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European Commission Grants Marketing Authorisation for Unituxin™ (dinutuximab) for the Treatment of Paediatric High-Risk Neuroblastoma

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., Aug. 17, 2015 /PRNewswire/ -- United Therapeutics Corporation (NASDAQ: UTHR) announced today that the European Commission (EC) has granted Marketing Authorisation for Unituxin™ (dinutuximab) for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplantation (ASCT). Unituxin is administered in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin.

Neuroblastoma is the most common extracranial solid cancer in childhood and the most common cancer in infancy, with an annual incidence in the European Union of approximately 1500 patients, of whom 50% are diagnosed as having high-risk disease.

The European approval was based on demonstration of improved event-free survival (EFS) and overall survival (OS) in a multicenter, open-label, randomized trial (ANBL0032) sponsored by the US National Cancer Institute under a Cooperative Research and Development Agreement with United Therapeutics and conducted by the Children's Oncology Group (COG).

Trial design and results

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. The primary intent-to-treat analysis found an improvement in EFS associated with dinutuximab immunotherapy plus isotretinoin as compared to isotretinoin alone. The two-year estimates of EFS were 66% among subjects receiving dinutuximab immunotherapy plus isotretinoin as compared with 48% in subjects receiving isotretinoin alone (log-rank test p = 0.033) although this difference did not reach formal statistical significance according to the pre-specified plan for interim analyses. In addition, OS was evaluated with 3 years of follow-up after the EFS analysis as a secondary endpoint with a significant improvement observed among ITT subjects randomly allocated to receive dinutuximab immunotherapy plus isotretinoin as compared with isotretinoin alone. The three-year estimates of OS were 80% compared with 67% among subjects receiving dinutuximab immunotherapy plus isotretinoin and isotretinoin alone, respectively (log-rank test p = 0.0165). Long-term overall survival was evaluated with five years of follow up after the EFS analysis and continued to demonstrate a survival advantage for patients who received dinutuximab immunotherapy compared to those who received isotretinoin alone. The five-year estimates of OS were 74% for dinutuximab immunotherapy compared to 57% for isotretinoin alone (log-rank test p = 0.030).

Frequently occurring adverse reactions

The most frequently occurring (more than 30% of patients) adverse reactions reported during the neuroblastoma studies were hypotension (67%), pain (66%), hypersensitivity (56%), pyrexia (53%), urticaria (49%), capillary leak syndrome (45%), anaemia (45%), hypokalaemia (41%), platelet count decreased (40%), hyponatraemia (37%), alanine aminotransferase increased (35%), decreased lymphocyte count (34%) and decreased neutrophil count (31%). Additional adverse reactions characteristic of an allergic response were also reported - including anaphylactic reaction (18%) and bronchospasm (4%).

Posology and method of administration

Unituxin is to be administered by intravenous infusion over five courses at a daily dose of 17.5 mg/m^2. It is administered on days 4-7 during courses 1, 3 and 5 (each course lasting approximately 24 days) and on days 8-11 during courses 2 and 4 (each course lasting approximately 28 days).

The treatment regimen consists of Unituxin, GM-CSF, IL-2, and isotretinoin, administered over six consecutive courses.

About Unituxin

Unituxin (dinutuximab) is a monoclonal chimeric antibody composed of murine variable heavy and light chain regions and the human constant region for the heavy chain kappa. Unituxin reacts specifically with the ganglioside GD2, which is highly expressed on the surface of the neuroblastoma cells and minimally expressed on the surface of normal human neurons, peripheral pain fibres, and skin melanocytes.

On 10 March 2015, Unituxin, in combination with GM-CSF, IL-2 and RA, became the first therapy to be approved by the US Food and Drug Administration for the treatment of paediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent multimodality therapy.

Unituxin carries a Boxed Warning alerting patients and health care professionals that Unituxin irritates nerve cells, causing severe pain that requires treatment with intravenous narcotics and can also cause nerve damage and life-threatening infusion reactions, including upper airway swelling, difficulty breathing, and low blood pressure, during or shortly following completion of the infusion. Unituxin may also cause other serious side effects including infections, eye problems, electrolyte abnormalities and bone marrow suppression. Full prescribing information is available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125516s000lbl.pdf.

Important EU Safety Information for Unituxin

- **This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.**

Contraindications
Hypersensitivity (Grade 4) to the active substance or to any of the excipients in Unituxin.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- **Allergic Reactions**
  - Antihistamine premedication (e.g. hydroxyzine or diphenhydramine) should be administered by intravenous injection approximately 20 minutes before starting each Unituxin infusion.
  - It is recommended that antihistamine medicinal product be repeated every 4-6 hours as required during infusion of Unituxin. Patients should be monitored for signs and symptoms of infusion reactions for 4 hours after the completion of the Unituxin infusion.
  - Epinephrine (adrenaline) and hydrocortisone for intravenous administration should be immediately available at the bedside during administration of dinutuximab to manage life-threatening allergic reactions.
  - It is recommended that treatment for such reactions include hydrocortisone administered by intravenous bolus, and epinephrine administered by intravenous bolus once every 3-5 minutes as necessary according to clinical response.
  - Depending on the severity of the allergic reaction, the rate of infusion should be reduced or treatment discontinued.

- **Capillary Leak Syndrome**
  - Capillary leak syndrome is more likely when dinutuximab is co-administered with IL-2. It is recommended to administer oral metolazone or intravenous furosemide every 6-12 hours as required. Supplemental oxygen, respiratory support, and albumin replacement therapy should be used as necessary according to clinical response.
  - Characteristic symptoms and signs include hypotension, generalized oedema, ascites, dyspnoea, pulmonary oedema and acute renal failure associated with hypoalbuminaemia and haemoconcentration.

- **Pain**
  - Severe pain (Grade 3 or 4) occurs most frequently during the first 4-day course of Unituxin, often subsiding over time with subsequent courses.
  - For severe pain, the Unituxin infusion rate should be decreased to 0.875 mg/m2/hour. Unituxin should be discontinued if pain is not adequately controlled despite infusion rate reduction and institution of maximum supportive measures.
  - Paracetamol should be administered orally 20 minutes prior to starting each dinutuximab infusion, and repeated every 4-6 hours as needed. Regular dosing every 4-6 hours is recommended when IL-2 is coadministered. If required for persistent pain, ibuprofen should be administered orally every 6 hours between doses of paracetamol. Ibuprofen should not be administered if there is evidence of thrombocytopenia, bleeding, or renal dysfunction.
  - An opioid, such as morphine sulphate, is recommended to be administered by intravenous infusion prior to each dinutuximab infusion and continued as an intravenous infusion during and until 2 hours after completion of the treatment. It is recommended that additional intravenous bolus doses of an opioid are administered as needed for

treatment of pain up to once every 2 hours during the dinutuximab infusion. If morphine is not tolerated, then fentanyl or hydromorphone may be utilised.
    - Lidocaine may be administered as an intravenous infusion (2 mg/kg in 50 mL of 0.9% sodium chloride) over 30 minutes prior to the start of each dinutuximab infusion and continued via intravenous infusion at 1 mg/kg/h up to 2 hours after completion of the treatment. Lidocaine infusion should be discontinued if the patient develops dizziness, perioral numbness, or tinnitus.
    - Gabapentin may be administered at the time of starting morphine premedication, at an oral dose of 10 mg/kg/day. The dose may be subsequently increased (up to a maximum of 60 mg/kg/day or 3600 mg/day) as needed for pain management.

- **Hypotension**
    - Intravenous sodium chloride 9 mg/mL (0.9%) solution for injection (10 mL/kg) should be administered over one hour just prior to the dinutuximab infusion. If hypotension occurs, this can be repeated, or intravenous albumin or packed red blood cells can be administered as clinically indicated.
      It is recommended that vasopressor therapy is also administered if necessary to restore an adequate perfusion pressure.

- **Neurological Disorders of the Eye**
    - Eye disorders may occur, especially with repeated courses. These changes usually resolve over time. Patients should have an ophthalmic examination before initiating therapy and be monitored for visual changes.

- **Hepatic Dysfunction**
    - Regular monitoring of liver function is recommended during dinutuximab immunotherapy.

- **Systemic Infections**
    - Patients typically have a central venous catheter in situ and as a consequence of prior ASCT are likely to be immunocompromised during therapy, and therefore, at risk of developing systemic infection.
    - Patients should have no evidence of systemic infection and any identified infection should be under control before beginning therapy.

- **Laboratory Test Abnormalities**
    - Electrolyte abnormalities occurring in at least 25% of patients who received Unituxin included hyponatraemia and hypokalaemia.

- **Atypical Haemolytic Uraemic Syndrome**
    - Haemolytic uraemic syndrome in the absence of documented infection and resulting in renal insufficiency, electrolyte abnormalities, anaemia, and hypertension has been reported. Supportive measures should be instituted including control of hydration status, electrolyte abnormalities, hypertension, and anaemia.

For the Summary of Product Characteristics, and detailed information on this medicinal product, please visit www.ema.europa.eu.

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, statements relating to the safety and benefits of Unituxin to children. 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 August 17, 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]