BRAND NAME: UNITUXIN

PROPER NAME: Dinutuximab

MANUFACTURER: United Therapeutics Corp.

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

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

BLA NO: 125516

REGULATORY MILESTONES:

- 12/04/1991 – IND submission
- 10/02/2002 – FDA placed IND 4308 on partial clinical hold
- 04/09/2003 – FDA removed partial hold
- 04/30/2003 – FDA placed IND 4308 on partial clinical hold
- 07/08/2003 – FDA removed partial hold
- 09/01/2005 – Type C meeting held between FDA and CPEP
- 05/30/2006 – FDA issued advice letter and requested for information
- 01/15/2009 – IND 4308 on partial clinical hold

- 04/03/2009 – FDA removed partial hold
- 12/20/2010 – FDA granted orphan drug status to ch14.18 for the treatment of neuroblastoma
- 01/27/2011 – Type B Pre-IND meeting with United Therapeutics (pIND110494)
- 03/09/2012 – IND application submission
- 04/09/2012 – Teleconference between DOP2, CMC, and UTC
- 04/11/2012 – FDA issued may proceed letter for IND 110494
- 12/11/2012 – Type C meeting
- 08/28/2013 – Informal teleconference between UTC and DOP2
- 12/20/2013 – Office of Orphan Products Development (OOPD) designated dinutuximab as a drug for a "rare pediatric disease" for the treatment of neuroblastoma
- 01/14/2014 – Type B pre-BLA CMC meeting
- 02/19/2014 – Type B pre-BLA meeting

US Approval	March 10, 2015
EU Approval	August 14, 2015 (withdrawn)
Health Canada Approval	November 29, 2018
TGA	March 17, 2020 (as Dinutuximab beta)

ADVISORY COMMITTEE:

This BLA for this new active moiety, first-in-class molecule was not referred for review to the Oncologic Drugs Advisory Committee (ODAC) for several reasons: the safety profile of dinutuximab is acceptable for the treatment of high-risk neuroblastoma, the evaluation of the safety data when used in the treatment of high-risk neuroblastoma did not raise significant safety or

efficacy issues that were unexpected for a drug in this population, and the composition of the committee is predominantly adult oncologists who do not treat this disease. Instead, FDA sought advice from two pediatric oncologists and a patient representative as Special Government Employees, who concurred that substantial evidence of effectiveness had been demonstrated and the risk/benefit assessment was favorable in this life-threatening disease with no satisfactory alternative therapies.

MANUFACTURING:

PARAMETER	DATA	REFERENCE
Manufacturer	United Therapeutics Corp.	
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.	1
Cell Substrate	Glycosylated chimeric IgG1 human/mouse monoclonal antibody (mAb)	3
Manufacturing platform	The upstream process consists of the thawing of a cell bank vial, cell expansion in a series of flasks, production in a bioreactor and recovery of the active substance. The active substance is purified with a series of chromatography, viral inactivation and filtration and ultra-/diafiltration steps.	3
Dose in vial/final container	17.5 mg/5 mL (3.5 mg/mL) in a single-use vial	1
Dose to patient	17.5 mg/m^2/day as a diluted intravenous infusion over 10 to 20 hours for 4 consecutive days for up to 5 cycles	1

1. Package insert - Unituxin
2. EPAR full - Unituxin
3. EPAR quality - Unituxin: EPAR - Public assessment report

4. FDA Review - Unituxin (dinutuximab)

CLINICAL TRIALS:

NCT	TRIAL PHASE	NO OF PATIENTS ENROLLED	TITLE	COUNTRIES
Clinical studies of ch14.18 in patients with Neuroblastoma				
NCT03098030	2, 3	483	Dinutuximab and Irinotecan Versus Irinotecan to Treat Subjects with Relapsed or Refractory Small Cell Lung Cancer	United States, India, Australia, Bulgaria, Italy, Canada, France, Georgia, Hong Kong, Poland, Taiwan, Romania, Korea, Republic of, Lithuania, Malaysia, Philippines, Russian Federation, Spain, Slovakia, Ukraine, Thailand, Hungary, United Kingdom
NCT00026312	3	1449	Isotretinoin with or without Dinutuximab, Aldesleukin, and Sargramostim Following Stem Cell Transplant in Treating Patients with Neuroblastoma	United States, Puerto Rico, Australia, New Zealand, Canada
NCT01041638	3	105	Monoclonal Antibody Ch14.18, Sargramostim, Aldesleukin, and Isotretinoin After Autologous Stem Cell Transplant in Treating Patients with Neuroblastoma	United States
NCT01418495	-	12	Pharmacokinetics of Ch14.18 in Younger Patients with High-Risk Neuroblastoma	United States
NCT01767194	2	73	Irinotecan Hydrochloride and Temozolomide with Temsirolimus or Dinutuximab in Treating Younger Patients with Refractory or Relapsed Neuroblastoma	United States, Puerto Rico, Australia, New Zealand, Canada
NCT01711554	1	27	Lenalidomide and Dinutuximab with or without	United States, Canada

			Isotretinoin in Treating Younger Patients with Refractory or Recurrent Neuroblastoma	
NCT01592045	1, 2	28	ch14.18 Pharmacokinetic Study in High-risk Neuroblastoma	United States

POST APPROVAL CHANGES

DATE	TYPE OF CHANGE	DESCRIPTION	LINK