Health Canada Approves Unituxin® For The Treatment Of Pediatric High-Risk Neuroblastoma

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SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., Nov. 29, 2018 /PRNewswire/ -- United Therapeutics Corporation (NASDAQ: UTHR) announced today that Health Canada has approved [Pr]Unituxin (dinutuximab for injection), in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA), for the treatment of high-risk neuroblastoma in pediatric patients who achieve at least a partial response to prior first-line multiagent, multimodality therapy. Unituxin was previously approved by the U.S. Food and Drug Administration in March 2015.

"We are delighted that Health Canada has approved our novel therapy, which has now provided hundreds of American children with freedom from cancer for over five years and counting," said Martine Rothblatt, Ph.D., Chairman and Chief Executive Officer of United Therapeutics. "We look forward to launching the product for Canadian patients during the first half of 2019."

"We are pleased that we can offer Canadian children an increased long-term survival advantage over previous standard of care," added Gil Golden, M.D., Ph.D., Chief Medical Officer of United Therapeutics. "In addition, we are testing dinutuximab in adult patients with small cell lung cancer, and have recently completed enrollment of our phase 3 clinical study of that indication."

About Unituxin

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.

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.**
- **Neurotoxicity**
  - **Unituxin causes serious neurologic adverse reactions including severe neuropathic pain and peripheral neuropathy.**
  - **Severe neuropathic pain occurs in the majority of patients.**
  - **Administer intravenous opioid prior to, during, and for 2 hours following completion of the Unituxin infusion.**
  - **In clinical studies of patients with high-risk neuroblastoma, severe (Grade 3) peripheral sensory neuropathy ranged from 2% to 9%.**
  - **In clinical studies of Unituxin and related GD2-binding antibodies, severe motor neuropathy has occurred. Resolution of motor neuropathy did not occur in all cases.**
  - **Discontinue Unituxin for severe unresponsive pain, severe sensory neuropathy, and 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. Severe urticaria occurred in 17 (13%) patients in the Unituxin/RA group but did not occur in the RA group. Serious adverse reactions consistent with anaphylaxis and resulting in permanent discontinuation of Unituxin occurred in 2 (1%) patients in the Unituxin/RA group. Additionally, 1 (0.1%) patient had multiple cardiac arrests and died within 24 hours after having received Unituxin in Study 2.

Neurotoxicity

- *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. For severe pain, decrease the Unituxin infusion rate to 0.875 mg/m^2/hour. Discontinue Unituxin if pain is not adequately controlled despite infusion rate reduction and institution of maximum supportive measures.
- *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. Permanently discontinue Unituxin in patients with peripheral motor neuropathy of Grade 2 or greater severity, Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks, or Grade 4 sensory neuropathy.
- *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. In Study 1, 3 (2%) patients in the Unituxin/RA group experienced blurred vision, compared to no patients in the RA group. Diplopia, mydriasis, and unequal pupillary size occurred in 1 patient each in the Unituxin/RA group, compared to no patients in the RA group. The duration of eye disorders occurring in Study 1 was not documented. In Study 3, eye disorders occurred in 16 (15%) patients, and in 3 (3%) patients resolution of the eye disorder was not documented. Among the cases with documented resolution, the median duration of eye disorders was 4 days (range: 0, 221 days).
    - 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 who experience loss of vision and in patients with recurrent eye disorder following dose reduction.
- *Prolonged Urinary Retention*: Urinary retention that persists for weeks to months following discontinuation of opioids has occurred in patients treated with Unituxin. Permanently discontinue Unituxin in patients with prolonged urinary retention that does not resolve with discontinuation of opioids.
- *Transverse Myelitis*: Transverse myelitis has occurred in patients treated with Unituxin. Promptly evaluate any patient with signs or symptoms such as weakness, paresthesia, sensory loss, or incontinence. Permanently discontinue Unituxin in patients who develop transverse myelitis.
- *Reversible Posterior Leukoencephalopathy Syndrome (RPLS)*: RPLS has occurred in patients treated with Unituxin. Institute appropriate medical treatment and permanently discontinue Unituxin in patients with signs and symptoms of RPLS (e.g., severe headache, hypertension, visual changes, lethargy, or seizures).

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 and institute supportive management in patients with symptomatic or severe capillary leak syndrome.

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 and institute supportive management in patients with symptomatic hypotension.

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.

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

- Electrolyte abnormalities occurring in at least 25% of patients who received Unituxin/RA in Study 1 included hyponatremia, hypokalemia, and hypocalcemia. 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

The most common serious adverse reactions (≥ 5%) are infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome.

The most common adverse drug reactions (≥ 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%). In post-approval use of Unituxin, the adverse reactions of prolonged urinary retention, transverse myelitis, and reversible posterior leukoencephalopathy syndrome were observed. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Please see Full Prescribing Information, including Boxed WARNING, for Unituxin, available at https://www.unituxin.com/wp-content/uploads/full-prescribing-information.pdf.

About United Therapeutics

United Therapeutics Corporation focuses on the strength of a balanced, value-creating biotechnology model. We are confident in our future thanks to our fundamental attributes, namely our obsession with quality and innovation, the power of our brands, our entrepreneurial culture and our bioinformatics leadership. We also believe that our determination to be responsible citizens – having a positive impact on patients, the environment and society – will sustain our success in the long term.

Through our wholly-owned subsidiary, Lung Biotechnology PBC, we are focused on addressing the acute national shortage of transplantable lungs and other organs with a variety of technologies that either delay the need for such organs or expand the supply. Lung Biotechnology is the first public benefit corporation subsidiary of a public biotechnology or pharmaceutical company. [uthr-g]

Forward-Looking Statements

Statements included in this press release concerning planned launch of Unituxin in Canada are "forward-looking statements" within the meaning of the safe harbor contained in the Private Securities Litigation Reform Act of 1995. These 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, which could cause actual results to differ materially from anticipated results. We are providing this information as of November 29, 2018, and 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.

SOURCE United Therapeutics Corporation

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