

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125516Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: September 12, 2014

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Subject: Review to determine if a REMS is necessary

Drug Name(s): dinutuximab (Unituxin)

Therapeutic Class: monoclonal antibody

Dosage and Route: 17.5mg/2/day for 4 days during each of 5 courses
of treatment

Application Type/Number: BLA 125516

Applicant/sponsor: United Therapeutics Corp

OSE RCM #: 2014-807
2014-855

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1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) dinutuximab (Unituxin). The sponsor, United Therapeutics Corporation (UTC), submitted a Biologics License Application (BLA) 125516 for dinutuximab with the proposed indication for the treatment of pediatric neuroblastoma. The sponsor was granted orphan drug status for the treatment of neuroblastoma in the US on December 20, 2010.

UTC submitted a risk management plan with identified risks of allergic reactions, capillary leak syndrome, hypotension, systemic infection/sepsis, pain, peripheral neuropathy, and neurological eye disorders. In this risk management plan, the Sponsor proposes to manage these events through routine pharmacovigilance and product labeling, and therefore did not submit a REMS.

1.1 BACKGROUND

Neuroblastoma is a malignancy that begins in the early stages of nerve cell formation in an embryo or fetus. This type of cancer primarily occurs in infants and young children, and is rarely found in children older than 10 years.¹ The median age at diagnosis is 17 months, and 40% of these cases are diagnosed before 1 year of age. More than 650-700 neuroblastoma cases are diagnosed in the United States each year, and is the third most common childhood cancer, accounting for 15% of pediatric cancer deaths.² Among newly diagnosed cases, 45% are classified as high risk, indicating a poorer prognosis and the need for intensive treatment. Depending on the patient's risks stratification, the current standard of care for neuroblastoma includes induction chemotherapy, surgical resection, myeloablative consolidation chemotherapy with autologous stem cell rescue, and radiation therapy to the primary tumor site.³ These treatments come with severe side effects and decreased quality of life, especially at such a young age. Abysmal survival rates are often seen in these circumstances. The three year event free survival rates are less than 15% in high risk (Stage IV) cases, and deaths are primarily due to disease progression.²

Dinutuximab – Dinutuximab, also known as ch14.18, is a chimeric monoclonal antibody (mAb) comprised of human and mouse genes. This compound reacts specifically with disialoganglioside (GD2), which are cells highly expressed on human tumors in the neuroectodermal region, and in melanoma cells.⁴ The mechanism of action is through lysis of tumor cells through the processes of antibody dependent cell-mediated

¹ <http://www.cancer.org/cancer/neuroblastoma/detailedguide/neuroblastoma-what-is-neuroblastoma> accessed 5/15/14.

² <http://www.uptodate.com/contents/epidemiology-pathogenesis-and-pathology-of-neuroblastoma> accessed 5/15/14.

³ Midcycle Meeting Clinical slides.

⁴ Clinical Overview (section 2.5), dinutuximab

cytotoxicity, and complement-dependent cytotoxicity.⁵ Dinutuximab was initially developed by the National Cancer Institute (NCI), and has been used in clinical studies for approximately 20 years prior to UTC obtaining ownership in July 2010. The proposed full indication for dinutuximab would be used in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin (RA) for high risk neuroblastoma (b) (4) treatment.³ Administration of dinutuximab would occur over a period of five cycles, in addition to several pre-medications in an attempt to ameliorate some of the common adverse events detailed below in the safety section. If approved, dinutuximab will be the first chimeric mAb specific to the GD2 antigen for the treatment of pediatric neuroblastoma.⁶

1.2 REGULATORY HISTORY

The review timeline for this application is Priority. Listed below are the pertinent regulatory history milestones for this BLA:

- December 20, 2010 – Orphan Drug Designation granted
- March 9, 2012 – IND 110494 submitted for dinutuximab
- April 11, 2014 – BLA application received
- July 9, 2014 – Midcycle meeting
- July 18, 2014 – Midcycle teleconference with the sponsor
- PDUFA (Action) date – December 10, 2014

2 MATERIALS REVIEWED

- UTC Clinical Modules (sections 2.5, 2.73, and 2.74) and Risk Management Plan submitted April 11, 2014
- UTC FDA Application Orientation Meeting, June 5, 2014
- Midcycle Meeting Slides, July 9, 2014
- Dinutuximab (Unituxin) draft label, August 27, 2014
- Midcycle Meeting Communication to the Sponsor (draft), September 2, 2014

3 RESULTS OF REVIEW

The clinical program for dinutuximab is extensive, spanning over a period of 20 years. NCI supported 8 clinical studies with dinutuximab (4 melanoma, 4 neuroblastoma), and when UTC took ownership in 2010, they began reformulating the drug, and subsequently performed a pharmacokinetic comparability study of the different dose and formulation of dinutuximab from the NCI dose to the UTC dose for the treatment of neuroblastoma. Three studies support the efficacy and safety data for this application as outlined below. In addition, along with adverse events that are duly noted in this chemotherapeutic setting, other severe toxicities were also documented with the use of dinutuximab. Clinical investigators were required to undergo web based protocol training from the sponsor for education on the management of adverse events. This training was not part of

⁵ UTC FDA Application Orientation Meeting, June 5, 2014

⁶ Parsons K, Neuroblastoma and Immunotherapy: Targeted Therapy for Children. Hematology/Oncology News Spring 2011

the risk management plan, but provided as a separate training for investigators that included information on the dosing cycle and schedules of dinutuximab and concomitant medications, as well as education and management on the adverse events noted in the risk management plan.

3.1 OVERVIEW OF CLINICAL PROGRAM

At the time of this writing, FDA clinical reviewers were still completing analysis of the safety and efficacy of the studies outlined below. The summary below provides a high level overview of the studies that support this application.

Key Efficacy Findings:

DIV-NB-301 (Study 1): This was an open-label multicenter study of 268 patients with randomization from October 26, 2001 – November 3, 2008. Patients were randomized in a 1:1 fashion to receive either RA 160mg/m²/day divided into daily doses, or dinutuximab + IL-2 + GM-CSF + RA given over a course of 5 cycles.⁴ The mean age at enrollment was 4.3 years (0.94 – 15.29 years), participants were predominately male (59%), and Caucasian (80%).⁴ Eighty-one percent of patients were diagnosed with Stage IV disease.

Dinutuximab was administered at a dose of 25 mg/m²/day (equivalent to 17.5 mg/m²/day for the UTC dose) on four consecutive days (Days 4-7) of courses 1-5. In courses 1, 3, and 5, GM-CSF was administered for 14 days at a dose of 250 mcg/m²/day. During courses 2 and 4, IL-2 was administered IV at a dose of 3.0 MIU/m²/day for 4 days during Week 1 and at a dose of 4.5 MIU/m²/day for 4 days during Week 2. During the last two weeks in each of the six courses, patients in the control and the dinutuximab arms were given oral RA at a dose of 160 mg/m²/day (given as 80 mg/m²/day twice daily).⁷

A total of 268 patients were randomized to the dinutuximab group (with the combination of GM-CSF, IL-2, and RA) and 106 patients were randomized to receive RA alone (RA group).⁷ Randomization was stopped on January 13, 2009 after the interim analysis showed positive outcomes in both the primary endpoint of event free survival (EFS) and secondary endpoint of overall survival (OS). Efficacy was determined from EFS which was defined as the first occurrence of relapse, progressive disease, secondary malignancy, or death. There was a statistically significant improvement in EFS (p = 0.0115) in the dinutuximab arm (29%) versus the RA arm (44%).⁷ At the time of this review, the median had not yet been reached for OS, but was approximately 7.5 years for the dinutuximab group, and 4 years for the RA group.

Approximately 72% of patients in the dinutuximab group completed study therapy, compared to 77% in the control (RA) group. The most common reason for discontinuation in the dinutuximab group was adverse reactions (19%), while progressive disease (17%), was the most common reason for discontinuation in the RA group.

DIV-NB-302 (Study 2): This is a continuation of DIV-NB-301, with the same patient population, with continuing enrollment. This study has been rolled over in to a single arm

⁷ Unituxin draft label, August 27, 2014

study (dinutuximab + cytokine combination + RA), and 747 patients have enrolled as of June 13, 2013.³

Study 3: This was a non-randomized, multi-center, non-controlled study conducted to more comprehensively assess the safety of dinutuximab given in combination with GM-CSF, IL-2 and RA, in addition to results from Study 1 and 2.⁷ Grade 1-5 adverse events were recorded during this study. There were 104 patients who received Unituxin and RA with GM-CSF and IL-2 77% of patients completing therapy.⁷ Patients had a mean age at enrollment of 5 years (1 – 27 years), were predominantly male (57%), and White (79%).

3.2 SAFETY CONCERNS

Adverse reactions determined by the sponsor that were deemed to be not related to the underlying disease include: allergic reactions, capillary leak syndrome, hypotension, sepsis, generalized pain, and peripheral neuropathy. These adverse events are outlined in the risk management plan, and clinical investigators were also required to undergo web-based training for the education and management of these adverse events. In study 1 and 2, FDA clinical reviewers also determined the most common serious grade 3-5 adverse drug reactions ($\geq 5\%$) in patients treated in the dinutuximab group were infections (7%), pain (49%), hypotension (16%), anaphylaxis, hypokalemia (36%), fever (39%), and capillary leak syndrome (23%).

Nasal congestion (20%), wheezing (15%), and hallucinations (10%) were adverse events reported in Study 3 that were not previously reported in Study 1 or 2.

Several pre-medications and concomitant medications have been outlined to assist with management of the adverse reactions that may occur such as: morphine sulfate, acetaminophen, lidocaine (if pain does not respond to morphine alone), gabapentin for pain, and antihistamines such as hydroxyzine or diphenhydramine for allergic and infusion reactions. The sponsor has proposed to include the adverse events below in the Warnings and Precautions section of the Unituxin draft label.

3.2.1 (b) (4) **Infusion reactions**⁷ – (b) (4)
[Redacted text block]

3.2.2 Capillary Leak Syndrome⁷ – (b) (4)
[Redacted text block]

(b) (4)

Reviewer Comment: *At the time of this review the analysis of the difference between capillary leak syndrome with and without co-administration with IL-2 was ongoing.*

3.2.3 Hypotension⁷ – (b) (4) hypotension was reported in 16% (n=22) of dinutuximab patients compared to no patients in the RA group.

(b) (4)

3.2.4 (b) (4) Infection | (b) (4) – (b) (4)

3.2.5 Pain and Peripheral Neuropathy⁷ – (b) (4)

3.2.6 Neurological Disorders of the Eye⁷ – (b) (4)

Deaths⁴: Out of a total of 1,144 subjects who received treatment with dinutuximab, 26 died (2%) within 30 days of study therapy. Disease or tumor related deaths accounted for 77% of these cases by investigators. Of the remaining cases that could not be directly attributed to disease progression, 4 died due to: systemic inflammatory response/capillary leak syndrome following an IL-2 overdose (1), pulmonary hemorrhage (1), cardiac arrest (1), intracranial hemorrhage (1). Sixteen percent (n = 182) of patients died >30 days after completing therapy. Ninety-five percent were considered to be disease/tumor related. The remaining deaths were as follows: 2 – infections, 1 – multi-organ failure, 5 – “other” causes. One of these cases was not recorded appropriately. The other four included: 1 – cardiopulmonary arrest due to metastatic disease, 1 – respiratory failure secondary to progressive disease, 2 – intracranial hemorrhage.

Nonclinical data⁴ – Hepatotoxicity has been noted in rats, primarily hepatocellular necrosis. Moderate increases in blood pressure (1 of 3 animals) were noted, and increases in heart rate (2 of 3 animals) were noted in cynomolgous monkeys. There appeared to be no effects on ECG or respiratory systems.

Embryo-fetal toxicity³ – The Agency waived embryo-fetal studies due to the age of the patient population. Dinutuximab is an IgG1 antibody, and can potentially cross the placental barrier, but the extent of its risk to pregnancy is unknown. FDA will be recommending a pregnancy category D rating.

Of note, since RA is part of the chemotherapeutic cycles, prescribers must undergo training and adhere to the iPLEDGE program requirements in order to prescribe this drug.

The applicant plans to communicate all safety events through labeling, and therefore did not submit a REMS.

4 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

Negotiations for PMR’s and PMC’s have not begun at this time.

5 DISCUSSION

Management of patients with neuroblastoma presents with many difficulties due to disease characteristics and the potential for severe adverse events that patients are likely to experience from current therapies. Cytotoxic chemotherapies with the use of camptothecins, topotecan and irinotecan in combination with cyclophosphamide and temozolomide have shown varying degrees of overall response rates (ORR) from 32% to 61% depending on the degree of malignancy and risk stratification of the patient.⁸

⁸ Morgenstern D et al. Current and Future Strategies for Relapsed Neuroblastoma: Challenges on the Road to Precision Therapy. *J Pediatr Hematol Oncol*; July 2013, 35(5): 337-347

Despite improvements in the treatment of neuroblastoma, overall survival rates still tend to be suboptimal, especially in patients presenting with high risk disease. There are currently no curative therapies, and ongoing management is focused on prolonging survival and relief of symptoms.

Dinutuximab is a chimeric mAb, being proposed for the treatment of high risk neuroblastoma, specifically in the maintenance phase of treatment, in combination with GM-CSF, IL-2, and RA throughout a course of six cycles. Results from Study 1 showed that there was a statistically significant improvement in EFS in the dinutuximab group (29%) versus the RA group (44%).⁷ At the time of this review, the median had not yet been reached for OS, but was approximately 7.5 years for the dinutuximab group, and 4 years for the RA group. Several adverse events were noted in patients who received dinutuximab, most commonly allergic and infusion related reactions, capillary leak syndrome, infections/sepsis, pain and peripheral neuropathy, and eye disorders.

In addition to IRB approval, the sponsors required additional web based training that investigators had to attest their completion, that focused on education of the adverse events listed above (also noted in the risk management plan), and outlined specific procedures on the management of these events, which included administration of pre-medications such as morphine and antihistamines as well as other supportive measures in an attempt to prevent or mitigate the adverse events. Although the sponsor required training of these events in the clinical trials, they did not submit a REMS, and proposed mitigating these adverse events in labeling.

RA is co-administered with dinutuximab, therefore investigators, and prescribers, will be required to complete the requirements associated with the iPLEDGE REMS program in order to prescribe this drug.

Despite several adverse events associated with dinutuximab, DRISK does not recommend having a REMS to mitigate these risks. The concomitant cytokines GM-CSF and IL-2 also present with severe side effects (commonly infection and infusion related reactions) that may be a contributory factor with the adverse event profile of dinutuximab. Due to the nature of the adverse events, and the concomitant medications expected to be given with each cycle, patients will receive dinutuximab in tertiary care hospitals with access to pediatric intensive care units. Likely prescribers of dinutuximab will be pediatric oncologists who are familiar with the management of the side effects of mAb's and cytokines; specifically IL-2 and many of whom were clinical investigators during the clinical trials of dinutuximab. The management of the adverse events will be communicated through the label. The DOSAGE AND ADMINISTRATION section of the label clearly describes premedication (b) (4) medication information that should be administered prior to each infusion (see section 2.4 of the label).

6 CONCLUSION

Data presented for dinutuximab in this patient population studied with Stage IV high risk neuroblastoma demonstrate that the benefits of dinutuximab outweigh the risks at this time in a patient population that presents with minimal treatment options. DRISK concurs with the Division of Oncology Products-2, that based on the available data and the potential benefits and risks of treatment, a REMS is not necessary. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit risk profile to be re-evaluated.

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/s/

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