Dosage and administration
pocket guide

Unituxin®
(dinutuximab)
Injection

Unituxin is a sterile, preservative-free, clear/colorless to slightly opalescent solution for IV infusion. Unituxin is supplied in single-use vials of 17.5 mg/5 mL.

Indication

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.

Important Safety Information for Unituxin

Boxed WARNING

Serious Infusion Reactions

- Serious and potentially life threatening infusion reactions (facial and upper airway edema, dyspnea, bronchospasm, stridor, urticaria, and hypotension) 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

Neurotoxicity

- Unituxin causes serious neurologic adverse reactions including severe neuropathic pain and peripheral neuropathy
- Severe neuropathic pain occurs in the majority of patients
- Administer intravenous opioid prior to, during, and for 2 hours following completion of the Unituxin infusion
- Severe (Grade 3) peripheral sensory neuropathy ranged from 2% to 9% in patients with neuroblastoma
- In clinical studies of Unituxin and related GD2-binding antibodies, severe motor neuropathy has occurred. Resolution of motor neuropathy did not occur in all cases
- Discontinue Unituxin for severe unresponsive pain, severe sensory neuropathy, and moderate to severe peripheral motor neuropathy.

Please see additional Important Safety Information on inside flap and Full Prescribing Information for Unituxin in pocket.

Prior to infusion[1]

» Verify that patients have adequate hematologic, respiratory, hepatic, and renal function prior to initiating each course of Unituxin
» Administer required premedication and hydration prior to initiation of each Unituxin infusion

Administering Unituxin[1]

17.5
mg/m²/d

0.875
mg/m²/h

The recommended dosage
Administer as an IV infusion over 10 to 20 hours for 4 consecutive days for a maximum of 5 cycles.

Rate of infusion for initial 30 minutes
The infusion rate can be gradually increased as tolerated to a maximum rate of 1.75 mg/m²/h. Follow dosage modification instructions for adverse reactions.

- Initiate infusion within 4 hours of preparation
- Do not administer as an IV push or bolus

Dose equivalency[2]

Formerly known as ch14.18, the concentration was modified during the commercial manufacturing process. The doses are equivalent in terms of total antibody amount.

17.5 mg/m²/d = **25 mg/m²/d**
Unituxin — NCI clinical trial drug

Discard instructions[1]

» Discard unused contents of the Unituxin vial
» Discard diluted Unituxin solution 24 hours after preparation

Please see additional Important Safety Information on reverse and Full Prescribing Information, including Boxed WARNING, for Unituxin in pocket.

Required Pretreatment and Guidelines for Pain Management[1]

IV Hydration

- Administer 0.9% sodium chloride injection, USP 10 mL/kg as an IV infusion over 1 hour just prior to initiating each Unituxin infusion

Analgesics

- Administer morphine sulfate (50 μg/kg) IV immediately prior to initiation of Unituxin and then continue as a morphine sulfate drip at an infusion rate of 20 to 50 μg/kg/h during and for 2 hours following completion of Unituxin
- Administer additional 25 to 50 μg/kg IV 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 IV morphine

Antihistamines and Antipyretics

- Administer an antihistamine such as diphenhydramine (0.5–1 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 (10-15 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 (5-10 mg/kg) every 6 hours as needed for control of persistent fever or pain

Infusion-Related Reactions
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/h
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
• *After resolution:* If signs and symptoms resolve rapidly, resume Unituxin at 50% of the previous rate and observe closely
• *First recurrence:* 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/h in an intensive care unit.
• *Second recurrence:* Permanently discontinue Unituxin.
Neurological Disorders of the Eye
• *Onset of reaction:* Discontinue Unituxin infusion until resolution.
• *After resolution:* Reduce the Unituxin dose by 50%.
• *First recurrence or if accompanied by visual impairment:* Permanently discontinue Unituxin

Dose Modification for Selected Unituxin Adverse Reactions[1] (continued)

Capillary Leak Syndrome
Moderate to severe but not life-threatening capillary leak syndrome
• *Onset of reaction:* Immediately interrupt Unituxin
• *After resolution:* Resume Unituxin infusion at 50% of the previous rate
Life-threatening capillary leak syndrome
• *Onset of reaction:* Discontinue Unituxin for the current cycle
• *After resolution:* In subsequent cycles, administer Unituxin at 50% of the previous rate
• *First recurrence:* Permanently discontinue Unituxin
Hypotension* requiring medical intervention
• *Onset of reaction*: Interrupt Unituxin infusion
• *After resolution:* Resume Unituxin 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/h
Severe Systemic Infection or Sepsis
• *Onset of reaction*: Discontinue Unituxin until resolution of infection, and then proceed with subsequent cycles of therapy

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

GM-CSF=granulocyte-macrophage colony-stimulating factor; IL-2=interleukin 2; IV=intravenous; NCI=National Cancer Institute; RA=13-cis-retinoic acid; USP=US Pharmacopeial Convention.

References: 1. Unituxin [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2017. 2. Data on file. United Therapeutics Corporation. Research Triangle Park, NC 27709. October 2014.

Please see Full Prescribing Information, including Boxed WARNING, for Unituxin in pocket. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Unituxin® (dinutuximab) Injection

United Therapeutics ONCOLOGY

US/UTX/0042 Printed in USA.

Clinical trial dosage regimen[1]

- The treatment regimen consists of Unituxin, GM-CSF, IL-2, and isotretinoin (RA)
- Unituxin infusion should be given over 10 to 20 hours

Cycles 1, 3, and 5 dosage regimen for Unituxin, GM-CSF, and RA (24 days in duration)

DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24
GM-CSF*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Unituxin†				X	X	X	X								
RA‡											X	X	X	X	X

*Granulocyte-macrophage colony-stimulating factor (GM-CSF):
250 μg/m^2/d, administered by either subcutaneous injection (recommended) or IV infusion administered over 2 hours.

† Unituxin: 17.5 mg/m^2/d, administered by diluted IV infusion over 10-20 hours (equivalent to 25 mg/m^2/d of clinical trial material).

‡ RA: for >12 kg body weight, 80 mg/m^2 orally twice daily for a total daily dose of 160 mg/m^2; for ≤12 kg body weight, 2.67 mg/kg orally twice daily for a total daily dose of 5.33 mg/kg (round dose up to nearest 10 mg).

Cycles 2 and 4 dosage regimen for Unituxin, IL-2, and RA (32 days in duration)

DAY	1	2	3	4	5	6	7	8	9	10	11	12-14	15-28	29-32
IL-2§	X	X	X	X				X	X	X	X			
Unituxin‖								X	X	X	X			
RA¶													X	

§Interleukin 2 (IL-2): 3 MIU/m^2/d administered by continuous IV infusion over 96 hours on days 1-4 and 4.5 MIU/m^2/d on days 8-11.

‖Unituxin: 17.5 mg/m^2/d, administered by diluted IV infusion over 10-20 hours (equivalent to 25 mg/m^2/d of clinical trial material).

¶RA: for >12 kg body weight, 80 mg/m^2 orally twice daily for a total daily dose of 160 mg/m^2; for ≤12 kg body weight, 2.67 mg/kg orally twice daily for a total daily dose of 5.33 mg/kg (round dose up to nearest 10 mg).

Cycle 6 consists of RA only

Adverse reactions should be managed by infusion interruption, infusion rate reduction, dose reduction, or permanent discontinuation of Unituxin (see Tables 3 and 4 of accompanying Full Prescribing Information).

Adverse reactions requiring permanent discontinuation of Unituxin[1]

- 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 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

For information on dosage modifications in the event of adverse reactions, please refer to the prescribing information.
Please see additional Important Safety Information on reverse and Full Prescribing Information, including Boxed WARNING, for Unituxin in pocket.

Important Safety Information for Unituxin (continued)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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.
- 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.

Neurotoxicity

- ***Pain:*** 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. 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.
- ***Peripheral Neuropathy:*** 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. 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.
- ***Neurological Disorders of the Eye:***
  - Neurological disorders of the eye experienced by two or more patients treated with Unituxin included blurred vision, photophobia, mydriasis, fixed or unequal pupils, optic nerve disorder, eyelid ptosis, and papilledema.
  - 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 who experience loss of vision and in patients with recurrent eye disorder following dose reduction.
- ***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 prolonged urinary retention that does not resolve with discontinuation of opioids.
- ***Transverse Myelitis:*** Transverse myelitis has occurred in patients treated with Unituxin. Promptly evaluate any patient with signs or symptoms such as weakness, paresthesia, sensory loss, or incontinence. Permanently discontinue Unituxin in patients who develop transverse myelitis.
- ***Reversible Posterior Leukoencephalopathy Syndrome (RPLS):*** RPLS has occurred in patients treated with Unituxin. Institute appropriate medical treatment and permanently discontinue Unituxin in patients with signs and symptoms of RPLS (e.g., severe headache, hypertension, visual changes, lethargy, or seizures).

Capillary Leak Syndrome

- 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.

- Depending on severity, manage by immediate interruption, infusion rate reduction or permanent discontinuation of Unituxin.

Hypotension

- 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.
- Depending on severity, manage by immediate interruption, infusion rate reduction or permanent discontinuation of Unituxin.

Infection

- 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%) of 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.

Bone Marrow Suppression

- 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 Unituxin therapy.

Electrolyte Abnormalities

- 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.
- Monitor serum electrolytes daily during therapy with Unituxin.

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 following receipt of the first cycle of Unituxin.
- Permanently discontinue Unituxin and institute supportive management.

Embryo-Fetal Toxicity

- Unituxin may cause fetal harm.
- 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.

ADVERSE REACTIONS

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

The most common adverse drug reactions (≥ 25%) in Unituxin/RA compared with RA alone are pain (85% vs. 16%), pyrexia (72% vs. 27%), thrombocytopenia (66% vs. 43%), lymphopenia (62% vs. 36%), infusion reactions (60% vs. 9%), hypotension (60% vs. 3%), hyponatremia (58% vs. 12%), increased alanine aminotransferase (56% vs. 31%), anemia (51% vs. 22%), vomiting (46% vs. 19%), diarrhea (43% vs. 15%), hypokalemia (43% vs. 4%), capillary leak syndrome (40% vs. 1%), neutropenia (39% vs. 16%), urticaria (37% vs. 3%), hypoalbuminemia (33% vs. 3%), increased aspartate aminotransferase (28% vs. 7%), and hypocalcemia (27% vs. 0%). In post-approval use of Unituxin, the adverse reactions of prolonged urinary retention, transverse myelitis, and reversible posterior leukoencephalopathy syndrome were observed. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

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