AURLUMYN™
(iloprost) Injection

US PRODUCT MONOGRAPH

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

SERB Pharmaceuticals

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Executive Summary

Though rare, at approximately 1000 cases annually in the US,[1] severe frostbite is a high-morbidity, high-cost injury that can result in significant disability from amputation of limbs and digits. If the person does not receive swift treatment or if the affected appendage does not undergo amputation, gangrene may lead to disease throughout the body, which could be life threatening. Cardiovascular collapse and sepsis can also occur. Traumatic digit amputations, such as amputations due to frostbite, are also detrimental to activities of daily living and work.[2,3] Furthermore, because the hands are so visible, digit amputation can lead to social withdrawal and reduced quality of life.[4]

The long-term impact of frostbite is poorly understood, but patients with frostbite have been reported to have long-term effects after amputation (eg, inability to work at same level prior to injury), peripheral neurologic damage that can be lifelong, paresthesias and hypersensitivity to cold exposure, neuropathic pain, and permanent cold injury–induced arthritis.[5]

The risk factors for frostbite, other than temperature, include physical immersion in water, wind chill, fatigue, malnutrition, smoking, alcohol and substance abuse, and medical comorbidities, such as peripheral vascular disease, diabetes, neuropathies, dementia, and mental illness.[1,6] Frostbite affects the unhoused population, industrial workers, and military personnel operating in cold regions, as well as people engaging in recreational activities, such as skiing, hiking, mountaineering, and ice climbing.[7,8]

Historically, guidelines for management of frostbite injuries were convened by the Wilderness Medical Society.[6] The proposed management of frostbite injuries can be divided into 3 phases: field treatment, immediate medical therapy (hospital or high-level field clinic), and post-thaw medical therapy. Field treatment aims to protect frozen tissue from further damage, while the hospital phase includes rapid rewarming of the frozen or partially frozen extremity in a 37°C-39°C recirculating antiseptic water bath for approximately 15-60 minutes until a red/purple color appears and the limb becomes soft and pliable.[6,9] Adequate pain management is required for rewarming, and additional warming should not be undertaken in the setting of an already-thawed extremity.[6] Imaging, such as angiography and multi-phase bone scintigraphy, if available, plays a critical role in initial evaluation of frostbite injuries and in monitoring response to treatment.[10]

Despite advancements in the standard of care (SoC) for frostbite, amputation of the affected extremity is still common practice and can range from an estimated 60%-83% for grade 3 frostbite (depending on the extent of the lesion to the intermediary or proximal phalanx) and 98%–100% for grade 4 frostbite.[11]

AURLUMYN is the first and only FDA-approved drug therapy to treat severe frostbite in adults to reduce the risk of digit amputations and received Priority Review and Orphan Drug designation for this indication. This product monograph is intended to provide comprehensive clinical information to healthcare providers who make treatment decisions for patients presenting with severe frostbite.

IMPORTANT SAFETY INFORMATION

INDICATION AND USAGE

AURLUMYN is a prostacyclin mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations. Effectiveness was established in young, healthy adults who suffered frostbite at high altitudes.

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Severe Frostbite Carries Significant Morbidity and Mortality Risk

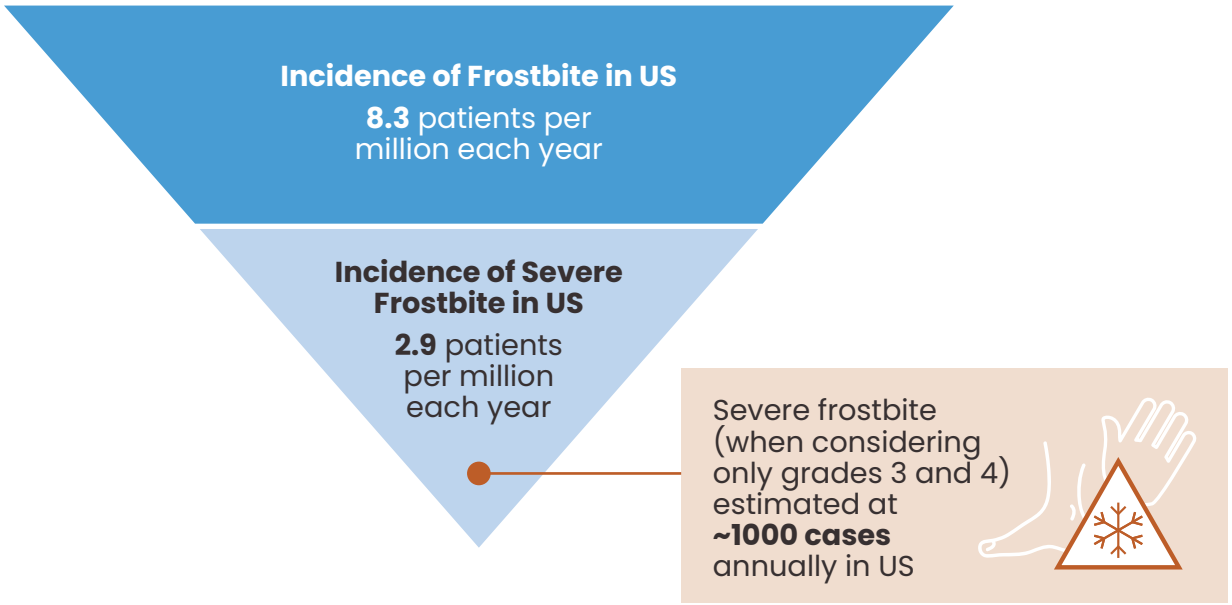
Frostbite Is Among the Most Serious Cold-Related Injuries[12]

Frostbite is an injury caused by extended exposure to freezing temperatures.[12] The spectrum of cold temperature–induced injury begins with frostnip where there is no injury to local skin tissues and progresses to pernio, which is a condition that arises from repeated exposure to near-freezing, dry environments.[12] Frostbite and, subsequently, severe frostbite are the most extreme injuries on the spectrum and consist of direct and indirect tissue damage secondary to freezing.[12] Restriction of blood flow to extremities combined with freezing temperatures results in the formation of ice crystals within body fluid that directly damages cells. The symptoms of frostbite include loss of feeling, waxy discoloration of the skin, swelling, and blisters.[13] Subsequent tissue necrosis may result in catastrophic amputation.[12]

While Severe Frostbite Is Rare in the US, It Has a Substantial Impact on Those It Affects

The incidence of severe frostbite in the US is 2.9 people per million each year.[1] This equates to approximately 1000 cases of severe frostbite (when considering only grades 3 and 4, described in more detail below) annually in the US.[1]

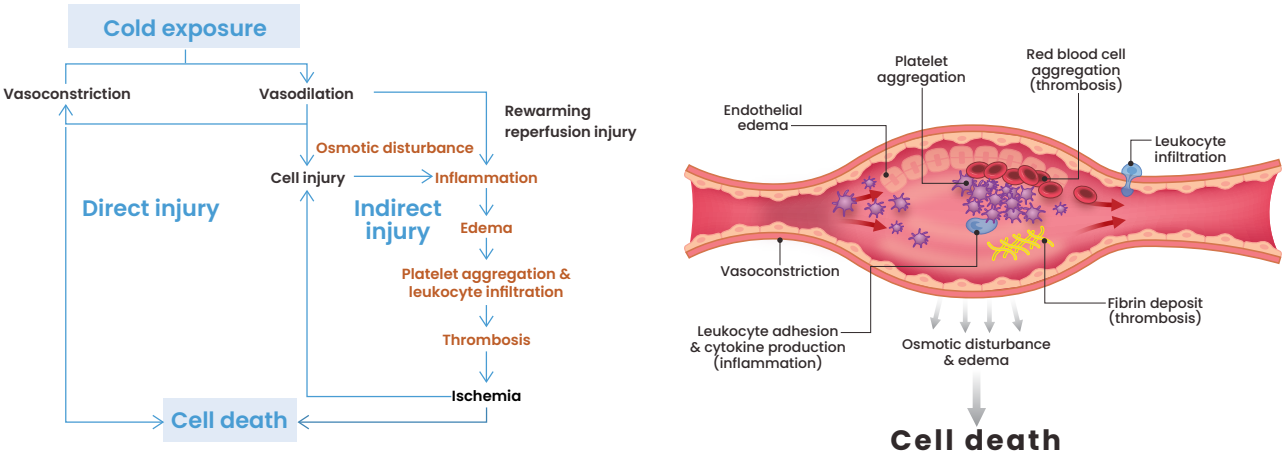
The populations at risk include cold-weather sports enthusiasts, industrial workers, the elderly, the unhoused population, and military personnel operating in cold regions.[7]



Direct and Indirect Injuries in Frostbite Lead to Cell Death

Low temperature results in a cycle of vasodilation and vasoconstriction, which leads to body cooling and decreased blood flow in the extremities (**Figure 1**).[12] Prolonged decreased blood flow and low temperatures cause ice crystals in the blood and tissues to ultimately freeze, causing a direct injury to cells. Damage to cells is the result of this direct injury and the indirect consequences of osmotic disturbances and inflammation. Inflammation leads to edema, platelet aggregation and leukocyte infiltration, and thrombosis, which further restrict blood flow to the impacted tissue. Ischemia ensues, and cells can die from the lack of oxygen.[12] Indirect injury continues after rewarming and reperfusion and remains an opportunity to improve outcomes for those impacted.[14]

Figure 1: Prolonged cold exposure results in direct and indirect injury, causing cell death.[12]



Traditional Management Does Not Adequately Prevent Amputation in Patients With Frostbite

The initial evaluation should look for reversible, ongoing, clinically important soft-tissue necrosis for potential intervention and treat trauma or hypothermia if present (**Figure 2**).[5] Rewarming is often the first line of treatment, which can lead to a reperfusion injury and subsequent inflammation.[6,12] Interventions, such as air drying, limb elevation, and systemic hydration, are recommended to prevent further tissue damage and restore blood flow.[6] Aspirin and ibuprofen are offered for anti-platelet, anti-inflammatory effects. Vasodilators and antiplatelet/fibrinolytic agents (eg, tissue plasminogen activator [tPA], heparin) can also be used in some cases. Off-label tPA administration is generally limited to hospital settings with intensive care monitoring capabilities. Contraindications for tPA include severe hypertension, recent trauma or stroke, and bleeding disorders.[6,15]

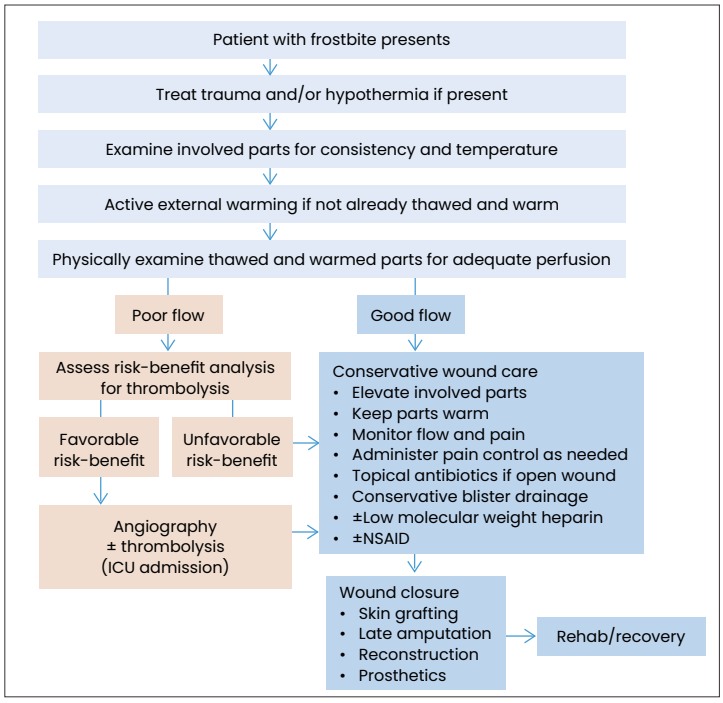


Figure 2: The current treatment algorithm for patients with frostbite.[5]

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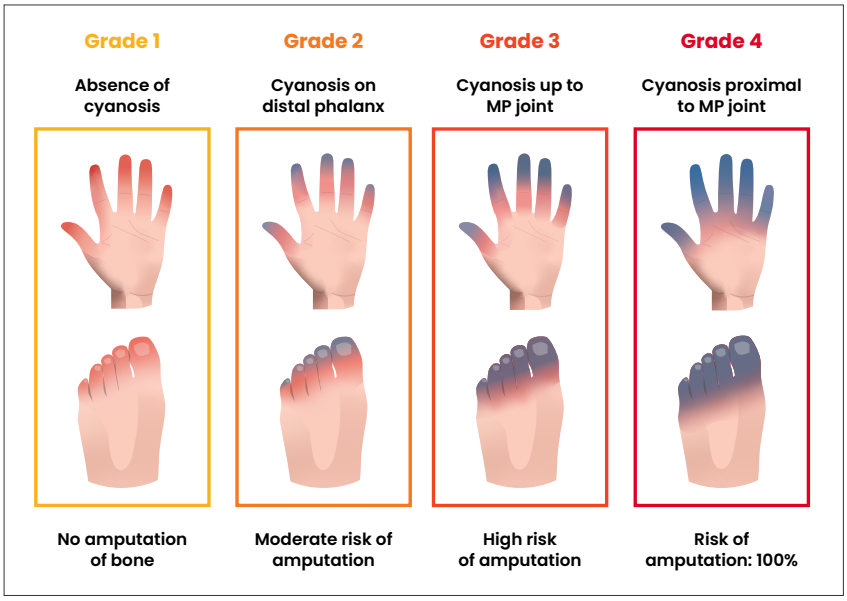
The Cauchy Classification Can Predict Risk of Amputation[11]

Emmanuel Cauchy proposed a classification for frostbite injuries in 2001 in order to predict outcomes for lesions or determine the probability of amputation (**Figure 3**). The system defines **4 grades of injury severity**: first grade, leading to recovery; second grade, leading to soft tissue amputation; third grade, leading to bone amputation; and fourth grade, leading to large amputation with systemic effects.[11]

On day 0 after rewarming, the **extent of the initial lesion** is used to determine the grade of the frostbite injury. Grade 1 injuries are absent of lesions, whereas grade 2 injuries have at least 1 lesion to the distal phalanx. The extent of initial lesion(s) for grade 3 and grade 4 injuries are to the intermediary and proximal phalanx and the carpal or tarsal, respectively.[11]

Figure 3: Cauchy classification system to assess frostbite severity.[11]



A **bone scan** on day 2 after rewarming is unnecessary for grade 1, but the scan would show tracer hypofixation for grade 2, tracer absence in the digit for grade 3, and absence to the carpal or tarsal for grade 4. Likewise, **blisters** are absent from grade 1 injuries, clear for grade 2, hemorrhagic to the digit for grade 3, and hemorrhagic to the carpal/tarsal for grade 4.[11]

The Wilderness Medical Society provides recommendations for the treatment of frostbite. In hospital or high-level field clinic, treatment of hypothermia, hydration, rapid rewarming of frozen tissues, systemic antibiotics, and tetanus prophylaxis are strongly recommended. Iloprost is recommended for grades 2-4 frostbite and intravenous (IV) or intra-arterial tPA is recommended for grades 3 and 4 frostbite.[6]

According to the Cauchy classification of frostbite, grade 1 injuries have a good **prognosis** with minimal amputation (**risk of amputation** of 0%-1%) or sequelae. Grade 2 injuries may necessitate tissue amputation and have resulting fingernail sequelae with a risk of amputation of 23%-39%. The prognosis of grade 3 injuries becomes poorer with a risk of amputation of 60%-83% of digits and subsequent functional sequelae. Grade 4 frostbite injuries have a risk of amputation of 98%-100% of limbs with possible systemic involvement and sepsis and functional sequelae moving forward.[11]

Table 1: The Cauchy classification of frostbite.

Frostbite injury of extremities					
Grade		**1**	**2**	**3**	**4**
Day 0 after rewarming	**Extent of initial lesion**	Absent	Distal phalanx	Intermediary and proximal phalanx	Carpal/tarsal
Day 2	**Bone scan**	Unnecessary	Tracer hypofixation	Tracer absent on digit	Tracer absent to carpal/tarsal
	Blisters	Absent	Clear	Hemorrhagic blisters on digit	Hemorrhagic blisters to carpal/tarsal
	Prognosis	• No amputation • No sequelae	• Tissue amputation • Fingernail sequelae	• Digit bone amputation • Functional sequelae	• Limb bone amputation • ± Systemic involvement • ± Sepsis • Functional sequelae
Risk of amputation[11,12]		0%-1%	23%-39%	60%-83%	98%-100%

Amputation Rates as Shown Across Multiple Studies Are Consistently High for Grade 3 and Grade 4 Frostbite

Several studies have reported the incidence of amputation in cases of severe frostbite, and there is an agreement as to the amputation rates of patients with grade 3 and grade 4 injuries.[16] Cauchy et al. defined the grades of frostbite injury by performing a retrospective review of French cases between 1985-1999 and found the amputation rate among patients with grade 3 frostbite was 60%-83%, whereas patients with grade 4 frostbite required amputations 98%-100% of the time.[11] Another study by Cauchy and colleagues published in 2011 reported a randomized control trial using patient data from 1996-2008. The study found that 58.3% of patients with grade 3 frostbite (and 47% of affected digits) required amputation, and both patients with grade 4 injuries (and all 9 impacted digits) needed to be amputated, which is consistent with their previous study.[17,18] A Canadian study by Crooks et al. reported that 44% of digits afflicted with grade 3 frostbite injuries needed to be amputated, and the amputation rate of digits with grade 4 frostbite was 95%.[19]

Severe Frostbite and Amputation Can Lead to Other Complications

Amputation and complications associated with severe frostbite are a significant burden to patients, the healthcare system, and society. Short-term complications include systemic involvement, sepsis, necrosis and the need for amputation, thrombosis, and gangrene.[11,13] Long-term complications include hyperhidrosis, cold-induced arthritis, functional impairment, cold sensitivity, consequences of limb loss, neuropathy, and chronic pain.[5,20] Frostbite can even lead to long-term disabilities. 13% of patients were unable to work at the same level they did prior to their injury, according to 1 study, and in the US military, 8% of patients were reassigned due to a frostbite injury.[21,22] A review of 493 patients with frostbite injury found that 69% of patients experienced long-term complications.[23]

Long-Term Complications[5,20]

- Neuropathy
- Chronic pain
- Cold hypersensitivity
- Hyperhidrosis
- Functional impairment
- Long-term effects of limb loss for individuals with amputation
- Cold injury-induced arthritis

Long-Term Disability[21,22]

- Case series report: 13% of patients were unable to work at same level prior to injury
- Study in US military: 8% of patients were reassigned due to frostbite injury

Frostbite Imposes a Substantial Economic Burden on the Healthcare System

Frostbite data have previously been compared to burn data due to their many similarities in classification and injury severity. Patients with frostbite injuries **require intensive care unit (ICU) care 26.5% of the time**, which is significantly more likely than burn injuries at 13.7% (*P*=.002). The **length of stay** in a hospital for a patient with frostbite injury is 8.1 days, whereas the length of stay for burn injuries is 4.0 days (*P*<.001). This adds up to significantly **higher hospital charges**. A frostbite injury can cost $43,400, whereas a burn injury costs $15,600 (*P*<.001).[24]

The National Inpatient Sample from 2016-2018 found an **overall incidence** of 2.9 severe frostbite patients per million each year in the US.[1] Of 8085 **hospital admissions**, 65% were for superficial frostbite, and 35% were for severe frostbite. The **estimated total charges** associated with primary hospitalization was $68,096, and the **average length of stay** was 9.4 days.[1]

Data from the 2016-2017 Nationwide Readmission Database of the Healthcare Cost and Utilization Project found an unplanned **readmission following frostbite injury rate** of 35.4% with an **average hospital length of stay** of 37.7 days and **average total cost** of $285,596.[25]

AURLUMYN: Product Overview

Indication and Usage[26]

AURLUMYN (iloprost) is a prostacyclin (PGI_2) mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations. Effectiveness was established in young, healthy adults who suffered frostbite at high altitudes.

IMPORTANT SAFETY INFORMATION *(cont.)*

Warnings and Precautions

- AURLUMYN may cause symptomatic hypotension. Correct hypotension prior to administration of AURLUMYN. Monitor vital signs while administering AURLUMYN.

Adverse Reactions

- Adverse events reported with the use of intravenous (IV) iloprost in patients with frostbite include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.

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Dosing and Administration

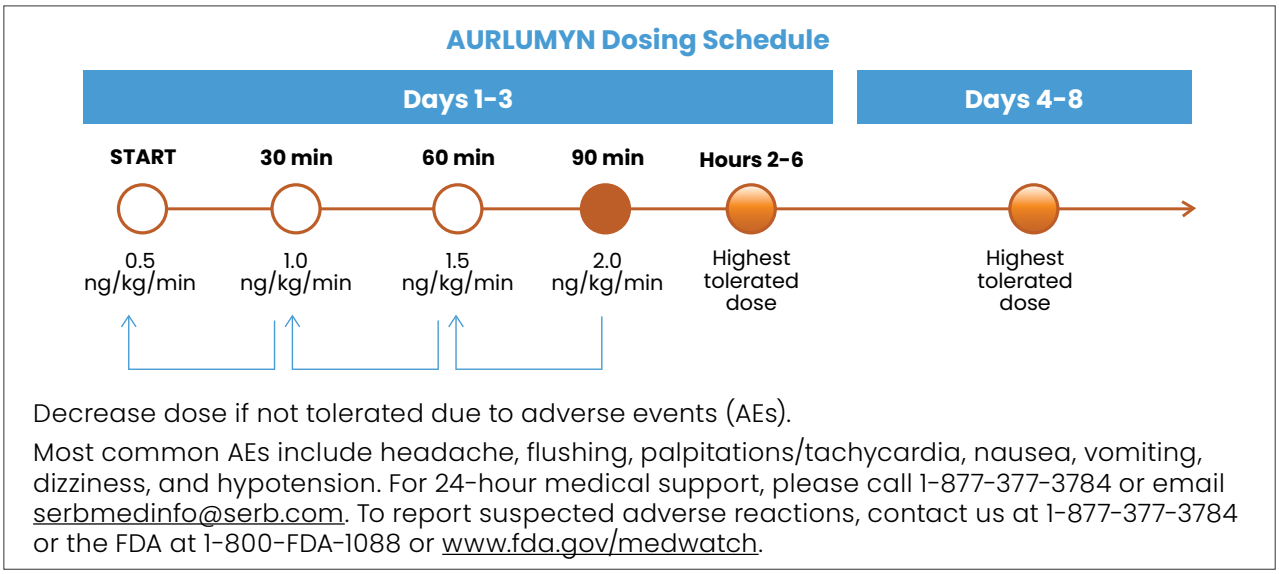
Recommended Dosage[26]

Monitor vital signs prior to the start of the infusion and with every dose increase.

Administer AURLUMYN as a continuous IV infusion over 6 hours each day for up to a maximum of 8 consecutive days.

- **Day 1:** Initiate the infusion at a rate of 0.5 ng/kg/min; increase in increments of 0.5 ng/kg/min every 30 minutes based on tolerability, up to 2 ng/kg/min
- **Days 2-3:** Repeat the dose titration steps described for day 1
- **Day 4 onward:** Initiate the infusion at the highest tolerated dose from the previous day; adjust the rate as needed based on tolerability

Figure 4: Administration regimen.[26]



Decrease dose if not tolerated due to adverse events (AEs).

Most common AEs include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension. For 24-hour medical support, please call 1-877-377-3784 or email serbmedinfo@serb.com. To report suspected adverse reactions, contact us at 1-877-377-3784 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Adverse reactions (eg, headache, flushing, jaw pain, myalgia, nausea, vomiting) may be dose limiting. If dose-limiting adverse reactions occur that cannot be tolerated by the patient, then decrease the dose in a stepwise manner by 0.5 ng/kg/min every 30 minutes until a tolerated dose is reached. If a dose-limiting adverse reaction occurs during administration of AURLUMYN at the starting dose, the infusion should be discontinued, and re-initiation of the infusion can be attempted after the event has resolved or been treated. If infusion is stopped at any point for a dose-limiting AE, infusion can be reinitiated at a previously tolerated dose/infusion rate once the event has resolved. The maximum tolerated dose should be maintained for the remaining 6-hour daily infusion.[26]

IMPORTANT SAFETY INFORMATION *(cont.)*

Use in Specific Populations

- Advise women not to breastfeed during treatment with AURLUMYN.
- The safety and efficacy of AURLUMYN in pediatric patients have not been established.
- Dosage adjustment is recommended in patients with moderate or severe hepatic impairment.
- In patients with eGFR <30 mL/min, dosage adjustment can be considered based on tolerability. The effect of dialysis on the clearance of AURLUMYN has not been evaluated.

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Dosing and Administration (cont.)

Preparation[26]

AURLUMYN comes as a 1 mL, 100 mcg/mL single-dose glass vial per carton and can be stored at room temperature.

- Use aseptic technique to prepare AURLUMYN
- Inspect the vial for particulate matter prior to administration. Do not use if the solution is discolored or cloudy or if foreign particles are present

Dilution[26]

1. Withdraw 1 mL (100 mcg) of AURLUMYN from vial
2. Transfer into 100 mL of 0.9% sodium chloride Injection, United States Pharmacopeia (USP) polyvinyl chloride (PVC) infusion bag to make a final concentration of 1 mcg/mL (1000 ng/mL)
3. Gently mix by slowly inverting the infusion bag—do not shake

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if visibly opaque particles, discoloration, or foreign particles are observed
- Immediately use diluted AURLUMYN infusion solution. If not used immediately, the diluted solution can be stored at room temperature (20°C-25°C [68°F-77°F]) for up to 4 hours

IMPORTANT SAFETY INFORMATION

INDICATION AND USAGE

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Dosing and Administration (cont.)

Administration[26]

Administer AURLUMYN as an IV infusion through a peripheral line or peripherally inserted central catheter using an infusion pump.

Use an infusion set with an in-line 0.22-micron or 0.2-micron filter.

Once diluted, AURLUMYN should be administered with an infusion pump that can support the minimum and maximum flow rates. The infusion pump used to administer AURLUMYN should:

- Be able to deliver rates 0.1-99.9 mL/h
- Adjust infusions rates with increments of 0.1 mL/h
- Be accurate to within 5% of programmed rate
- Be positive pressure driven (continuous or pulsatile)
- Have a reservoir and infusion line set made of PVC

Infusion rates may be calculated using the following formula:

$$\text{Infusion Rate (mL/h)} = \frac{\text{[Dose (ng/kg/min) x Weight (kg) x 60 min/h]}}{\text{Final Concentration (1000 ng/mL)}}$$

IMPORTANT NOTE: Avoid inadvertent administration of a bolus of the drug. Do not flush the catheter without withdrawing residual drug from the catheter system. Discard any unused portion.

IMPORTANT SAFETY INFORMATION *(cont.)*

Warnings and Precautions

- AURLUMYN may cause symptomatic hypotension. Correct hypotension prior to administration of AURLUMYN. Monitor vital signs while administering AURLUMYN.

Adverse Reactions

- Adverse events reported with the use of intravenous (IV) iloprost in patients with frostbite include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.

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Dosing and Administration (cont.)

Use in Patients With Hepatic Impairment[26]

Patients with moderate or severe hepatic impairment (Child-Pugh Class B or C): Initiate dosage at 0.25 ng/kg/min for 30 minutes, then continue titration in 0.5 ng/kg/min increments every 30 minutes according to tolerability to a maximum dose of 2 ng/kg/min.

Use in Patients With Renal Impairment[26]

Patients with renal impairment with estimated glomerular filtration rate (eGFR) <30 mL/min: Initiate and titrate dosing per recommended dosage. If patient cannot tolerate the starting dose of 0.5 ng/kg/min, the dose can be lowered to 0.25 ng/kg/min. The effect of dialysis on AURLUMYN exposure has not been evaluated. For patients requiring intermittent hemodialysis, consider AURLUMYN administration after the end of hemodialysis. Alternatively, hemodialysis can be started at least 1 hour after the end of AURLUMYN infusion.

IMPORTANT SAFETY INFORMATION *(cont.)*

Use in Specific Populations

- Advise women not to breastfeed during treatment with AURLUMYN.
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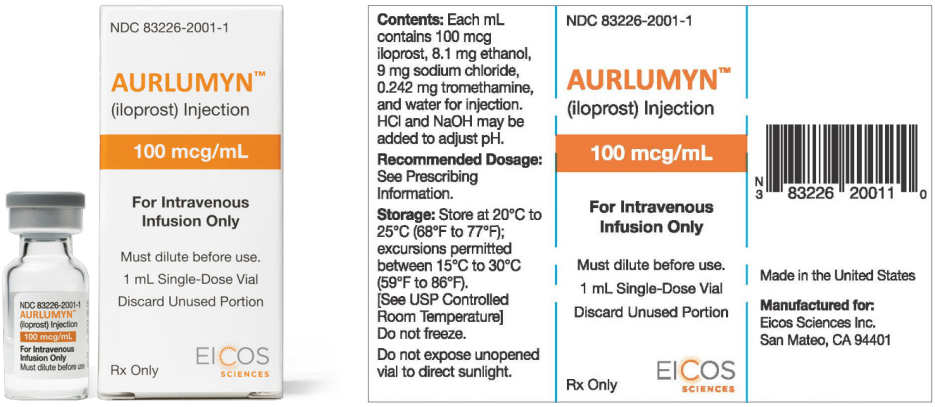
How Supplied[26]

AURLUMYN (iloprost) injection is a clear, colorless sterile solution supplied as a 100 mcg/mL single-dose glass vial per carton.

National Drug Code (NDC) (carton and vial): 83226-2001-1



Storage and Handling[26,27]

- AURLUMYN has a 30-month shelf life from the date of manufacture when stored at 20°C-25°C (68°F-77°F). The expiration date is printed on each AURLUMYN carton
- Unopened vials of AURLUMYN are stable until the date indicated on the package when stored at 20°C-25°C (68°F-77°F), with excursions permitted to 15°C-30°C (59°F-86°F)
- Unopened vials should be kept in the carton and not exposed to direct sunlight. DO NOT FREEZE

IMPORTANT SAFETY INFORMATION

INDICATION AND USAGE

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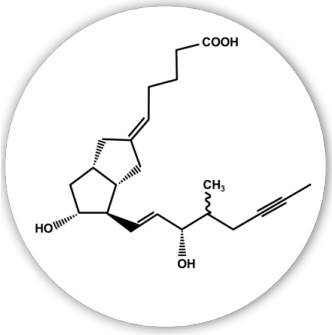
AURLUMYN: The First and Only FDA-Approved Drug Therapy to Treat Severe Frostbite in Adults

AURLUMYN Is a Synthetic Analog of Prostacyclin That Can Reduce Risk of Digit Amputations in Adults With Severe Frostbite[26]

Description

AURLUMYN contains iloprost, a synthetic analog of prostacyclin (PGI_2). The chemical name for iloprost is (5E)-[3aS,4R,5R,6aS)-5-hydroxy-4-[(1E)-(3S,4RS)-3-hydroxy-4-methyloct-1-en-6-ynyl]-hexahydropentalen-2(1H)-ylidene]pentanoic acid. Iloprost consists of a mixture of the 4R and 4S diastereoisomers at a ratio of approximately 53:47. Iloprost is an oily substance, which is soluble in methanol, ethanol, ethyl acetate, acetone, and pH 7 buffer, sparingly soluble in buffer pH 9, and very slightly soluble in distilled water, buffer pH 3, and buffer pH 5. The molecular formula of iloprost is $C_{22}H_{32}O_4$, and its molecular weight is 360.49. The structural formula is shown below:



AURLUMYN injection is a clear, colorless, sterile solution formulated for IV use. AURLUMYN is supplied in single-use glass vials containing 1 mL per vial. Each mL of the solution contains 100 mcg (0.1 mg) of iloprost as the active ingredient and the following inactive ingredients: 8.1 mg ethanol, 9 mg sodium chloride, and 0.242 mg tromethamine. Hydrochloric acid and sodium hydroxide is added to adjust pH to 8.3. The solution contains no preservatives.

IMPORTANT SAFETY INFORMATION *(cont.)*

Warnings and Precautions

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Adverse Reactions

- Adverse events reported with the use of intravenous (IV) iloprost in patients with frostbite include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.

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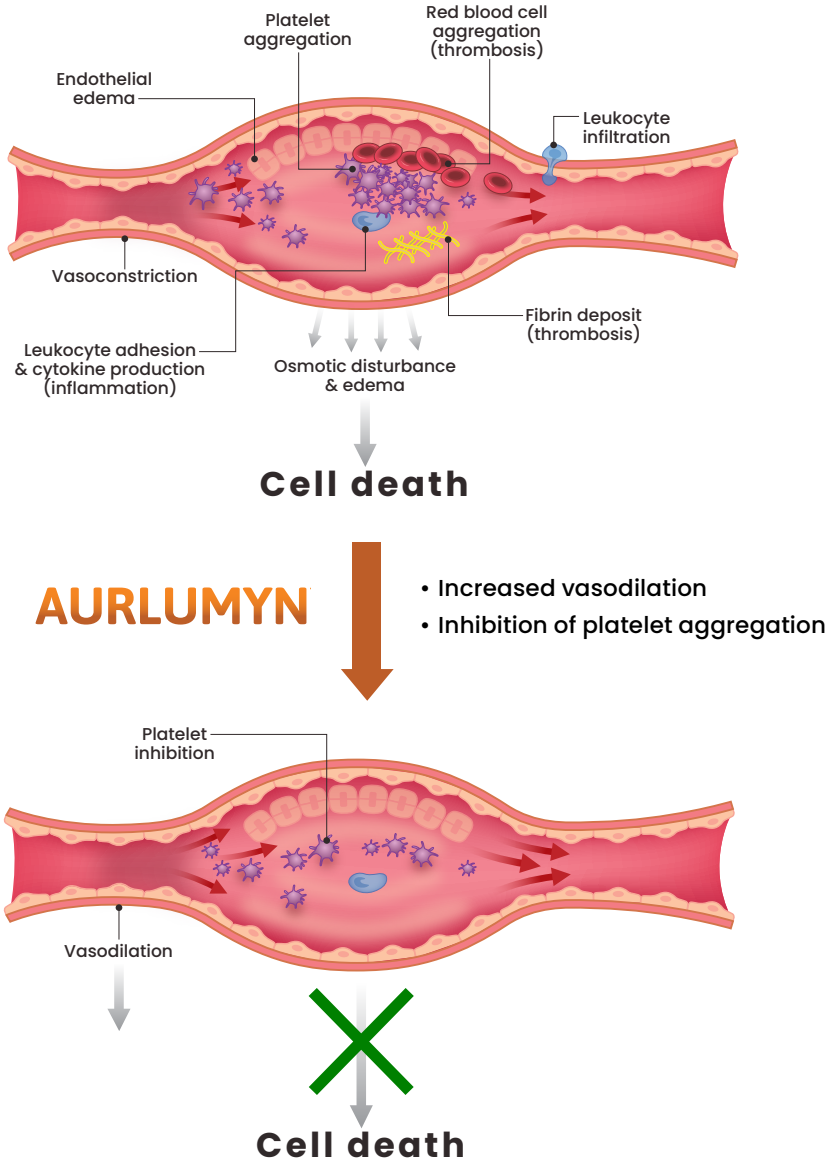
AURLUMYN: The First and Only FDA-Approved Drug Therapy to Treat Severe Frostbite in Adults (cont.)

Mechanism of Action[26]

AURLUMYN is a synthetic analog of prostacyclin. AURLUMYN is a vasodilator and inhibits platelet aggregation.



IMPORTANT SAFETY INFORMATION *(cont.)*

Use in Specific Populations

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Pharmacokinetics (PK)

General[26]

AURLUMYN administered intravenously has linear PK over the dose range of 1-3 ng/kg/min. The half-life of AURLUMYN is 20-30 minutes.

Absorption and Distribution[26]

Following IV infusion, the apparent steady-state volume of distribution was 0.7-0.8 L/kg in healthy subjects. AURLUMYN is approximately 60% protein-bound, mainly to albumin, and this ratio is concentration-independent in the range of 30-3000 pg/mL.

Metabolism and Excretion[26]

In vitro studies reveal that cytochrome P450–dependent metabolism plays only a minor role in the biotransformation of AURLUMYN. AURLUMYN is metabolized principally via ß-oxidation of the carboxyl side chain. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form. In animal experiments, tetranor-iloprost was pharmacologically inactive.

Clearance in normal subjects was approximately 20 mL/min/kg.

A mass-balance study using intravenously and orally administered [^{3}H]-iloprost in healthy subjects (n=8) showed recovery of 81% of total radioactivity over 14 hours after dose, with 68% and 12% recoveries in urine and feces, respectively.

Drug Interactions[26]

IV infusion of AURLUMYN had no effect on the PK of digoxin. Acetylsalicylic acid did not alter the clearance (PK) of AURLUMYN.

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Clinical Development Overview

There is a body of evidence supporting the efficacy and safety of iloprost IV* in the treatment of severe frostbite (**Table 2**).

Table 2: Clinical development overview.

Pivotal data				
Study	**Study design**	**Location**	**Study size**	**Primary endpoints/ effectiveness outcome**
Cauchy et al. *N Engl J Med.* 2011; Cheguillaume. *Hum Med Pathol.* 2011[17,18]	Randomized, controlled, open-label study	Single center in France	47 patients with severe distal frostbite	Evaluated number of patients with amputation predicted by bone scan. Amputation status assessed 3 months after treatment
Published literature with iloprost IV* in frostbite				
Study	**Study design**	**Location**	**Study size**	**Endpoints**
Crooks et al. *CJEM.* 2022[19]	Retrospective, observational study	Multicenter in Canada	90 patients with frostbite injuries	Evaluated rate of affected digits amputated, stratified by frostbite severity
Poole et al. *CMAJ Open.* 2021[28]	Retrospective series of cases	Single center in Canada	142 patients with grade 2-4 frostbite	Evaluated number of digits salvaged compared to number of digits affected
Magnan et al. *Medicina (Kaunas).* 2021[29]	Prospective and retrospective, nonrandomized study	Multicenter in France and Switzerland	58 patients with grade 3-4 frostbite	Evaluated number of preserved segments and rate of amputated segments

Safety data evaluating AURLUMYN in patients with systemic sclerosis are also included in the safety section of this document.

*Study was conducted in a different formulation of iloprost IV.

IMPORTANT SAFETY INFORMATION *(cont.)*

Warnings and Precautions

- AURLUMYN may cause symptomatic hypotension. Correct hypotension prior to administration of AURLUMYN. Monitor vital signs while administering AURLUMYN.

Adverse Reactions

- Adverse events reported with the use of intravenous (IV) iloprost in patients with frostbite include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Iloprost IV* Pivotal Trial Study Design

The Pivotal Trial Was Designed to Assess Risk for Amputation in Patients With Severe Frostbite[17,18]

The efficacy of iloprost IV for the treatment of severe frostbite to reduce the risk of digit amputations was evaluated in a randomized, controlled, open-label trial that enrolled adult patients with severe frostbite. Severe frostbite was defined as having at least 1 digit (finger or toe) with frostbite grade 3 (lesion extending just past the proximal phalanx) or grade 4 (lesion extending proximal to the metacarpal or metatarsal joint). The trial randomized 47 patients at a single site between 1996-2008. The primary endpoint was the presence of an anomaly (absence of uptake) in the bone phase of a technetium 99m (Tc-99m) scan performed 7 days after initial clinical presentation of frostbite (BS2 bone scintigraphy anomaly) in at least 1 finger or toe affected by severe frostbite. This BS2 bone scintigraphy anomaly was used to predict risk of amputation. An additional follow-up was performed 3 months after treatment to confirm amputation. These data were obtained for 40/47 patients, which was concordant with the bone scintigraphy results (**Figure 5**).

Figure 5: Iloprost IV pivotal trial study design.[17,27]

Randomized, Controlled, Open-Label Study of Iloprost IV for the Treatment of Severe Frostbite (1996-2008)

Patient with frostbite

Rapid warming protocol:
Aspirin 250 mg direct IV
buflomedil 400 mg IV 1 hour
Warm bath 38°C 1 hour

Clinical assessment

≥Severe frostbite (grades 3 and 4)
Clinical and paraclinical assessment, inclusion criteria met information and informed consent (n=46)

Non-serious frostbite only (grades 1 and 2)
Supportive care

Primary efficacy endpoint: number of patients with amputation predicted by bone scan following 8 days of treatment
- Amputation status assessed 3 months after treatment to confirm predicted outcome based on scintigraphy

Secondary efficacy endpoint: number of digits with amputation predicted by bone scan

Randomization

	Day 0	Day 1-day 7
Control Buflomedil (alpha blocker vasodilator)		**Buflomedil** 400 mg IV over 1 h **Aspirin** 250 mg direct IV
Iloprost IV (prostacyclin analog)	**Iloprost IV** 0.5-2 ng/kg/min IV over 6 h	**Iloprost IV** 0.5-2 ng/kg/min IV over 6 h *6 h later:* **Aspirin** 250 mg direct IV
Iloprost IV+rtPA (prostacyclin analog)+rtPA	**rtPA** GUSTO protocol (≤100 mg in 90 min) *0.5 h later:* **Iloprost IV** 0.5-2 ng/kg/min IV over 6 h	**Iloprost IV** 0.5-2 ng/kg/min IV over 6 h *6 h later:* **Aspirin** 250 mg direct IV

Each patient underwent a first scintigraphy (BS1) on day 2 or 3, repeated 5 days later (BS2).

Inclusion and Exclusion Criteria[17,18]

The pivotal trial included adults with severe distal frostbite.

Table 3: Iloprost IV pivotal trial inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• **Patients with severe distal frostbite** Severe distal frostbite is defined by the presence (after performing conventional emergency treatment combining rapid warming in water at 38°C for 1 hour, aspirin 250 mg by direct IV, and buflomedil 400 mg IV over 1 hour) of ≥1 toe or finger with ≥1 fully cyanotic phalanx. This corresponds to frostbite grades 3 and 4 of the new frostbite classification	• A pathology or associated treatment contradicting the use of aspirin, buflomedil, iloprost IV, or recombinant tissue-type plasminogen activator (rtPA) • Patients with associated significant secondary trauma • Moderate or severe associated hypothermia • Minor patients without legal guardian authorization • A psychological state that does not allow for proper compliance with and monitoring of the treatment

*Study was conducted in a different formulation of iloprost IV.

IMPORTANT SAFETY INFORMATION *(cont.)*

Use in Specific Populations

- Advise women not to breastfeed during treatment with AURLUMYN.
- The safety and efficacy of AURLUMYN in pediatric patients have not been established.
- Dosage adjustment is recommended in patients with moderate or severe hepatic impairment.
- In patients with eGFR <30 mL/min, dosage adjustment can be considered based on tolerability. The effect of dialysis on the clearance of AURLUMYN has not been evaluated.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Iloprost IV Pivotal Trial Study Design (cont.)

Baseline Demographics[18,27]

Baseline characteristics were consistent across study arms (**Table 4**).

Table 4: Iloprost IV pivotal trial baseline demographics.

	Study arm		
	Control (n=15)	**Iloprost IV (n=16)**	**Iloprost IV+rtPA (n=16)**
Mean age, y	35.4	29.3	34.7
Males, %	80	100	100
Comorbidities, %	Diabetes: 0 Smoking: 6.4 Raynaud's disease: 4.2		
Causes of frostbite, %	Sports activities: 95.7		
Frostbite severity, n/N (%)	Grade 2: 1/15 (6.7)* Grade 3: 12/15 (80)* Grade 4: 2/15 (13.3)*	Grade 2: 0/16 (0)* Grade 3: 14/16 (87.5)* Grade 4: 2/16 (12.5)*	Grade 2: 0/16 (0)* Grade 3: 10/16 (62.5)* Grade 4: 6/16 (37.5)*
Location of frostbite, n (%)	Feet: 7 (47) Hands: 6 (40) Hands and feet: 2 (13)	Feet: 7 (44) Hands: 1 (6) Hands and feet: 8 (50)	Feet: 4 (25) Hands: 7 (44) Hands and feet: 5 (31)
Time to treatment, n (%)	≤12 h: 6 (40) ≤24 h: 10 (66.7)	≤12 h: 11 (68.7) ≤24 h: 15 (93.7)	≤12 h: 14 (87.5) ≤24 h: 14 (87.5)

*Study was conducted in a different formulation of iloprost IV.

IMPORTANT SAFETY INFORMATION

INDICATION AND USAGE

AURLUMYN is a prostacyclin mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations. Effectiveness was established in young, healthy adults who suffered frostbite at high altitudes.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

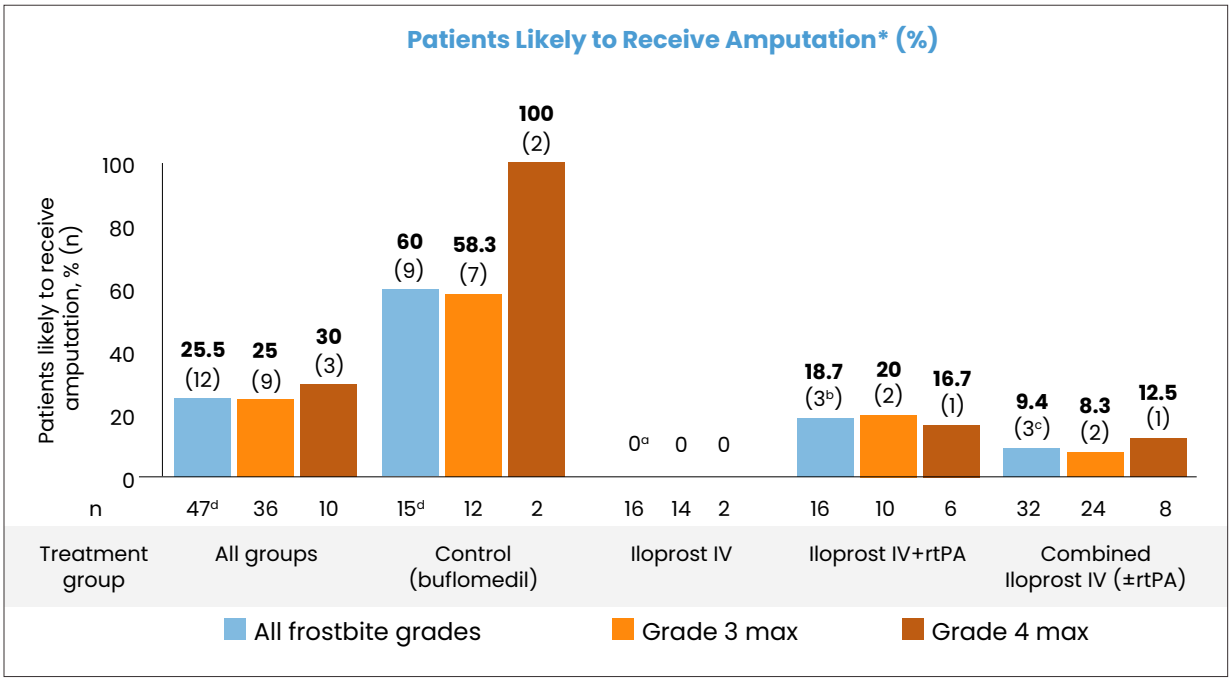
Iloprost IV Pivotal Trial Efficacy Data

Primary Endpoint: Number of Patients With Predicted Amputation

The primary endpoint was the number of patients with amputation predicted by bone scan following 8 days of treatment. The amputation status was assessed 3 months after treatment to confirm the outcome predicted by scintigraphy in a post hoc analysis.[18,27]

Iloprost IV significantly decreased the likelihood of amputation in patients with severe frostbite. The prognostic risk of amputation regardless of frostbite grade was 60.0% (control), 0.0% (iloprost IV), and 18.7% (iloprost IV+rtPA). The iloprost IV and iloprost IV+rtPA treatment groups had a statistically significant lower risk of amputation vs the control group (*P*<.001 and *P*<.03, respectively). When the 2 iloprost IV groups were combined (ie, iloprost IV and iloprost IV+rtPA), the risk of amputation was significantly lower than in the control group: 9.4% vs 60.0% (*P*<.001) (**Figure 6**).[17,18]

Figure 6: Primary endpoint: proportion of patients predicted to receive amputation.*[,18]



*Likelihood of amputation was determined by the presence of a radiotracer anomaly in ≥1 digit in the bone phase of technetium scintigraphy after 8 days of treatment.

[a]*P*=.0002 vs control; [b]*P*<.0290 vs control; [c]*P*=.0005 vs control; [d]One patient enrolled in the control group was found to have only grade 2 frostbite.

IMPORTANT SAFETY INFORMATION *(cont.)*

Warnings and Precautions

- AURLUMYN may cause symptomatic hypotension. Correct hypotension prior to administration of AURLUMYN. Monitor vital signs while administering AURLUMYN.

Adverse Reactions

- Adverse events reported with the use of intravenous (IV) iloprost in patients with frostbite include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

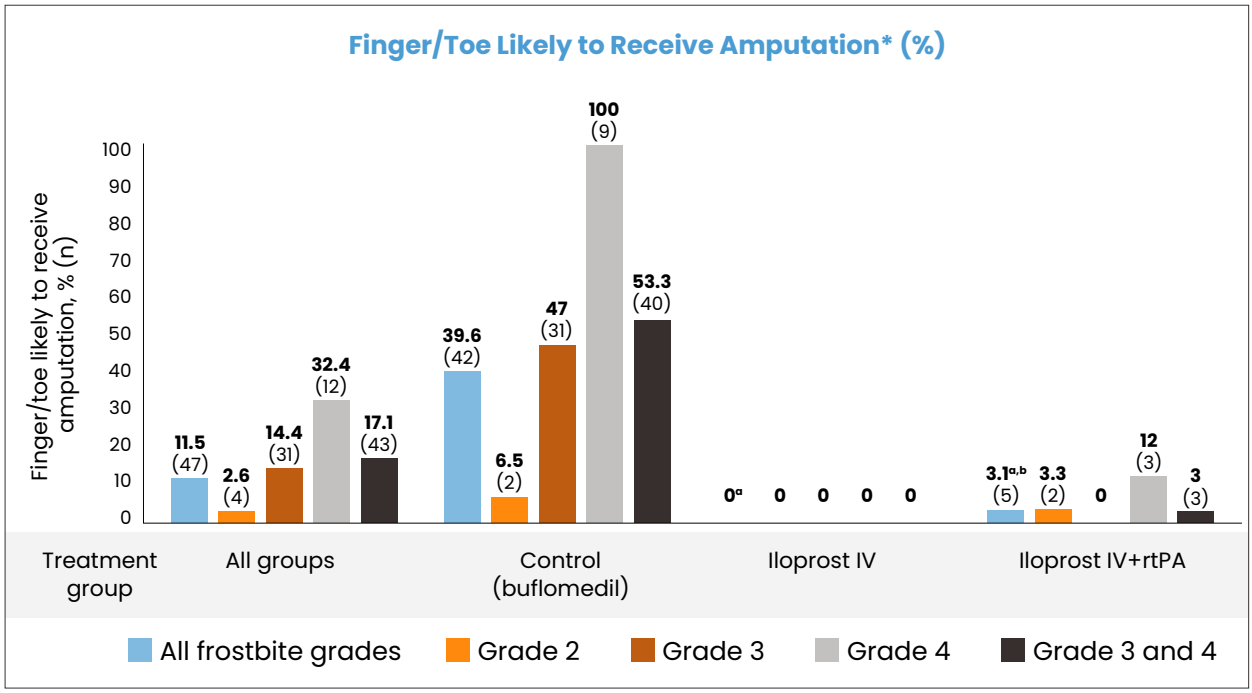
Iloprost IV Pivotal Trial Efficacy Data (cont.)

Secondary Endpoint: Number of Digits With Predicted Amputation

The secondary endpoint was number of digits with amputation predicted by bone scan following 8 days of treatment.[18]

A decrease in the likelihood of finger and toe amputations in patients with severe frostbite was observed in the iloprost IV group. In all frostbite grades combined and regardless of the time to treatment, the risk of amputation of a finger or toe with frostbite treated with buflomedil was 39.6%. No digits (0 fingers or toes out of 142) were amputated in patients treated with iloprost IV alone and 3.1% were amputated (5 out of 159) in patients treated with iloprost IV+rtPA. The difference was statistically significant (*P*<.001) in both cases. There was no significant difference between the patients treated with iloprost IV alone and those treated with iloprost IV+rtPA (*P*>.06) (**Figure 7**).[17,18]

Figure 7: Secondary endpoint: number of digits predicted to be amputated.*[,17,18]



*Likelihood of amputation was determined by the presence of a radiotracer anomaly in at ≥1 digit in the bone phase of technetium scintigraphy after 8 days of treatment.

[a]*P*<.001 vs control; [b]*P*>.06 vs iloprost IV alone.

IMPORTANT SAFETY INFORMATION *(cont.)*

Use in Specific Populations

- Advise women not to breastfeed during treatment with AURLUMYN.
- The safety and efficacy of AURLUMYN in pediatric patients have not been established.
- Dosage adjustment is recommended in patients with moderate or severe hepatic impairment.
- In patients with eGFR <30 mL/min, dosage adjustment can be considered based on tolerability. The effect of dialysis on the clearance of AURLUMYN has not been evaluated.

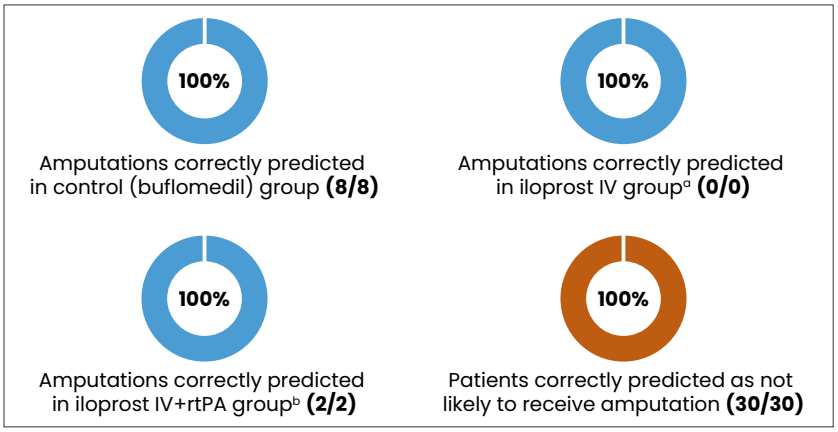
Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Iloprost IV Pivotal Trial Efficacy Data (cont.)

Follow-Up to Confirm Actual Amputation Rates After Treatment[27]

Additional follow-up data confirming amputation were consistent with the bone scintigraphy results in the primary endpoint. Confirmatory amputation outcomes were obtained 3 months after treatment for 40/47 patients. 3-month post-treatment data were not available for 5 patients who did not have the presence of a radiotracer anomaly, and 1 patient in the control group and 1 patient in the iloprost IV+rtPA group who did have the presence of a radiotracer anomaly. Bone scintigraphy reliably predicted likelihood of amputation in 40/40 (100%) of patients for whom 3-month follow-up data were available (**Figure 8**).

Figure 8: 40 of 40 (100%) amputation outcomes correctly predicted (of patients for whom 3-month follow-up data were available).



[a]*P*=.0005 vs control; [b]*P*=.0209 vs control.

Pivotal Trial Safety Findings[27]

Iloprost IV was well tolerated with no serious AEs or discontinuations noted in the pivotal trial (**Table 5**).

Table 5: Common AEs from the combined iloprost IV group.

	Combined iloprost IV (±rtPA) (n=32)
Vasomotor AEs, n (%)	18 (56.4)*
Headache, n (%)	17 (53.1)
Flushing, n (%)	(55)[a]
Nausea, n (%)	8 (25)
Palpitations, n (%)	5 (15.6)
Vomiting, n (%)	2 (6.2)
Bleeding, n (%)	0 (0)[b]
AEs leading to dose adjustment, n (%)	10 (31.2)
AEs leading to discontinuation, n (%)	0 (0)

*Calculated by the sponsor.
[a]n not available; % shown from Cauchy, 2011; [b]Cauchy, 2011 reported local, regional, or systemic bleeding complications in 0 patients in the iloprost IV arm, iloprost IV+rtPA arm, or SoC arm.

IMPORTANT SAFETY INFORMATION

INDICATION AND USAGE

AURLUMYN is a prostacyclin mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations. Effectiveness was established in young, healthy adults who suffered frostbite at high altitudes.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Iloprost IV* Retrospective Study Was Designed to Assess Rate of Digit Amputation by Frostbite Severity[19]

Crooks Study Design

Patient with frostbite injuries[a] from April 2017-April 2020 (n=525)

Initial screening of triage note, visit diagnosis, and ED consults placed

Charts included if:
- Grade 2-4 frostbite
- Plastic surgery consultation

Participants included in study (n=90)

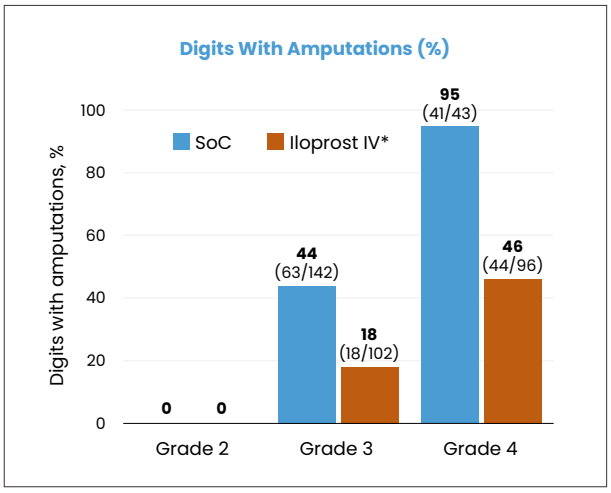
Historical control[b] (n=64)

Participants treated with iloprost IV for 5 days[c] (n=26)
- Complete 5-day course (n=23)
- Incomplete 5-day course (n=3)
  Discontinued iloprost IV due to low injury severity (n=2)
- Minor AEs (n=6)
- AE resulting in dose lowering (n=5)
- AE resulting in discontinued iloprost IV (n=1)

[a]Consecutive patients who presented to Calgary emergency departments (EDs); [b]Historical control: patients prior to February 2019 who were managed with SoC (local best practice without iloprost IV); [c]Iloprost IV group: patients from February 2019 onward who were managed with a 5-day iloprost IV infusion protocol.

This was a multicenter, retrospective, observational study of iloprost IV for the treatment of frostbite. The primary effectiveness outcome was the rate of affected digits amputated, stratified by frostbite severity.

Crooks Results



No digit amputations were required for patients with grade 2 injuries in either group. The rates of digital amputations were lower in the iloprost IV cohort vs SoC cohort for grade 3 and grade 4 injuries. The rate of grade 3 frostbite in the iloprost IV group was 18/102 (18%) vs the SoC group was 63/142 (44%). The rate of grade 4 frostbite in the iloprost IV group was 44/96 (46%) vs the SoC group, which was 41/43 (95%). There were no predefined serious AEs with iloprost IV reported. Minor AEs, including headache and tachycardia, occurred in 6 (23%) patients.

*Study was conducted in a different formulation of iloprost IV.

IMPORTANT SAFETY INFORMATION *(cont.)*

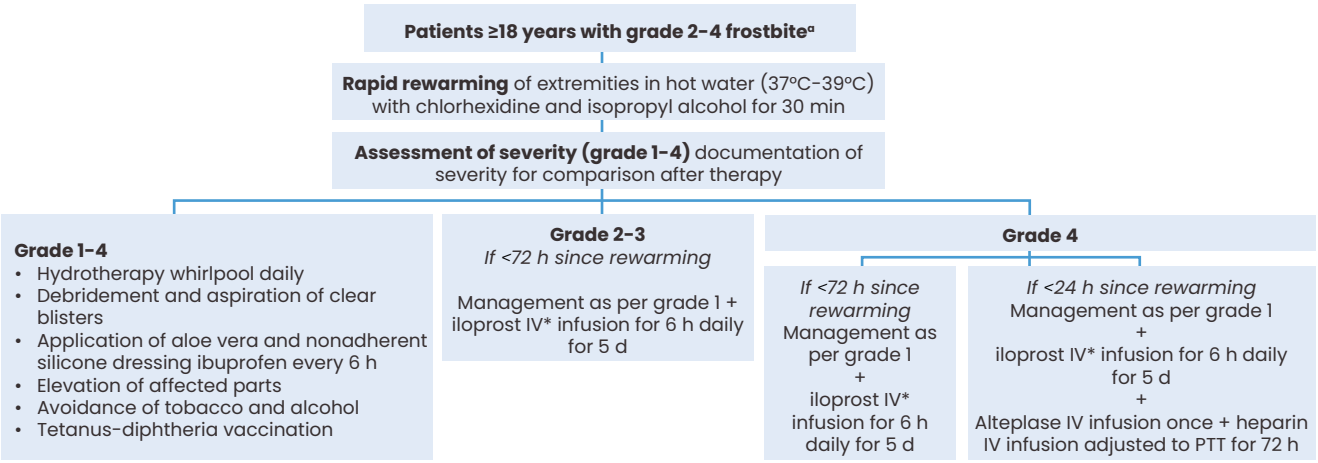
Warnings and Precautions

- AURLUMYN may cause symptomatic hypotension. Correct hypotension prior to administration of AURLUMYN. Monitor vital signs while administering AURLUMYN.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

All Digits Were Salvaged in Patients With Grade 3 Frostbite and 50% of Digits Were Salvaged in Patients With Grade 4 Frostbite[28]

Poole Study Design

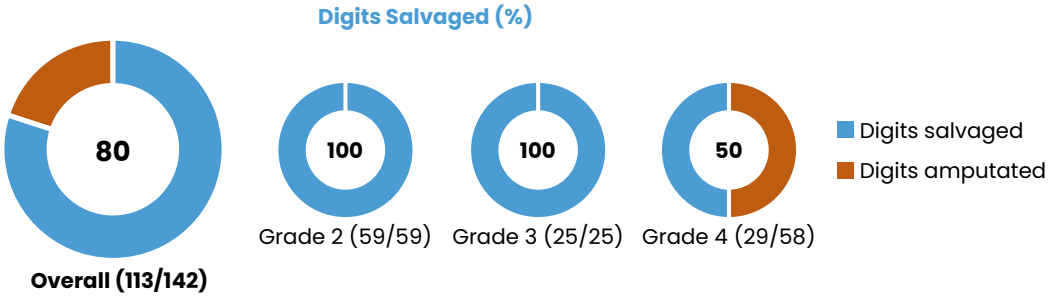


[a]Patients who presented to Whitehorse General Hospital, a rural and remote hospital, with grade 2–4 frostbite and treated with iloprost IV between February 9, 2015–February 8, 2020.

PTT, partial thromboplastin time.

This was a single-center retrospective series of cases in Whitehorse, Yukon Territory, Canada studying the use of iloprost IV for 5 days in patients with grade 2-4 frostbite. Exclusion criteria included patients who presented 72 hours or more after rewarming, and the primary outcome was the number of digits salvaged compared to the number of digits affected. The study was conducted in a location that sees many athletes for extreme outdoor sports. The study included patients ≥18 years of age with frostbite. Precipitating events for patients included sports (45%), alcohol use (27%), car accident/breakdown (14%), work/labor (9%), and psychiatric disorders (4%). Patients had grade 2 (45%), grade 3 (23%), or grade 4 (32%) frostbite.

Poole Results



142 digits in 22 patients were included: 59 as grade 2; 25 as grade 3; and 58 as grade 4. Four patients required amputation. All 29 digits amputated had grade 4 frostbite, with the majority of digits amputated (19) from 1 patient. The most common AE was headache in 50% of patients. One patient had bleeding from an altercation injury and was also receiving anticoagulant for venous thromboembolism prophylaxis, which may have contributed to the bleeding. One patient developed a duodenal ulcer thought to be related to the use of ibuprofen (2400 mg/d for 5 days) without a gastric-protecting agent. Of 5 patients receiving alteplase and heparin, 2 had bleeding requiring blood transfusion, which is an expected risk associated with thrombolytic and anticoagulant use.

*Study was conducted in a different formulation of iloprost IV.

IMPORTANT SAFETY INFORMATION *(cont.)*

Adverse Reactions

- Adverse events reported with the use of intravenous (IV) iloprost in patients with frostbite include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Improved Rate of Preserved Digits With Severe Frostbite Injuries Was Observed With the Addition of Hyperbaric Oxygen to Standardized Treatment With Iloprost IV[a,29]

	Prospective cohort (2013-2019): SOS-frostbite group	Retrospective cohort (2000-2012): Control group
Study type		
Study criteria	28 patients • Grade 3, 4 frostbite • SOS-frostbite protocol (standardized treatment with iloprost IV+HBO[b]) • Medical care delay <72 h	30 patients • Grade 3, 4 frostbite • Standardized treatment with iloprost IV • Medical care delay <72 h
Efficacy results	**85%** of injured segments[c] were preserved in patients treated with **iloprost IV alone**	**98%** of injured segments[c] were preserved in patients treated with **iloprost IV and HBO**

- Magnan et al. conducted an observational study in 2021 that included 58 patients
- The ratio of amputation of injured digits were compared in patients with severe frostbite injuries who received iloprost IV±hyperbaric oxygen (HBO)
- Improved rates of preserved digits were observed with the addition of HBO to the standardized treatment protocol with iloprost IV

[a]Frostbitten extremities were rewarmed and patients were given oral aspirin. Patients with injuries graded 3 or 4 were hospitalized for 7 days to receive daily iloprost IV infusions, aspirin, antibiotics, and wound care with topical hyaluronic acid; [b]For HBO treatment, patients received their first HBO session as soon as possible after the first iloprost IV infusion (range 1-6 hours post infusion) for 150 minutes at 2.5 atmospheres absolute (ATA) once daily during iloprost IV treatment and for 7 additional days after (14 HBO sessions in total); [c]Each phalanx and each metacarpal or metatarsal is defined as a segment.

IMPORTANT SAFETY INFORMATION *(cont.)*

Use in Specific Populations

- Advise women not to breastfeed during treatment with AURLUMYN.
- The safety and efficacy of AURLUMYN in pediatric patients have not been established.
- Dosage adjustment is recommended in patients with moderate or severe hepatic impairment.
- In patients with eGFR <30 mL/min, dosage adjustment can be considered based on tolerability. The effect of dialysis on the clearance of AURLUMYN has not been evaluated.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Updates to Clinical Practice Guidelines to Include Iloprost IV[6]

Wilderness Medical Society Clinical Practice Guidelines (2024)[6]

1. Treat hypothermia or serious trauma
2. Rapidly rewarm until soft and pliable to the touch
3. Ibuprofen
4. Pain medication
5. Tetanus prophylaxis
6. Air dry
7. Debridement
8. Topical aloe vera
9. Dry, bulky dressings
10. Elevate
11. Systemic hydration
12. Thrombolytic therapy
13. **Iloprost IV: consider for deep frostbite (grades 2-4)***
14. Examination and imagery to identify surgical margins

- In the absence of large-scale randomized trials and in light of available evidence, iloprost IV should be considered a first-line therapy for grade 3-4 frostbite <48 hours after thawing and possible for up to 72 hours.[6]
- It should be given as soon as possible after rewarming.[6]
- Authors suggest use of iloprost IV for deep frostbite extending to the distal interphalangeal joint or more proximal (grades 2-4), up to 72 hours after rewarming, but ideally as soon as possible.[6]
  - *Recommendation: Strong recommendation, low quality evidence*

*AURLUMYN is indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations.[26]

Of note, iloprost IV was not commercially available when authors met in 2022 to update **the American Burn Association Clinical Practice Guidelines** on the Treatment of Severe Frostbite.[30]

IMPORTANT SAFETY INFORMATION

INDICATION AND USAGE

AURLUMYN is a prostacyclin mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations. Effectiveness was established in young, healthy adults who suffered frostbite at high altitudes.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Safety Information

Adverse Events[26]

AEs reported with the use of IV AURLUMYN in patients with frostbite from the published literature include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.

Pre-marketing safety data on AURLUMYN were obtained from 116 patients with systemic sclerosis receiving AURLUMYN in 2 multicenter, double-blind, randomized, placebo-controlled studies in patients with systemic sclerosis experiencing symptomatic digital ischemic episodes (Raynaud's phenomenon). Patients received IV AURLUMYN administered as a continuous infusion over 6 hours each day for 5 consecutive days, and the dose was adjusted according to individual tolerability within the range of 0.5-2.0 ng/kg/min. The observed safety profile in these patients was similar to that observed with IV AURLUMYN.

The Most Common AEs Observed With Iloprost IV* in the Cauchy 2011, Crooks 2022, and Poole 2021 Studies Were Headache, Nausea, and Flushing[27]

	Cauchy, 2011 Iloprost IV±tPA*,[17] (n=32)	Crooks, 2022 Iloprost IV±tPA and heparin*,[19] (n=26)	Poole, 2021 Iloprost IV±tPA and heparin*,[a,28] (n=22)
AE, n (%)			
Headache	17 (53.1)	3 (11.5)	11 (50)
Flushing	(55)[b]	NR	8 (36)
Nausea	8 (25)	NR	6 (27)
Palpitations	5 (15.6)	NR	NR
Tachycardia	NR	3 (11.5)	8 (36)[c]
Vomiting	2 (6.2)	NR	2 (9)
Dizziness	NR	NR	2 (9)
Hypotension	NR	NR	1 (4)[d]
Bleeding	0	NR	1 (4)
AEs leading to dose adjustment, n (%)	**10 (31.2)**	**5 (19.2)**	**0**
AEs leading to discontinuation, n (%)	**0**	**1 (3.8)**	**0**

*Study was conducted in a different formulation of iloprost IV.
[a]Only AURLUMYN-associated AEs are captured in the table; tPA-associated AEs occurred in 2/5 patients treated with tPA (40%);
[b]It was unclear whether these data were for the iloprost-treated patients and AURLUMYN+tPA–treated patients or for all patients;
[c]Tachycardia was defined as a heart rate of >100 beats/min; [d]Hypotension was defined as blood pressure of <90/50 mm Hg.

NR, not reported.

IMPORTANT SAFETY INFORMATION *(cont.)*

Warnings and Precautions

- AURLUMYN may cause symptomatic hypotension. Correct hypotension prior to administration of AURLUMYN. Monitor vital signs while administering AURLUMYN.

Adverse Reactions

- Adverse events reported with the use of intravenous (IV) iloprost in patients with frostbite include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Safety Information (cont.)

Contraindications[26]

None.

Warnings and Precautions[26]

AURLUMYN is a systemic vasodilator and may cause symptomatic hypotension. Correct hypotension prior to administration of AURLUMYN. Monitor vital signs while administering AURLUMYN. Consider temporary discontinuation of concomitant vasodilator or other antihypertensive medications while administering AURLUMYN to reduce potential additive hypotensive effects. Consider down-titration or discontinuation of AURLUMYN if hypotension persists despite discontinuation of other antihypertensives and fluid resuscitation.

Drug Interactions[26]

IV infusion of AURLUMYN had no effect on the PK of digoxin. Acetylsalicylic acid did not alter the clearance (PK) of AURLUMYN.

IMPORTANT SAFETY INFORMATION *(cont.)*

Use in Specific Populations

- Advise women not to breastfeed during treatment with AURLUMYN.
- The safety and efficacy of AURLUMYN in pediatric patients have not been established.
- Dosage adjustment is recommended in patients with moderate or severe hepatic impairment.
- In patients with eGFR <30 mL/min, dosage adjustment can be considered based on tolerability. The effect of dialysis on the clearance of AURLUMYN has not been evaluated.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Use in Specific Populations

Pregnancy[26]

Risk Summary

There are no available data with AURLUMYN during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are limited published cases of inhaled AURLUMYN use during pregnancy, primarily during the second and third trimesters, that have not identified a drug-associated risk of adverse maternal or fetal outcomes. In animal reproductive studies, administration of continuous IV AURLUMYN to pregnant Han-Wistar rats during organogenesis at doses 2-times the maximum recommended human dose on a mg/m^2 basis resulted in adverse developmental outcomes. However, there were no adverse developmental outcomes with oral or IV administration of AURLUMYN to pregnant Sprague-Dawley rats, rabbits, and monkeys at doses 1111-, 1061-, and 12-times, respectively, the maximum recommended human dose by C_{max}.

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Lactation[26]

Risk Summary

There are no data on the presence of AURLUMYN in human milk, the effects on the breastfed infant, or the effects on milk production. AURLUMYN is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions, advise women not to breastfeed during treatment with AURLUMYN.

Pediatric Use[26]

Safety and efficacy in pediatric patients have not been established.

Geriatric Use[26]

Clinical studies of AURLUMYN did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently than younger subjects. Other reported clinical experience with AURLUMYN has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

IMPORTANT SAFETY INFORMATION

INDICATION AND USAGE

AURLUMYN is a prostacyclin mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations. Effectiveness was established in young, healthy adults who suffered frostbite at high altitudes.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Use in Specific Populations (cont.)

Hepatic Impairment[26]

In an IV AURLUMYN study in patients with liver cirrhosis, the mean clearance in Child-Pugh Class B subjects (n=5) was approximately 10 mL/min/kg (half that of healthy subjects based on a cross-study comparison). In patients with moderate or severe hepatic impairment (Child-Pugh Class B or C), use a lower starting dose of 0.25 ng/kg/min.

Renal Impairment[26]

In a study of IV infusion of AURLUMYN on a dialysis-free day in adults with kidney failure receiving intermittent hemodialysis treatment (n=7), the mean AUC_{0-4h} was 230 pg*h/mL compared to 54 pg*h/mL in patients with kidney failure (n=8) not requiring intermittent dialysis. The half-life was similar in both groups. The mean AUC_{0-4h} was 48 pg*h/mL in normal subjects in a different study. In patients with renal impairment with eGFR less than 30 mL/min, the dose can be lowered to 0.25 ng/kg/min if the patient cannot tolerate the starting dose of 0.5 ng/kg/min.

The effect of dialysis on the clearance of AURLUMYN has not been evaluated. For patients requiring intermittent hemodialysis, consider AURLUMYN administration after the end of hemodialysis. Alternatively, hemodialysis can be started at least 1 hour after the end of AURLUMYN infusion.

IMPORTANT SAFETY INFORMATION *(cont.)*

Warnings and Precautions

- AURLUMYN may cause symptomatic hypotension. Correct hypotension prior to administration of AURLUMYN. Monitor vital signs while administering AURLUMYN.

Adverse Reactions

- Adverse events reported with the use of intravenous (IV) iloprost in patients with frostbite include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Summary

AURLUMYN is the first and only FDA-approved drug therapy to treat severe frostbite in adults to reduce the risk of digit amputations.[26] AURLUMYN received Priority Review and Orphan Drug designation from the FDA for this indication.[27]

Severe frostbite is a serious but rare condition occurring approximately 2.9 people per million in the US.[1] When exposed to cold for too long, both direct and indirect injuries occur leading to cellular death in extremities.[12]

Frostbite carries a significant burden for patients, healthcare and society with short-term and long-term complications, expensive medical costs, and lengthy hospital stays.[1,11,13,20,25]

Despite advancements in the SoC for frostbite, amputation of the affected extremity is still common practice and can range from an estimated 60%–83% for grade 3 frostbite (depending on the extent of the lesion to the intermediary or proximal phalanx) and 98%–100% for grade 4 frostbite.[11]

In the pivotal trial for iloprost IV, efficacy was shown in preventing the need for amputation among patients with grade 3 and grade 4 frostbite:

- Prognostic risk of amputation: control (buflomedil), 60.0%, iloprost IV alone: 0.0% (*P*=.0002 vs control), and iloprost IV+rtPA, 18.7% (*P*<.0290 vs control)[17]
- Confirmatory follow-up data showed that bone scintigraphy reliably predicted likelihood of amputation in 40/40 (100%) of patients for whom 3-month follow-up data were available[27]

AURLUMYN was well tolerated, with no predefined serious AEs reported in clinical trials.[27]

AEs reported with the use of IV AURLUMYN in patients with frostbite from the published literature include headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.[27]

IMPORTANT SAFETY INFORMATION *(cont.)*

Use in Specific Populations

- Advise women not to breastfeed during treatment with AURLUMYN.
- The safety and efficacy of AURLUMYN in pediatric patients have not been established.
- Dosage adjustment is recommended in patients with moderate or severe hepatic impairment.
- In patients with eGFR <30 mL/min, dosage adjustment can be considered based on tolerability. The effect of dialysis on the clearance of AURLUMYN has not been evaluated.

Please see Indication and Important Safety Information throughout and scan QR code on page 36 for full Prescribing Information for AURLUMYN.

Important Safety Information

INDICATION AND USAGE

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IMPORTANT SAFETY INFORMATION

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- In patients with eGFR <30 mL/min, dosage adjustment can be considered based on tolerability. The effect of dialysis on the clearance of AURLUMYN has not been evaluated.

To report suspected adverse reactions, contact us at 1-877-377-3784 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Abbreviations

AE=adverse event
ATA=atmospheres absolute
AUC=area under the curve
BS=bone scintigraphy
C_{max}=maximum serum concentration
ED=emergency department
eGFR=estimated glomerular filtration rate
FDA=Food and Drug Administration
HBO=hyperbaric oxygen
ICU=intensive care unit
IV=intravenous
MP=metacarpophalangeal
NDC=National Drug Code
NR=not reported
NSAID=nonsteroidal anti-inflammatory drug
PGI_2=prostacyclin
PK=pharmacokinetics
PTT=partial thromboplastin time
PVC=polyvinyl chloride
rtPA=recombinant tissue-type plasminogen activator
SoC=standard of care
Tc-99m=technetium 99m
tPA=tissue plasminogen activator
USP=United States Pharmacopeia

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AURLUMYN™
(iloprost) Injection

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