PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**UNITUXIN®**

Dinutuximab for injection

3.5 mg/mL Injection for Intravenous Use

Antineoplastic

United Therapeutics Corp.
Research Triangle Park, NC
27709, USA

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PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

[Pr]Unituxin® (dinutuximab for injection) 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 high-risk neuroblastoma in pediatric patients who achieve at least a partial response to prior first-line multiagent, multimodality therapy *[see CLINICAL TRIALS]*.

2 CONTRAINDICATIONS

[Pr]Unituxin® (dinutuximab for injection) is contraindicated in patients with a history of anaphylaxis to dinutuximab, IL-2, GM-CSF, RA, or any excipients in the medicinal product. See Dosage Forms, Strengths, Composition, and Packaging for a complete listing of ingredients.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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 4 hours following completion of each Unituxin infusion. Immediately interrupt Unituxin for severe infusion reactions and permanently discontinue Unituxin for anaphylaxis *[see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS]*.**

Neurotoxicity

- **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 peripheral motor neuropathy has also been reported. Discontinue for severe unresponsive pain, severe sensory neuropathy, and moderate to severe peripheral motor neuropathy *[see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS]*.**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Verify that patients have adequate hematologic, respiratory, hepatic, and renal function prior to initiating each course of [Pr]Unituxin® *[see CLINICAL TRIALS]*.
- Administer required premedication and hydration prior to initiation of each Unituxin infusion *[see Recommended Dose and Dosage Adjustment]*.

4.2 Recommended Dose and Dosage Adjustment

4.2.1 Recommended Dose

- The recommended dose of Unituxin is 17.5 mg/m^2/day administered as an intravenous infusion over 10 to 20 hours for 4 consecutive days for a maximum of 5 cycles (Table 1 and Table 2) *[see CLINICAL TRIALS and Administration]*.
- Initiate at an infusion rate of 0.875 mg/m^2/hour for 30 minutes. The infusion rate can be gradually increased as tolerated to a maximum rate of 1.75 mg/m^2/hour. Follow dose modification instructions for adverse reactions *[see Recommended Dose and Dosage Adjustment]*.

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

Cycle Day	1 through 3	4	5	6	7	8 through 24[a]
Unituxin		X	X	X	X	

[a] 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[a]
Unituxin		X	X	X	X	

[a] Cycles 2 and 4 are 32 days in duration.

4.2.2 Required Pre-treatment and Guidelines for Pain Management and Infusion Reactions

4.2.2.1 Required Pre-treatment and Guidelines for Pain Management and Infusion Reactions During all Unituxin-Administered Courses

Intravenous Hydration

- Administer 0.9% Sodium Chloride Injection as an intravenous infusion over 1 hour just prior to initiating each Unituxin infusion.

Analgesics

- Administer morphine sulfate at 50 mcg/kg intravenously immediately prior to initiation of Unituxin infusion and then continue as a morphine sulfate drip at an infusion rate of 20-50 mcg/kg/hour during and for 2 hours following completion of Unituxin infusion.
- Administer additional 25-50 mcg/kg intravenous doses of morphine sulfate up to every 2 hours as needed for pain, followed by a clinically appropriate increase in the morphine sulfate infusion rate in clinically stable patients.
- Other pain control should be considered as necessary. Consideration of using fentanyl or hydromorphone if morphine sulfate is not tolerated. Lidocaine or gabapentin can be considered as co-analgesics in conjunction with morphine infusion.

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 infusion and as tolerated every 4 to 6 hours during the Unituxin infusion.
- Administer an antipyretic such as 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. For persistent pain or fever despite acetaminophen and morphine sulfate, administer ibuprofen (5 to 10 mg/kg) every 6 hours as needed.

4.2.2.2 Required Pretreatment and Guidelines for Pain Management and Infusion Reaction When IL-2 is Administered Alone (Course 2 and 4, Course Days 0-3)

Antihistamines and Antipyretics

- Acetaminophen and ibuprofen should be administered as noted in 4.2.2.1 above. Acetaminophen is recommended before IL-2 administration and every six hours around the clock during IL-2 administration.
- Diphenhydramine is administered as needed for allergic reactions or nausea with dosing as described in 4.2.2.1. For nausea, it is recommended to start 10 minutes before IL-2 and continued every 4 to 6 hours as needed.

4.2.3 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, ADVERSE REACTIONS, and CLINICAL TRIALS]*.

Table 3 Adverse Reactions Requiring Permanent Discontinuation of Unituxin

Grade 3 or 4 anaphylaxis or Grade 4 infusion reactions
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 or greater peripheral motor neuropathy
Urinary retention that persists following discontinuation of opioids
Transverse myelitis
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Subtotal or total vision loss
Grade 4 hyponatremia despite appropriate fluid management
Grade 4 hypokalemia despite interventions to correct deficiency
Atypical hemolytic uremic syndrome
Grade 4 capillary leak syndrome (if recurs after 50% dose reduction following Grade 4 reaction in previous cycle)

Table 4 Dose Modification for Selected Unituxin Adverse Reactions

Infusion-related reactions *[see WARNINGS AND PRECAUTIONS]*	
Mild to moderate adverse reactions such as transient rash, fever, rigors, and localized urticaria that respond promptly to symptomatic treatment	
Onset of reaction:	Reduce Unituxin infusion rate to 50% of the previous rate and monitor closely.
After resolution:	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	
Onset of reaction:	Immediately interrupt Unituxin infusion.
After resolution:	If signs and symptoms resolve rapidly, resume Unituxin infusion at 50% of the previous rate and observe closely.
First recurrence:	Discontinue Unituxin infusion 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.
Second recurrence:	Permanently discontinue Unituxin.
Neurological disorders of the eye *[see WARNINGS AND PRECAUTIONS]*	
Onset of reaction:	Discontinue Unituxin infusion and current Unituxin cycle until resolution.
After resolution:	In subsequent cycles, reduce the Unituxin dose by 50%.
First recurrence or if accompanied by visual impairment:	Permanently discontinue Unituxin.
Capillary leak syndrome *[see WARNINGS AND PRECAUTIONS]*	
Moderate to severe but not life-threatening capillary leak syndrome	
Onset of reaction:	Immediately interrupt Unituxin infusion.
After resolution:	Resume Unituxin infusion at 50% of the previous rate.
Life-threatening capillary leak syndrome	
Onset of reaction:	Discontinue Unituxin infusion for the current cycle.
After resolution:	In subsequent cycles, administer Unituxin infusion at 50% of the previous rate.
First recurrence:	Permanently discontinue Unituxin.

Hypotension[a] requiring medical intervention *[see WARNINGS AND PRECAUTIONS]*	
Onset of reaction:	Interrupt Unituxin infusion.
After resolution:	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	
Onset of reaction:	Discontinue Unituxin until resolution of infection, and then proceed with subsequent cycles of therapy.

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

4.3 Administration

- Administer Unituxin only as an intravenous infusion diluted in 0.9% Sodium Chloride, USP *[see Recommended Dose and Dosage Adjustment]*. **Do not administer Unituxin as an intravenous push or bolus.**
- Once diluted, initiate infusion within 4 hours.

4.4 Preparation

- 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 [36°F to 46°F]). **Do not freeze.**
- Discard diluted Unituxin solution 24 hours after preparation.

4.5 Missed Dose

Not Applicable

5 OVERDOSAGE

Pr Unituxin® is only administered in a professional setting by experienced practitioners. During clinical trials no cases of dinutuximab for injection overdose have been reported. In clinical trials, scheduled dinutuximab for injection doses of up to 120 mg/m^2 (60 mg/m^2/day) have been administered with an adverse reaction profile similar to those described under *ADVERSE REACTIONS*.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 5 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Intravenous Infusion	17.5 mg/5 mL (3.5 mg/mL) solution in a single-use vial	Histidine (20 mM), Hydrochloric Acid (to adjust pH), Polysorbate 20 (0.05%), Sodium Chloride (150 mM), Water for Injection.

[Pr]Unituxin® is supplied in cartons containing 1 vial.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information regarding Infusion Reactions and Neurotoxicity.

General

Serious Infusion Reactions

Serious infusion reactions including anaphylaxis and serum sickness requiring urgent intervention including blood pressure support, bronchodilator therapy, corticosteroids, infusion rate reduction, infusion interruption, or permanent discontinuation of [Pr]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 DIV-NB-301, 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 DIV-NB-302.

Prior to each Unituxin dose, administer required intravenous hydration and premedication with antihistamines, analgesics, and antipyretics *[see Recommended Dose and Dosage Adjustment]*. 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 the Unituxin infusion 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 Recommended Dose and Dosage Adjustment]*.

Capillary Leak Syndrome

In study DIV-NB-301, 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 the Unituxin infusion or discontinue Unituxin and institute supportive management in patients with symptomatic or severe capillary leak syndrome *[see Recommended Dose and Dosage Adjustment]*. Capillary leak syndrome is more likely when Unituxin is co-administered with interleukin-2 (IL-2). It is recommended to administer oral metolazone or intravenous furosemide every 6–12 hours as required. Supplemental oxygen, respiratory support, and albumin replacement therapy should be used as necessary according to clinical response.

Pain

In study DIV-NB-301, 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 2 hours following completion of the Unituxin infusion *[see Recommended Dose and Dosage Adjustment]*.

For severe pain, decrease the Unituxin infusion rate to 0.875 mg/m^2/hour. Discontinue Unituxin if pain is not adequately controlled despite infusion rate reduction and institution of maximum supportive measures *[see Recommended Dose and Dosage Adjustment]*.

Cardiovascular

Hypotension

In study DIV-NB-301, 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 the Unituxin infusion 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 Recommended Dose and Dosage Adjustment]*.

Endocrine and Metabolism

Electrolyte Abnormalities

Electrolyte abnormalities occurring in at least 25% of patients who received Unituxin/RA in study DIV-NB-301 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.

Neurologic

Transverse Myelitis

Transverse myelitis has occurred in patients treated with Unituxin. Promptly evaluate any patient with signs or symptoms of transverse myelitis such as weakness, paresthesia, sensory loss, or incontinence. Permanently discontinue Unituxin in patients who develop transverse myelitis *[see Recommended Dose and Dosage Adjustment and Post-Market Adverse Reactions]*.

Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has occurred in patients treated with Unituxin. Institute appropriate medical treatment and permanently discontinue Unituxin in patients with signs and symptoms of RPLS (eg, severe headache, hypertension, visual changes, lethargy, or seizures) *[see Recommended Dose and Dosage Adjustment and Post-Market Adverse Reactions]*.

Peripheral Neuropathy

In study DIV-NB-301, 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 DIV-NB-301 was not documented. In study DIV-NB-303, 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.

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 peripheral motor neuropathy of Grade 2 or greater severity, Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks, or Grade 4 sensory neuropathy *[see Recommended Dose and Dosage Adjustment]*.

Ophthalmologic

Neurological Disorders of the Eye

Neurological disorders of the eye experienced by 2 or more patients treated with Unituxin in Studies DIV-NB-301, DIV-NB-302, or DIV-NB-303 included blurred vision, photophobia, mydriasis, fixed or unequal pupils, optic nerve disorder, eyelid ptosis, and papilledema.

In study DIV-NB-301, 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 DIV-NB-301 was not documented. In study DIV-NB-303, 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 (min, max) duration of eye disorders was 4 days (0, 221 days).

Interrupt Unituxin infusion in patients experiencing persistent dilated pupil with sluggish light reflex or other visual disturbances. Discontinue the current Unituxin cycle. Upon resolution, if continued treatment with Unituxin is warranted, then decrease the Unituxin infusion dose by 50% in future cycles. 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 Recommended Dose and Dosage Adjustment]*.

Renal

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 2 patients enrolled in study DIV-NB-302 following receipt of the first cycle of Unituxin. Atypical hemolytic uremic syndrome recurred following rechallenge with Unituxin in 1 patient. Permanently discontinue Unituxin and institute supportive management for signs of hemolytic uremic syndrome.

Prolonged Urinary Retention

Urinary retention that persists for weeks to months following discontinuation of opioids has occurred in patients treated with Unituxin. Permanently discontinue Unituxin in patients with urinary retention that does not resolve following discontinuation of opioids *[see Recommended Dose and Dosage Adjustment and Post-Market Adverse Reactions]*.

Sexual Health Reproduction, Function, Fertility

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 2 months after the last dose of Unituxin *[see Special Populations and ACTION AND CLINICAL PHARMACOLOGY]*.

7.1 Special Populations

7.1.1 Females of Reproductive Potential

Unituxin may cause fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for two months after the last dose of Unituxin.

7.1.2 Pregnant Women

Based on its mechanism of action, ^{Pr}Unituxin® may cause fetal harm when administered to a pregnant woman *[see ACTION AND CLINICAL PHARMACOLOGY]*. 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 general population of major congenital anomalies is ~4% and still births is <1% in Canada.

7.1.3 Breast-feeding

There is no information available on the presence of dinutuximab in human breast milk, the effects of the drug on the breast-fed infant, or the effects of the drug on breast milk production.

However, human immunoglobulin G (IgG) is present in human breast milk. Because of the potential for serious adverse reactions in a breast-fed infant, advise a nursing woman to discontinue breast-feeding during treatment with Unituxin.

7.1.4 Pediatrics

The safety and effectiveness of Unituxin as part of multi-agent, multimodality therapy have been established in pediatric patients with high-risk neuroblastoma. *See ADVERSE REACTIONS, ACTION AND CLINICAL PHARMACOLOGY, and CLINICAL TRIALS sections for details regarding supporting evidence*.

7.1.5 Geriatrics

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

7.1.6 Use in Renal Impairment

Unituxin has not been studied in patients with renal impairment.

7.1.7 Use in Hepatic Impairment

Unituxin has not been studied in patients with hepatic impairment.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The data described below reflect exposure to [Pr]Unituxin® at the recommended dose and schedule in 1021 patients with high-risk neuroblastoma enrolled in an open label, randomized (study DIV-NB-301) or single arm clinical trials (studies DIV-NB-302 and DIV-NB-303). 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 GM-CSF, IL-2 and RA. Treatment commenced within 95 days post autologous stem cell transplant in study DIV-NB-301, within 210 days of autologous stem cell transplant in study DIV-NB-302, and within 110 days of autologous stem cell transplant in study DIV-NB-303.

Unituxin has been associated with neurologic adverse reactions thought to be resulting from the binding to GD2 not located at the tumor site (see Warnings and Precautions for guidance). Most of these adverse reactions, including transverse myelitis, resolved following discontinuation of Unituxin and initiation of appropriate medical therapy.

8.2 Clinical Trial Adverse Reactions (Pediatrics)

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Study DIV-NB-301

In a randomized, open label, multi-center study (DIV-NB-301), 134 patients received dinutuximab for injection 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 for injection. A total of 106 randomized patients received RA alone (RA group) *[see DOSAGE AND ADMINISTRATION and CLINICAL TRIALS]*. 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 DIV-NB-301, 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 (≥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 (≥5%) in the Unituxin/RA group were infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome.

Study DIV-NB-302

Study DIV-NB-302 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 DIV-NB-302 was similar to that observed in study DIV-NB-301.

Study DIV-NB-303

Study DIV-NB-303 was a multicenter, single arm safety study of dinutuximab for injection in combination with GM-CSF, IL-2 and RA. In study DIV-NB-303, adverse events of all Common Terminology Criteria for Adverse Events (CTCAE) grades and laboratory data were systematically and comprehensively collected. Of 104 patients enrolled and treated in study DIV-NB-303, 77% of patients completed study therapy. In general, the adverse reaction profile of dinutuximab observed in study DIV-NB-303 was similar to that observed in studies DIV-NB-301 and DIV-NB-302. The following adverse reactions not previously reported in study DIV-NB-301 were reported in at least 10% of patients in study DIV-NB-303: nasal congestion (20%) and wheezing (15%).

Table 6 lists the adverse reactions, including laboratory values, reported in at least 2% of patients from study DIV-NB-301.

Table 6 Adverse Reactions Occurring in at Least 2% of Subjects in the Dinutuximab Group

Adverse Reaction	Control Group DIV-NB-301 Randomized (N=108) %	Dinutuximab Group DIV-NB-301 Randomized (N=141) %
Blood and Lymphatic System Disorders		
Anemia	21.3	53.9
Febrile neutropenia	0	3.5
Cardiac Disorders		
Sinus tachycardia	0	15.6
Tachycardia	0.9	9.2
Supraventricular tachycardia	0	2.1
Ear and Labyrinth Disorders		
Hearing impaired	5.6	5.7
Endocrine Disorders		
Hypothyroidism	1.9	3.5
Hyperthyroidism	0	2.8
Eye Disorders		
Vision blurred	0	2.1
Photophobia	1.9	2.8
Gastrointestinal Disorders		
Abdominal pain	8.3	57.4
Vomiting	18.5	43.3
Diarrhea	14.8	44.0
Nausea	2.8	9.9
Constipation	1.9	7.1
Cheilitis	3.7	4.3
Abdominal pain upper	0.9	4.3
Stomatitis	0.9	3.5
Lower gastrointestinal hemorrhage	0	2.1
General Disorders and Administration Site Conditions		
Pyrexia	26.9	73.0
Pain	5.6	51.8
Face Edema	0	12.1
Fatigue	1.9	6.4
Irritability	0	4.3
Edema peripheral	0	6.4
Chills	0	7.8
Injection site reaction	0	4.3
Edema	0	6.4
Non-cardiac chest pain	0	4.3
Immune System Disorders		
Hypersensitivity	7.4	56.7
Anaphylactic reaction	0.9	26.2
Cytokine release syndrome	0	4.3
Infections and Infestations		
Device related infection	10.2	17.7
Infection susceptibility increased	5.6	9.9
Enterocolitis infection	1.9	7.1
Urinary tract infection	2.8	2.8

Adverse Reaction	Control Group DIV-NB-301 Randomized (N=108) %	Dinutuximab Group DIV-NB-301 Randomized (N=141) %
Staphylococcal bacteremia	3.7	10.6
Upper respiratory tract infection	2.8	2.1
Lung infection	1.9	2.1
Otitis media	1.9	3.5
Bacteremia	0.9	2.1
Bacillus infection	0.9	3.5
Klebsiella bacteremia	0.9	3.5
Clostridium difficile colitis	0.9	2.1
Herpes zoster	0.9	3.5
Streptococcal bacteremia	0	2.1
Osteomyelitis	0	2.1
Wound infection	0	2.1
Escherichia urinary tract infection	0	2.1
Investigations		
Platelet count decreased	40.7	66.0
Lymphocyte count decreased	35.2	67.4
Alanine aminotransferase increased	30.6	53.9
White blood cell count decreased	14.8	37.6
Neutrophil count decreased	15.7	41.8
Aspartate aminotransferase increased	6.5	27.0
Gamma-Glutamyl transferase increased	0	4.3
Weight increased	0	10.6
Blood creatinine increased	5.6	14.9
Blood alkaline phosphatase increased	6.5	6.4
Blood bilirubin increased	4.6	8.5
Weight decreased	0	2.8
Blood culture positive	0.9	2.8
Metabolism and Nutrition Disorders		
Hypoalbuminemia	2.8	34.0
Hyponatremia	12.0	56.7
Hypokalemia	4.6	43.3
Hypocalcemia	0	25.5
Hypertriglyceridemia	11.1	17.0
Hyperglycemia	3.7	18.4
Hypophosphatemia	2.8	20.6
Decreased appetite	4.6	14.9
Hypomagnesemia	0.9	12.1
Hyperkalemia	3.7	5.7
Hypoglycemia	0	3.5
Hypercalcemia	7.4	7.8
Acidosis	0	5.7
Hypermagnesemia	0.9	3.5
Dehydration	1.9	3.5
Hypernatremia	0.9	2.8

Adverse Reaction	Control Group DIV-NB-301 Randomized (N=108) %	Dinutuximab Group DIV-NB-301 Randomized (N=141) %
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	3.7	17.0
Back pain	0.9	12.1
Neck pain	0	4.3
Musculoskeletal chest pain	1.9	7.8
Myalgia	0.9	4.3
Arthralgia	1.9	6.4
Bone pain	0.9	4.3
Nervous System Disorders		
Neuralgia	0	9.2
Headache	3.7	7.8
Peripheral sensory neuropathy	0.9	7.1
Peripheral motor neuropathy	3.7	6.4
Psychiatric Disorders		
Agitation	1.9	4.3
Psychotic disorder	0	2.1
Euphoric mood	0	2.1
Renal and Urinary Disorders		
Proteinuria	2.8	14.9
Hematuria	0.9	7.8
Urinary retention	0	7.1
Urinary tract obstruction	0	2.1
Respiratory, Thoracic, and Mediastinal Disorders		
Hypoxia	1.9	26.2
Cough	1.9	9.9
Dyspnea	0.9	5.7
Bronchospasm	0	5.0
Oropharyngeal pain	0	3.5
Rhinitis allergic	0.9	2.1
Epistaxis	3.7	2.8
Skin and Subcutaneous Tissue Disorders		
Urticaria	2.8	44.7
Pruritus	0.9	10.6
Dry skin	14.8	16.3
Rash papular	4.6	8.5
Erythema multiforme	5.6	5.0
Vascular Disorders		
Hypotension	2.8	63.1
Capillary leak syndrome	0.9	41.8
Hypertension	6.5	13.5
Flushing	0	2.1

8.3 Less Common Clinical Trial Adverse Reactions

The following events occur with a frequency below the cut-off for common and very common adverse reactions (<2%):

- Blood and Lymphatic: Atypical hemolytic uremic syndrome
- Eye: Mydriasis, Unequal pupils
- Immune System: Serum sickness
- Infections and Infestations: Sepsis
- Neurologic/Nervous System: Myelitis, Reversible Posterior Leukoencephalopathy Syndrome
- Hemorrhages including gastrointestinal/gastric hemorrhage, hematochezia, rectal hemorrhage, hematemesis, upper gastrointestinal hemorrhage, hemorrhage urinary tract, renal hemorrhage, respiratory tract hemorrhage, disseminated intravascular coagulation, and catheter site hemorrhage

8.4 Immunogenicity

As with all therapeutic proteins, there is potential for patients treated with dinutuximab to develop anti-drug antibodies. In clinical studies of pediatric patients treated with dinutuximab, 68 of 414 (16.4%) tested positive for anti-dinutuximab binding antibodies and 38 of 414 (9.24%) tested positive for neutralizing antibodies. Plasma concentrations of dinutuximab, especially trough levels, tended to be lower in patients with human anti-chimeric antibodies (HACA). In light of insufficient data, no claim can be made regarding any correlation between the detection of these antibodies and allergic reactions.

The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay and for these reasons, comparison of the incidence of antibodies to dinutuximab with the incidence of antibodies to other products may be misleading.

8.5 Post-Market Adverse Reactions

In addition to the adverse reactions discussed in the previous sections, the following adverse reactions have been identified during post-approval use of Unituxin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Neurotoxicity including transverse myelitis

9 DRUG INTERACTIONS

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

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 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).

This binding to normal cells of neuroectodermal origin has been proposed as an explanation for the pain and neurotoxicity observed in the clinic. 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.

10.2 Pharmacodynamics

Non-clinical studies demonstrate that dinutuximab-induced neurotoxicity is likely due to the induction of mechanical allodynia that may be mediated by reactivity of dinutuximab with GD2 antigen located on the surface of peripheral nerve fibers and/or myelin.

Severe allergic reactions are more likely when dinutuximab is co-administered with IL-2. Therefore, caution should be taken when both medicinal products are combined.

Cardiovascular events including increased heart rate and blood pressure were observed in clinical studies; however, no effects on QTc interval or other cardiac monitoring parameters were identified in the cardiovascular sub-study of DIV-NB-302.

10.3 Pharmacokinetics

Table 7 Summary of Unituxin Pharmacokinetic Parameters in High Risk Pediatric Neuroblastoma Patients

	C_{max}	T_{max}	$t_{½}$ (h)	$AUC_{0-\infty}$	CL	Vd
Multiple Dose Mean	11.45 mcg/mL	74.72 h	197.5 h	1822 mcg.h/mL	0.026 L/h	7.2 L

Absorption: No formal metabolism studies have been conducted. Absorption is considered to be 100% of the administered dose.

Distribution: The pharmacokinetics of dinutuximab was evaluated by a non-compartmental pharmacokinetic analysis in a clinical study of ^{Pr}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 mg/m^2/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 11.45 mcg/mL (20%, coefficient of variation [CV]). The mean volume of distribution at steady state (Vd_{ss}) was 7.2 L (56%).

Metabolism: Dinutuximab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Classical biotransformation studies have not been performed.

Elimination: The clearance was 0.026 L/hour (0.63 L/day) and increased with body size. The terminal half-life was 197.5 hours (8.23 days). A covariate analysis with the population pharmacokinetic analysis conducted on all clinical data available suggests that the disposition of dinutuximab is not altered by age, race, gender, concomitant medications (IL-2, GM-CSF) and the presence of capillary leak syndrome, or renal or hepatic impairment. However, the presence of HACA appears to increase the clearance parameter in the model of dinutuximab by approximately 60%.

Special Populations and Conditions

Pediatrics: *[see Pediatrics]*

Geriatrics: No formal pharmacokinetic studies were conducted in geriatric patients *[see Geriatrics].*

Pregnancy and Breast-feeding: No formal pharmacokinetic studies were conducted in patients who were pregnant or breast-feeding *[see Pregnant Women and Breast-feeding].*

Hepatic Insufficiency: No formal pharmacokinetic studies were conducted in patients with hepatic impairment.

Renal Insufficiency: No formal pharmacokinetic studies were conducted in patients with renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store [Pr]Unituxin® vials under refrigeration at 2°C to 8°C (36°F to 46°F) until time of use. **DO NOT FREEZE OR SHAKE** the vial. Keep the vial in the outer carton in order to protect from light. Discard unused contents of the vial.

Store the diluted Unituxin solution under refrigeration (2°C to 8°C [36°F to 46°F]). Discard diluted Unituxin solution 24 hours after preparation.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Avoid contact with skin or eyes. For skin contact, wash affected area immediately with soap and water and contact physician. For eye contact, flush eyes immediately with large amounts of water and contact physician.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Dinutuximab

Chemical name: Immunoglobulin G1, anti-(ganglioside GD2) (human-Mus musculus monoclonal ch14.18 heavy chain), disulfide with human-Mus musculus monoclonal ch14.18 light chain, dimer

Molecular formula and molecular mass: The molecular weight of dinutuximab is in the range of 147,625 Da to 150,744 Da.

Structural formula: The heavy chain has 443 amino acids and 1 glycosylation site (Asn 293), molecular weight 49750 Da to 50075.4 Da. The light chain has 220 amino acids and a molecular weight of 24070.9 Da.

Physicochemical properties: Dinutuximab is a glycosylated chimeric IgG1 human/mouse monoclonal antibody (mAb), produced in a murine myeloma cell (SP2/0 hybridoma cell). It incorporates human constant regions for the heavy chain IgG1 and the kappa light chain, along with the murine variable regions targeted specifically against human disialoganglioside (GD2) to which dinutuximab binds. Dinutuximab is a clear, colorless, to slightly opalescent liquid.

14 CLINICAL TRIALS

The safety and effectiveness of [Pr]Unituxin® was evaluated in a randomized, open-label, multicenter trial conducted in pediatric patients with high-risk neuroblastoma (study DIV-NB-301). 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.

14.1 Trial Design and Study Demographics

Table 8 Summary of Patient Demographics for Pivotal and Main Supportive Clinical Trials in Pediatrics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age in years (Range in years)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age in years (Range in years)
DIV-NB-301 (ANBL-0032)	Phase III randomized study of chimeric antibody 14.18 (dinutuximab) in high-risk neuroblastoma following myeloablative therapy and autologous stem cell rescue	Dinutuximab for injection: 25 mg/m^2/day IV over 5 to 20 hours x 4 days Courses 1-5 GM-CSF: 250 mcg/m^2/day IV or SC over 2 hours x 14 days Courses 1, 3, and 5 IL-2: up to 4.5 MIU/m^2/day IV x 8 days Courses 2 and 4 RA: 80 mg/m^2/dose BID PO x 14 days, Courses 1-6	Neuroblastoma: 251 enrolled, 226 randomized, of which 113 were assigned to dinutuximab immunotherapy + RA, 113 were assigned to RA only, and 25 were non-randomly assigned to dinutuximab immunotherapy (as of 13 January 2009 data cut)	4.3 (0.94 to 15.29)
DIV-NB-302 (ANBL-0032)	Open-label, non-randomized, efficacy and safety study of dinutuximab for injection + GM-CSF + IL-2 + RA in patients with neuroblastoma	Dinutuximab for injection: 25 mg/m^2/day IV over 10 to 20 hours x 4 days Courses 1-5 GM-CSF: 250 mcg/m^2/day IV or SC over 2 hours x 14 days Courses 1, 3, and 5 IL-2: up to 4.5 MIU/m^2/day IV x 8 days Courses 2 and 4 RA: 80 mg/m^2/dose BID PO x 14 days Courses 1-6	838 subjects enrolled per data cut from 31 December 2013.	4.5 (0.75 to 29.4)
DIV-NB-303 (ANBL-0931)	Open-label, safety study of dinutuximab for injection + GM-CSF + IL-2 + RA in patients with neuroblastoma	Dinutuximab for injection: 25 mg/m^2/day IV over 10 to 20 hours x 4 days Courses 1-5 GM-CSF: 250 mcg/m^2/day IV or SC over 2 hours x 14 days Courses 1, 3, and 5 IL-2: up to 4.5 MIU/m^2/day IV x 8 days Courses 2 and 4 RA: 80 mg/m^2/dose BID PO x 14 days Courses 1-6	105 enrolled, 104 treated	4.8 (1 to 27)
DIV-NB-201	Open label randomized, comparative pharmacokinetic study in patients with neuroblastoma	Dinutuximab for injection: 25 mg/m^2/day or 17.5 mg/m^2/day IV over 10 to 20 hours x 4 days Courses 1-5 [a] GM-CSF 250 mcg/m^2/day IV or SC over 2 hours x 14 days Courses 1, 3, and 5 IL-2: up to 4.5 MIU/m^2/day IV x 8 days Courses 2 and 4 RA: 80 mg/m^2/dose BID PO x 14 days, Courses 1-6	28	3.9 (0.76 to 8.8)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age in years (Range in years)

[a] Study DIV-NB-201 was designed to evaluate the comparability of two dinutuximab products: the product used in clinical trials at 25 mg/m^2/day and the other intended for commercial production at 17.5 mg/m^2/day. The results demonstrated comparability between the two products at these doses.

BID = twice daily; CSR = clinical study report; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL-2 = interleukin-2; IV = intravenous(ly); PO = by mouth; RA = 13-cis-retinoic acid; SC = subcutaneous

Table 9 Summary of Baseline Demographics for ITT Population of DIV-NB-301

Characteristics	RA Alone (n=113)	Immunotherapy + RA (n=113)	Overall (n=226)
Age at Enrollment (years): Mean (range)	4.0 (0.94-13.29)	4.3 (0.95-15.29)	4.1 (0.94-15.29)
Age at Enrollment Category: n (%)			
Adolescent (12-18 years)	1 (0.9%)	4 (3.5%)	5 (2.2%)
Child (2-12 years)	94 (83.2%)	97 (85.8%)	191 (84.5%)
Infant/Toddler (28 days to 2 years)	18 (15.9%)	12 (10.6%)	30 (13.3%)
Gender: Male/Female (%)	57/43	63/37	60/40
Ethnicity: n (%)			
Hispanic or Latino	11 (10%)	11 (10%)	22 (10%)
Not Hispanic or Latino	96 (85%)	100 (89%)	196 (87%)
Unknown	6 (5%)	2 (2%)	8 (4%)
Race: n (%)			
White	90 (80%)	95 (84%)	185 (82%)
Black or African American	8 (7%)	8 (7%)	16 (7%)
Asian	4 (4%)	2 (2%)	6 (3%)
Native Hawaiian or Other Pacific Islander	2 (2%)	0	2 (1%)
Multiple	2 (2%)	1 (1%)	3 (1%)
Other/Unknown	7 (6%)	7 (6%)	14 (6%)
Pre-ASCT Response: n (%)			
CR	38 (34%)	40 (35%)	78 (35%)
VGPR	49 (43%)	47 (42%)	96 (43%)
PR	26 (23%)	26 (23%)	52 (23%)
Number of Days Post-Final ASCT: mean ± SD	77 ± 12.0	75 ± 8.7	76 ± 10.5
INSS Stage: n (%)			
Stage 2a	0	4 (4%)	4 (2%)
Stage 3	16 (14%)	10 (9%)	26 (12%)
Stage 4	92 (81%)	89 (79%)	181 (80%)
Stage 4s	0	2 (2%)	2 (1%)
MYCN: n (%)			
Amplified	45 (40%)	36 (32%)	81 (36%)
Non-amplified	51 (45%)	52 (46%)	103 (46%)
Missing	17 (15%)	25 (22%)	42 (19%)
DNA ploidy: n (%)			
Diploid	46 (41%)	35 (31%)	81 (36%)
Hyperdiploid	48 (43%)	49 (43%)	97 (43%)
Missing	19 (17%)	29 (26%)	48 (21%)
Tumor Histology: n (%)			
Favorable	5 (4%)	4 (4%)	9 (4%)
Unfavorable	81 (72%)	68 (60%)	149 (66%)
Missing	27 (24%)	41 (36%)	68 (30%)
Baseline Absolute Phagocyte Count	17153 ± 74215	11767 ± 50411	14460 ± 63356

Characteristics	RA Alone (n=113)	Immunotherapy + RA (n=113)	Overall (n=226)
(count/mcL): Mean ± SD			

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 phagocyte count (≥ 1000 cells/mcL), adequate hepatic function (total bilirubin <1.5 x the upper limit of normal and alanine aminotransferase (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 m^2). 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 5 cycles of dinutuximab for injection in combination with GM-CSF (Table 10) or IL-2 (Table 11) plus RA, followed by 1 cycle of RA alone. Patients randomized to the RA arm received 6 cycles of RA. Dinutuximab for injection was administered at a dose of 17.5 mg/m^2/day (equivalent to 25 mg/m^2/day of clinical trials material – see reference to this study and footnote "a" in Table 8) on 4 consecutive days. Patients in both treatment arms received 6 cycles of RA at a dose of 160 mg/m^2/day orally (for patients weighing >12 kg) or 5.33 mg/kg/day (for patients weighing ≤12 kg) in 2 divided doses for 14 consecutive days.

Table 10 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 [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Unituxin [b]				X	X	X	X								
RA [c]											X	X	X	X	X

GM-CSF = granulocyte-macrophage colony-stimulating factor; RA = 13-cis-retinoic acid

[a] GM-CSF: 250 µg/m^2/day, administered by either subcutaneous injection (recommended) or IV infusion administered over 2 hours.

[b] Unituxin: 17.5 mg/m^2/day, administered by diluted IV infusion over 10–20 hours.

[c] RA: for >12 kg body weight, 80 mg/m^2 orally twice daily for a total dose of 160 mg/m^2/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 11 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 [a]	X	X	X	X				X	X	X	X			
Unituxin [b]								X	X	X	X			
RA [c]													X	

IL-2 = interleukin-2; RA = 13-cis-retinoic acid

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

[b] Unituxin: 17.5 mg/m^2/day, administered by diluted IV infusion over 10-20 hours.

[c] RA: for >12 kg body weight, 80 mg/m^2 orally twice daily for a total dose of 160 mg/m^2/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).

14.2 Study Results

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. Efficacy results on all randomized patients are shown in Table 12.

Table 12 Results of Study DIV-NB-301 in High-risk Neuroblastoma

Efficacy Parameter		**Unituxin/RA arm n=113**	**RA arm n=113**
EFS	No. of Events (%)	40 (35%)	54 (48%)
	Median (95% CI) (years)	NR (3.4, NR)	2.0 (1.3, NR)
	Hazard Ratio (95% CI) [a]	0.59 (0.39, 0.89)	
	p-value (log-rank test) [a]	0.0124	
Efficacy Parameter		**Unituxin/RA arm n=114**	**RA arm n=114**
OS [b]	No. of Events (%)	28 (25%)	44 (39%)
	Median (95% CI) (years)	NR (7.5, NR)	NR (4.4, NR)
	Hazard Ratio (95% CI) [b]	0.60 (0.37, 0.96)	
	p-value [b]	0.0351	

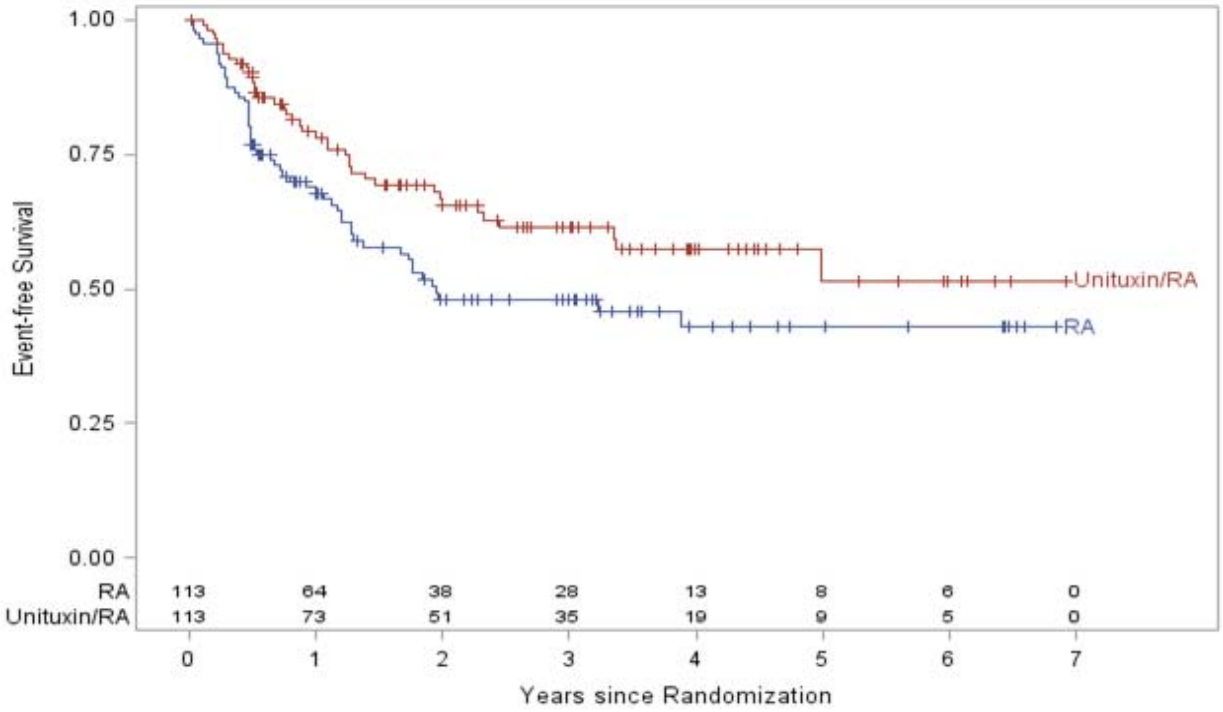
CI = confidence interval; EFS = event-free survival; INSS = International Neuroblastoma Staging System; NR = not reached; OS = overall survival; RA = 13-cis-retinoic acid

[a] Hazard ratio and p-value were calculated using multivariate Cox proportional hazard regression model with treatment, age at diagnosis category, age at enrollment category, INSS stage, and pre-autologous stem cell transplantation (ASCT) response as explanatory variables.

[b] Based on an additional 3 years of follow up. Hazard ratio and p-value were calculated using multivariate Cox proportional hazard regression model with treatment, DNA ploidy, and pre-ASCT response as explanatory variables. The p-value for OS is not adjusted for multiplicity.

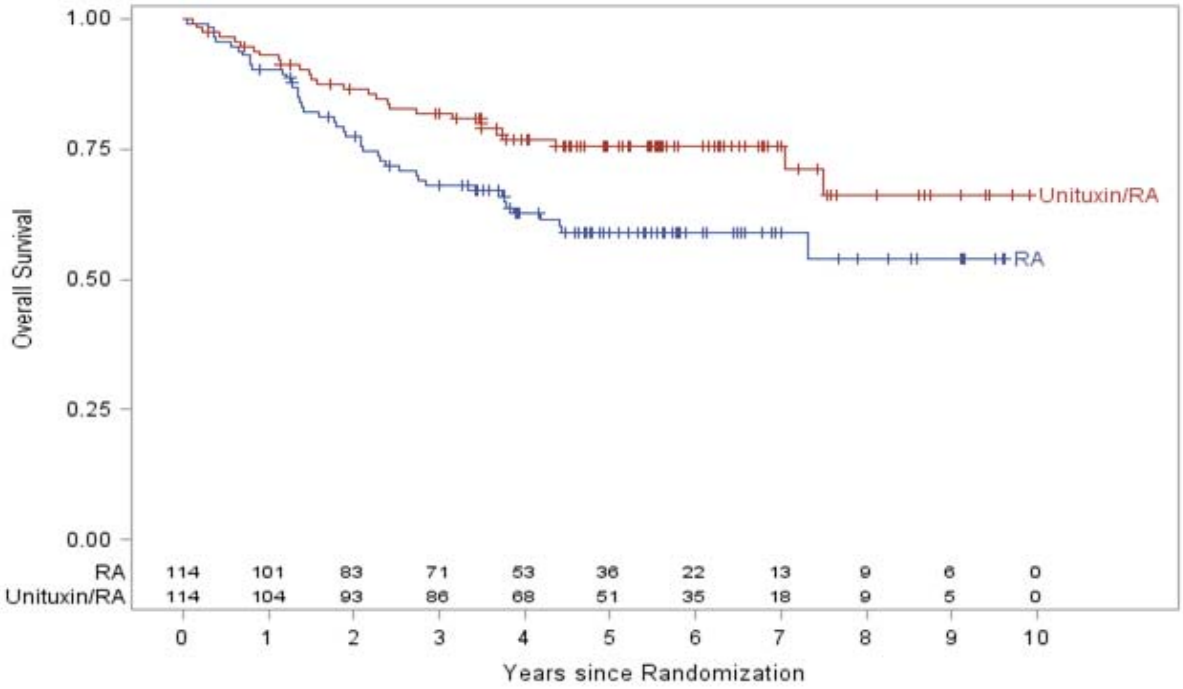
The Kaplan-Meier curve of EFS is shown in Figure 1. The Kaplan-Meier curve of OS is shown in Figure 2.

Figure 1 Kaplan-Meier Curve of Event-Free Survival



RA = 13-cis-retinoic acid

Figure 2 Kaplan-Meier Curve of Overall Survival



RA = 13-cis-retinoic acid

15 MICROBIOLOGY

Not Applicable

16 NON-CLINICAL TOXICOLOGY

- ***General Toxicology (single and repeat-dose studies)***

  Traditional animal studies were not conducted prior to the use of dinutuximab in the pivotal clinical trial, ANBL0032. Toxicology studies have been conducted in rats and non-human primates to investigate clinical findings observed in the clinical trial population. Overall, no new safety concerns have been identified through the non-clinical toxicology studies conducted; no mortality occurred during these studies despite higher exposure to the test agent, dinutuximab.

- ***Carcinogenicity***

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

- ***Genotoxicity***

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

- ***Reproductive and Developmental Toxicology***

  Dedicated studies examining the effects of dinutuximab on male and female fertility and early embryonic development, embryofetal development, or pre and postnatal development have not been conducted. In repeat-dose toxicity studies, no clear effects on reproductive organs were observed in rats.

- ***Special Toxicology Studies***

  A combined cardiovascular and respiratory safety pharmacology study was conducted in three conscious male cynomolgus monkeys with 14 mg/kg dinutuximab administered via a 10-hour IV infusion. No respiratory system effects were noted. Cardiovascular system effects, including moderate increases in blood pressure (in one animal) and heart rate (in two animals), when compared with the control, were observed from 5 to 24 hours after the start of dosing. However, no statistically significant changes in group mean values were noted for blood pressure or heart rate at any time point. No change in QTc was observed, and the administration of dinutuximab had no direct effect on any ECG parameter.

- ***Juvenile Toxicity***

  A single-cycle IV tolerability study of dinutuximab in the juvenile cynomolgus monkey at doses of 0, 3, 10, or 30 mg/kg/day given for 4 consecutive days (total doses per 4-day cycle of 12, 40, and 120 mg/kg, respectively), was conducted. There was no mortality during the study. There was no dinutuximab-related effect on electrocardiology, neurological evaluation, nerve conduction velocity, or urinalysis parameters. An extensive peripheral neuropathy with nerve fiber degeneration extending into the dorsal funiculi of the spinal cord and further into the medulla oblongata was observed across doses without clear dose-relationship and was persistent beyond the cessation of dosing at the end of the 24-day recovery period. In addition, minimal degeneration and/or gliosis of the white matter in the cerebrum were observed at the high dose. A no-observed-adverse-effect level (NOAEL) could not be established for this study. However, it should be noted that these total per cycle doses are approximately 6-, 21-, and 63-fold higher than the human 1.9 mg/kg total cycle dose and lead to exposures approximately 20- to 70-fold higher than those observed in the clinical studies.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrUNITUXIN®
Dinutuximab for injection

If you are a patient or parent of a child who will be receiving **Unituxin**, read this carefully before you or your child start receiving **Unituxin** and each time treatment is received. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about pre-existing medical conditions and treatment and ask if there is any new information about **Unituxin**.

Serious Warnings and Precautions

Infusion Reactions

- **Serious and potentially life-threatening infusion reactions and anaphylaxis have occurred in patients treated with Unituxin. Immediately report any signs or symptoms, such as facial or lip swelling, urticaria, difficulty breathing, lightheadedness, or dizziness that can occur during or within 24 hours following the infusion.**

Neurologic Reactions

- **Unituxin can cause severe pain, sensory and motor neuropathy, prolonged urinary retention, and transverse myelitis. Promptly report severe or worsening pain and signs and symptoms such as numbness, tingling, burning, weakness, or inability to urinate.**

What is Unituxin used for?

- Unituxin is used to treat high-risk neuroblastoma in babies, children and adolescents.
- Neuroblastomas are cancers that start in early nerve cells (called *neuroblasts*) in the body. Neuroblastoma is classified as 'high risk' if the cancer has spread to various parts of the body and contains certain types of cells. High-risk neuroblastomas are more likely to come back again after treatment than those of lower risk.
- To reduce the risk of the cancer coming back, Unituxin is given at the last stage of the treatment to eliminate small amounts of disease that may still be present after the cancer has responded to chemotherapy, surgery, and an autologous (self-donating) blood cell transplant.
- Unituxin has been shown to delay the progression or relapse of the disease and to increase survival.

How does Unituxin work?

Unituxin is an antibody therapy, which means it acts similarly to the natural antibodies produced by the human body. Antibodies have the job of recognizing viruses, bacteria, and anything else that doesn't belong in the body so that the immune system can fight them off.

As an antibody therapy, Unituxin can help the immune system recognize and fight the neuroblastoma cells.

Unituxin recognizes and attaches to a cell surface substance called 'GD2'. GD2 is found on the surface of neuroblastoma and other GD2 expressing cells. When Unituxin attaches to the GD2 substance on the cancer cells, the patient's immune system starts to attack these cells

and kill them. Unituxin also binds to GD2 on nerve cells. This is why pain is the most common side effect of Unituxin.

What are the ingredients in Unituxin?
Medicinal ingredients: dinutuximab
Non-medicinal ingredients: histidine, hydrochloric acid (to adjust pH), polysorbate 20, sodium chloride, and water for injection.

Unituxin comes in the following dosage forms:
Single-use vials containing 17.5 mg/5 mL (3.5 mg/mL) of dinutuximab in solution.

Do not use Unituxin if:
- You or your child are allergic to dinutuximab.

To help avoid side effects and ensure proper use, talk to your healthcare professional about any health conditions or problems you or your child may have before taking Unituxin, including if you or your child:

- have ever had fits (convulsions)
- have liver problems
- have a low number of white blood cells or platelets in your blood – shown in tests
- have breathing problems such as shortness of breath when resting
- have kidney problems
- have any infections
- have had a serious allergic reaction to previous cancer therapies
- have had a serious allergic reaction to medications used to manage pain (narcotics or opioid medications)
- take steroids or other medications that lower immune response

Tell your healthcare professional about all the medicines you or your child take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with Unituxin:
Prior to receiving Unituxin, tell your doctor or nurse if you or your child are taking, have recently taken, or might take during Unituxin therapy, any other medicines. This includes medicines obtained without a prescription and herbal medicines.
In particular, tell your doctor or nurse if you or your child have recently received medication that may affect the immune system such as:

- medicines called “corticosteroids” – such medications can alter the activity of your immune system, which is important for Unituxin to work.
- “intravenous immunoglobulin” – you or your child should not have this type of medicine in the 2 weeks before Unituxin treatment and for at least 1 week after Unituxin treatment has finished.

How to take Unituxin:
Unituxin will be given to you or your child by a doctor or nurse while in the hospital. It is given as an intravenous infusion.
Unituxin is given along with other medicines (IL-2, GM-CSF, and RA) as part of the treatment regimen.

Usual Dose:
Unituxin will be given in 5 monthly cycles, and the Unituxin infusion is given for 4 days in a row each cycle. The usual dose of Unituxin is 17.5 mg/m^2/day. M^2 is a measurement of body surface area and your doctor will work out the dose based on this measurement of patient body size and weight.

Overdose:

It is unlikely you or your child will receive an overdose of Unituxin as it is only administered in a professional setting by experienced healthcare professionals. If you think you or your child have received too much Unituxin and are experiencing any side effects noted below, then speak with your healthcare professional immediately.

Missed Dose:
It is very important for you or your child to keep all appointments to receive Unituxin. If you miss an appointment, ask your doctor when to schedule the next dose.

What should I expect on Unituxin treatment days?
The healthcare team will tell you exactly when to arrive at the hospital, if you are not already there. Expect to arrive a few hours earlier than the Unituxin infusion will begin in order to receive certain pre-treatment medications. These pre-treatments can help guard against possible side effects.

Each Unituxin dose will be given over 10 to 20 hours. Ask your healthcare team how long you should plan to stay in the hospital with each treatment cycle.

What are possible side effects from using Unituxin?
Like all medications, this medicine, can cause side effects. Your healthcare team will use various medications before, during, and after the Unituxin infusion to help prevent some of these side effects. Some side effects can be related to the rate of the Unituxin infusion, and your healthcare team will know how and when to adjust the Unituxin infusion rate. You or your child may still experience side effects after you leave the hospital. If you have questions or concerns about side effects, contact your healthcare professional.

Side effects may include:

Very common:

- Pain including abdominal pain, back pain and pain in your legs or arms, fever
- Allergic reactions up to anaphylaxis, itching, hives, low oxygen in your blood, swelling in your face
- Loss of appetite, weight gain
- Dry skin
- Diarrhea
- Increased heart rate, low blood pressure that may make you feel dizzy or faint, or high blood pressure
- Abnormal tests such as low platelets, low red or white blood cells, low level of albumin (this can cause swelling and make you feel weak and tired), abnormal liver function, low level of potassium, sodium, calcium, magnesium or phosphates, high level of glucose, creatinine or triglycerides, protein in your urine.

Common:

- Cough, difficulty breathing
- Chills, swelling in arms and legs, feeling tired
- Headache
- Constipation, blood in stool, vomiting
- Not being able to urinate, blood in your urine
- Higher risk of getting infections (especially from the devices used to give you the medicine), such as blood or gut infections
- Skin problems where the injection was given, such as a red rash with small bumps
- Abnormal blood tests, such as low levels of magnesium or glucose, or high levels of acids, calcium, or potassium.

Uncommon:

- Serum sickness – an illness similar to an allergy
- Abnormal heart rhythm
- Neuropathy – tingling, burning, or weakness in the arms or legs.

Serious Side Effects and What to Do About Them:

Below are listed serious side effects that may occur during or after treatment with Unituxin. When any of these side effects occur, in all cases contact your healthcare professional and discuss the next course of action.

Serious side effects
Symptom / effect
VERY COMMON Pain *Pain can occur in the stomach, throat, chest, face, hands, feet, legs or arms (such as numbness, tingling, or burning), back, neck, joint, bone, muscle, mouth, eye, genitals*
Hypersensitivity/Anaphylactic reaction/Infusion reactions *Symptoms may include a skin rash, hives, swelling in the face or throat, dizziness, a rapid heartbeat or palpitations, being short of breath and difficulty breathing, fever, vomiting, aches and pains in your joints*
COMMON Neurological disorders of the eye *Blurred vision, being sensitive to light, the pupils of your eyes staying large ('dilated')*
Capillary leak syndrome *Symptoms may include swelling of the arms, legs and other parts of your body, rapid drop in blood pressure, light headedness and breathing difficulties, kidney failure*
RARE Transverse myelitis *Symptoms may include reduced sensation or weakness or the inability to control urine*
Atypical hemolytic uremic syndrome (aHUS) *This is an illness that affects the blood system and kidneys; symptoms may include flu-like symptoms that do not go away, confusion, lethargy, loss of appetite, or dark colored urine*

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Swelling in the back part of the brain; symptoms may include high blood pressure, headache, fits, change in vision or behavior, feeling drowsy or tired

If you or your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

You may also contact United Therapeutics Corporation at 1-866-458-6479 to report suspected side effects/adverse events.

Storage:
Unituxin will be stored in the hospital or clinic where it is given to you or your child. The vials are stored in a refrigerator (2°C to 8°C [36°F to 46°F]) until they need to be used. The vials must not be frozen or shaken. The vials are kept in their carton to protect from light.

Keep out of reach and sight of children.

If you want more information about Unituxin:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); or by calling the customer service line at 1-877-864-8437.

This leaflet was prepared by United Therapeutics Corp., North Carolina, USA 27709.

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