United Therapeutics CORPORATION

PO Box 14186
55 T.W. Alexander Dr
Research Triangle Park, NC 27709
Tel 919-485-8350
Fax 919-485-8352

June 2017

IMPORTANT DRUG WARNING

Subject: Recently Identified Serious Neurologic Risks of UNITUXIN® (dinutuximab)

- **Prolonged urinary retention**
- **Transverse myelitis**
- **Reversible posterior leukoencephalopathy (RPLS)**

Dear Health Care Provider:

The purpose of this letter is to inform you of important safety information for UNITUXIN (dinutuximab), 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.

Information regarding newly identified serious risks of prolonged urinary retention, transverse myelitis, and reversible posterior leukoencephalopathy were identified in post-marketing reports and have been added to the WARNINGS and PRECAUTIONS section of the UNITUXIN prescribing information. The prescribing information for UNITUXIN contains a BOXED WARNING for neurotoxicity.

Recommended Prescriber Actions

Counsel patients and caregivers about these newly identified risks of UNITUXIN.

Recommended actions are summarized below: (*see Section 5, Warnings and Precautions, and Section 17, Patient Counseling Information*)

- **RPLS**: 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). [*see Dosage and Administration (2.3) and Postmarketing Experience (6.3)*].

  Inform patients and caregivers of the risk of RPLS and to immediately report signs or symptoms such as severe headache, hypertension, visual changes, lethargy, or seizures.

- **Transverse myelitis**: Promptly evaluate any patient with signs or symptoms of transverse myelitis such as weakness, paresthesia, sensory loss, or incontinence. Permanently discontinue Unituxin in patients who develop transverse myelitis. [*see Dosage and Administration (2.3) and Postmarketing Experience (6.3)*].

Inform patients and caregivers of the risk of severe pain, sensory and motor neuropathy, prolonged urinary retention, and transverse myelitis, and to promptly report severe or worsening pain and signs and symptoms such as numbness, tingling, burning, weakness, or inability to urinate.

- **Prolonged urinary retention:** Permanently discontinue Unituxin in patients with urinary retention that does not resolve following discontinuation of opioids [*see Dosage and Administration (2.3) and Postmarketing Experience (6.3)*].

  Inform patients and caregivers of the risk of severe pain, sensory and motor neuropathy, prolonged urinary retention, and transverse myelitis, and to promptly report severe or worsening pain and signs and symptoms such as numbness, tingling, burning, weakness, or inability to urinate.

Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Reporting Adverse Events
Health care providers and patients are encouraged to report adverse events in patients taking UNITUXIN to United Therapeutics at drugsafety@unither.com. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

You may also contact our Global Medical Information group at 1-877-522-2950 or druginformation@unither.com if you have any questions about the information contained in this letter or the safe and effective use of UNITUXIN.

This letter is not intended as a complete description of the benefits and risks related to the use of UNITUXIN. Please refer to the enclosed full prescribing information, including the BOXED WARNINGs.

Sincerely,

Gil Golden, MD, PhD
Sr. Vice President and Chief Medical Officer