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RESEARCH**

*APPLICATION NUMBER:*

**125516Orig1s000**

**OFFICE DIRECTOR MEMO**

### Office Director Decisional Memo for Regulatory Action

<b>Date</b>	Electronic stamp date
<b>From</b>	Richard Pazdur, MD
<b>Subject</b>	Office Director Decisional Memo
<b>BLA #</b>	125516
<b>Applicant Name</b>	United Therapeutics Corporation
<b>Date of Submission</b>	April 11, 2014
<b>PDUFA Goal Date</b>	March 10, 2015
<b>Proprietary Name / Established (USAN) Name</b>	Unituxin injection/ dinutuximab
<b>Dosage Forms / Strength</b>	Injection for intravenous use/ 17.5 mg/5 mL (3.5 mg/mL) solution in a single-use vial
<b>Proposed Indication(s)</b>	UNITUXIN (dinutuximab) is indicated for high-risk neuroblastoma <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span> treatment, in combination with granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), and isotretinoin (RA)
<b>Recommended Action for NME:</b>	<i>Approval</i>

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Division Director	Patricia Keegan
Regulatory Project Manager Review	Gina Davis
Medical Officer Review	Martha Donoghue
Statistical Review	Sirisha Mushti
Pharmacology Toxicology Review	Dubravka Kufrin
OBP Reviews	Chikako Torigoe, & Jibril Abdus-Samad
CMC Microbiology Review	Lakshmi Narasimhan & Colleen Thomas,
Clinical Pharmacology Review	Jingyu Yu
OPDP	Carole Broadnax
OSI	Lauren Iacono-Connor
CDTL Review	Suzanne Demko
OSE/DMEPA	Otto Townsend
OSE/DRISK	Naomi Redd
ODE IV/ DPMH Consult	Erica Wynn

OND=Office of New Drugs  
 OBP=Office of Biotechnology Product  
 CDTL=Cross-Discipline Team Leader  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management  
 ODE IV= Office of Drug Evaluation IV DPMH=Division of Pediatric and Maternal Health

## 1. Introduction and Background

On April 11, 2014, United Therapeutics Corporation submitted a BLA for Unituxin (dinutuximab) for high-risk neuroblastoma (b) (4) treatment, in combination with granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), and isotretinoin (RA). 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. Dinutuximab binds specifically to the GD2 disialoganglioside, which is expressed in both benign and malignant tissues (neuroblastoma) of neuroectodermal origin.

Neuroblastoma is a cancer of the sympathetic nervous system, most commonly arising in neural tissue within the adrenal glands, but may also arise in the paraspinal ganglia in the abdomen, chest, and spinal cord. Neuroblastoma is slightly more common in boys, and occurs in approximately 1 out of 100,000 children. Approximately 90% of patients are diagnosed under age 5 years and the median age at diagnosis is 19 months.<sup>1</sup> There were an estimated 600 to 700 new cases of neuroblastoma in the United States in 2014.<sup>2</sup>

The prognosis of patients with advanced stage neuroblastoma (International Neuroblastoma Staging System (INSS) stage 4 disease) is dependent on age at diagnosis and other prognostic factors (e.g., MYCN amplification), with a 5-year disease-free survival rate of 50%–80% in children diagnosed before 18 months of age and 3% in children/young adult patients between 10 and 21 years of age.<sup>3</sup>

### FDA-approved drugs for treatment of neuroblastoma

Cyclophosphamide, injection was approved on November 16, 1959. It is FDA-approved for the treatment of neuroblastoma. The basis for approval is not clearly stated in the labeling, which stated that neuroblastoma is one of several cancers that “are often susceptible to cyclophosphamide treatment.”

Doxorubicin Hydrochloride was approved on December 23, 1987. It is FDA-approved for the treatment of neuroblastoma. The basis for approval is not described in product labeling, which stated that “doxorubicin HCl has been used successfully to produce regression in disseminated neoplastic conditions such as neuroblastoma.”

Vincasar PFS (vincristine sulfate PFS) was approved on July 17, 1987. It is FDA-approved for the treatment of neuroblastoma. The basis for approval is not described in product labeling, which states vincristine sulfate injection has been shown to be useful in combination with other oncolytic agents in neuroblastoma.

### Clinical Practice Guidelines – Neuroblastoma Treatment (PDQ)<sup>4</sup>

- Induction chemotherapy consisting of cisplatin and etoposide alternating with vincristine, cyclophosphamide and doxorubicin
- Maximum feasible surgical resection
- Consolidation chemotherapy consisting of myeloablative chemotherapy (either carboplatin/etoposide/melphalan or busulfan/melphalan) supported by autologous stem cell rescue
- Radiation to the primary tumor site and metaiodobenzylguanidine (MIBG)-positive bony metastatic sites, either before, during or after myeloablative therapy
- For patients who achieve a partial, very good partial, or complete response to induction chemotherapy, six cycles of “maintenance therapy” with chimeric 14.18 in combination with GM-CSF, IL-2, and RA.

<sup>1</sup> London WB, Castleberry RP, Matthay KK, et al.: Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. *J Clin Oncol* 23 (27): 6459-65, 2005.

<sup>2</sup> <http://www.cancer.org/cancer/neuroblastoma/detailedguide/neuroblastoma-key-statistics>. Accessed February 28, 2015.

<sup>3</sup> [http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional/page1#section\\_1.7](http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional/page1#section_1.7). Accessed on February 29, 2015.

<sup>4</sup> Neuroblastoma Treatment (PDQ®), “Treatment Option Overview for Neuroblastoma” at <http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional/page4#Reference4.8>. Accessed on May 23, 2014.

## 2. Chemistry, Manufacturing, and Controls (CMC)

There are no issues that would preclude approval from a CMC perspective. The CMC discipline has provided an overall acceptability recommendation of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 18 months from the date of manufacture when stored at 2°C to 8°C (36° - 46° F).

Analytical comparability between the NCI-manufactured dinutuximab and the initial lots of UTC-manufactured dinutuximab supported extrapolation of safety and efficacy in Study ANBL0032 (DIV-NB-301 and DIV-NB-302) to the UTC product for commercial marketing. However, during review of the BLA, it was noted the ADCC activity of dinutuximab manufactured by UTC had greater variability, with later lots having two-fold higher ADCC activity than earlier lots, which were used to establish the safety of dinutuximab in Study DIV-NB-303. Based on this observed difference, additional CMC and manufacturing information were requested during review. The submission of these additional data was deemed a major amendment, extending the review clock. Review of the CMC data did not identify additional analytical differences between the NCI- and UTC-sourced products.

## 3. Nonclinical Pharmacology/Toxicology

There are no issues from a nonclinical perspective that would preclude approval.

The mechanism of action of dinutuximab is through specific binding to the GD2 antigen on normal and malignant human cells which results in complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC).

The BLA contained the results of a single 28-day repeat-dose toxicology study in Sprague-Dawley rats. Animals in this study showed signs of developing a strong anti-drug antibody response, suggesting that longer term chronic toxicology studies in rats would be of limited value. The liver was identified as a potential target organ with increases in liver weight, mild increases in AST, ALT, and cholesterol along with minimal microscopic findings of hepatocellular necrosis, pericentral vein/interlobular fibrosis, and centrilobular congestion. The majority of changes in the rats demonstrated evidence of reversibility within a 6 week recovery period. Though there were no histopathological indications of an effect of dinutuximab on peripheral nerves in this study, ch14.18 has been shown to bind to GD2 in rats. Literature reports of studies submitted to this BLA showed decreases in mechanical pain threshold in rats, indicating that the rat was a relevant species for toxicology studies.

Normal tissue cross-reactivity studies demonstrated GD2-specific antibody binding to peripheral nerves across multiple species. Non-clinical studies confirmed evidence of neurologic effects. In rats treated with dinutuximab or related anti-GD2 antibodies, a decreased mechanical pain threshold was consistently demonstrated with persistence up to 48 hours after the last dose of an anti-GD2 antibody. A safety pharmacology study, limited to cardiovascular and respiratory parameters, was conducted in cynomolgus monkeys. Increased heart rate and blood pressure were observed, but no respiratory findings noted and no evidence of prolongation of QTc.

Based on the median age of the proposed patient population (90% of patients less than 5 years of age), the Agency agreed that reproductive and developmental toxicology studies would not be required to support the BLA for dinutuximab for the treatment of high risk neuroblastoma. Dinutuximab is not indicated for females of reproductive potential. Based on its mechanism of action, ADCC-mediated and CDC-mediated lysis of GD2-expressing cells, and the ability of IgG1 antibodies to cross the placental barrier, dinutuximab may cause fetal harm. Pregnancy Category D is recommended.

## 4. Clinical Pharmacology

There are no clinical pharmacology issues that would preclude approval. The dose selected for study in DIV-NB-301 was based on the maximum tolerated dose of dinutuximab, when administered in combination with RA and GM-CSF RA and IL-2, in a single trial, Study CCG -0935A. Since PK samples were not obtained in Study DIV-NB-301 or DIV-NB-302, exposure-response relationships for efficacy or for toxicity could not be conducted to further investigate the optimal dose of dinutuximab.

In order to support extrapolation of the safety and efficacy data obtained with the NCI-sourced dinutuximab in Study DIV-NB-301 to the UTC-manufactured product, UTC conducted Study DIV-NB-201. Study DIV-NB-201 was a multi-center, randomized, open-label, two-sequence, cross-over, comparative PK and safety study. The trial was conducted in 28 patients with high-risk neuroblastoma who met the eligibility criteria for Study DIV-NB-301 and who received the same treatment regimen as the experimental arm of Study DIV-NB-301. Following completion of induction chemotherapy and myeloablative therapy with autologous stem cell rescue, patients were randomly assigned to one of the two treatment sequences

- UTC-manufactured dinutuximab Cycles 1 & 2 → NCI-manufactured dinutuximab Cycles 3-5
- NCI-manufactured dinutuximab in Cycles 1 & 2 → UTC-manufactured dinutuximab Cycles 3-5

Comparable PK exposure between the to-be-marketed dinutuximab manufactured by UTC and the clinical trial dinutuximab manufactured by NCI was demonstrated based on both the population PK model-based assessment and non-compartmental analysis.

The PK profile of dinutuximab was characterized in a population pharmacokinetic (popPK) analysis with data from 36 patients enrolled in Study DIV-NB-302 (n=9) and study DIV-NB-201 (n=27). Based on this analysis, the terminal half-life was estimated to be 10 days. There was insufficient data to allow an evaluation of the PK with chronic dosing, however treatment is limited to 5 cycles. There was insufficient data to evaluate the effect of intrinsic factors, such as age, gender, race, weight, underlying disease, and organ dysfunction, on exposure.

Mass balance and metabolism studies were not performed; such studies are not generally performed for proteins which are catabolized into amino acids. Drug interaction studies for dinutuximab and GM-CSF or IL-2 or RA were not performed, however the potential for interactions is considered to be low for dinutuximab, as with other monoclonal antibodies.

The incidence of anti-drug antibodies (ADA) to dinutuximab was evaluated in 414 patients enrolled in Studies DIV-NB-302, DIV-NB-303, and DIV-NB-201 using analytically validated assays, which demonstrated a 20% (83/414) incidence of binding antibodies and 4% (15/414) incidence of neutralizing antibodies to dinutuximab; these included 11 patients with evidence of ADA prior to dinutuximab dosing.

## 5. Clinical Microbiology

Not applicable.

## 6. Clinical/Statistical-Efficacy

This BLA was primarily supported by a demonstration of improved event-free survival (EFS) and overall survival (OS) in a multicenter, open-label, randomized trial (Study DIV-NB-301) conducted by the Children's Oncology Group. Prior to enrollment, patients had achieved at least a partial response to prior therapy for newly diagnosed high-risk neuroblastoma, consisting of induction combination chemotherapy, maximum feasible surgical resection, and myeloablative consolidation chemotherapy, and also received autologous stem cell transplant and radiation therapy.

The trial randomized (1:1) 226 patients to either the dinutuximab/RA arm or the RA alone arm. Patients in each arm received six cycles of treatment. The dinutuximab/RA arm consisted of dinutuximab in combination with GM-CSF and RA (cycles 1, 3, and 5), dinutuximab in combination with IL-2 and RA (cycles 2 and 4), and RA (cycle 6). Patients were 11 months to 15 years of age (median age 3.8 years).

The major efficacy outcome measure was investigator-assessed EFS, defined as the time from randomization to the first occurrence of relapse, progressive disease, secondary malignancy, or death. At the seventh interim analysis, an improvement in EFS [HR 0.57 (95% CI: 0.37, 0.89); p = 0.01, log-rank test] was demonstrated and four remaining patients undergoing treatment on the RA arm crossed over to receive dinutuximab/RA. The median EFS was not reached (3.4 years, NR) in the dinutuximab/RA arm and was 1.9 years (1.3, NR) in the RA arm. An analysis of overall survival

(OS) conducted three years later documented an improvement in OS in the dinutuximab/RA arm compared to the RA arm [HR 0.58 (95% CI: 0.37, 0.91)]. At the time of this survival analysis, median OS had not been reached in either arm.

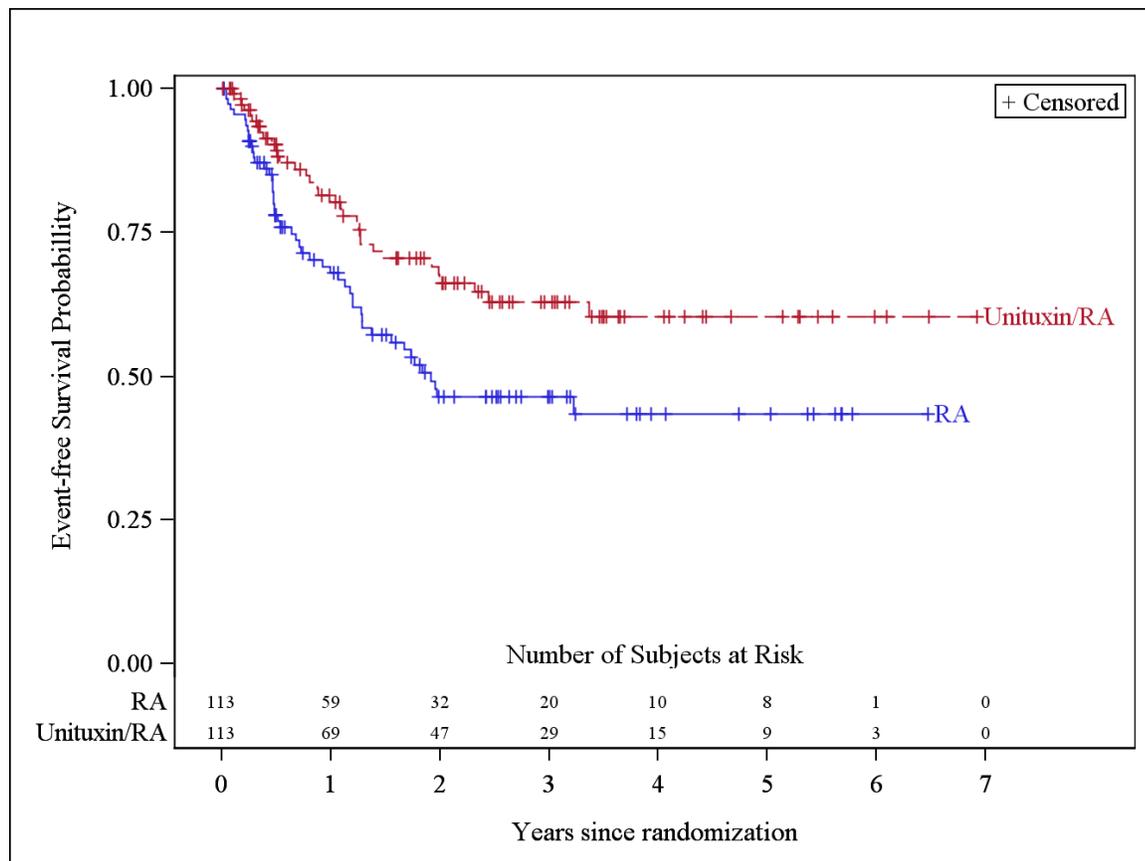
Efficacy Parameter		Unituxin/ RA arm n=113	RA arm n=113
EFS	No. of Events (%)	33 (29%)	50 (44%)
	Median (95% CI) (years)	NR (3.4 ,NR)	1.9 (1.3, NR)
	Hazard Ratio (95% CI)	0.57 (0.37, 0.89)	
	p-value (log-rank test) <sup>1</sup>	0.01	
OS <sup>2</sup>	No. of Events (%)	31 (27%)	48 (42%)
	Median (95% CI)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

NR = not reached

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

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

Kaplan-Meier Curves of Event-Free Survival in Study DIV-NB-301



## 7. Safety

Safety data was evaluated in 134 patients. The most common (greater than or equal to 25%) adverse drug reactions in the dinutuximab/RA group were pain, pyrexia, thrombocytopenia, 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 (greater than or equal to 5%) serious adverse reactions in the dinutuximab/RA group were infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome.

Seventy-one percent of patients in the dinutuximab/RA arm and 77% of patients in the RA alone arm completed planned treatment. The most common reason for premature discontinuation of study therapy was adverse reactions in the dinutuximab/RA group (19%) and progressive disease (17%) in the RA group.

Unituxin labeling includes a Boxed Warning for serious infusion reactions and for neuropathic pain and peripheral neuropathy as well as a Contraindication for use in patients with a history of anaphylaxis to dinutuximab.

## 8. Advisory Committee Meeting

This first-in-class molecule was not referred to the Oncologic Drugs Advisory Committee (ODAC) because the committee is comprised predominantly of adult oncologists. 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 positive in this serious disease with no satisfactory alternative therapies.

## 9. Pediatrics

Orphan drug designation was granted for dinutuximab on December 20, 2010, for the treatment of neuroblastoma, therefore dinutuximab is exempt from the requirements of the Pediatric Research Equity Act (PREA).

## 10. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.
- Risk Benefit Assessment: The prognosis of patients with advanced stage neuroblastoma (stage 4 disease) is influenced by age at diagnosis and other prognostic factors, with a 5-year disease-free survival rate of 50%–80% in children diagnosed before 18 months of age and 3% in children/young adults patients between 10 and 21 years of age. In the patient population enrolled in Study DIV-NB-301, 80% had INSS Stage 4 disease and the median age was 3.8 years, with only 3% of patients less than 18 months of age; the anticipated 5-year survival rates would be less than 50% and in some patients, as low as 5%. There have been no drugs approved for treatment of this disease since 1987. Patients with high-risk neuroblastoma are typically treated on clinical protocols employing sequential multimodality that includes combination chemotherapy, myeloablative therapy with stem cell support, surgical debulking, and radiation to sites of disease, followed by retinoic acid for up to 6 months. The background therapy in this disease is also toxic and considered acceptable in light of the life-threatening nature of the disease.

Study DIV-NB-301 demonstrated a 42% improvement in event-free survival (median EFS in the control arm 1.9 years) with a trend in improved overall survival; these findings were present at multiple time-points as the study results matured and were present across relevant subgroups. While the study design of DIV-NB-301 isolated the effects of retinoic acid, it did not isolate the treatment effects of concomitant cytokines (GM-CSF and IL-2) administered to enhance ADCC. At the doses administered, these agents alone are unlikely to account for these improvements in EFS and OS, based on external data described in product labeling for each of these drugs.

When dinutuximab is administered according to the package insert and with optimal medical management which includes intravenous hydration and concomitant medications, this regimen requires administration in a hospital setting for management of dinutuximab-induced pain. In addition, careful patient selection based on adequate end-organ function and monitoring in a hospital/acute care setting are required to mitigate the risks and potential for death

due to the potential serious risks of serious infusion reactions, capillary leak syndrome, and hypotension. The most common severe and life-threatening adverse reactions of dinutuximab are neuropathic pain (51%), pyrexia (40%), infusion-related reactions (25%), capillary leak syndrome (23%), hypotension (16%), sepsis (16%), device-related infection (16%), diarrhea (13%), urticaria (13%) and hypoxia (12%).

The benefits of dinutuximab outweigh these serious and sometimes fatal risks, which are commonly accepted in the pediatric oncology community by both healthcare providers, patients, and their parents, as the price of improvement in overall survival and delaying time to relapse. However, additional studies should be conducted to confirm or rule out the role of GM-CSF, IL-2, and retinoic acid to determine if toxicity can be reduced with removal of ineffective drugs from this complex and toxic treatment regimen.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies  
A REMS is not required to ensure safe use. Treatment of patients with high-risk neuroblastoma is limited to pediatric oncologists at tertiary or specialized medical centers. These specialists are familiar with the risks of dinutuximab and there has been extensive experience through the expanded access program which enrolled more than 750 patients. In addition, the clinical review team and DRISK do not recommend requirement of a REMS.
- Recommendation for other Postmarketing Requirements and Commitments  
See action letter.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TAMY E KIM  
03/10/2015

RICHARD PAZDUR  
03/10/2015