DRUG NAME: Dinutuximab

SYNONYM(S): ch14.18[1]

COMMON TRADE NAME(S): UNITUXIN®

CLASSIFICATION: molecular targeted therapy

*The information below is adapted from predominantly **pediatric** sources; special considerations for adults may apply.*

MECHANISM OF ACTION:

Dinutuximab is a human-murine IgG1 kappa monoclonal antibody that targets glycolipid disialoganglioside (GD2). Dinutuximab induces cell lysis via antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity in cells overexpressing GD2. Dinutuximab is an immunosuppressive agent.[2,3]

PHARMACOKINETICS:

Distribution	two-compartment model with first order pharmacokinetics[4]	
	cross blood brain barrier?	no[4]
	volume of distribution	0.4 L/kg or 5.4-7.2 L (children)[5-7]
	plasma protein binding	no information found
Metabolism	likely metabolized into small peptides and amino acids by proteolytic enzymes	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	clearance increased by ~60% if human anti-chimeric antibody present[5]	
	urine	no information found
	feces	no information found
	terminal half life	5.1-7.5 days (adult)[8,9]; 2.8-10 days (children)[7,10]
	clearance	0.5 L/day/m^2 (adult)[6]; 0.21-0.6 L/day or 2 L/day/m^2 (children)[5-7]
Children	clearance is ~4 fold higher in children than adults and appears to be age dependent[6]	

Adapted from standard reference[5] unless specified otherwise.

USES:

Primary uses:

*Neuroblastoma

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to dinutuximab or mouse proteins[5]

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Caution:
- potentially ***life-threatening infusion reactions*** are reported; prehydration and routine premedications are recommended prior to each infusion[5]
- avoid co-administration of systemic ***corticosteroids*** and ***immunosuppressants*** with dinutuximab due to potential interference with dinutuximab's mechanism of action; corticosteroids may be used for the management of serious hypersensitivity or infusion-related reactions due to dinutuximab[2]
- intravenous ***immune globulin*** may interfere with dinutuximab's mechanism of action; avoid administration within two weeks before or one week after dinutuximab infusion[2,5]
- ***severe neuropathic pain*** is expected with dinutuximab; opioids and co-analgesics are pre-emptively started prior to initiation of dinutuximab[5]
- immune response to ***vaccines*** may be diminished by dinutuximab[3]
- ***live attenuated vaccines*** should not be administered during treatment and for at least three months after the last dose of dinutuximab due to risk of enhanced vaccine adverse effects[3]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: In animal studies, no clear effects on reproductive organs were reported.[5]

Pregnancy: Human and animal studies are not available, however, IgG1 monoclonal antibodies are known to cross the placenta, with the highest proportion being transferred during the third trimester. Therefore, dinutuximab is expected to be transmitted from mother to fetus. Based on its mechanism of action, dinutuximab may cause fetal harm. Females of reproductive potential should use effective contraception while on dinutuximab and for two months after treatment has been discontinued.[5]

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[11,12]
Incidence data in the Side Effects table is based on dinutuximab monotherapy data where possible. In some cases, incidence data has been based on combination therapy (with isotretinoin and GM-CSF or interleukin-2[3,5,13]) and this is indicated with an asterisk (*).

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (4%)[14]
	disseminated intravascular coagulation* (<2%)[5]
	leukopenia (1%)[15]
	thrombocytopenia (1%)[15]
cardiac	cardiac arrest* (<1%)[2]
	tachycardia (3-11%)
eye	ocular symptoms (5-12%)[15,16]; see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low[17]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	abdominal pain* (57%)[5]
	diarrhea (6-11%)
	nausea/vomiting (15-18%)
general disorders and administration site conditions	*extravasation hazard:* none[18]
	edema (12-18%)
	fever (79-100%)
	pain despite analgesic prophylaxis (21-33%); see paragraph following **Side Effects** table
immune system	***hypersensitivity reaction*** (7%)[15]; in combination with interleukin-2* (57%, severe 26%)[5,13]; see paragraph following **Side Effects** table
	serum sickness (7%)[15]
infections and infestations	urinary tract infection (1-7%)
injury, poisoning, and procedural complications	***infusion related reaction**** (≥26%, severe 26%)[5]; see paragraph following **Side Effects** table
investigations	C-reactive protein elevation without evidence of infection (56-64%)
	liver enzyme abnormalities (11-13%)
metabolism and nutrition	anorexia* (15%)[5]
	hypoalbuminemia* (33-34%)[3,5]
	hypocalcemia* (26%)[5]
	hypokalemia* (43%, severe 37%)[5]
	hyponatremia* (57%, severe 23%)[5]
nervous system	***neuropathic pain**** (≥52%, severe 52%)[13]; see paragraph following **Side Effects** table
	peripheral motor neuropathy* (6%, severe 1%)[3,5]; see paragraph following **Side Effects** table
	peripheral sensory neuropathy* (7-9%, severe 1%)[3,5]; see paragraph following **Side Effects** table
	reversible posterior leukoencephalopathy syndrome* (<1%)[3,5]
	transverse myelitis* (<1%)[3,5]
renal and urinary	atypical hemolytic uremic syndrome* (<1%)[5]
	proteinuria (1%)[15]
	urinary retention* (7%)[5]; may persist for weeks to months (<1%)[3]
respiratory, thoracic and mediastinal	***pulmonary obstruction, stridor*** (6-14%, severe 6-14%)
	cough (43-54%); dry, treatment resistant
	dyspnea* (6%)[5]
	hypoxia* (24-26%)[3,5]
	pruritus (21-25%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
skin and subcutaneous tissue	rash, papular* (9%)[5]
	urticaria (54-61%)
vascular	***capillary leak syndrome*** (5-11%, severe 1-4%); in combination with interleukin-2* (40%, severe 23%)[3,13]
	hypertension (2-4%)
	hypotension (12-18%); in combination therapy* (60%, severe 18%)[3,13]

Adapted from standard reference[14,15] unless specified otherwise.

Hypersensitivity or ***infusion reactions*** occur in 7% of patients receiving single-agent dinutuximab. However, ***serious*** reactions (e.g., facial and upper airway edema, dyspnea, bronchospasm, stridor, urticaria, and hypotension) are reported in up to 26% of patients receiving dinutuximab combination therapy. Reactions may be life-threatening. Distinguishing infusion reactions from hypersensitivity reactions may not be possible due to overlapping symptoms. Reactions generally occur during the dinutuximab infusion or within 24 hours of its completion. Prehydration and premedications, including an antihistamine, antipyretic, and analgesic are recommended for each dinutuximab infusion. Reactions may be managed by reducing the infusion rate, temporary interruption of the infusion, or permanent discontinuation of dinutuximab depending on the severity of the reaction. Dinutuximab re-challenges should be initiated at a slower infusion rate. Following a second episode of a severe or prolonged infusion reaction, additional premedications and intensive care measures may be required. Permanently discontinue dinutuximab for a grade 4 infusion reaction, grade 3 or 4 anaphylaxis, or the third episode of a prolonged or severe reaction.[2,5]

Ocular symptoms are reported in up to 12% of patients receiving dinutuximab monotherapy and up to 15% of patients receiving combination therapy. Symptoms may include blurred vision, accommodation deficit, photophobia, mydriasis, fixed or unequal pupils, optic nerve disorders, eyelid ptosis, and/or papilledema. Ocular symptoms correspond to parasympathetic denervation and are not associated with neuroblastoma involvement of the orbital structures.[5,16] With dinutuximab monotherapy, symptoms may begin after any cycle and usually improve or resolve completely over two to twelve months despite further treatment with dinutuximab.[16] Median duration of ocular disorders during combination therapy is 4 days; however, some patients may experience a prolonged period of symptoms before resolution (e.g., up to 8 months has been reported). Dinutuximab infusion interruption and dose reduction is recommended for patients experiencing visual disturbances. Permanent discontinuation is recommended for patients with recurrent eye disorders following dose reduction and in patients who experience vision loss.[5]

Pain despite analgesic prophylaxis is common during dinutuximab infusions.[5,15] Pain is experienced with both monotherapy (up to 33%)[15] and combination therapy (85%),[5] with a decline in incidence with successive cycle numbers.[5,15] Pain during monotherapy is predominantly described as deep visceral pain in the back or abdomen and less frequently as pain in the extremities.[15] With combination therapy, it is reported as generalized pain, involving the abdomen, extremities, or back, or as neuralgias, musculoskeletal chest pain, or arthralgias.[5] Analgesia, including intravenous opioids, is recommended prior to, throughout, and after the dinutuximab infusion to prevent and manage pain. Severe pain may require dinutuximab rate reduction or discontinuation in addition to supportive measures.[3,5]

Severe ***peripheral neuropathy*** and ***neuropathic pain*** is associated with dinutuximab. The mechanism is not clearly understood, but it is proposed that antibody binding to GD2 on peripheral nerve fibers and/or myelin results in neuropathic pain. The average duration of peripheral sensory neuropathy is nine days (range 3 to 163 days). The average duration of motor neuropathy has not been defined. Analgesia, including intravenous opioids, is recommended prior to, throughout, and after the dinutuximab infusion to prevent and manage pain. Permanent discontinuation of dinutuximab is recommended for grade 2 or greater peripheral motor neuropathy and grade 4 sensory neuropathy, or grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks.[5]

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INTERACTIONS: no information found

SUPPLY AND STORAGE:

***Injection*:** Unither Biotec Inc. supplies dinutuximab in 17.5 mg preservative-free, single use vials in a concentration of 3.5 mg/mL. Refrigerate. Protect from light. Do not shake.[5]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[5]	do NOT use
Intermittent infusion[5]	over 10 to 20 hours (starting rate of 0.875 mg/m^2/h; after 30 minutes, gradually increase rate as tolerated to a maximum of 1.75 mg/m^2/h)
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy.

***Children*:**

BC Cancer usual dose noted in ***bold, italics***

Intravenous:	Cycle Length: 24-32 days[5]:	Cycles 1, 3, and 5: 17.5 mg/m^2 IV once daily for 4 consecutive days starting on day 4 (total dose per cycle 70 mg/m^2) Cycles 2 and 4: 17.5 mg/m^2 IV once daily for 4 consecutive days starting on day 8 (total dose per cycle 70 mg/m^2)

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BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
	21 days[19]:	Cycles 1 to 17: 17.5 mg/m^2 IV once daily for 4 consecutive days starting on day 2 (total dose per cycle 70 mg/m^2)
Concurrent radiation:	no information found	
Dosage in renal failure:	no information found	
Dosage in hepatic failure:	no information found	
Dosage in dialysis:	no information found	

REFERENCES:

1. Keyel ME, Reynolds CP. Spotlight on dinutuximab in the treatment of high-risk neuroblastoma: development and place in therapy. Biologics: Targets and Ther 2019;13:1-12
2. AHFS Drug Information® (database on the Internet). Dinutuximab. Lexi-Comp Inc., 2019. Available at: http://online.lexi.com. Accessed 29 May, 2019
3. Lexicomp Online® (database on the Internet). Dinutuximab. Lexi-Comp Inc., 2019. Available at: http://online.lexi.com. Accessed 29 May, 2019
4. Greenwood KL, Foster JH. The safety of dinutuximab for the treatment of pediatric patients with high-risk neuroblastoma. Expert Opin on Drug Safety 2018;17(12):1257-1262
5. Unither Biotec Inc. for United Therapeutics Corp. UNITUXIN® product monograph. Magog, Quebec; 28 November 2018
6. Desai AV, Fox E, Smith LM, et al. Pharmacokinetics of the chimeric anti-GD2 antibody, ch14.18, in children with high risk neuroblastoma. Cancer Chemother Pharmacol 2014;74:1047-1055
7. United Therapeutics Corp. UNITUXIN® US product monograph. Silver Spring, Maryland; March 2015
8. Saleh MN, Khazaeli MB, Wheeler RH, et al. Phase I trial of the chimeric anti-GD2 monoclonal antibody ch14.18 in patients with malignant melanoma. Hum Antibodies Hybridomas 1992;3(1):19-24
9. Murray JL, Kleinerman ES, Jia SF, et al. Phase Ia/Ib trial of anti-GD2 chimeric monoclonal antibody 14.18 (ch14.18) and recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) in metastatic melanoma. J Immunother Emphas Tumor Immunol 1996;19(3):206-217
10. Uttenreuther-Fischer MM, Huang CS, Yu AL. Pharmacokinetics of human-mouse chimeric anti-GD2 mAb ch14.18 in a phase I trial in neuroblastoma patients. Cancer Immunol Immunother 1995;41:331-338
11. Rebecca Deyell MD. BC Children's Hospital. Personal communication. 27 June2019
12. Jennifer Kendrick. Clinical Pharmacy Specialist, Children's and Women's Health Centre of British Columbia. Personal communication. 9 July2019
13. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 2010;363(14):1324-1334
14. Simon T, Hero B, Faldum A, et al. Infants with stage 4 neuroblastoma: the impact of the chimeric anti-GD2-antibody ch14.18 consolidation therapy. Klin Padiatr 2005;217:147-152
15. Simon T, Hero B, Faldum A, et al. Consolidation treatment with chimeric anti-GD2-antibody ch14.18 in children older than 1 year with metastatic neuroblastoma. J Clin Oncol 2004;22(17):3549-3557
16. Kremens B, Hero B, Esser J, et al. Ocular symptoms in children treated with human-mouse chimeric anti-GD2 mAb ch14.18 for neuroblastoma. Cancer Immunol Immunother 2002;51:107-110
17. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 Dec 2018
18. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; January 2016
19. Mody R, Naranjo A, Van Ryn C, et al. Randomized phase II trial of irinotecan/temozolomide (I/T) with temsirolimus (TEM) or dinutuximab (DIN) in children with refractory or relapsed neuroblastoma: A report from the Children's Oncology Group (COG). Lancet Oncol 2017;18(7):946-957

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