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FDA Approves Unituxin™ (dinutuximab) for the Treatment of Pediatric High-Risk Neuroblastoma

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., March 10, 2015 /PRNewswire/ -- United Therapeutics Corporation (NASDAQ: UTHR) announced today that the United States Food and Drug Administration (FDA) has approved Unituxin™ (dinutuximab) Injection (formerly called ch14.18), 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. Neuroblastoma is the most common extracranial solid cancer in childhood and the most common cancer in infancy, with an annual incidence in the United States of approximately 700 patients, of whom 50% are diagnosed as having high-risk disease. Unituxin is a chimeric biologic antibody that induces cell lysis of GD2-expressing cells through antibody-dependent cell-mediated cytoxicity (ADCC) and complement-dependent cytoxicity (CDC) and is part of an immunotherapeutic regimen to treat pediatric high-risk neuroblastoma.

The approval was based on demonstration of improved event-free survival (EFS) and overall survival (OS) in a multicenter, open-label, randomized trial (ANBL0032) conducted by the Children's Oncology Group (COG). The trial randomized (1:1) 226 patients to either the Unituxin/13-cis-retinoic acid (RA) arm or the RA alone arm. Patients in each arm received six cycles of treatment. The Unituxin/RA arm consisted of Unituxin in combination with granulocyte macrophage-colony stimulating factor and RA (cycles 1, 3, and 5), Unituxin in combination with interleukin-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 Unituxin/RA. The median EFS was not reached (3.4 years, NR) in the Unituxin/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 Unituxin/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.

The most common serious adverse reactions (greater than or equal to 5%) are infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome.

The most common adverse drug reactions (greater than or equal to 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%).

"This approval has been a collaborative effort between the National Cancer Institute (NCI), the Children's Oncology Group and United Therapeutics for the first approved therapy for pediatric high-risk neuroblastoma," said Roger Jeffs, Ph.D., United Therapeutics' President and Co-Chief Executive Officer. "We are grateful for the FDA's thorough review and collaboration on this program, and we look forward to expanding our research efforts in the area of pediatric oncology."

"The FDA approval of dinutuximab represents the culmination of a remarkably productive collaboration between researchers of the NCI-supported Children's Oncology Group, the manufacturing and clinical research groups of NCI, and the oncology team at United Therapeutics," said Malcolm Smith, MD, Ph.D., Associate Branch Chief, Pediatrics in the Cancer Therapy Evaluation Program at NCI. Children with neuroblastoma will benefit from this collaboration, and the drug development pathway blazed by dinutuximab will likely be followed in the future to develop other novel agents directed against pediatric cancer therapeutic targets."

"After decades of pursuits, I am pleased to see that dinutuximab has received FDA approval and may now benefit high risk neuroblastoma patients," said Alice Yu, M.D., Ph.D., University of California San Diego and Principle Investigator of the registration study conducted by the COG. "This is not only the first successful immunotherapeutic to target a non-protein antigen, but also to be developed from an Investigational New Drug application through phase 3 trials largely through investigator-initiated effort and NCI support."

The recommended dose and schedule for Unituxin is 17.5 mg/m^2/day as a diluted intravenous infusion over 10 to 20 hours for 4 consecutive days for a maximum of 5 cycles. Patients require intravenous treatment with opioids prior to, during, and for 2 hours following the Unituxin infusion to mitigate neuropathic pain. Prior to each Unituxin dose, administer required intravenous hydration and premedication with antihistamines, analgesics, and antipyretics.

In connection with the Unituxin approval, United Therapeutics agreed to certain postmarketing requirements (PMRs) and certain postmarketing commitments (PMCs). PMRs and PMCs are studies that sponsors conduct after FDA approval to gather additional information about a product's safety, efficacy, or optimal use. PMRs are required studies, whereas a sponsor voluntarily commits to conduct PMCs.

About Unituxin

Unituxin (dinutuximab) is a disialoganglioside, GD2-binding chimeric monoclonal antibody (formerly called ch14.18) 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. The safety and effectiveness of Unituxin was evaluated in a randomized, open-label, multicenter trial conducted in pediatric patients with high-risk neuroblastoma. All patients had received prior therapy consisting of induction combination chemotherapy, maximum feasible surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and radiation therapy to residual soft tissue disease.

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
- **Neuropathy**
  - Unituxin causes severe neuropathic pain 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 was observed in adults. Resolution of motor neuropathy was not documented in all cases
  - Discontinue Unituxin for severe unresponsive pain, severe sensory neuropathy, or moderate to severe peripheral motor neuropathy

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
- **Pain and Peripheral Neuropathy**
  - *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.
  - *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
- **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
- **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 with recurrent eye disorder following dose reduction and in patients who experience loss of vision
- **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

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Please see Full Prescribing Information including **Boxed WARNING** for Unituxin, available at http://www.unither.com/UFullPrescribingInformation.PDF.

About United Therapeutics

United Therapeutics Corporation is a biotechnology company focused on the development and commercialization of innovative products to address the unmet medical needs of patients with chronic and life-threatening conditions.

Forward-looking Statements

Statements included in this press release that are not historical in nature are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include, among others, United Therapeutics' intention to expand its research efforts in the area of pediatric oncology, the benefit of Unituxin to children, and future development of other novel agents. These forward-looking statements are subject to certain risks and uncertainties, such as those described in our periodic reports filed with the Securities and Exchange Commission, that could cause actual results to differ materially from anticipated results. Consequently, such forward-looking statements are qualified by the cautionary statements, cautionary language and risk factors set forth in our periodic reports and documents filed with the Securities and Exchange Commission, including our most recent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K. We claim the protection of the safe harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. We are providing this information as of March 10, 2015, and we assume no obligation to update or revise the information contained in this press release whether as a result of new information, future events or any other reason. [uthr-g]

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