no patients in the RA group. The duration of eye disorders occurring in Study 1 was not documented. In Study 3, eye disorders occurred in 16 (15%) patients, and in 3 (3%) patients resolution of the eye disorder was not documented. Among the cases with documented resolution, the median duration of eye disorders was 4 days (range: 0, 221 days).

Interrupt Unituxin in patients experiencing dilated pupil with sluggish light reflex or other visual disturbances that do not cause visual loss. Upon resolution and if continued treatment with Unituxin is warranted, decrease the Unituxin dose by 50%. Permanently discontinue Unituxin in patients with recurrent signs or symptoms of an eye disorder following dose reduction and in patients who experience loss of vision [see *Dosage and Administration* (2.3)].

5.7 Bone Marrow Suppression

In Study 1, severe (Grade 3 or 4) thrombocytopenia (39% vs. 25%), anemia (34% vs. 16%), neutropenia (34% vs. 13%), and febrile neutropenia (4% vs. 0 patients) occurred more commonly in patients in the Unituxin/RA group compared to patients treated with RA alone. Monitor peripheral blood counts closely during therapy with Unituxin.

5.8 Electrolyte Abnormalities

Electrolyte abnormalities occurring in at least 25% of patients who received Unituxin/RA in Study 1 included hyponatremia, hypokalemia, and hypocalcemia. Severe (Grade 3 or 4) hypokalemia and hyponatremia occurred in 37% and 23% of patients in the Unituxin/RA group respectively compared to 2% and 4% of patients in the RA group. In a study of a related anti-GD2 antibody conducted in 12 adult patients with metastatic melanoma, 2 (13%) patients developed syndrome of inappropriate antidiuretic hormone secretion resulting in severe hyponatremia. Monitor serum electrolytes daily during therapy with Unituxin.

5.9 Atypical Hemolytic Uremic Syndrome

Hemolytic uremic syndrome in the absence of documented infection and resulting in renal insufficiency, electrolyte abnormalities, anemia, and hypertension occurred in two patients enrolled in Study 2 following receipt of the first cycle of dinutuximab. Atypical hemolytic uremic syndrome recurred following rechallenge with Unituxin in one patient. Permanently discontinue Unituxin and institute supportive management for signs of hemolytic uremic syndrome.

5.10 Embryo-Fetal Toxicity

Based on its mechanism of action, Unituxin may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment, and for two months after the last dose of Unituxin [see *Use in Specific Populations* (8.1, 8.3) and *Clinical Pharmacology* (12.1)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Infusion Reactions [see *Boxed Warning* and *Warnings and Precautions* (5.1)]
- Pain and Peripheral Neuropathy [see *Boxed Warning* and *Warnings and Precautions* (5.2)]
- Capillary Leak Syndrome [see *Warnings and Precautions* (5.3)]

- Hypotension [see *Warnings and Precautions (5.4)*]
- Infection [see *Warnings and Precautions (5.5)*]
- Neurological Disorders of the Eye [see *Warnings and Precautions (5.6)*]
- Bone Marrow Suppression [see *Warnings and Precautions (5.7)*]
- Electrolyte Abnormalities [see *Warnings and Precautions (5.8)*]
- Atypical Hemolytic Uremic Syndrome [see *Warnings and Precautions (5.9)*]
- Embryo-Fetal Toxicity [see *Warnings and Precautions (5.10)*]

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

The data described below reflect exposure to Unituxin at the recommended dose and schedule in 1021 patients with high-risk neuroblastoma enrolled in an open label, randomized (Study 1) or single arm clinical trials (Study 2 and Study 3). Prior to enrollment, patients received therapy consisting of induction combination chemotherapy, maximum feasible surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and radiation therapy to residual soft tissue disease. Patients received Unituxin in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis-retinoic acid (RA). Treatment commenced within 95 days post autologous stem cell transplant in Study 1, within 210 days of autologous stem cell transplant in Study 2, and within 110 days of autologous stem cell transplant in Study 3.

Study 1

In a randomized, open label, multi-center study (Study 1), 134 patients received dinutuximab in combination with GM-CSF, IL-2 and RA (Unituxin/RA group), including 109 randomized patients and 25 patients with biopsy-proven residual disease who were non-randomly assigned to receive dinutuximab. A total of 106 randomized patients received RA alone (RA group) [see *Dosage and Administration (2)* and *Clinical Studies (14)*]. Patients had a median age at enrollment of 3.8 years (range: 0.94 to 15.3 years), and were predominantly male (60%) and White (82%). In Study 1, adverse reactions of Grade 3 or greater severity were comprehensively collected, but adverse reactions of Grade 1 or 2 severity were collected sporadically and laboratory data were not comprehensively collected.

Approximately 71% of patients in the Unituxin/RA group and 77% of patients in the RA group completed planned treatment. The most common reason for premature discontinuation of study therapy was adverse reactions in the Unituxin/RA group (19%) and progressive disease (17%) in the RA group.

The most common adverse drug reactions ($\geq 25\%$) in the Unituxin/RA group were pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatremia, increased alanine aminotransferase, anemia, vomiting, diarrhea, hypokalemia, capillary leak syndrome, neutropenia, urticaria, hypoalbuminemia, increased aspartate aminotransferase, and hypocalcemia. The most common serious adverse reactions ($\geq 5\%$) in the Unituxin/RA group were infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome.

Table 5 lists the adverse reactions reported in at least 10% of patients in the Unituxin/RA group for which there was a between group difference of at least 5% (all grades) or 2% (Grade 3 or greater severity).

Table 5: Selected Adverse Reactions Occurring in at Least 10% of Patients in the Unituxin/RA Group in Study 1

Adverse Reaction ^{1,2}	Unituxin/RA (N=134)		RA (N=106)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General Disorders and Administration Site Conditions				
Pain ³	85	51	16	6
Pyrexia	72	40	27	6
Edema	17	0	0	0
Blood and Lymphatic System Disorders⁴				
Thrombocytopenia	66	39	43	25
Lymphopenia ⁴	62	51	36	20
Anemia	51	34	22	16
Neutropenia	39	34	16	13
Immune System Disorders				
Infusion reactions	60	25	9	1
Vascular Disorders				
Hypotension	60	16	3	0
Capillary leak syndrome ⁵	40	23	1	0
Hemorrhage ⁶	17	6	6	3
Hypertension	14	2	7	1
Metabolism and Nutrition Disorders				
Hyponatremia ⁴	58	23	12	4
Hypokalemia ⁴	43	37	4	2
Hypoalbuminemia ⁴	33	7	3	0
Hypocalcemia ⁴	27	7	0	0
Hypophosphatemia ⁴	20	8	3	0
Hyperglycemia ⁴	18	6	4	1
Hypertriglyceridemia ⁴	16	1	11	1
Decreased appetite	15	10	5	4
Hypomagnesemia ⁴	12	2	1	0
Investigations				
Increased alanine aminotransferase ⁴	56	23	31	3
Increased aspartate aminotransferase ⁴	28	10	7	0
Increased serum creatinine ⁴	15	2	6	0
Increased weight	10	0	0	0

Adverse Reaction ^{1,2}	Unituxin/RA (N=134)		RA (N=106)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Vomiting	46	6	19	3
Diarrhea	43	13	15	1
Nausea	10	2	3	1
Skin and Subcutaneous Tissue Disorders				
Urticaria	37	13	3	0
Respiratory, Thoracic and Mediastinal Disorders				
Hypoxia	24	12	2	1
Cardiac Disorders				
Tachycardia ⁷	19	2	1	0
Infections and Infestations				
Sepsis	18	16	9	9
Device related infection	16	16	11	11
Renal and Urinary Disorders				
Proteinuria ⁴	16	0	3	1
Nervous System Disorders				
Peripheral neuropathy	13	3	6	0

¹ Includes adverse reactions that occurred in at least 10% of patients in the Unituxin/RA group with at least a 5% (All Grades) or 2% (Grades 3-5) absolute higher incidence in the Unituxin/RA group compared to the RA group.

² Adverse drug reactions were graded using CTCAE version 3.0.

³ Includes preferred terms abdominal pain, abdominal pain upper, arthralgia, back pain, bladder pain, bone pain, chest pain, facial pain, gingival pain, infusion related reaction, musculoskeletal chest pain, myalgia, neck pain, neuralgia, oropharyngeal pain, pain, pain in extremity, and proctalgia.

⁴ Based on investigator reported adverse reactions.

⁵ One Grade 5 adverse reaction.

⁶ Includes preferred terms gastrointestinal hemorrhage, hematochezia, rectal hemorrhage, hematemesis, upper gastrointestinal hemorrhage, hematuria, hemorrhage urinary tract, renal hemorrhage, epistaxis, respiratory tract hemorrhage, disseminated intravascular coagulation, catheter site hemorrhage, hemorrhage and hematoma.

⁷ Includes preferred terms tachycardia and sinus tachycardia.

Table 6 compares the per-patient incidence of selected adverse reactions occurring during cycles containing dinutuximab in combination with GM-CSF (Cycles 1, 3, and 5) with cycles containing dinutuximab in combination with IL-2 (Cycles 2 and 4).

Table 6: Comparison of Adverse Events by Treatment Cycle in the Unituxin/RA Group in Study 1

Preferred Term ^{1,2}	All Grades		Severe	
	GM-CSF N=134 (%)	IL-2 ³ N=127 (%)	GM-CSF N=134 (%)	IL-2 ³ N=127 (%)
General Disorders and administration site conditions				
Pyrexia	55	65	10	37
Pain ⁵	77	61	43	35
Blood and Lymphatic System Disorders⁴				
Thrombocytopenia	62	61	31	33
Lymphopenia	54	61	33	50
Anemia	42	42	21	24
Neutropenia	25	32	19	28
Immune System Disorders				
Infusion reactions	47	54	10	20
Vascular Disorders				
Hypotension	43	54	5	16
Capillary leak syndrome	22	36	11	20
Metabolism and Nutrition Disorders⁴				
Hyponatremia	36	55	5	21
Hypokalemia	26	39	13	33
Hypoalbuminemia	29	29	3	5
Hypocalcemia	20	21	2	6
Investigations⁴				
Increased alanine aminotransferase	43	48	15	13
Aspartate aminotransferase increased	16	21	4	7
Gastrointestinal Disorders				
Diarrhea	31	37	6	13
Vomiting	33	35	3	2
Skin and Subcutaneous Tissue Disorders				
Urticaria	25	29	7	7

Abbreviations: GM-CSF: granulocyte-macrophage colony-stimulating factor; IL-2: interleukin-2.

¹ Includes preferred terms with a per-patient incidence of at least 20% in the Unituxin and RA group for either IL-2 or GM-CSF containing cycles.

² Adverse drug reactions were graded using CTCAE version 3.0.

³ Seven patients who received GM-CSF in Cycle 1 discontinued prior to starting Cycle 2.

⁴ Based on investigator reported adverse reactions.

⁵ Includes preferred terms abdominal pain, abdominal pain upper, arthralgia, back pain, bladder pain, bone pain, chest pain, facial pain, gingival pain, infusion related reaction, musculoskeletal chest pain, myalgia, neck pain, neuralgia, oropharyngeal pain, pain, pain in extremity, and proctalgia.

Study 2 and Study 3

Study 2 was a single arm, multicenter expanded access trial that enrolled patients with high-risk neuroblastoma (N=783). The reported adverse event profile of dinutuximab in Study 2 was similar to that observed in Study 1.

Study 3 was a multicenter, single arm safety study of dinutuximab in combination with GM-CSF, IL-2 and RA. In Study 3, adverse events of all CTCAE grades and laboratory data were

systematically and comprehensively collected. Of 104 patients enrolled and treated in Study 3, 77% of patients completed study therapy. In general, the adverse reaction profile of dinutuximab observed in Study 3 was similar to that observed in Study 1 and Study 2. The following adverse reactions not previously reported in Study 1 were reported in at least 10% of patients in Study 3: nasal congestion (20%) and wheezing (15%). Table 7 provides the per-patient incidence of laboratory abnormalities in Study 3.

Table 7: Per-Patient Incidence of Selected (≥ 5% Grade 3-4) Laboratory Abnormalities in Study 3

Laboratory Test ¹	Grade ²	
	All Grades %	Grades 3-4 %
Hematology		
Anemia	100	46
Neutropenia	99	63
Thrombocytopenia	98	49
Chemistry		
Hypoalbuminemia	100	8
Hypocalcemia	97	7
Hyponatremia	93	36
Hyperglycemia	87	6
Aspartate Aminotransferase Increased	84	8
Alanine Aminotransferase Increased	83	13
Hypokalemia	82	41
Hypophosphatemia	78	6
Urinalysis³		
Urine protein	66	ND
Red blood cell casts	38	ND

ND: not determined

¹ Laboratory abnormalities with a per-patient incidence of at least 20% (all grades) and at least a 5% per-patient incidence of severe (Grade 3 or 4) laboratory abnormalities.

² Based on CTCAE version 4.0.

³ Urinalysis results were reported as positive or negative without assessment of grade.

6.2 Immunogenicity

As with all therapeutic proteins, patients treated with Unituxin may develop anti-drug antibodies. In clinical studies, 52 of 284 (18%) patients from Study 2 and 13 of 103 (13%) patients from Study 3 tested positive for anti-dinutuximab binding antibodies. Neutralizing antibodies were detected in 3.6% of patients who were tested for anti-dinutuximab binding antibodies in Study 2 and Study 3. However, due to the limitations of the assay, the incidence of neutralizing antibodies may not have been reliably determined.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to Unituxin with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with dinutuximab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, Unituxin may cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no studies in pregnant women and no reproductive studies in animals to inform the drug-associated risk. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. Advise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There is no information available on the presence of dinutuximab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. However, human IgG is present in human milk. Because of the potential for serious adverse reactions in a breastfed infant, advise a nursing woman to discontinue breastfeeding during treatment with Unituxin.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Unituxin may cause fetal harm [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment and for two months after the last dose of Unituxin.

8.4 Pediatric Use

The safety and effectiveness of Unituxin as part of multi-agent, multimodality therapy have been established in pediatric patients with high-risk neuroblastoma based on results of an open-label, randomized (1:1) trial conducted in 226 patients aged 11 months to 15 years (median age 3.8 years) (Study 1). Prior to enrollment, patients achieved at least a partial response to prior first-line therapy for high-risk neuroblastoma consisting of induction combination chemotherapy, maximum feasible surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and received radiation therapy to residual soft tissue disease. Patients randomized to the Unituxin/13-cis-retinoic acid (RA) arm (Unituxin/RA) received up to five cycles of Unituxin in combination with alternating cycles of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-2 (IL-2) plus RA, followed by one cycle of RA alone. Patients randomized to the RA arm received up to six cycles of RA monotherapy. Study 1 demonstrated an improvement in event-free survival and overall survival in patients in the Unituxin/RA arm compared to those in the RA arm [see *Adverse Reactions (6)*, *Clinical Pharmacology (12)*, *Clinical Studies (14)*].

8.5 Geriatric Use

The safety and effectiveness of Unituxin in geriatric patients have not been established.

8.6 Renal Impairment

Unituxin has not been studied in patients with renal impairment.

8.7 Hepatic Impairment

Unituxin has not been studied in patients with hepatic impairment.

11 DESCRIPTION

Unituxin (dinutuximab) is a chimeric monoclonal antibody composed of murine variable heavy and light chain regions and the human constant region for the heavy chain IgG1 and light chain kappa. Unituxin binds to the glycolipid disialoganglioside (GD2). Dinutuximab is produced in the murine myeloma cell line, SP2/0.

Unituxin is a sterile, preservative-free, clear/colorless to slightly opalescent solution for intravenous infusion. Unituxin is supplied in single-use vials of 17.5 mg/5mL. Each vial contains 3.5 mg/mL of dinutuximab, histidine (20mM), polysorbate 20 (0.05%), sodium chloride (150 mM), and water for injection; hydrochloric acid is added to adjust pH to 6.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dinutuximab binds to the glycolipid GD2. This glycolipid is expressed on neuroblastoma cells and on normal cells of neuroectodermal origin, including the central nervous system and peripheral nerves. Dinutuximab binds to cell surface GD2 and induces cell lysis of GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

12.3 Pharmacokinetics

The pharmacokinetics of dinutuximab was evaluated by a population pharmacokinetic analysis in a clinical study of Unituxin in combination with GM-CSF, IL-2, and RA. In this study, 27 children with high-risk neuroblastoma (age: 3.9 ± 1.9 years) received up to 5 cycles of Unituxin at $17.5 \text{ mg/m}^2/\text{day}$ as an intravenous infusion over 10 to 20 hours for 4 consecutive days every 28 days. The observed maximum plasma dinutuximab concentration (C_{max}) was 11.5 mcg/mL [20%, coefficient of variation (CV)]. The mean volume of distribution at steady state ($V_{\text{d}_{\text{ss}}}$) was 5.4 L (28%). The clearance was 0.21 L/day (62%) and increased with body size. The terminal half-life was 10 days (56%).

No formal pharmacokinetic studies were conducted in patients with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted to evaluate the carcinogenic or mutagenic potential of dinutuximab.

Dedicated studies examining the effects of dinutuximab on fertility in animals have not been conducted. No clear effects on reproductive organs were observed in general toxicology studies conducted in rats.

13.2 Animal Toxicology and/or Pharmacology

Non-clinical studies suggest that dinutuximab-induced neuropathic pain is mediated by binding of the antibody to the GD2 antigen located on the surface of peripheral nerve fibers and myelin and subsequent induction of CDC and ADCC activity.

14 CLINICAL STUDIES

The safety and effectiveness of Unituxin was evaluated in a randomized, open-label, multicenter trial conducted in pediatric patients with high-risk neuroblastoma (Study 1). All patients had received prior therapy consisting of induction combination chemotherapy, maximum feasible surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and radiation therapy to residual soft tissue disease. Patients were randomized between Day 50 and Day 77 post-autologous stem cell transplantation.

Patients were required to have achieved at least a partial response prior to autologous stem cell transplantation, have no evidence of disease progression following completion of front-line multi-modality therapy, have adequate pulmonary function (no dyspnea at rest and peripheral arterial oxygen saturation of at least 94% on room air), adequate hepatic function (total bilirubin < 1.5 x the upper limit of normal and ALT < 5 x the upper limit of normal), adequate cardiac function (shortening fraction of > 30% by echocardiogram, or if shortening fraction abnormal, ejection fraction of 55% by gated radionuclide study), and adequate renal function (glomerular filtration rate at least 70 mL/min/1.73 m²). Patients with systemic infections or a requirement for concomitant systemic corticosteroids or immunosuppressant usage were not eligible for enrollment.

Patients randomized to the Unituxin/RA arm received up to five cycles of dinutuximab (clinical trials material) in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) (Table 8) or interleukin-2 (IL-2) (Table 9) plus 13-cis-retinoic acid (RA), followed by one cycle of RA alone. Patients randomized to the RA arm received six cycles of RA. Dinutuximab was administered at a dose of 17.5 mg/m²/day (equivalent to 25 mg/m²/day of clinical trials material) on four consecutive days. Patients in both treatment arms received six cycles of RA at a dose of 160 mg/m²/day orally (for patients weighing more than 12 kg) or 5.33 mg/kg/day (for patients weighing less than or equal to 12 kg) in two divided doses for 14 consecutive days.

Table 8: Dosage Regimen in the Unituxin/RA Arm for Cycles 1, 3, and 5

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24
GM-CSF ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Unituxin ²				X	X	X	X								
RA ³											X	X	X	X	X

¹ GM-CSF: 250 µg/m²/day, administered by either subcutaneous injection (recommended) or IV infusion administered over 2 hours.

² Unituxin: 17.5 mg/m²/day, administered by diluted IV infusion over 10–20 hours.

³ RA: for >12 kg body weight, 80 mg/m² orally twice daily for a total dose of 160 mg/m²/day; for ≤12 kg body weight, 2.67 mg/kg orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

Table 9: Dosage Regimen in the Unituxin/RA Arm for Cycles 2 and 4

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12-14	15-28	29-32
IL-2 ¹	X	X	X	X				X	X	X	X			
Unituxin ²								X	X	X	X			
RA ³													X	

¹ IL-2: 3 MIU/m²/day administered by continuous IV infusion over 96 hours on Days 1-4 and 4.5 MIU/m²/day on Days 8-11.

² Unituxin: 17.5 mg/m²/day, administered by diluted IV infusion over 10-20 hours.

³ RA: for >12 kg body weight, 80 mg/m² orally twice daily for a total dose of 160 mg/m²/day; for ≤12 kg body weight, 2.67 mg/kg orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

A total of 226 patients were randomized, 113 patients to each arm. In general, demographic and baseline tumor characteristics were similar across study arms. Across the study population, 60% were male, the median age was 3.8 years and 3% of patients were less than 1.5 years, 82% were White and 7% were Black. The majority (80%) of patients had International Neuroblastoma Staging System Stage 4 disease. Thirty-five percent of patients had a complete response, 43% had a very good partial response, and 23% had a partial response to therapy received prior to autologous stem cell transplant. Forty-six percent of patients had neuroblastoma that was not

MYCN-amplified, 36% had tumors with known MYCN-amplification, and MYCN status was unknown or missing in 19% of patients. Forty-three percent of patients had hyperdiploid tumors, 36% had diploid tumors, and DNA ploidy status was unknown or missing in 21% of patients.

The major efficacy outcome measure was investigator-assessed event-free survival (EFS), defined as the time from randomization to the first occurrence of relapse, progressive disease, secondary malignancy, or death. Overall survival (OS) was also evaluated. After observing a numerical improvement in EFS based on the seventh interim analysis, the Data Monitoring Committee recommended termination of accrual. Efficacy results are shown in Table 10.

Table 10: Efficacy Results

Efficacy Parameter		Unituxin/ RA arm n=113	RA arm n=113
EFS	No. of Events (%)	33 (29%)	50 (44%)
	Median (95% CI) (years)	NR (3.4 ,NR)	1.9 (1.3, NR)
	Hazard Ratio (95% CI)	0.57 (0.37, 0.89)	
	p-value (log-rank test) ¹	0.01	
OS ²	No. of Events (%)	31 (27%)	48 (42%)
	Median (95% CI) (years)	NR (7.5,NR)	NR (3.9,NR)
	Hazard Ratio (95% CI)	0.58 (0.37,0.91)	

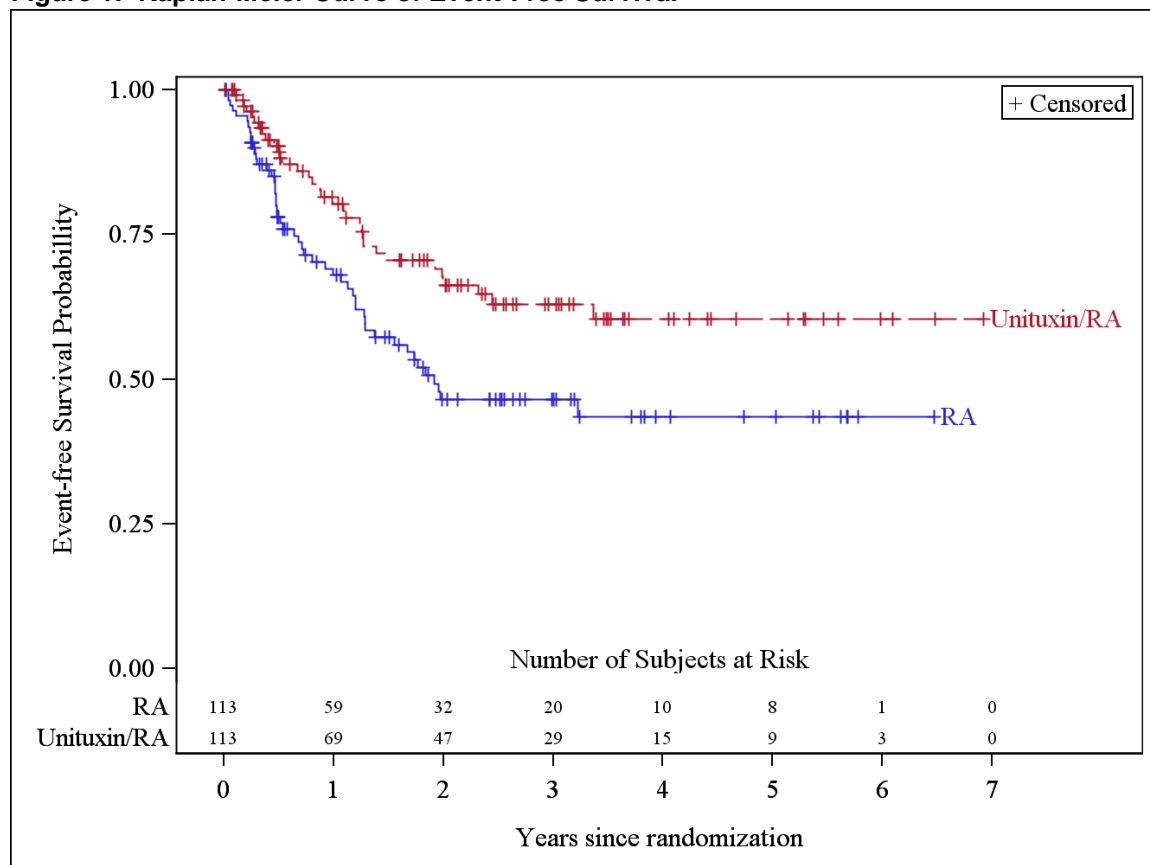
NR = not reached

¹ Compared to the allocated alpha of 0.01 pre-specified for the seventh interim analysis of EFS

² Based on an additional three years of follow up after the seventh interim analysis of EFS

The Kaplan-Meier curve of EFS is shown in Figure 1.

Figure 1: Kaplan-Meier Curve of Event-Free Survival



16 HOW SUPPLIED / STORAGE AND HANDLING

Unituxin is supplied in a carton containing one 17.5 mg/5 mL (3.5 mg/mL) single-use vial.

NDC 66302-014-01

Store Unituxin vials under refrigeration at 2°C to 8°C until time of use. Do not freeze or shake the vial. Keep the vial in the outer carton in order to protect from light.

17 PATIENT COUNSELING INFORMATION

- Serious Infusion Reactions**
 Inform patients and caregivers of the risk of serious infusion reactions and anaphylaxis and to immediately report any signs or symptoms, such as facial or lip swelling, urticaria, difficulty breathing, lightheadedness or dizziness that occur during or within 24 hours following the infusion [see *Warnings and Precautions* (5.1)].
- Pain and Peripheral Neuropathy**
 Inform patients and caregivers of the risk of severe pain and peripheral sensory and motor neuropathy and to promptly report severe or worsening pain and signs and symptoms of neuropathy such as numbness, tingling, burning, or weakness [see *Warnings and Precautions* (5.2)].

- *Capillary Leak Syndrome*
Inform patients and caregivers of the risk of capillary leak syndrome and to immediately report any signs or symptoms [see *Warnings and Precautions* (5.3)].
- *Hypotension*
Inform patients and caregivers of the risk of hypotension during the infusion and to immediately report any signs or symptoms [see *Warnings and Precautions* (5.4)].
- *Infection*
Inform patients and caregivers of the risk of infection following treatment and to immediately report any signs or symptoms [see *Warnings and Precautions* (5.5)].
- *Neurological Disorders of the Eye*
Inform patients and caregivers of the risk of neurological disorders of the eye and to promptly report signs or symptoms such as blurred vision, photophobia, ptosis, diplopia, or unequal pupil size [see *Warnings and Precautions* (5.6)].
- *Bone Marrow Suppression*
Inform patients and caregivers of the risk of bone marrow suppression, and to promptly report signs or symptoms of anemia, thrombocytopenia, or infection [see *Warnings and Precautions* (5.7)].
- *Electrolyte Abnormalities*
Inform patients and caregivers of the risk of electrolyte abnormalities including hypokalemia, hyponatremia, and hypocalcemia, and to report any signs or symptoms such as seizures, heart palpitations, and muscle cramping [see *Warnings and Precautions* (5.8)].
- *Atypical Hemolytic Uremic Syndrome*
Inform patients and caregivers of the risk of hemolytic uremic syndrome and to report any signs or symptoms such as fatigue, dizziness, fainting, pallor, edema, decreased urine output, or hematuria [see *Warnings and Precautions* (5.9)].
- *Embryo-Fetal Toxicity*
Advise women of reproductive potential of the potential risk to the fetus if administered during pregnancy and the need for use of effective contraception during and for at least two months after completing therapy [see *Warnings and Precautions* (5.10)].

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