Understanding Antibody Therapy

Treatment for Pediatric High-Risk Neuroblastoma

UNITUXIN® (dinutuximab) INJECTION, FOR INTRAVENOUS USE

Indication

Unituxin is used to treat children with high-risk neuroblastoma who have had some success with prior first-line treatments. Granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA) are part of the treatment regimen with Unituxin.

Important Safety Information for Unituxin

Boxed WARNING

- Serious Infusion Reactions
  - **Unituxin can cause serious and potentially life-threatening infusion reactions. These include excess fluid in tissue, noisy or difficult breathing, a feeling of narrowing in the throat, rash, and low blood pressure.**
  - **Tell your healthcare professional right away if you notice any of the following on the day of, or the day after, the infusion: facial or lip swelling, rash, difficulty breathing, lightheadedness, or dizziness. Patients who experience severe infusion reactions should stop receiving treatment with Unituxin.**
- Neurotoxicity
  - **Unituxin causes serious neurologic adverse reactions including severe neuropathic pain (nerve pain) and peripheral neuropathy (weakness, pain and/or numbness in hands, feet, legs or arms).**
  - **Severe neuropathic pain occurs in the majority of patients. Pain medication given prior to, during, and for 2 hours following treatment can help manage the pain.**
  - **Tell your healthcare professional about severe or worsening pain and signs and symptoms of neuropathy such as numbness, tingling, burning, or weakness experienced during treatment with Unituxin. Depending on the severity of pain, patients may need to stop treatment.**

CONTRAINDICATIONS

Patients who are allergic to dinutuximab should not take Unituxin.

WARNINGS AND PRECAUTIONS

Serious Infusion Reactions

- In a clinical study, 35 (26%) patients taking Unituxin experienced severe (Grade 3 or 4) infusion reactions. Serious infusion reactions included swelling of the face and upper airway, difficult or abnormal breathing, bronchospasm, rash and hives, and low blood

Important Safety Information for Unituxin (continued)

pressure. Urgent intervention included blood pressure support, bronchodilator therapy, corticosteroids, infusion rate reduction, infusion interruption, or permanent discontinuation of Unituxin.

- Infusion reactions generally happen during or within 24 hours after treatment with Unituxin. Tell your healthcare professional right away if you notice any signs or symptoms of serious infusion reactions, including facial or lip swelling, rash, difficulty breathing, lightheadedness, or dizziness, that occur during or within 24 hours following infusion. Your healthcare professional will decide whether treatment should be stopped temporarily or permanently.

Neurotoxicity

- ***Pain:***
  - Your healthcare professional will administer medication before, during, and after treatment to help manage pain. Tell your healthcare professional right away about any severe or worsening pain.
  - In a clinical study, 114 (85%) patients taking Unituxin experienced pain despite pre-treatment with pain medicine including morphine sulfate infusion. Severe (Grade 3) pain occurred in 68 (51%) patients taking Unituxin compared to 5 (5%) patients who were not taking Unituxin. Pain typically occurred during the Unituxin infusion and was most commonly reported as stomach pain, generalized pain, pain in the arms or legs, back pain, nerve pain, muscle and bone pain of the chest, and joint pain.
  - If severe pain is experienced, your healthcare professional may reduce the speed at which Unituxin is given. Unituxin may be stopped if pain is not adequately controlled through medical intervention.
- ***Peripheral Neuropathy:***
  - Symptoms of neuropathy (may include numbness, tingling, burning), or weakness. Report any signs or symptoms of neuropathy immediately to your healthcare provider.
  - In a clinical study, severe (Grade 3) peripheral sensory neuropathy occurred in 2 (1%) patients and severe peripheral motor neuropathy occurred in 2 (1%) patients taking Unituxin compared to zero patients who were not taking Unituxin.
  - Treatment with Unituxin may need to be permanently discontinued in patients with Grade 2 peripheral motor neuropathy, Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks, or Grade 4 sensory neuropathy.

Important Safety Information for Unituxin (continued)

- ***Neurological Disorders of the Eye:***
  - Neurological disorders of the eye can be serious. Tell your healthcare professional immediately if you experience blurred vision, sensitivity to light, drooping of the upper eyelid, double vision, optic disc swelling, or fixed or unequal pupil size as these can be signs and symptoms of a neurological disorder of the eye. Patients who experience neurological disorders of the eye may need to have the Unituxin dose reduced or permanently stopped.
  - In clinical studies, neurological disorders of the eye experienced by 2 or more patients treated with Unituxin included blurred vision, sensitivity to light, dilated pupils, an inability to move the eyelid, fixed or unequal pupils, optic nerve disorder, drooping of the eyelid, and swelling.
- ***Prolonged Urinary Retention:***
  - Urinary retention (inability to completely empty the bladder) that persists for weeks to months after stopping opioids has occurred in patients treated with Unituxin. Report to your healthcare provider persistent urinary retention that does not resolve after having stopped opioid therapy. If you experience prolonged urinary retention, your healthcare professional will decide whether treatment should be stopped.
- ***Transverse Myelitis:***
  - Transverse myelitis has occurred in patients treated with Unituxin. Symptoms may include weakness, tingling or burning sensation, reduced sensation, or inability to control urine. Report signs or symptoms of transverse myelitis immediately to your healthcare provider. Your healthcare professional will determine if you have transverse myelitis and stop treatment as necessary.
- ***Reversible Posterior Leukoencephalopathy Syndrome (RPLS):***
  - RPLS is swelling in the back part of the brain. It has occurred in patients treated with Unituxin. Symptoms may include severe headache, high blood pressure, change in vision, feeling drowsy or tired, or seizures (fits). Report signs or symptoms immediately to your healthcare provider. Unituxin may be stopped in patients with signs and symptoms of RPLS.

Capillary Leak Syndrome

- Capillary leak syndrome is a potentially life-threatening condition in which fluid and proteins leak out of tiny blood vessels and flow into surrounding tissue. This leads to dangerously low blood pressure. If severe capillary leak syndrome is experienced, the speed at which Unituxin is given may need to be interrupted, reduced, or permanently stopped.

Important Safety Information for Unituxin (continued)

- Signs and symptoms of capillary leak syndrome include swelling of the arms, legs, and other parts of the body; shock; lightheadedness; weakness; fatigue; nausea; and rapid drop in blood pressure. Immediately report any signs or symptoms of capillary leak syndrome to your healthcare professional.
- In a clinical study, severe (Grades 3 to 5) capillary leak syndrome occurred in 31 (23%) patients taking Unituxin and in no patients who were not taking Unituxin.

Low Blood Pressure

- In a clinical study, 22 (16%) patients taking Unituxin experienced severe (Grade 3 or 4) low blood pressure. Fluids will be given by your healthcare professional prior to treatment with Unituxin. Blood pressure should be watched closely during Unituxin treatment. Tell your healthcare professional right away if you experience any changes in breathing, dizziness or lightheadedness, fainting, or dehydration (symptoms may include unusual thirst, urinating less often than usual, dark colored urine, dry skin, or tiredness). Patients who get low blood pressure may need to have the speed at which Unituxin is given reduced or permanently stopped.

Infection

- In a clinical study, 17 (13%) patients experienced severe (Grade 3 or 4) bacteremia that required urgent intervention, and 24 (18%) patients experienced sepsis. Closely monitor for signs and symptoms of systemic infection such as fever or tiredness. Tell your healthcare professional if you notice any signs of an infection.
- Patients who develop systemic infection will need to temporarily stop treatment with Unituxin until the infection resolves.

Bone Marrow Suppression

- Patients taking Unituxin may have slow blood clotting. This is due to a lowering of the number of platelets in the blood. Unituxin may also cause low red blood cell count (anemia) and low white blood cell count. This may make patients more likely to develop an infection.
- In a clinical study, severe (Grade 3 or 4) platelet deficiency (39% vs. 25%), low red blood cell count (34% vs. 16%), low white blood cell count (34% vs. 13%), and fever along with a low white blood cell count (4% vs. 0 patients) occurred more commonly in patients who were taking Unituxin than in patients who were not taking Unituxin.

Important Safety Information for Unituxin (continued)

Electrolyte Abnormalities

- In a clinical study, electrolyte abnormalities occurring in at least 25% of patients who received Unituxin included low levels of sodium, low levels of potassium, and low levels of calcium in the bloodstream. Your healthcare professional will monitor these levels. Tell your healthcare professional about any seizures; a feeling that the heart is beating too hard or too fast, skipping a beat, or fluttering; or muscle cramping.

Atypical Hemolytic Uremic Syndrome

- Patients taking Unituxin may experience kidney problems, electrolyte abnormalities, low red blood cell count, or high blood pressure. Patients who experience these side effects may need to permanently stop treatment with Unituxi n. Tell your healthcare professional about any fatigue, dizziness, fainting, extreme skin paleness, swelling, less urine output than normal, or blood in the urine.

Tell your healthcare professional if you are pregnant before taking Unituxin.

- Unituxin may cause harm to an unborn child. Women who are taking Unituxin should use effective birth control measures during treatment and for 2 months after the last dose of Unituxin.

COMMON SERIOUS ADVERSE REACTIONS

The following is a list of the most common serious adverse reactions seen in 5% or more of patients taking Unituxin:

- Infections
- Infusion reactions
- Low levels of potassium in the blood
- Low blood pressure
- Pain
- Fever
- Capillary leak syndrome (a potentially life-threatening condition in which fluid and proteins leak out of tiny blood vessels and flow into surrounding tissue, leading to dangerously low blood pressure)

COMMON ADVERSE REACTIONS

The following is a list of the most common adverse reactions seen in 25% or more of patients taking Unituxin:

- Pain
- Fever
- Slow blood clotting

Important Safety Information for Unituxin (continued)

- Reduced ability to fight infections
  (low levels of white blood cells of various kinds)
- Infusion reactions
- Low blood pressure
- Low levels of sodium in the blood
- Increased levels of the enzyme alanine aminotransferase in the blood
- Low red blood cell count
- Vomiting
- Diarrhea
- Low levels of potassium in the blood
- Capillary leak syndrome
- Hives
- Low levels of albumin in the blood
- Increased levels of the enzyme aspartate aminotransferase
- Low levels of calcium in the blood

The following side effects have also been observed in patients taking Unituxin after approval: prolonged urinary retention (inability to completely empty the bladder), transverse myelitis, and reversible posterior leukoencephalopathy (swelling in the back part of the brain).

Tell your healthcare professional about any side effect seen during treatment with Unituxin. These are not all the possible side effects of Unituxin.

For more information, talk to your healthcare professional.

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.

UTXISIdtcMAR17

Table of Contents

As your child begins the next phase of treatment for high-risk pediatric neuroblastoma, you probably have many questions.

This book can provide answers to some of those questions, as well as connect you with resources, information, and support that can help you navigate the journey ahead.

This book is intended for informational purposes and is not intended as treatment advice. It is not meant to replace conversations with your child's healthcare team. You should reach out to them with any questions you have regarding your child's treatment. Your child's healthcare team is your main source of information about your child's care and treatment.

Selected Important Safety Information for Unituxin

CONTRAINDICATIONS
Patients who are allergic to dinutuximab should not take Unituxin.

Please see complete Important Safety Information on pages 2 to 7 and Full Prescribing Information, including Boxed WARNING, for Unituxin in the brochure pocket.

Unituxin®
(dinutuximab)
Injection

Chapter 1

Understanding the Body's Immune System

The Immune System Protects and Defends the Body

Before we talk about antibody therapy, let's review how the body's immune system works.

The immune system is made up of an army of many different cells that work together to protect the body from getting sick.

In a healthy body, the immune system targets and helps to eliminate threats.

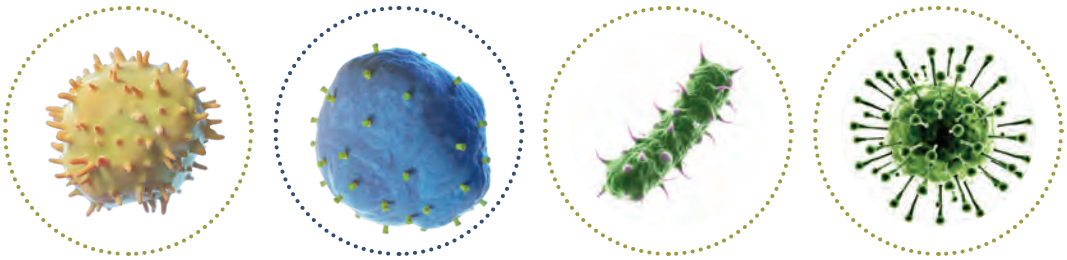
Threats can come in many forms, like bacteria or viruses. Sometimes, the body's own cells change and become harmful.

Cancer is an example of this, where either because of genetic or environmental causes, normal cells become harmful. Sometimes they live longer than healthy cells, and can multiply quickly.

Selected Important Safety Information for Unituxin

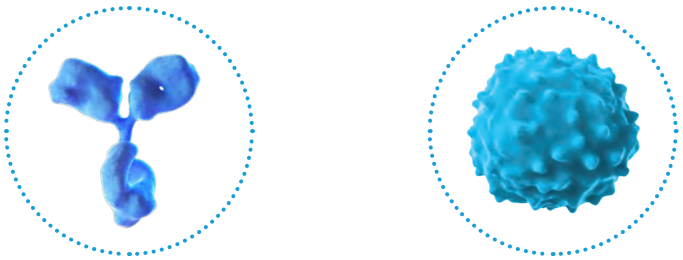
Low Blood Pressure

- In a clinical study, 22 (16%) patients taking Unituxin experienced severe (Grade 3 or 4) low blood pressure. Fluids will be given by your healthcare professional prior to treatment with Unituxin. Blood pressure should be watched closely during Unituxin treatment. Tell your healthcare professional right away if you experience any changes in breathing, dizziness or lightheadedness, fainting, or dehydration (symptoms may



Abnormal Cell | Neuroblastoma Tumor Cell | Bacteria | Virus

Foreign/Enemy Cells



Antibody | White Blood Cell

Immune System

include unusual thirst, urinating less often than usual, dark colored urine, dry skin, or tiredness). Patients who get low blood pressure may need to have the speed at which Unituxin is given reduced or permanently stopped.

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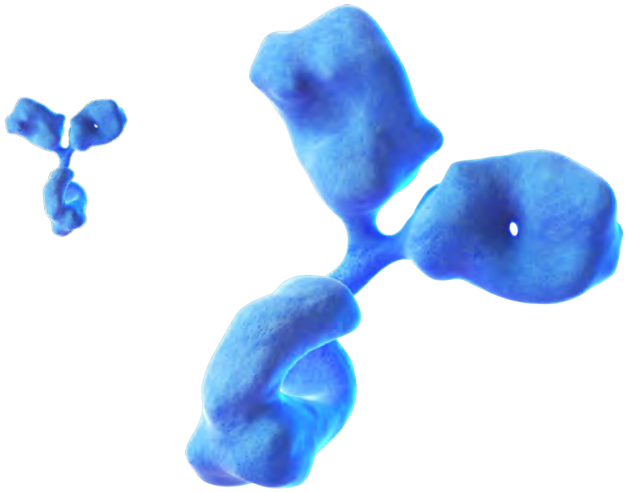
Immune System: Antibodies and White Blood Cells

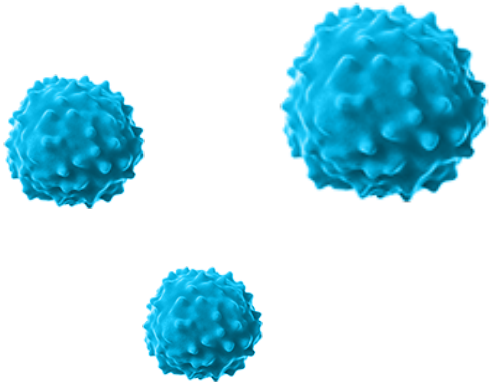
Antibody

Antibodies are "Y-shaped" proteins that act like detectives looking for foreign or abnormal cells in the body.



White Blood Cell

White blood cells patrol the bloodstream to defend the body by attacking and destroying the invading cells.



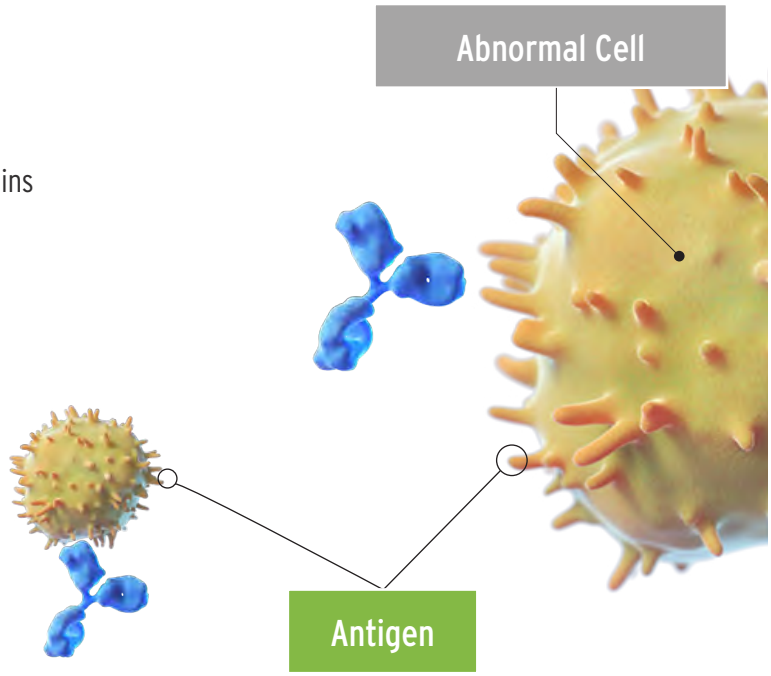
Selected Important Safety Information for Unituxin

Capillary Leak Syndrome

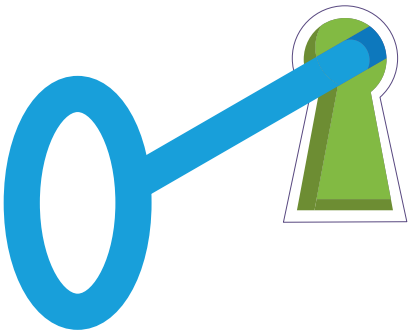
- Capillary leak syndrome is a potentially life-threatening condition in which fluid and proteins leak out of tiny blood vessels and flow into surrounding tissue. This leads to dangerously low blood pressure. If severe capillary leak syndrome is experienced, the speed at which Unituxin is given may need to be interrupted, reduced, or permanently stopped.

Antigen

Cells have proteins on their surface. These proteins are called ANTIGENS.



Each antibody matches a specific antigen much like a key matches a lock.



- Signs and symptoms of capillary leak syndrome include swelling of the arms, legs, and other parts of the body; shock; lightheadedness; weakness; fatigue; nausea; and rapid drop in blood pressure. Immediately report any signs or symptoms of capillary leak syndrome to your healthcare professional.

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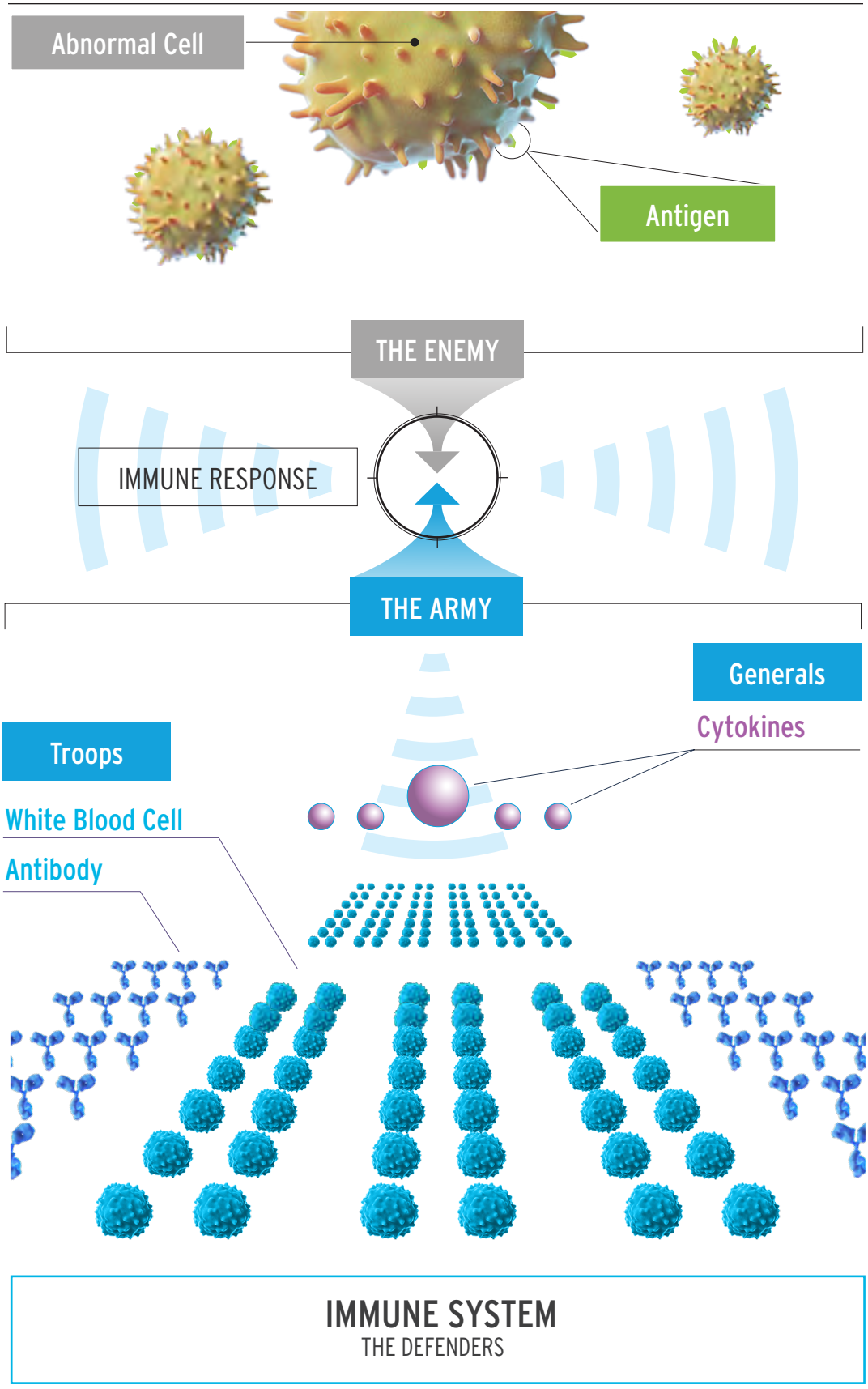

IMMUNE SYSTEM
THE DEFENDERS

The War Between Good Cells and Bad Cells

When antibodies find the antigens on the abnormal cells, they bind (attach) to them.

Once attached, the antibodies can recruit other cells to join the body's immune response.

An immune response is how the body defends itself against the invading foreign cells (enemy cells). It is like an army being called to battle.

In this battle, the foreign cells are the enemy and the body's immune system is the army. The antibodies and white blood cells are some of the army's specialized troops, and the **CYTOKINES** are like the generals that gather and organize the troops. They make sure there are enough troops (white blood cells) to fight the battle and that the troops are communicating with each other.

Definitions

Cytokines: *Proteins that help organize an immune response by gathering white blood cells.*

Selected Important Safety Information for Unituxin

Tell your healthcare professional if you are pregnant before taking Unituxin.

- Unituxin may cause harm to an unborn child. Women who are taking Unituxin should use effective birth control measures during treatment and for 2 months after the last dose of Unituxin.

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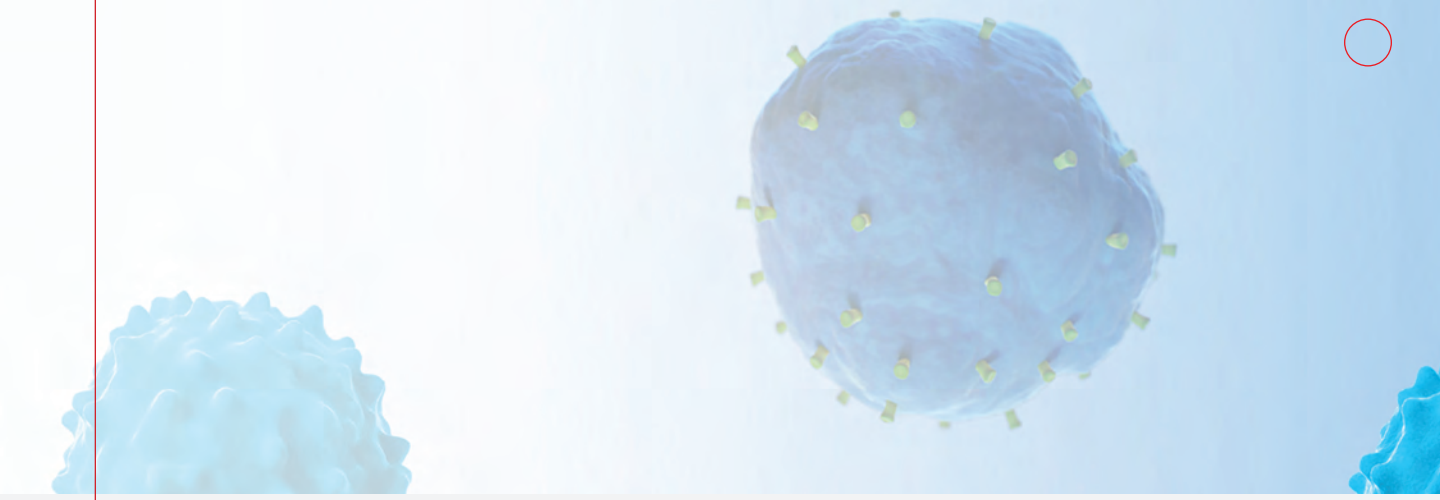
The Immune System Is Affected by Neuroblastoma

- In a child with neuroblastoma, the immune system is weak (immunosuppressed)
- Neuroblastoma cells are also able to hide from the immune system
- If the immune system cannot find the cancer cells, then it cannot make antibodies to destroy them



Bone Marrow Suppression

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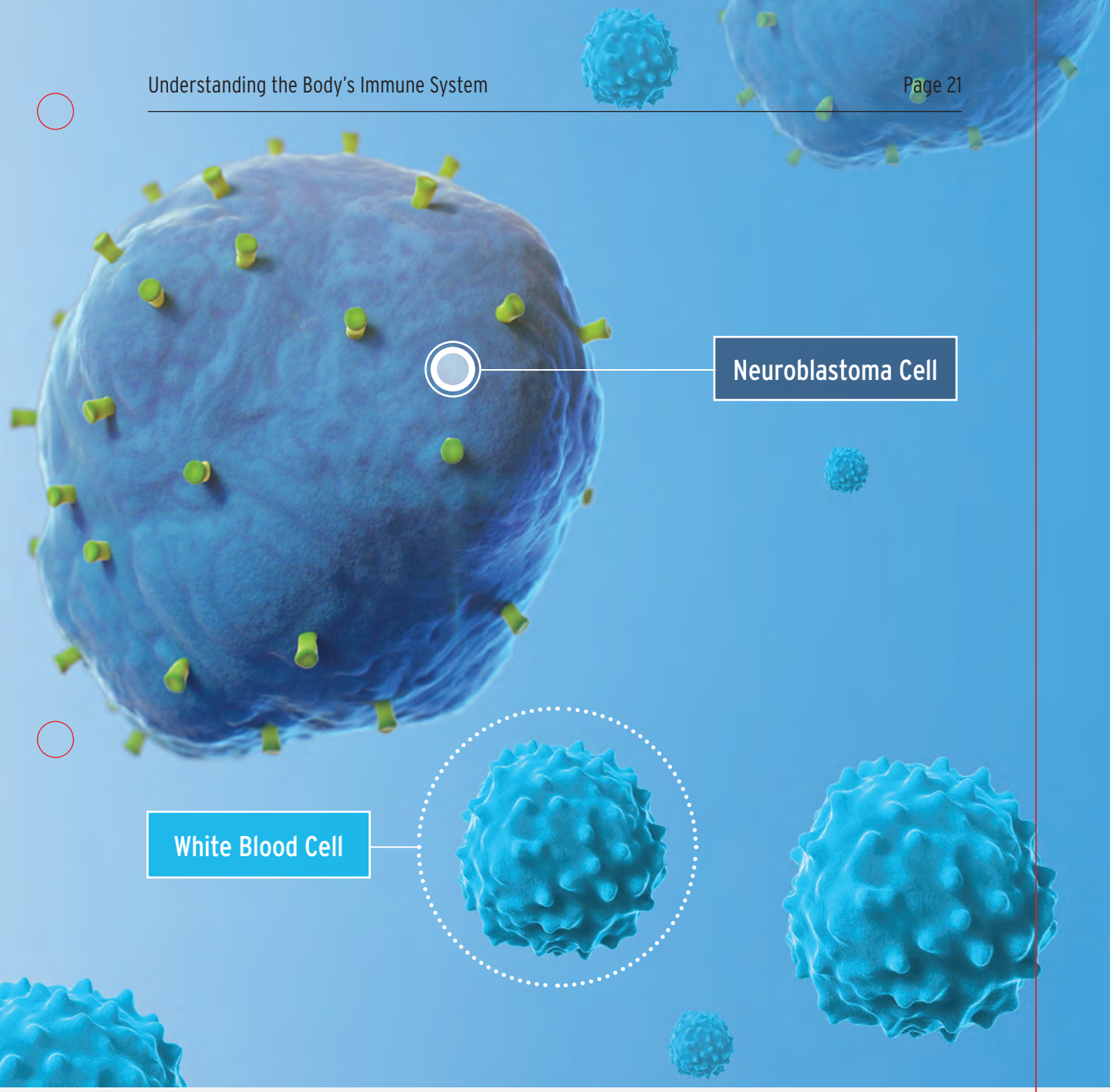

- In a clinical study, severe (Grade 3 or 4) platelet deficiency (39% vs. 25%), low red blood cell count (34% vs. 16%), low white blood cell count (34% vs. 13%), and fever along with a low white blood cell count (4% vs. 0 patients) occurred more commonly in patients who were taking Unituxin than in patients who were not taking Unituxin.

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Injection

Chapter 2

Understanding How Unituxin Works

What Is Unituxin?

Unituxin is a MONOCLONAL ANTIBODY.

Scientists make it in a lab.

It targets the antigen GD2.

Definitions

***Monoclonal antibody**: Immune system protein, made by scientists in a lab, that can be specialized to target different cells.*

- ***Peripheral Neuropathy:***
  - Symptoms of neuropathy (may include numbness, tingling, burning), or weakness. Report any signs or symptoms of neuropathy immediately to your healthcare provider.
  - In a clinical study, severe (Grade 3) peripheral sensory neuropathy occurred in 2 (1%) patients and severe peripheral motor neuropathy occurred in 2 (1%) patients taking Unituxin compared to zero patients who were not taking Unituxin.

What Is GD2?

The **GD2 ANTIGEN** is a protein found in high levels on the surface of neuroblastoma cells.

GD2 is also found on some noncancerous cells in the body (nerve cells and pain fibers).

Selected Important Safety Information for Unituxin

- Treatment with Unituxin may need to be permanently discontinued in patients with Grade 2 peripheral motor neuropathy, Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks, or Grade 4 sensory neuropathy.

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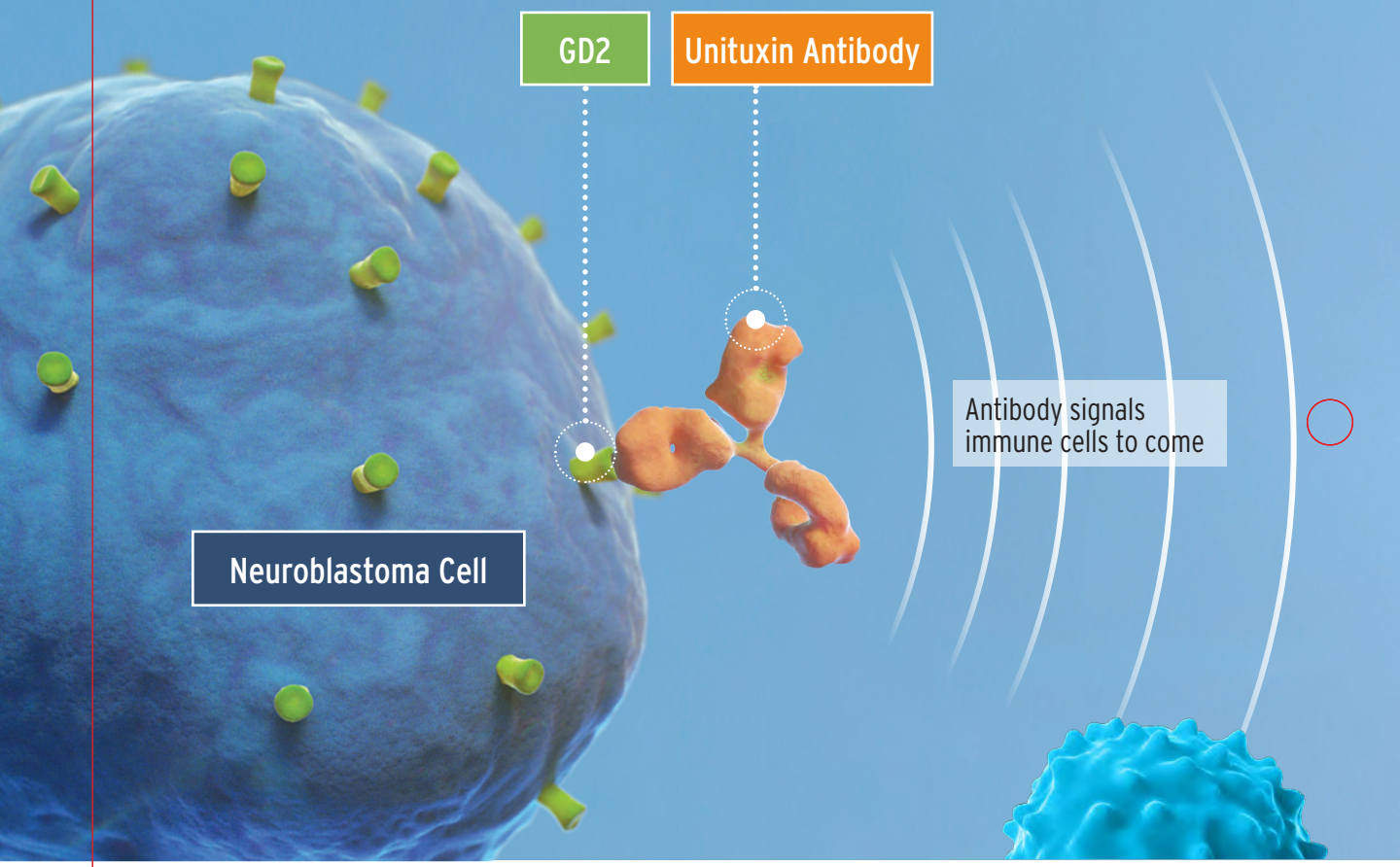
Injection

How Does Unituxin Work?

The Unituxin antibody helps the body find the neuroblastoma cells by attaching to the GD2 antigen found on their cell surface.

Once attached, the antibody sends a signal to the immune system, and white blood cells and other types of immune cells are sent to destroy the neuroblastoma cells.



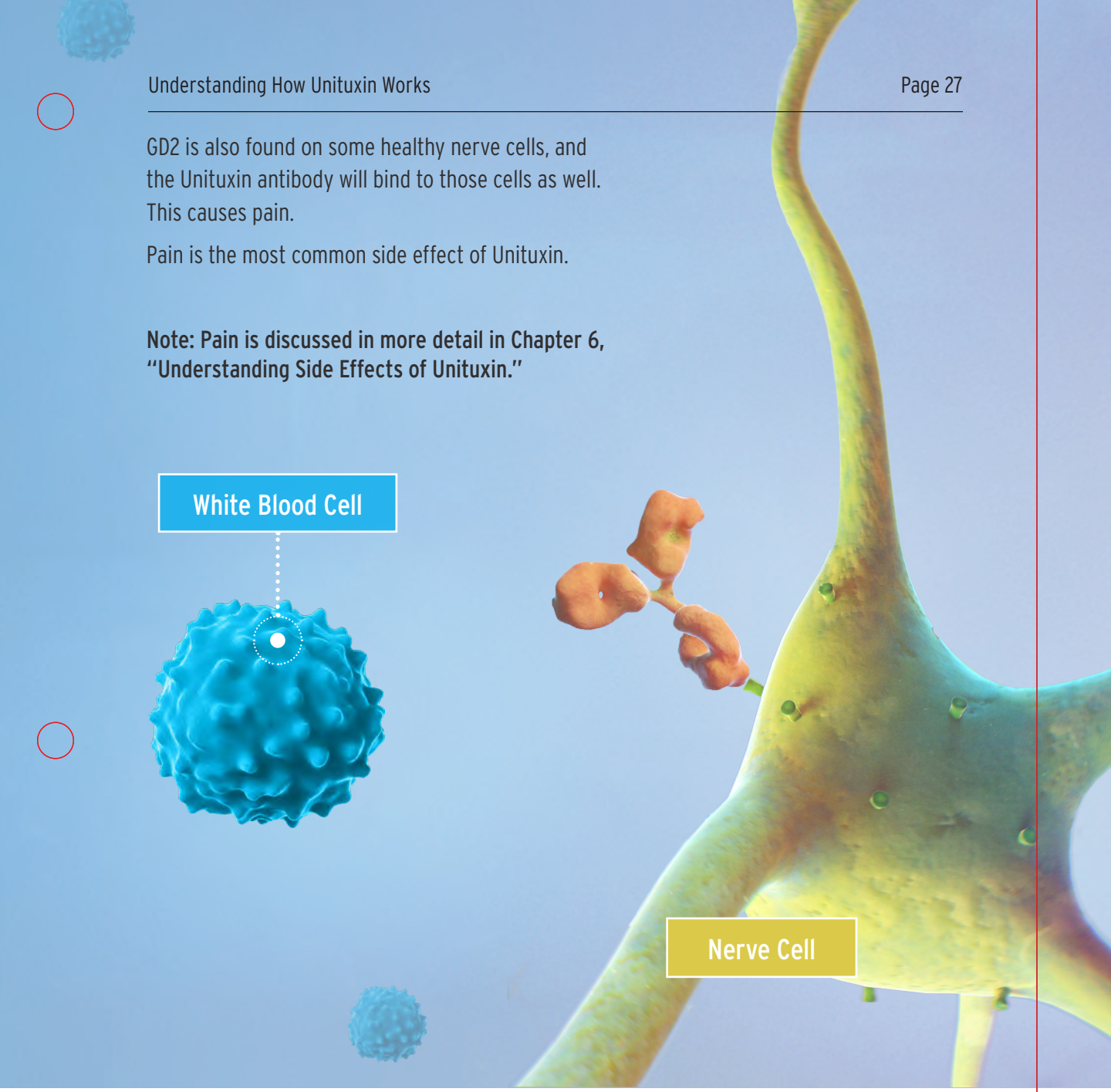
Selected Important Safety Information for Unituxin

- ***Pain:***
  - Your healthcare professional will administer medication before, during, and after treatment to help manage pain. Tell your healthcare professional right away about any severe or worsening pain.
  - In a clinical study, 114 (85%) patients taking Unituxin experienced pain despite pre-treatment with pain medicine including morphine sulfate infusion. Severe (Grade 3) pain occurred in 68 (51%) patients taking Unituxin compared to 5 (5%) patients

GD2 is also found on some healthy nerve cells, and the Unituxin antibody will bind to those cells as well. This causes pain.

Pain is the most common side effect of Unituxin.

Note: Pain is discussed in more detail in Chapter 6, "Understanding Side Effects of Unituxin."



who were not taking Unituxin. Pain typically occurred during the Unituxin infusion and was most commonly reported as stomach pain, generalized pain, pain in the arms or legs, back pain, nerve pain, muscle and bone pain of the chest, and joint pain.

- If severe pain is experienced, your healthcare professional may reduce the speed at which Unituxin is given. Unituxin may be stopped if pain is not adequately controlled through medical intervention.

Chapter 3

Understanding How Unituxin Was Studied

Unituxin Has Been Studied for Over 20 Years in Over 2000 Patients

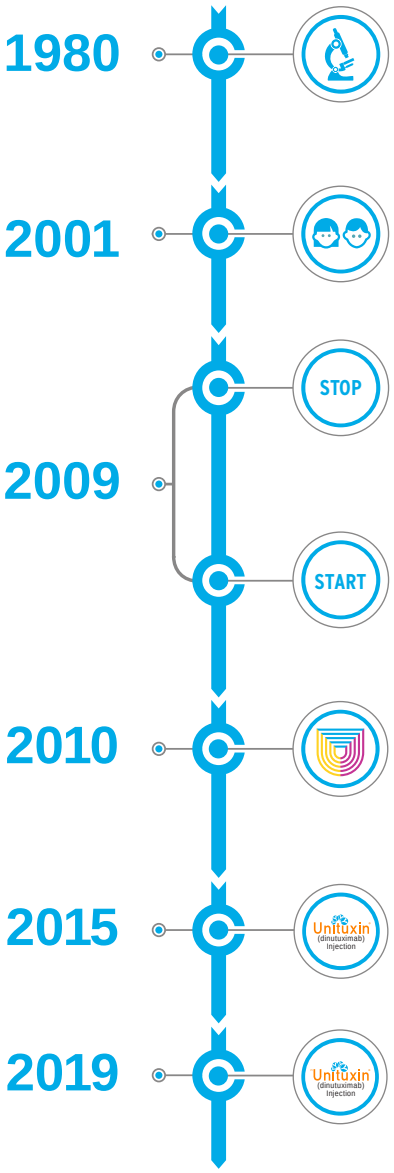
Unituxin (then known as **CH14.18** or chimeric 14.18) was developed by the National Cancer Institute (NCI) in the 1980s.

It was then studied for many more years in multiple clinical trials by the Children's Oncology Group (COG), the world's largest organization devoted exclusively to pediatric cancer research.

Selected Important Safety Information for Unituxin

Serious Infusion Reactions

- In a clinical study, 35 (26%) patients taking Unituxin experienced severe (Grade 3 or 4) infusion reactions. Serious infusion reactions included swelling of the face and upper airway, difficult or abnormal breathing, bronchospasm, rash and hives, and low blood pressure. Urgent intervention included blood pressure support, bronchodilator therapy, corticosteroids, infusion rate reduction, infusion interruption, or permanent discontinuation of Unituxin.



- Infusion reactions generally happen during or within 24 hours after treatment with Unituxin. Tell your healthcare professional right away if you notice any signs or symptoms of serious infusion reactions, including facial or lip swelling, rash, difficulty breathing, lightheadedness, or dizziness, that occur during or within 24 hours following infusion. Your healthcare professional will decide whether treatment should be stopped temporarily or permanently.

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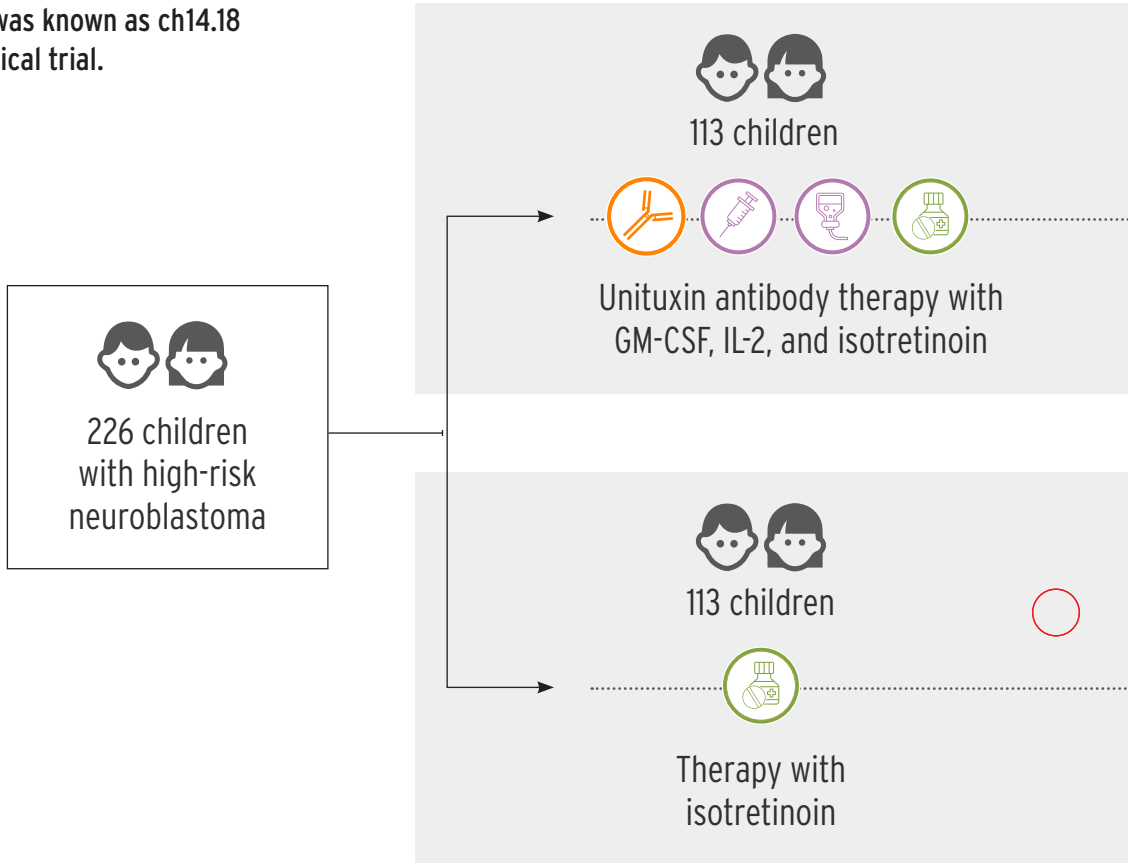
Unituxin® (dinutuximab) Injection

Results of the Children's Oncology Group Clinical Trial, ANBL0032

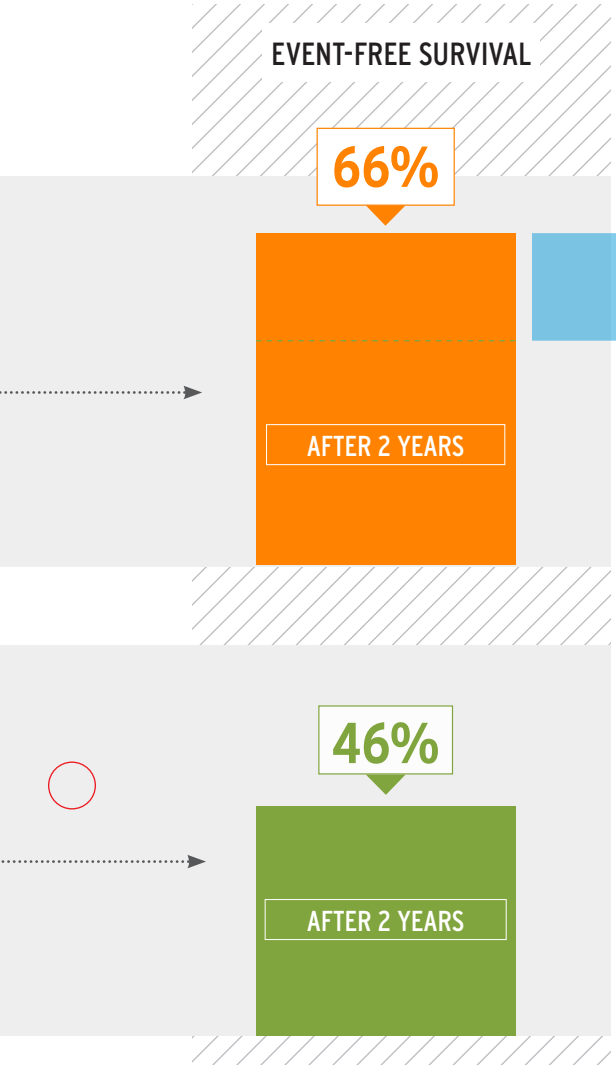
Unituxin was known as ch14.18 in the clinical trial.



Treatment Schedule

Unituxin was given for a total of 5 cycles (Cycles 1-5). Cycles 1, 3, and 5 used Unituxin, GM-CSF, and isotretinoin. Cycles 2 and 4 used Unituxin, IL-2, and isotretinoin. In the last cycle, Cycle 6, isotretinoin was given alone.

- ***Prolonged Urinary Retention:***
  - Urinary retention (inability to completely empty the bladder) that persists for weeks to months after stopping opioids has occurred in patients treated with Unituxin. Report to your healthcare provider persistent urinary retention that does not resolve after having stopped opioid therapy. If you experience prolonged urinary retention, your healthcare professional will decide whether treatment should be stopped.



20% IMPROVEMENT IN EVENT-FREE SURVIVAL

A landmark study published in *The New England Journal of Medicine* in 2010 showed that Unituxin (with GM-CSF, IL-2, and isotretinoin) improved the 2-year event-free survival (EFS) by 20% when compared to isotretinoin alone.

It proved so effective that randomization stopped, and all patients enrolled in the study were given antibody therapy with GM-CSF, IL-2, and isotretinoin.

Definitions

***Event-free survival (EFS)**: A medical research term that defines the amount of time a patient lives without the disease, the disease getting worse, a new cancer developing, or the patient dying while being treated.*

Chapter 4

What to Expect During Antibody Therapy

How Is Unituxin Given?

- Unituxin infusion given through the vein over 10 to 20 hours
- Given daily for 4 days in a row

Some side effects can be related to the rate of the Unituxin infusion.

Your healthcare provider will know how and when to adjust the Unituxin infusion rate if this occurs. You can learn more about side effects in Chapter 5.

Side effects will be discussed in greater detail in the next chapter.

Selected Important Safety Information for Unituxin

Serious Infusion Reactions

- In a clinical study, 35 (26%) patients taking Unituxin experienced severe (Grade 3 or 4) infusion reactions. Serious infusion reactions included swelling of the face and upper airway, difficult or abnormal breathing, bronchospasm, rash and hives, and low blood pressure. Urgent intervention included blood pressure support, bronchodilator therapy, corticosteroids, infusion rate reduction, infusion interruption, or permanent discontinuation of Unituxin.

Pre-medications Given Before the Unituxin Antibody Infusion:

There are many expected side effects with Unituxin antibody therapy.

Your healthcare team will use various medications to help prevent some of these side effects. They include:

- Intravenous fluids bolus
- Medications for allergic reaction such as Benadryl®
- Medications for fever such as Tylenol®
- Strong medications for pain such as morphine
- Additional medications may be used as decided by your child's healthcare team

– Infusion reactions generally happen during or within 24 hours after treatment with Unituxin. Tell your healthcare professional right away if you notice any signs or symptoms of serious infusion reactions, including facial or lip swelling, rash, difficulty breathing, lightheadedness, or dizziness, that occur during or within 24 hours following infusion. Your healthcare professional will decide whether treatment should be stopped temporarily or permanently.

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Unituxin® (dinutuximab) Injection

Hospital Admission

Your child will be admitted to the hospital either the day before or early in the morning on the day they start their antibody **INFUSION**.

This is done so that the **HEALTHCARE TEAM** can perform any necessary blood work and make sure the antibody infusion starts on time.

Each hospital is a little different. Find out from your child's healthcare team what day your child will be admitted for each treatment cycle.

Selected Important Safety Information for Unituxin

Infection

- In a clinical study, 17 (13%) patients experienced severe (Grade 3 or 4) bacteremia that required urgent intervention, and 24 (18%) patients experienced sepsis. Closely monitor for signs and symptoms of systemic infection such as fever or tiredness. Tell your healthcare professional if you notice any signs of an infection.
- Patients who develop systemic infection will need to temporarily stop treatment with Unituxin until the infection resolves.

Length of Stay in the Hospital

The antibody infusion is given for 4 days in a row. The amount of time your child will spend in the hospital will depend on how they react to treatment.

Talk with your healthcare team about how many days they expect your child will need to stay in the hospital.

Definitions

Healthcare team: *The team of experts caring for your child in the hospital (doctors, nurse practitioners, nurses, etc)*

Chapter 5

Understanding Side Effects of Unituxin

Common Side Effects of Unituxin

The following is a list of the most common adverse reactions seen in 25% or more of patients taking Unituxin:

- Pain (85%)
- Fever (72%)
- Low levels of platelets in blood (66%)
- Low levels of lymphocytes (62%)
- Infusion reactions (60%)
- Low blood pressure (60%)
- Low levels of sodium in the blood (58%)
- Increased levels of the enzyme alanine aminotransferase in the blood (56%)
- Low red blood cell count (51%)
- Vomiting (46%)
- Diarrhea (43%)
- Low levels of potassium inthe blood (43%)
- Capillary leak syndrome (40%)
- Low levels of neutrophils (39%)
- Hives (37%)
- Low levels of albumin in the blood (33%)
- Increased levels of the enzyme aspartate aminotransferase (28%)
- Low levels of calcium in the blood (27%)

Some side effects of Unituxin require your child's infusion to be slowed, paused, or even stopped until the side effects have resolved. The Unituxin infusion may have to be permanently discontinued in some cases.

Serious Side Effects of Unituxin

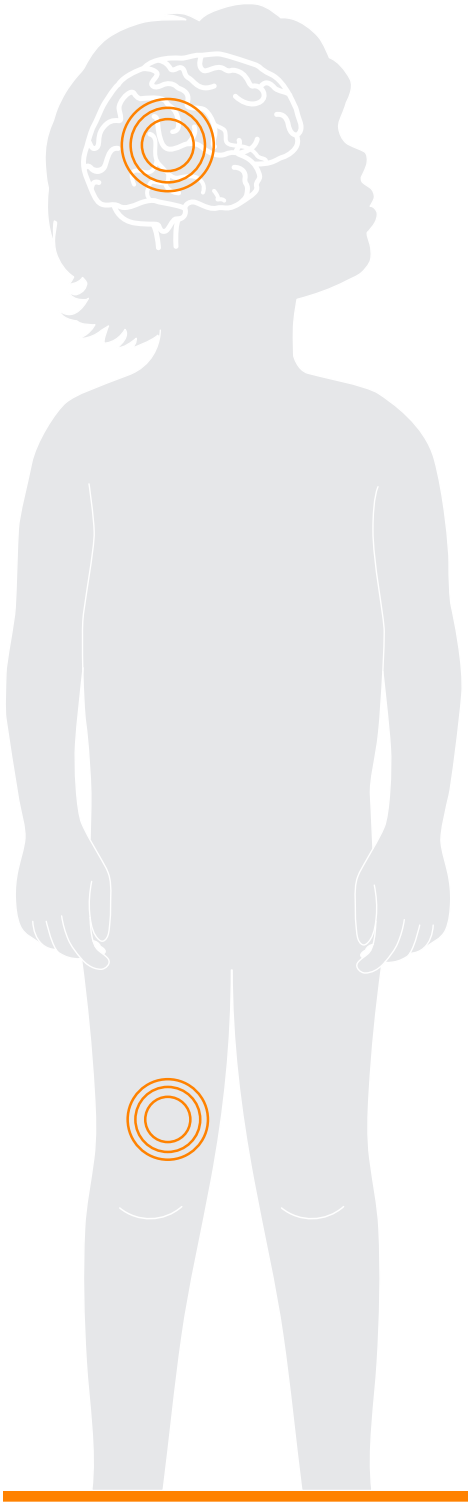
The following is a list of the serious side effects experienced by patients taking Unituxin:

- Neurologic disorders of the eye
- Prolonged urinary retention
- Infection
- Transverse myelitis
- Reversible posterior leukoencephalopathy syndrome (RPLS)
- Atypical hemolytic uremic syndrome

Let's take a closer look!

This is not a complete list of side effects. For a complete list of side effects seen with Unituxin, please see Full Prescribing Information, including Boxed WARNING, for Unituxin in the front of this booklet.

Unituxin® (dinutuximab) Injection



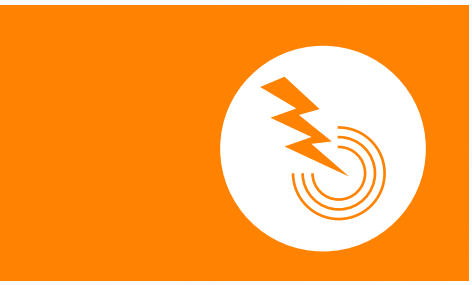
Pain

Pain typically occurred during the Unituxin infusion and was most commonly reported as stomach pain, generalized pain, pain in the arms or legs, back pain, nerve pain, muscle and bone pain of the chest, and joint pain.

85%
of patients had pain during the Unituxin infusion.

The GD2 antigen found on neuroblastoma cells is also found on nerve cells and pain fibers.

When Unituxin binds to GD2 on nerve cells and pain fibers, it causes pain.



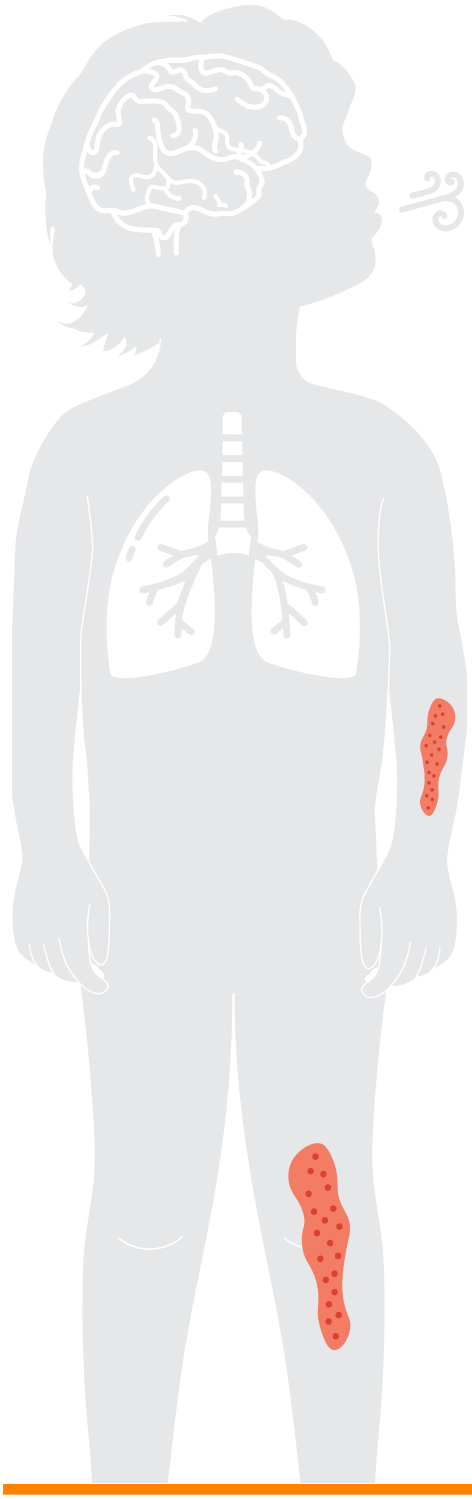
To help lessen the pain, your child will receive pain medicine (such as morphine) continuously during the Unituxin infusion.

Your child's pain will be monitored while the Unituxin is infusing.

Your child may require additional doses of pain medication or an increase in the dose of their pain medication.

If severe pain is experienced, your healthcare professional may reduce the speed at which Unituxin is given. Unituxin may be stopped if pain is not adequately controlled through medical intervention.

It can be very difficult for a child to explain the type of pain they are feeling. As a parent, you know your child best. Speak up and let your healthcare providers know if you notice your child is uncomfortable.



Infusion Reactions

An exaggerated response by the immune system to a foreign substance.

60%
of patients had symptoms of an **INFUSION REACTION**.

1% of patients experienced anaphylaxis.

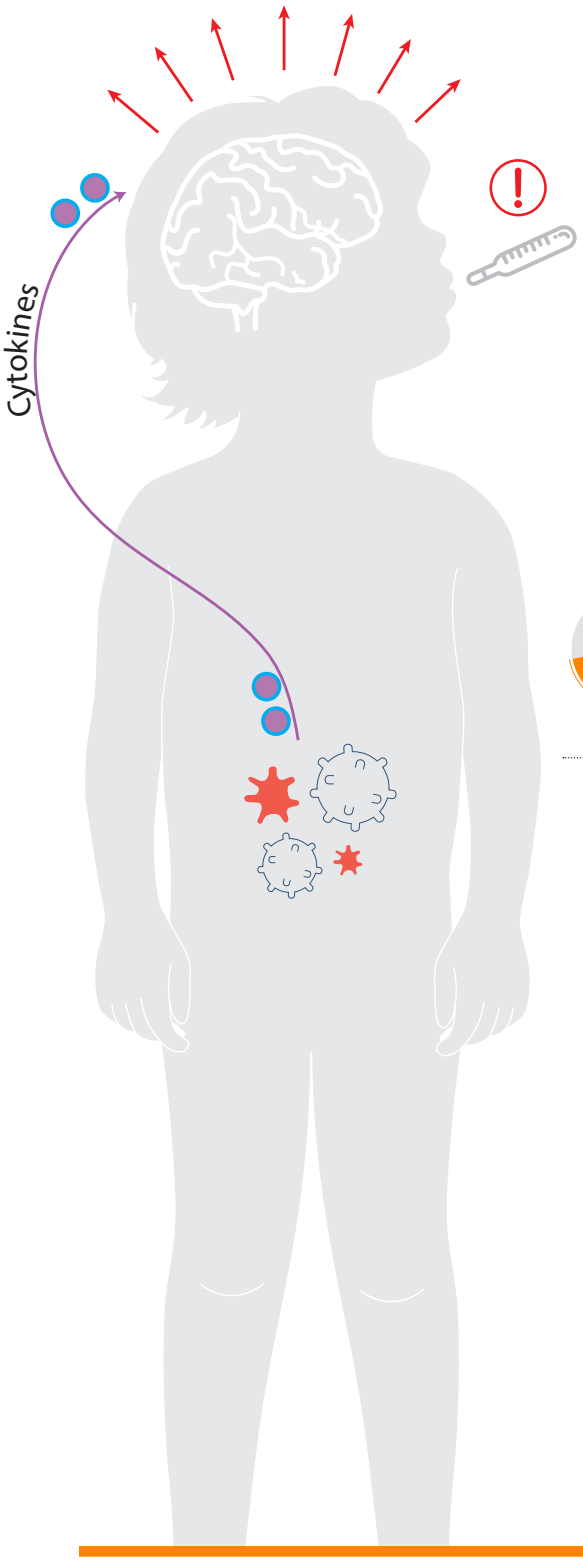
In the clinical trial, infusion reactions were more common when Unituxin was given with IL-2.

Reactions can range from mild to severe. Symptoms may include rashes, hives, cough, wheezing, facial swelling, or anaphylaxis.

Your child will be given medicine (such as Benadryl®) during the infusion to help prevent reactions.

The infusion will be slowed down, stopped, or permanently discontinued if your child develops a serious reaction.

Tell your healthcare providers right away if your child has a rash, is coughing, if their lips or face are swelling, if they are having a hard time breathing, or if you are worried about any other symptoms.



Fever

Fever is a sign that the immune system has been activated and is one of the ways the body defends itself. The body uses cytokines and other proteins to communicate this message to the brain.

72%

72% of patients experienced fever during the Unituxin infusion.

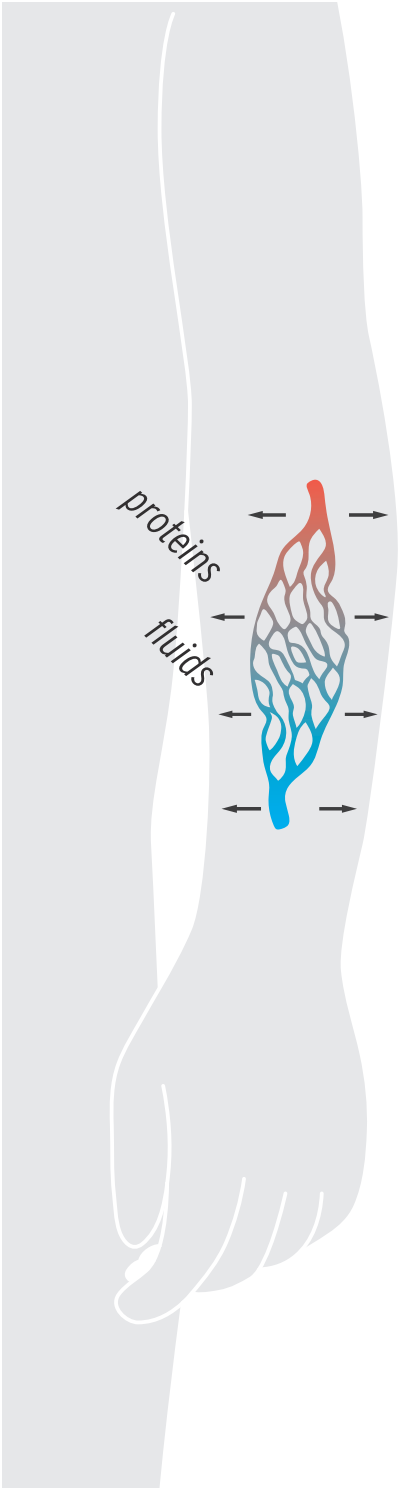
Symptoms of fever may include the skin feeling warm or hot to the touch, sweating, or shivering.

Your child will be given medicine (such as Tylenol®) to control fever during the Unituxin infusion.

Your child's temperature will be checked frequently during the infusion.

Your healthcare providers will follow their hospital guidelines for fever (which may include blood cultures and/or antibiotics).

Tell your healthcare providers right away if your child appears feverish, is sweating, or is shivering.



Capillary Leak Syndrome

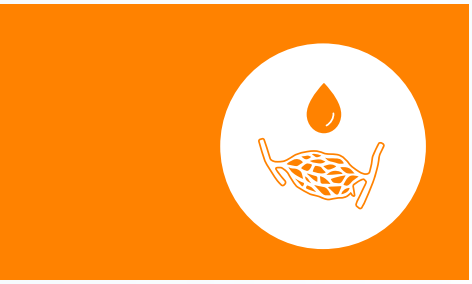
When the immune system is activated and there are high levels of cytokines present, small blood vessels (capillaries) may dilate and leak fluid into surrounding tissues.

40%
of patients who received Unituxin developed **CAPILLARY LEAK SYNDROME**.

In the clinical trial, capillary leak syndrome was more common when Unituxin was given with IL-2.

Capillary leak syndrome develops slowly over time, but can be life-threatening.

Symptoms may include swelling in hands and feet, puffiness around the eyes, weight gain, decreased urination, concentrated urine, and low blood pressure.

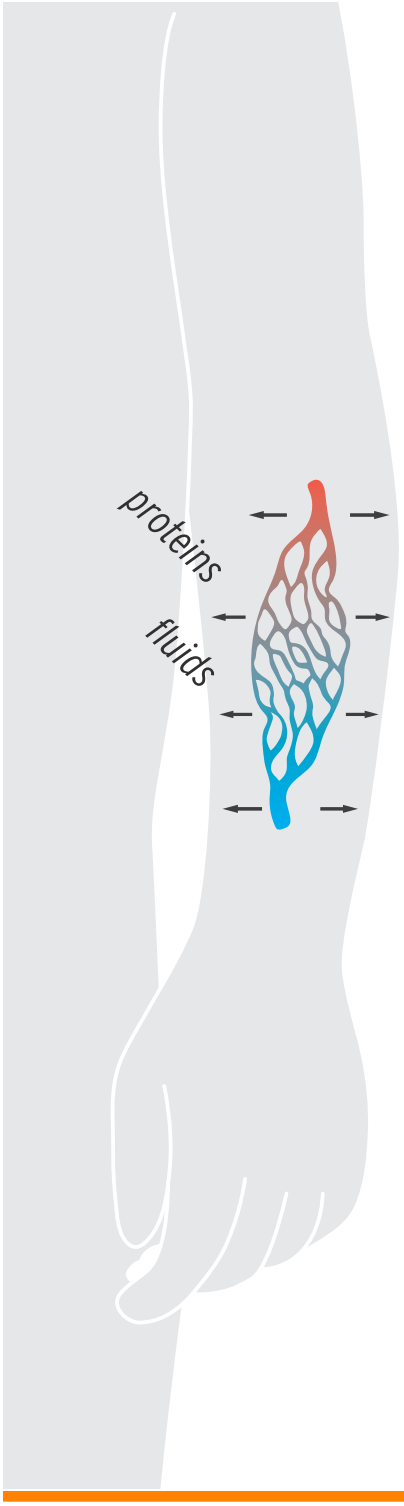


Your child's vital signs, weight, fluid intake, and urine output will be monitored closely.

The infusion may be slowed down or stopped if your child develops moderate-to-severe capillary leak.

Make sure to always tell the nurse how much your child drinks and how much urine they produce.

Tell your healthcare providers if you notice your child has any swelling, is not urinating, or if they feel lightheaded, dizzy, or weak.



Low Blood Pressure

Low blood pressure (HYPOTENSION) happens when the pressure within the blood vessels is less than normal.

60%
of patients receiving Unituxin experienced low blood pressure.

Low blood pressure can be a direct side effect of the Unituxin infusion. It can also be a late sign of capillary leak syndrome.

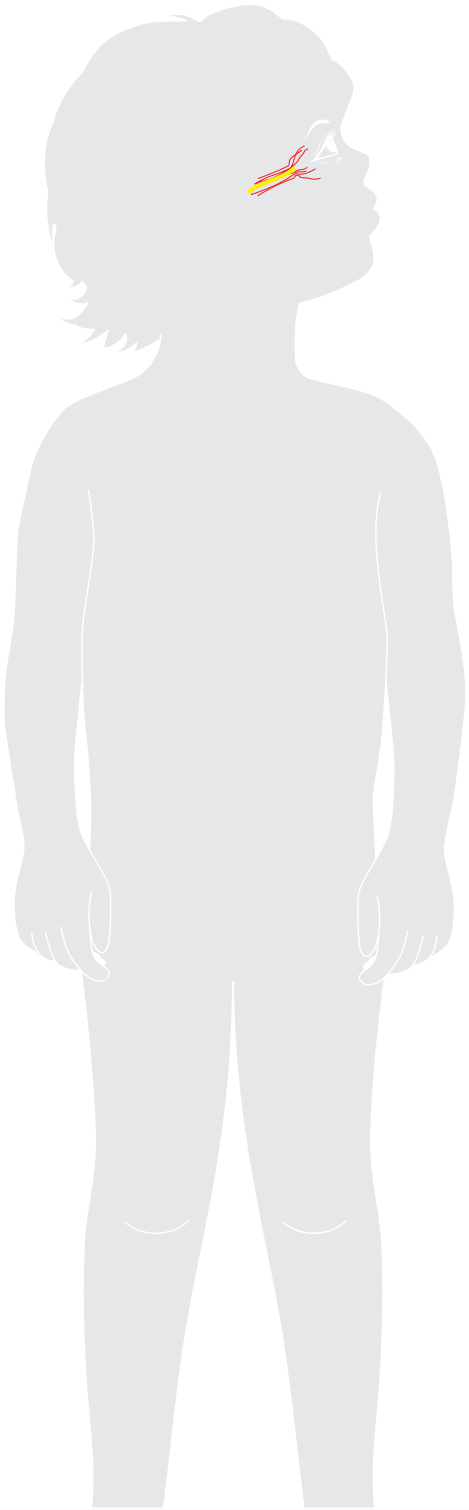
Symptoms of low blood pressure may include dizziness, lightheadedness, nausea, or fainting.

Your child will be given intravenous fluids prior to the start of Unituxin to help prevent low blood pressure.

Your child's blood pressure will be checked frequently during the Unituxin infusion.

The Unituxin infusion may be slowed down or stopped if your child develops low blood pressure.

Tell your healthcare providers if your child is dizzy, lightheaded, or nauseous.



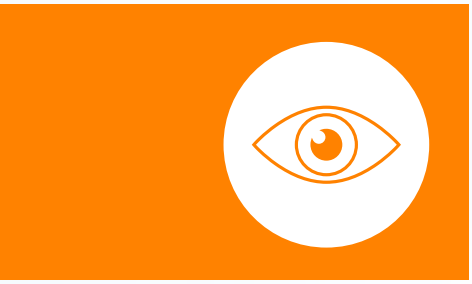
Neurological Disorders of the Eye

Visual changes can occur when a child is receiving Unituxin.

Fewer than 10%
of patients receiving Unituxin experienced visual changes.

In some patients, these visual changes did not resolve.

Symptoms may include blurry vision, double vision, sensitivity to light, dilated pupils, unequal pupils, or drooping of the eyelid.



Your child's eyes will be monitored closely during the infusion of Unituxin.

The infusion will be permanently stopped if your child develops vision loss.

Tell your healthcare providers right away if your child has any change in vision or vision loss.

Chapter 6

Tips for Parents & Caregivers

As you adjust to the routine of antibody therapy, you may find new and improved ways to help manage the journey. Below are a few tips that other families have found to be useful.

Speak Up

As a parent or caregiver, no one knows your child better than you. You have an important role in helping the healthcare team manage your child's care. Always pay close attention to any changes in your child's condition, and tell your healthcare team immediately if you notice any changes or are concerned.

Use a Calendar

Each cycle of antibody therapy is a little different. Following a treatment calendar can help you keep track of the busy schedule. Understanding the order of events in each cycle can help you to plan ahead before clinic appointments and hospital admissions. It may also help you to anticipate when you may need to take time off work and schedule childcare for siblings.

Keep a Journal

It may be helpful to record notes about medications and other information to help you better understand the regimen and your child's progress during each cycle. Please go to *Unituxin.com* where you can download and print a caregiver journal that can be used for notes.

Don't Forget to Fill Prescriptions

It is important to be sure that your child has an adequate supply of home medications prior to leaving the hospital or your clinic appointment. Ask your healthcare provider or pharmacist if you have any questions about your child's medications.

Take Care of Your Family

It is not uncommon for siblings to have a difficult time understanding why their brother or sister is sick. Siblings can often feel forgotten and may need additional attention and support because the child with cancer requires so much focus. For more information on helping siblings cope, you can visit the SuperSibs page of the Alex's Lemonade Stand website at *www.alexslemonade.org/campaign/supersibs3.*

Ask for Help

Caring for a child with cancer can affect you physically as well as emotionally. It is important to reach out to friends and family for support during this time. Be specific about what you need. Sometimes help with chores can be just as valuable as a listening ear.

Chapter 7

Parent & Caregiver Resources

Links, Resources, & Further Reading

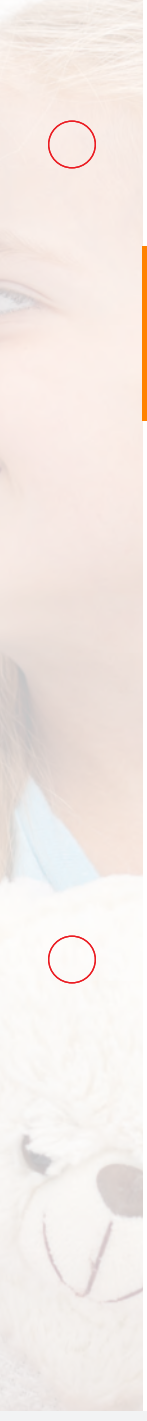
By reaching out to organizations and support groups, you can find parents and families who have also traveled the neuroblastoma journey. They can provide useful tips and information to help you navigate your child's treatment journey.

Children's Neuroblastoma Cancer Foundation

Children's Neuroblastoma Cancer Foundation (CNCF)
www.cncfhope.org

The Children's Neuroblastoma Cancer Foundation is a source of information and resources on neuroblastoma.

United Therapeutics Corporation is not affiliated with any of these organizations. The information provided by these organizations is meant for informational purposes only. It is not meant to replace your child's healthcare team's medical advice. For more information about Unituxin, visit www.unituxin.com/caregiver.



Alex's Lemonade Stand Foundation for Childhood Cancer
www.alexslemonade.org

Alex's Lemonade Stand SuperSibs
www.alexslemonade.org/campaign/supersibs

Association of Cancer Online Resources (Neuroblastoma Group)
www.acor.orglistservs/join288

Arms Wide Open Childhood Cancer Foundation
www.awoccf.org

Band of Parents
www.bandofparents.org

Children's Neuroblastoma Cancer Foundation
www.cncfhope.org

Kids' Cancer Research Foundation
www.endkidscancer.org

Neuroblastoma Consortium
www.neuroblastomaconsortium.org

Solving Kids' Cancer
www.solvingkidscancer.org

The EVAN Foundation
www.theevanfoundation.org

The NANT Foundation (New Approaches to Neuroblastoma Therapy)
www.nant.org

The Children's Oncology Group (COG)
https://childrensoncologygroup.org/index.php/patients-and-families

Clinical Trials
https://clinicaltrials.gov/ct2/results?term=neuroblastoma&Search=Search

For more information about Unituxin, visit www.unituxin.com/caregiver.

Please see complete Important Safety Information on pages 2 to 7 and Full Prescribing Information, including Boxed WARNING, for Unituxin in the brochure pocket.

Unituxin® (dinutuximab) Injection

Chapter 8

Glossary of Commonly Used Terms

Glossary

Antibody: *A Y-shaped protein that helps the immune system find foreign or abnormal cells.*

Antigen: *Protein on cells that acts as a marker and can also cause an immune response. These proteins are targeted by antibodies.*

Blood pressure: *The strength of your blood pushing against the sides of your blood vessels.*

Capillary leak syndrome: *A condition in which fluid and proteins leak out of tiny blood vessels and flow into surrounding tissues.*

Ch14.18 or chimeric 14.18: *The name used for Unituxin during the clinical trial.*

Cytokines: *Proteins that help organize an immune response by gathering white blood cells.*

Event-free survival: *A medical research term that defines the amount of time a patient lives without the disease, the disease getting worse, a new cancer developing, or the patient dying while being treated.*

GD2 antigen: *A protein found on the surface of neuroblastoma cells and some noncancerous cells (nerve cells and pain fibers). GD2 is short for glycolipid disialoganglioside.*

GM-CSF: *Granulocyte-macrophage colony-stimulating factor, a drug (cytokine) that boosts the number of white blood cells.*

Hypotension: *Low blood pressure.*

Healthcare team: *The team of experts caring for your child in the hospital (doctors, nurse practitioners, nurses, etc).*

IL-2: *Interleukin-2, a type of drug (cytokine) that activates and boosts the number of white blood cells.*

Infusion: *The administration of a medicine into the bloodstream.*

Infusion rate: *The speed at which an infusion is set to deliver medicine.*

Infusion reaction: *A state of exaggerated immune response to a foreign substance or medication.*

Isotretinoin (ISOT), also called retinoic acid (RA): *A pill that encourages neuroblastoma cells to mature.*

Monoclonal antibodies: *Immune system proteins, made by scientists in a lab, that can be specialized to target different cells.*

Neuroblastoma: *A cancer found in developing nerve cells.*

United Therapeutics
ONCOLOGY

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use UNITUXIN safely and effectively. See Full Prescribing Information for UNITUXIN.

UNITUXIN® (dinutuximab) injection, for intravenous use
Initial U.S. Approval: 2015

WARNING: SERIOUS INFUSION REACTIONS AND NEUROTOXICITY

See full prescribing information for complete boxed warning.

- **Infusion Reactions: Life-threatening infusion adverse reactions occur with Unituxin. Administer required prehydration and premedication. Immediately interrupt for severe infusion reactions and permanently discontinue for anaphylaxis *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.1)]*.**
- **Neurotoxicity: Unituxin causes severe neuropathic pain. Administer intravenous opioid prior to, during, and for 2 hours following completion of the Unituxin infusion. Severe peripheral sensory neuropathy ranged from 2% to 9% in patients with neuroblastoma. Severe peripheral motor neuropathy has also been reported. Discontinue for severe unresponsive pain, severe sensory neuropathy, and moderate to severe peripheral motor neuropathy *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.2)]*.**

----------RECENT MAJOR CHANGES----------

- Warnings and Precautions, Neurotoxicity (5.2) 03/2017

----------INDICATIONS AND USAGE----------

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. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- 17.5 mg/m^2/day as a diluted intravenous infusion over 10 to 20 hours for 4 consecutive days for up to 5 cycles. (2.1, 2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Injection: 17.5 mg/5 mL (3.5 mg/mL) in a single-use vial. (3)

----------CONTRAINDICATIONS----------

- History of anaphylaxis to dinutuximab. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Neurological Disorders of the Eye: Interrupt Unituxin for dilated pupil with sluggish light reflex or other visual disturbances and permanently discontinue Unituxin for recurrent eye disorders or loss of vision. (5.2)
- Prolonged Urinary Retention and Transverse Myelitis: Permanently discontinue Unituxin and institute supportive care. (5.2)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Permanently discontinue Unituxin and institute supportive care for signs and symptoms of RPLS. (5.2)
- Capillary leak syndrome and hypotension: Administer required prehydration and monitor patients closely during treatment. Depending upon severity, manage by interruption, infusion rate reduction, or permanent discontinuation. (5.3, 5.4)
- Infection: Interrupt until resolution of systemic infection. (5.5)
- Bone marrow suppression: Monitor peripheral blood counts during Unituxin therapy. (5.6)
- Electrolyte abnormalities: Monitor serum electrolytes closely. (5.7)
- Atypical hemolytic uremic syndrome: Permanently discontinue Unituxin and institute supportive management. (5.8)
- Embryo-Fetal toxicity: May cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception. (5.9, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

The most common adverse drug reactions (≥ 25%) are pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatremia, increased alanine aminotransferase, anemia, vomiting, diarrhea, hypokalemia, capillary leak syndrome, neutropenia, urticaria, hypoalbuminemia, increased aspartate aminotransferase, and hypocalcemia. (5, 6.1)

The most common serious adverse reactions (≥ 5%) are infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome. (5, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFUSION REACTIONS AND NEUROTOXICITY

Infusion Reactions

- **Serious and potentially life-threatening infusion reactions 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 (*2.2, 2.3, 5.1*).**

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, Grade 3 peripheral sensory neuropathy occurred in 2% to 9% of patients. 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 (*2.2, 2.3, 5.2*).

1 INDICATIONS AND USAGE

Unituxin (dinutuximab) is 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 *[see Clinical Studies (14)].*

2 DOSAGE AND ADMINISTRATION

- Verify that patients have adequate hematologic, respiratory, hepatic, and renal function prior to initiating each course of Unituxin *[see Clinical Studies (14)].*
- Administer required premedication and hydration prior to initiation of each Unituxin infusion *[see Dosage and Administration (2.2)]*.

2.1 Recommended Dose

- The recommended dose of Unituxin is 17.5 mg/m^2/day administered as an intravenous infusion over 10 to 20 hours for 4 consecutive days for a maximum of 5 cycles (Tables 1 and 2) *[see Dosage and Administration (2.4) and Clinical Studies (14)]*.
- Initiate at an infusion rate of 0.875 mg/m^2/hour for 30 minutes. The infusion rate can be gradually increased as tolerated to a maximum rate of 1.75 mg/m^2/hour. Follow dose modification instructions for adverse reactions *[see Dosage and Administration (2.3)]*.

Table 1: Schedule of Unituxin Administration for Cycles 1, 3, and 5

Cycle Day	1 through 3	4	5	6	7	8 through 24*
Unituxin		X	X	X	X	

*Cycles 1, 3, and 5 are 24 days in duration.

Table 2: Schedule of Unituxin Administration for Cycles 2 and 4

Cycle Day	1 through 7	8	9	10	11	12 through 32*
Unituxin		X	X	X	X	

*Cycles 2 and 4 are 32 days in duration.

2.2 Required Pre-treatment and Guidelines for Pain Management

Intravenous Hydration

- Administer 0.9% Sodium Chloride Injection, USP 10 mL/kg as an intravenous infusion over one hour just prior to initiating each Unituxin infusion.

Analgesics

- Administer morphine sulfate (50 mcg/kg) intravenously immediately prior to initiation of Unituxin and then continue as a morphine sulfate drip at an infusion rate of 20 to 50 mcg/kg/hour during and for two hours following completion of Unituxin.
- Administer additional 25 mcg/kg to 50 mcg/kg intravenous doses of morphine sulfate as needed for pain up to once every 2 hours followed by an increase in the morphine sulfate infusion rate in clinically stable patients.
- Consider using fentanyl or hydromorphone if morphine sulfate is not tolerated.
- If pain is inadequately managed with opioids, consider use of gabapentin or lidocaine in conjunction with intravenous morphine.

Antihistamines and Antipyretics

- Administer an antihistamine such as diphenhydramine (0.5 to 1 mg/kg; maximum dose 50 mg) intravenously over 10 to 15 minutes starting 20 minutes prior to initiation of Unituxin and as tolerated every 4 to 6 hours during the Unituxin infusion.
- Administer acetaminophen (10 to 15 mg/kg; maximum dose 650 mg) 20 minutes prior to each Unituxin infusion and every 4 to 6 hours as needed for fever or pain. Administer ibuprofen (5 to 10 mg/kg) every 6 hours as needed for control of persistent fever or pain.

2.3 Dosage Modifications

Manage adverse reactions by infusion interruption, infusion rate reduction, dose reduction, or permanent discontinuation of Unituxin (Table 3 and Table 4) *[see Warnings and Precautions (5), Adverse Reactions (6), and Clinical Studies (14)]*.

Table 3: Adverse Reactions Requiring Permanent Discontinuation of Unituxin

Grade 3 or 4 anaphylaxis
Grade 3 or 4 serum sickness
Grade 3 pain unresponsive to maximum supportive measures
Grade 4 sensory neuropathy or Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks
Grade 2 or greater peripheral motor neuropathy
Urinary retention that persists following discontinuation of opioids
Transverse myelitis
Reversible posterior leukoencephalopathy syndrome (RPLS)
Subtotal or total vision loss
Grade 4 hyponatremia despite appropriate fluid management

Table 4: Dose Modification for Selected Unituxin Adverse Reactions

Infusion-related reactions *[see Warnings and Precautions (5.1)]*	
Mild to moderate adverse reactions such as transient rash, fever, rigors, and localized urticaria that respond promptly to symptomatic treatment	
Onset of reaction:	Reduce Unituxin infusion rate to 50% of the previous rate and monitor closely.
After resolution:	Gradually increase infusion rate up to a maximum rate of 1.75 mg/m^2/hour.
Prolonged or severe adverse reactions such as mild bronchospasm without other symptoms, angioedema that does not affect the airway	
Onset of reaction:	Immediately interrupt Unituxin.
After resolution:	If signs and symptoms resolve rapidly, resume Unituxin at 50% of the previous rate and observe closely.
First recurrence:	Discontinue Unituxin until the following day.
	If symptoms resolve and continued treatment is warranted, premedicate with hydrocortisone 1 mg/kg (maximum dose 50 mg) intravenously and administer Unituxin at a rate of 0.875 mg/m^2/hour in an intensive care unit.
Second recurrence:	Permanently discontinue Unituxin.

Neurological Disorders of the Eye *[see Warnings and Precautions (5.2)]*	
Onset of reaction:	Discontinue Unituxin infusion until resolution.
After resolution:	Reduce the Unituxin dose by 50%.
First recurrence or if accompanied by visual impairment:	Permanently discontinue Unituxin.
Capillary leak syndrome *[see Warnings and Precautions (5.3)]*	
Moderate to severe but not life-threatening capillary leak syndrome	
Onset of reaction:	Immediately interrupt Unituxin.
After resolution:	Resume Unituxin infusion at 50% of the previous rate.
Life-threatening capillary leak syndrome	
Onset of reaction:	Discontinue Unituxin for the current cycle.
After resolution:	In subsequent cycles, administer Unituxin at 50% of the previous rate.
First recurrence:	Permanently discontinue Unituxin.
Hypotension* requiring medical intervention *[see Warnings and Precautions (5.4)]*	
Onset of reaction:	Interrupt Unituxin infusion.
After resolution:	Resume Unituxin infusion at 50% of the previous rate. If blood pressure remains stable for at least 2 hours, increase the infusion rate as tolerated up to a maximum rate of 1.75 mg/m^2/hour.
Severe systemic infection or sepsis *[see Warnings and Precautions (5.5)]*	
Onset of reaction:	Discontinue Unituxin until resolution of infection, and then proceed with subsequent cycles of therapy.

*Symptomatic hypotension, systolic blood pressure (SBP) less than lower limit of normal for age, or SBP decreased by more than 15% compared to baseline.

2.4 Instructions for Preparation and Administration

Preparation

- Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the outer carton. **DO NOT FREEZE OR SHAKE** vials.
- Inspect visually for particulate matter and discoloration prior to administration. Do not administer Unituxin and discard the single-use vial if the solution is cloudy, has pronounced discoloration, or contains particulate matter.
- Aseptically withdraw the required volume of Unituxin from the single-use vial and inject into a 100 mL bag of 0.9% Sodium Chloride Injection, USP. Mix by gentle inversion. Do not shake. Discard unused contents of the vial.

- Store the diluted Unituxin solution under refrigeration (2°C to 8°C). Initiate infusion within 4 hours of preparation.
- Discard diluted Unituxin solution 24 hours after preparation.

Administration

- Administer Unituxin as a diluted intravenous infusion only *[see Dosage and Administration (2.1)]*. **Do not administer Unituxin as an intravenous push or bolus.**

3 DOSAGE FORMS AND STRENGTHS

Injection: 17.5 mg/5 mL (3.5 mg/mL) solution in a single-use vial.

4 CONTRAINDICATIONS

Unituxin is contraindicated in patients with a history of anaphylaxis to dinutuximab.

5 WARNINGS AND PRECAUTIONS

5.1 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.

In Study 1, 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.

Prior to each Unituxin dose, administer required intravenous hydration and premedication with antihistamines, analgesics, and antipyretics *[see Dosage and Administration (2.2)]*. Monitor patients closely for signs and symptoms of infusion reactions during and for at least 4 hours following completion of each Unituxin infusion in a setting where cardiopulmonary resuscitation medication and equipment are available.

For mild to moderate infusion reactions such as transient rash, fever, rigors, and localized urticaria that respond promptly to antihistamines or antipyretics, decrease the Unituxin infusion rate and monitor closely. Immediately interrupt or permanently discontinue Unituxin and institute supportive management for severe or prolonged infusion reactions. Permanently discontinue Unituxin and institute supportive management for life-threatening infusion reactions *[see Dosage and Administration (2.3)]*.

5.2 Neurotoxicity

Pain

In Study 1, 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. Pain typically occurred during the Unituxin infusion and was most commonly reported as abdominal pain, generalized pain, extremity pain, back pain, neuralgia, musculoskeletal chest pain, and arthralgia.

Premedicate with analgesics including intravenous opioids prior to each dose of Unituxin and continue analgesics until two hours following completion of Unituxin *[see Dosage and Administration (2.2)]*.

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 *[see Dosage and Administration (2.3)]*.

Peripheral Neuropathy

In Study 1, 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. No patients treated with RA alone experienced severe peripheral neuropathy. The duration and reversibility of peripheral neuropathy occurring in Study 1 was not documented. In Study 3, no patients experienced peripheral motor neuropathy. Among the 9 (9%) patients who experienced peripheral sensory neuropathy of any severity, the median (min, max) duration of peripheral sensory neuropathy was 9 (3, 163) days.

In a study of a related anti-GD2 antibody conducted in 12 adult patients with metastatic melanoma, 2 (13%) patients developed severe motor neuropathy. One patient developed lower extremity weakness and inability to ambulate that persisted for approximately 6 weeks. Another patient developed severe lower extremity weakness resulting in an inability to ambulate without assistance that lasted for approximately 16 weeks and neurogenic bladder that lasted for approximately 3 weeks. Complete resolution of motor neuropathy was not documented in this case.

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 *[see Dosage and Administration (2.3)]*.

Neurological Disorders of the Eye

Neurological disorders of the eye experienced by two or more patients treated with Unituxin in Studies 1, 2, or 3 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 with recurrent signs or symptoms of an eye disorder following dose reduction and in patients who experience loss of vision *[see Dosage and Administration (2.3)]*.

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 urinary retention that does not resolve following discontinuation of opioids *[see Dosage and Administration (2.3) and Postmarketing Experience (6.3)]*.

Transverse Myelitis

Transverse myelitis has occurred in patients treated with Unituxin. 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)].*

Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (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) *[see Dosage and Administration (2.3) and Postmarketing Experience (6.3)]*.

5.3 Capillary Leak Syndrome

In Study 1, 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. Additionally, capillary leak syndrome was reported as a serious adverse reaction in 9 (6%) patients in the Unituxin/RA group and in no patients treated with RA alone. Immediately interrupt or discontinue Unituxin and institute supportive management in patients with symptomatic or severe capillary leak syndrome *[see Dosage and Administration (2.3)]*.

5.4 Hypotension

In Study 1, 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. Immediately interrupt or discontinue Unituxin and institute supportive management in patients with symptomatic hypotension, systolic blood pressure (SBP) less than lower limit of normal for age, or SBP that is decreased by more than 15% compared to baseline *[see Dosage and Administration (2.2, 2.3)]*.

5.5 Infection

In Study 1, 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%) 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 *[see Dosage and Administration (2.3)]*.

5.6 Bone Marrow Suppression

In Study 1, 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 therapy with Unituxin.

5.7 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. In a study of a related anti-GD2 antibody conducted in 12 adult patients with metastatic melanoma, 2 (13%) patients

developed syndrome of inappropriate antidiuretic hormone secretion resulting in severe hyponatremia. Monitor serum electrolytes daily during therapy with Unituxin.

5.8 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 enrolled in Study 2 following receipt of the first cycle of dinutuximab. Atypical hemolytic uremic syndrome recurred following rechallenge with Unituxin in one patient. Permanently discontinue Unituxin and institute supportive management for signs of hemolytic uremic syndrome.

5.9 Embryo-Fetal Toxicity

Based on its mechanism of action, Unituxin may cause fetal harm when administered to a pregnant woman. 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 *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Infusion Reactions *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Neurotoxicity, including Pain, Peripheral Neuropathy, Neurological Disorders of the Eye, Prolonged Urinary Retention, Transverse Myelitis, and Reversible Posterior Leukoencephalopathy Syndrome *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Capillary Leak Syndrome *[see Warnings and Precautions (5.3)]*
- Hypotension *[see Warnings and Precautions (5.4)]*
- Infection *[see Warnings and Precautions (5.5)]*
- Bone Marrow Suppression *[see Warnings and Precautions (5.6)]*
- Electrolyte Abnormalities *[see Warnings and Precautions (5.7)]*
- Atypical Hemolytic Uremic Syndrome *[see Warnings and Precautions (5.8)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in clinical practice.

The data described below reflect exposure to Unituxin at the recommended dose and schedule in 1021 patients with high-risk neuroblastoma enrolled in an open label, randomized (Study 1) or single arm clinical trials (Study 2 and Study 3). Prior to enrollment, patients received 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. Patients received Unituxin in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis-retinoic acid (RA). Treatment commenced within 95 days post autologous stem cell transplant in Study 1, within 210 days of autologous stem cell transplant in Study 2, and within 110 days of autologous stem cell transplant in Study 3.

<u>Study 1</u>

In a randomized, open label, multi-center study (Study 1), 134 patients received dinutuximab in combination with GM-CSF, IL-2 and RA (Unituxin/RA group), including 109 randomized patients and 25 patients with biopsy-proven residual disease who were non-randomly assigned to receive dinutuximab. A total of 106 randomized patients received RA alone (RA group) *[see Dosage and Administration (2) and Clinical Studies (14)]*. Patients had a median age at enrollment of

3.8 years (range: 0.94 to 15.3 years), and were predominantly male (60%) and White (82%). In Study 1, adverse reactions of Grade 3 or greater severity were comprehensively collected, but adverse reactions of Grade 1 or 2 severity were collected sporadically and laboratory data were not comprehensively collected.

Approximately 71% of patients in the Unituxin/RA group and 77% of patients in the RA group completed planned treatment. The most common reason for premature discontinuation of study therapy was adverse reactions in the Unituxin/RA group (19%) and progressive disease (17%) in the RA group.

The most common adverse drug reactions (≥ 25%) in the Unituxin/RA group were pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatremia, increased alanine aminotransferase, anemia, vomiting, diarrhea, hypokalemia, capillary leak syndrome, neutropenia, urticaria, hypoalbuminemia, increased aspartate aminotransferase, and hypocalcemia. The most common serious adverse reactions (≥ 5%) in the Unituxin/RA group were infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome.

Table 5 lists the adverse reactions reported in at least 10% of patients in the Unituxin/RA group for which there was a between group difference of at least 5% (all grades) or 2% (Grade 3 or greater severity).

Table 5: Selected Adverse Reactions Occurring in at Least 10% of Patients in the Unituxin/RA Group in Study 1

	Unituxin/RA (N=134)		**RA (N=106)**	
Adverse Reaction[1,2]	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
General Disorders and Administration Site Conditions				
Pain[3]	85	51	16	6
Pyrexia	72	40	27	6
Edema	17	0	0	0
Blood and Lymphatic System Disorders[4]				
Thrombocytopenia	66	39	43	25
Lymphopenia[4]	62	51	36	20
Anemia	51	34	22	16
Neutropenia	39	34	16	13
Immune System Disorders				
Infusion reactions	60	25	9	1
Vascular Disorders				
Hypotension	60	16	3	0
Capillary leak syndrome[5]	40	23	1	0
Hemorrhage[6]	17	6	6	3
Hypertension	14	2	7	1
Metabolism and Nutrition Disorders				
Hyponatremia[4]	58	23	12	4
Hypokalemia[4]	43	37	4	2
Hypoalbuminemia[4]	33	7	3	0
Hypocalcemia[4]	27	7	0	0
Hypophosphatemia[4]	20	8	3	0

Adverse Reaction[1,2]	Unituxin/RA (N=134)		RA (N=106)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hyperglycemia[4]	18	6	4	1
Hypertriglyceridemia[4]	16	1	11	1
Decreased appetite	15	10	5	4
Hypomagnesemia[4]	12	2	1	0
Investigations				
Increased alanine aminotransferase[4]	56	23	31	3
Increased aspartate aminotransferase[4]	28	10	7	0
Increased serum creatinine[4]	15	2	6	0
Increased weight	10	0	0	0
Gastrointestinal Disorders				
Vomiting	46	6	19	3
Diarrhea	43	13	15	1
Nausea	10	2	3	1
Skin and Subcutaneous Tissue Disorders				
Urticaria	37	13	3	0
Respiratory, Thoracic and Mediastinal Disorders				
Hypoxia	24	12	2	1
Cardiac Disorders				
Tachycardia[7]	19	2	1	0
Infections and Infestations				
Sepsis	18	16	9	9
Device related infection	16	16	11	11
Renal and Urinary Disorders				
Proteinuria[4]	16	0	3	1
Nervous System Disorders				
Peripheral neuropathy	13	3	6	0

[1] Includes adverse reactions that occurred in at least 10% of patients in the Unituxin/RA group with at least a 5% (All Grades) or 2% (Grades 3-5) absolute higher incidence in the Unituxin/RA group compared to the RA group.

[2] Adverse drug reactions were graded using CTCAE version 3.0.

[3] Includes preferred terms abdominal pain, abdominal pain upper, arthralgia, back pain, bladder pain, bone pain, chest pain, facial pain, gingival pain, infusion related reaction, musculoskeletal chest pain, myalgia, neck pain, neuralgia, oropharyngeal pain, pain, pain in extremity, and proctalgia.

[4] Based on investigator reported adverse reactions.

[5] One Grade 5 adverse reaction.

[6] Includes preferred terms gastrointestinal hemorrhage, hematochezia, rectal hemorrhage, hematemesis, upper gastrointestinal hemorrhage, hematuria, hemorrhage urinary tract, renal hemorrhage, epistaxis, respiratory tract hemorrhage, disseminated intravascular coagulation, catheter site hemorrhage, hemorrhage and hematoma.

[7] Includes preferred terms tachycardia and sinus tachycardia.

Table 6 compares the per-patient incidence of selected adverse reactions occurring during cycles containing dinutuximab in combination with GM-CSF (Cycles 1, 3, and 5) with cycles containing dinutuximab in combination with IL-2 (Cycles 2 and 4).

Table 6: Comparison of Adverse Events by Treatment Cycle in the Unituxin/RA Group in Study 1

Preferred Term[1,2]	All Grades		Severe	
	GM-CSF N=134 (%)	IL-2[3] N=127 (%)	GM-CSF N=134 (%)	IL-2[3] N=127 (%)
General Disorders and administration site conditions				
Pyrexia	55	65	10	37
Pain[5]	77	61	43	35
Blood and Lymphatic System Disorders[4]				
Thrombocytopenia	62	61	31	33
Lymphopenia	54	61	33	50
Anemia	42	42	21	24
Neutropenia	25	32	19	28
Immune System Disorders				
Infusion reactions	47	54	10	20
Vascular Disorders				
Hypotension	43	54	5	16
Capillary leak syndrome	22	36	11	20
Metabolism and Nutrition Disorders[4]				
Hyponatremia	36	55	5	21
Hypokalemia	26	39	13	33
Hypoalbuminemia	29	29	3	5
Hypocalcemia	20	21	2	6
Investigations[4]				
Increased alanine aminotransferase	43	48	15	13
Aspartate aminotransferase increased	16	21	4	7
Gastrointestinal Disorders				
Diarrhea	31	37	6	13
Vomiting	33	35	3	2
Skin and Subcutaneous Tissue Disorders				
Urticaria	25	29	7	7

Abbreviations: GM-CSF: granulocyte-macrophage colony-stimulating factor; IL-2: interleukin-2.

[1] Includes preferred terms with a per-patient incidence of at least 20% in the Unituxin and RA group for either IL-2 or GM-CSF containing cycles.

[2] Adverse drug reactions were graded using CTCAE version 3.0.

[3] Seven patients who received GM-CSF in Cycle 1 discontinued prior to starting Cycle 2.

[4] Based on investigator reported adverse reactions.

[5] Includes preferred terms abdominal pain, abdominal pain upper, arthralgia, back pain, bladder pain, bone pain, chest pain, facial pain, gingival pain, infusion related reaction, musculoskeletal chest pain, myalgia, neck pain, neuralgia, oropharyngeal pain, pain, pain in extremity, and proctalgia.

Study 2 and Study 3

Study 2 was a single arm, multicenter expanded access trial that enrolled patients with high-risk neuroblastoma (N=783). The reported adverse event profile of dinutuximab in Study 2 was similar to that observed in Study 1.

Study 3 was a multicenter, single arm safety study of dinutuximab in combination with GM-CSF, IL-2 and RA. In Study 3, adverse events of all CTCAE grades and laboratory data were systematically and comprehensively collected. Of 104 patients enrolled and treated in Study 3, 77% of patients completed study therapy. In general, the adverse reaction profile of dinutuximab observed in Study 3 was similar to that observed in Study 1 and Study 2. The following adverse reactions not previously reported in Study 1 were reported in at least 10% of patients in Study 3: nasal congestion (20%) and wheezing (15%). Table 7 provides the per-patient incidence of laboratory abnormalities in Study 3.

Table 7: Per-Patient Incidence of Selected (≥ 5% Grade 3-4) Laboratory Abnormalities in Study 3

Laboratory Test[1]	Grade[2]	
	All Grades %	Grades 3-4 %
Hematology		
Anemia	100	46
Neutropenia	99	63
Thrombocytopenia	98	49
Chemistry		
Hypoalbuminemia	100	8
Hypocalcemia	97	7
Hyponatremia	93	36
Hyperglycemia	87	6
Aspartate Aminotransferase Increased	84	8
Alanine Aminotransferase Increased	83	13
Hypokalemia	82	41
Hypophosphatemia	78	6
Urinalysis[3]		
Urine protein	66	ND
Red blood cell casts	38	ND

ND: not determined

[1] Laboratory abnormalities with a per-patient incidence of at least 20% (all grades) and at least a 5% per-patient incidence of severe (Grade 3 or 4) laboratory abnormalities.

[2] Based on CTCAE version 4.0.

[3] Urinalysis results were reported as positive or negative without assessment of grade.

6.2 Immunogenicity

As with all therapeutic proteins, patients treated with Unituxin may develop anti-drug antibodies. In clinical studies, 52 of 284 (18%) patients from Study 2 and 13 of 103 (13%) patients from Study 3 tested positive for anti-dinutuximab binding antibodies. Neutralizing antibodies were detected in 3.6% of patients who were tested for anti-dinutuximab binding antibodies in Study 2 and Study 3. However, due to the limitations of the assay, the incidence of neutralizing antibodies may not have been reliably determined.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to Unituxin with the incidences of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Unituxin. Because these 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.

- Neurotoxicity: prolonged urinary retention, transverse myelitis, and reversible posterior leukoencephalopathy syndrome (RPLS) *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with dinutuximab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, Unituxin may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no studies in pregnant women and no reproductive studies in animals to inform the drug-associated risk. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. Advise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There is no information available on the presence of dinutuximab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. However, human IgG is present in human milk. Because of the potential for serious adverse reactions in a breastfed infant, advise a nursing woman to discontinue breastfeeding during treatment with Unituxin.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Unituxin may cause fetal harm *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for two months after the last dose of Unituxin.

8.4 Pediatric Use

The safety and effectiveness of Unituxin as part of multi-agent, multimodality therapy have been established in pediatric patients with high-risk neuroblastoma based on results of an open-label, randomized (1:1) trial conducted in 226 patients aged 11 months to 15 years (median age 3.8 years) (Study 1). Prior to enrollment, patients achieved at least a partial response to prior first-line therapy for high-risk neuroblastoma consisting of induction combination chemotherapy, maximum feasible surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and received radiation therapy to residual soft tissue disease. Patients randomized to the Unituxin/13-cis-retinoic acid (RA) arm (Unituxin/RA) received up to

five cycles of Unituxin in combination with alternating cycles of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-2 (IL-2) plus RA, followed by one cycle of RA alone. Patients randomized to the RA arm received up to six cycles of RA monotherapy. Study 1 demonstrated an improvement in event-free survival and overall survival in patients in the Unituxin/RA arm compared to those in the RA arm *[see Adverse Reactions (6), Clinical Pharmacology (12), and Clinical Studies (14)]*.

8.5 Geriatric Use

The safety and effectiveness of Unituxin in geriatric patients have not been established.

8.6 Renal Impairment

Unituxin has not been studied in patients with renal impairment.

8.7 Hepatic Impairment

Unituxin has not been studied in patients with hepatic impairment.

11 DESCRIPTION

Unituxin (dinutuximab) is a chimeric monoclonal antibody composed of murine variable heavy and light chain regions and the human constant region for the heavy chain IgG1 and light chain kappa. Unituxin binds to the glycolipid disialoganglioside (GD2). Dinutuximab is produced in the murine myeloma cell line, SP2/0.

Unituxin is a sterile, preservative-free, clear/colorless to slightly opalescent solution for intravenous infusion. Unituxin is supplied in single-use vials of 17.5 mg/5 mL. Each vial contains 3.5 mg/mL of dinutuximab, histidine (20 mM), polysorbate 20 (0.05%), sodium chloride (150 mM), and water for injection; hydrochloric acid is added to adjust pH to 6.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dinutuximab binds to the glycolipid GD2. This glycolipid is expressed on neuroblastoma cells and on normal cells of neuroectodermal origin, including the central nervous system and peripheral nerves. Dinutuximab binds to cell surface GD2 and induces cell lysis of GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

12.3 Pharmacokinetics

The pharmacokinetics of dinutuximab was evaluated by a population pharmacokinetic analysis in a clinical study of Unituxin in combination with GM-CSF, IL-2, and RA. In this study, 27 children with high-risk neuroblastoma (age: 3.9±1.9 years) received up to 5 cycles of Unituxin at 17.5 mg/m^2/day as an intravenous infusion over 10 to 20 hours for 4 consecutive days every 28 days. The observed maximum plasma dinutuximab concentration (C_{max}) was 11.5 mcg/mL [20%, coefficient of variation (CV)]. The mean volume of distribution at steady state (Vd_{ss}) was 5.4 L (28%). The clearance was 0.21 L/day (62%) and increased with body size. The terminal half-life was 10 days (56%).

No formal pharmacokinetic studies were conducted in patients with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted to evaluate the carcinogenic or mutagenic potential of dinutuximab.

Dedicated studies examining the effects of dinutuximab on fertility in animals have not been conducted. No clear effects on reproductive organs were observed in general toxicology studies conducted in rats.

13.2 Animal Toxicology and/or Pharmacology

Non-clinical studies suggest that dinutuximab-induced neuropathic pain is mediated by binding of the antibody to the GD2 antigen located on the surface of peripheral nerve fibers and myelin and subsequent induction of CDC and ADCC activity.

14 CLINICAL STUDIES

The safety and effectiveness of Unituxin was evaluated in a randomized, open-label, multicenter trial conducted in pediatric patients with high-risk neuroblastoma (Study 1). 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. Patients were randomized between Day 50 and Day 77 post-autologous stem cell transplantation.

Patients were required to have achieved at least a partial response prior to autologous stem cell transplantation, have no evidence of disease progression following completion of front-line multi-modality therapy, have adequate pulmonary function (no dyspnea at rest and peripheral arterial oxygen saturation of at least 94% on room air), adequate hepatic function (total bilirubin < 1.5 x the upper limit of normal and ALT < 5 x the upper limit of normal), adequate cardiac function (shortening fraction of > 30% by echocardiogram, or if shortening fraction abnormal, ejection fraction of 55% by gated radionuclide study), and adequate renal function (glomerular filtration rate at least 70 mL/min/1.73 m^2). Patients with systemic infections or a requirement for concomitant systemic corticosteroids or immunosuppressant usage were not eligible for enrollment.

Patients randomized to the Unituxin/RA arm received up to five cycles of dinutuximab (clinical trials material) in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) (Table 8) or interleukin-2 (IL-2) (Table 9) plus 13-cis-retinoic acid (RA), followed by one cycle of RA alone. Patients randomized to the RA arm received six cycles of RA. Dinutuximab was administered at a dose of 17.5 mg/m^2/day (equivalent to 25 mg/m^2/day of clinical trials material) on four consecutive days. Patients in both treatment arms received six cycles of RA at a dose of 160 mg/m^2/day orally (for patients weighing more than 12 kg) or 5.33 mg/kg/day (for patients weighing less than or equal to 12 kg) in two divided doses for 14 consecutive days.

Table 8: Dosage Regimen in the Unituxin/RA Arm for Cycles 1, 3, and 5

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24
GM-CSF[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Unituxin[2]				X	X	X	X								
RA[3]											X	X	X	X	X

[1] GM-CSF: 250 µg/m^2/day, administered by either subcutaneous injection (recommended) or IV infusion administered over 2 hours.

[2] Unituxin: 17.5 mg/m^2/day, administered by diluted IV infusion over 10–20 hours.

[3] RA: for >12 kg body weight, 80 mg/m^2 orally twice daily for a total dose of 160 mg/m^2/day; for ≤12 kg body weight, 2.67 mg/kg orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

Table 9: Dosage Regimen in the Unituxin/RA Arm for Cycles 2 and 4

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12-14	15-28	29-32

IL-2[1]	X	X	X	X				X	X	X	X			
Unituxin[2]								X	X	X	X			
RA[3]													X	

[1] IL-2: 3 MIU/m^2/day administered by continuous IV infusion over 96 hours on Days 1-4 and 4.5 MIU/m^2/day on Days 8-11.

[2] Unituxin: 17.5 mg/m^2/day, administered by diluted IV infusion over 10-20 hours.

[3] RA: for >12 kg body weight, 80 mg/m^2 orally twice daily for a total dose of 160 mg/m^2/day; for ≤12 kg body weight, 2.67 mg/kg orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

A total of 226 patients were randomized, 113 patients to each arm. In general, demographic and baseline tumor characteristics were similar across study arms. Across the study population, 60% were male, the median age was 3.8 years and 3% of patients were less than 1.5 years, 82% were White and 7% were Black. The majority (80%) of patients had International Neuroblastoma Staging System Stage 4 disease. Thirty-five percent of patients had a complete response, 43% had a very good partial response, and 23% had a partial response to therapy received prior to autologous stem cell transplant. Forty-six percent of patients had neuroblastoma that was not MYCN-amplified, 36% had tumors with known MYCN-amplification, and MYCN status was unknown or missing in 19% of patients. Forty-three percent of patients had hyperdiploid tumors, 36% had diploid tumors, and DNA ploidy status was unknown or missing in 21% of patients.

The major efficacy outcome measure was investigator-assessed event-free survival (EFS), defined as the time from randomization to the first occurrence of relapse, progressive disease, secondary malignancy, or death. Overall survival (OS) was also evaluated. After observing a numerical improvement in EFS based on the seventh interim analysis, the Data Monitoring Committee recommended termination of accrual. Efficacy results are shown in Table 10.

Table 10: Efficacy Results

Efficacy Parameter		**Unituxin/ RA arm n=113**	**RA arm n=113**
EFS	No. of Events (%)	33 (29%)	50 (44%)
	Median (95% CI) (years)	NR (3.4, NR)	1.9 (1.3, NR)
	Hazard Ratio (95% CI)	0.57 (0.37, 0.89)	
	p-value (log-rank test)[1]	0.01	
OS[2]	No. of Events (%)	31 (27%)	48 (42%)
	Median (95% CI) (years)	NR (7.5, NR)	NR (3.9, NR)
	Hazard Ratio (95% CI)	0.58 (0.37, 0.91)	

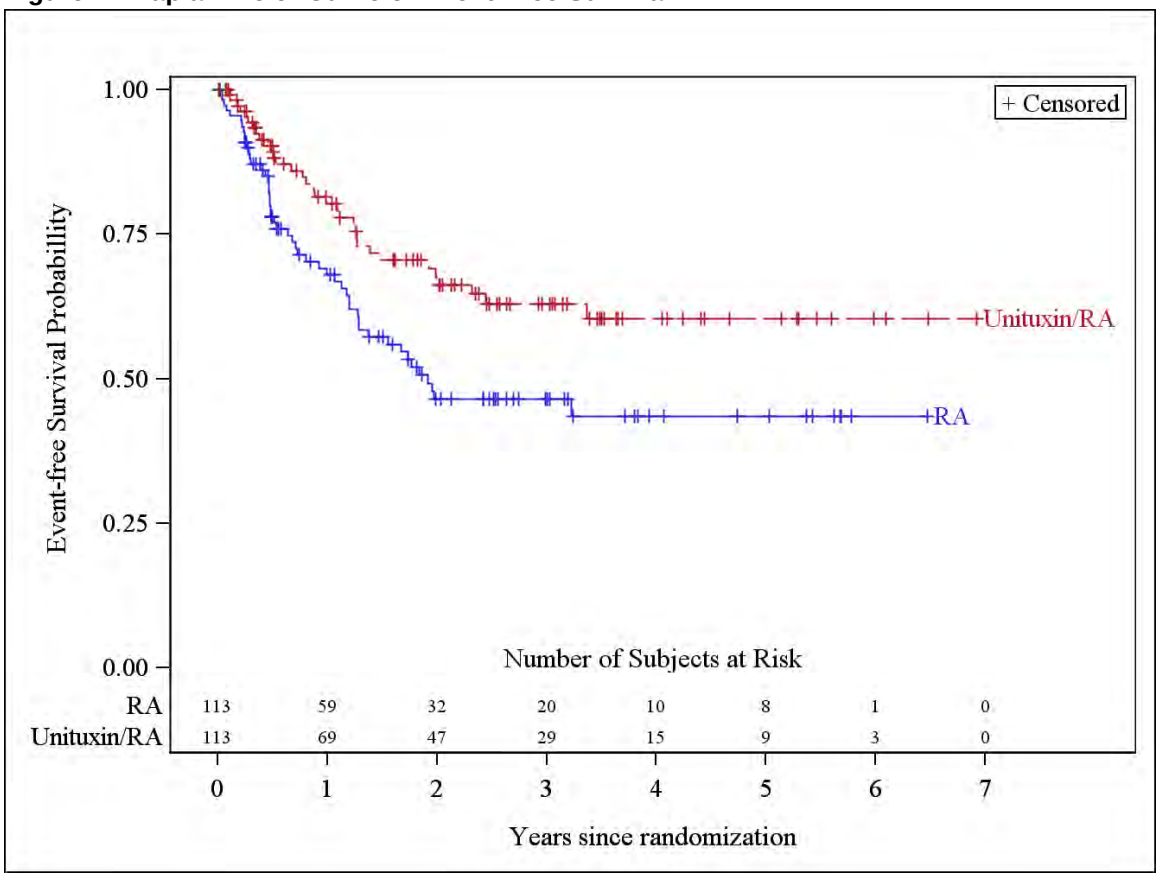
NR = not reached

[1] Compared to the allocated alpha of 0.01 pre-specified for the seventh interim analysis of EFS

[2] Based on an additional three years of follow up after the seventh interim analysis of EFS

The Kaplan-Meier curve of EFS is shown in Figure 1.

Figure 1: Kaplan-Meier Curve of Event-Free Survival



16 HOW SUPPLIED / STORAGE AND HANDLING

Unituxin is supplied in a carton containing one 17.5 mg/5 mL (3.5 mg/mL) single-use vial.

NDC 66302-014-01

Store Unituxin vials under refrigeration at 2°C to 8°C until time of use. Do not freeze or shake the vial. Keep the vial in the outer carton in order to protect from light.

17 PATIENT COUNSELING INFORMATION

- *Serious Infusion Reactions*
  Inform patients and caregivers of the risk of serious infusion reactions and anaphylaxis and to immediately report any signs or symptoms, such as facial or lip swelling, urticaria, difficulty breathing, lightheadedness or dizziness that occur during or within 24 hours following the infusion *[see Warnings and Precautions (5.1)]*.
- *Pain, Peripheral Neuropathy, Prolonged Urinary Retention, and Transverse Myelitis*
  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 *[see Warnings and Precautions (5.2)]*.

- *Neurological Disorders of the Eye*
  Inform patients and caregivers of the risk of neurological disorders of the eye and to promptly report signs or symptoms such as blurred vision, photophobia, ptosis, diplopia, or unequal pupil size *[see Warnings and Precautions (5.2)]*.
- *Reversible Posterior Leukoencephalopathy Syndrome (RPLS)*
  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 *[see Warnings and Precautions (5.2)]*.
- *Capillary Leak Syndrome*
  Inform patients and caregivers of the risk of capillary leak syndrome and to immediately report any signs or symptoms *[see Warnings and Precautions (5.3)]*.
- *Hypotension*
  Inform patients and caregivers of the risk of hypotension during the infusion and to immediately report any signs or symptoms *[see Warnings and Precautions (5.4)]*.
- *Infection*
  Inform patients and caregivers of the risk of infection following treatment and to immediately report any signs or symptoms *[see Warnings and Precautions (5.5)]*.
- *Bone Marrow Suppression*
  Inform patients and caregivers of the risk of bone marrow suppression, and to promptly report signs or symptoms of anemia, thrombocytopenia, or infection *[see Warnings and Precautions (5.6)]*.
- *Electrolyte Abnormalities*
  Inform patients and caregivers of the risk of electrolyte abnormalities including hypokalemia, hyponatremia, and hypocalcemia, and to report any signs or symptoms such as seizures, heart palpitations, and muscle cramping *[see Warnings and Precautions (5.7)]*.
- *Atypical Hemolytic Uremic Syndrome*
  Inform patients and caregivers of the risk of hemolytic uremic syndrome and to report any signs or symptoms such as fatigue, dizziness, fainting, pallor, edema, decreased urine output, or hematuria *[see Warnings and Precautions (5.8)]*.
- *Embryo-Fetal Toxicity*
  Advise women of reproductive potential of the potential risk to the fetus if administered during pregnancy and the need for use of effective contraception during and for at least two months after completing therapy *[see Warnings and Precautions (5.9)]*.

Unituxin manufactured by:

United Therapeutics Corp.
Silver Spring, MD 20910
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