



Administration of Iloprost (AURLUMYN™)

ICD-10 Coordination & Maintenance
Committee Update
March 2025

AURLUMYN™ (iloprost) injection, for intravenous use, is the first and only drug therapy approved in the U.S. for the treatment of frostbite¹

AURLUMYN™ (iloprost) injection, for intravenous use, is a prostacyclin mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations²

- AURLUMYN™ was approved by the FDA on February 13, 2024, under Priority Review (NDA sponsor, EICOS Sciences)
 - Earlier, Orphan Drug designation was granted for the treatment of frostbite
- SERB Pharmaceuticals acquired AURLUMYN™ globally on October 18, 2024
- No intravenous form of iloprost was available in the U.S. until FDA approval of AURLUMYN™

- Outside the U.S., an intravenous formulation of iloprost has been available, with published use in frostbite dating back to 1994³



- Since 2019, the Wilderness Medical Society Practice Guidelines have recognized intravenous iloprost as the first-line treatment of deep or severe frostbite (Strong Recommendation)^{4,5}

"This approval provides patients with the first-ever treatment option for severe frostbite. Having this new option provides physicians with a tool that will help prevent the lifechanging amputation of one's frostbitten fingers or toes"

Norman Stockbridge, MD, PhD, Director of Cardiology and Nephrology, FDA's Center for Drug Evaluation and Research¹

Frostbite is a thermal injury caused when tissue is exposed to freezing temperatures

Frostbite cases in the urban setting are most often in conjunction with⁶⁻⁸

Elderly/Geriatric
Trauma
Hypothermia
Physical disability
Psychosocial issues
Vehicular-related incident
Work-related and recreational activities
Smoking
Unstable housing
No/Inadequate home heating

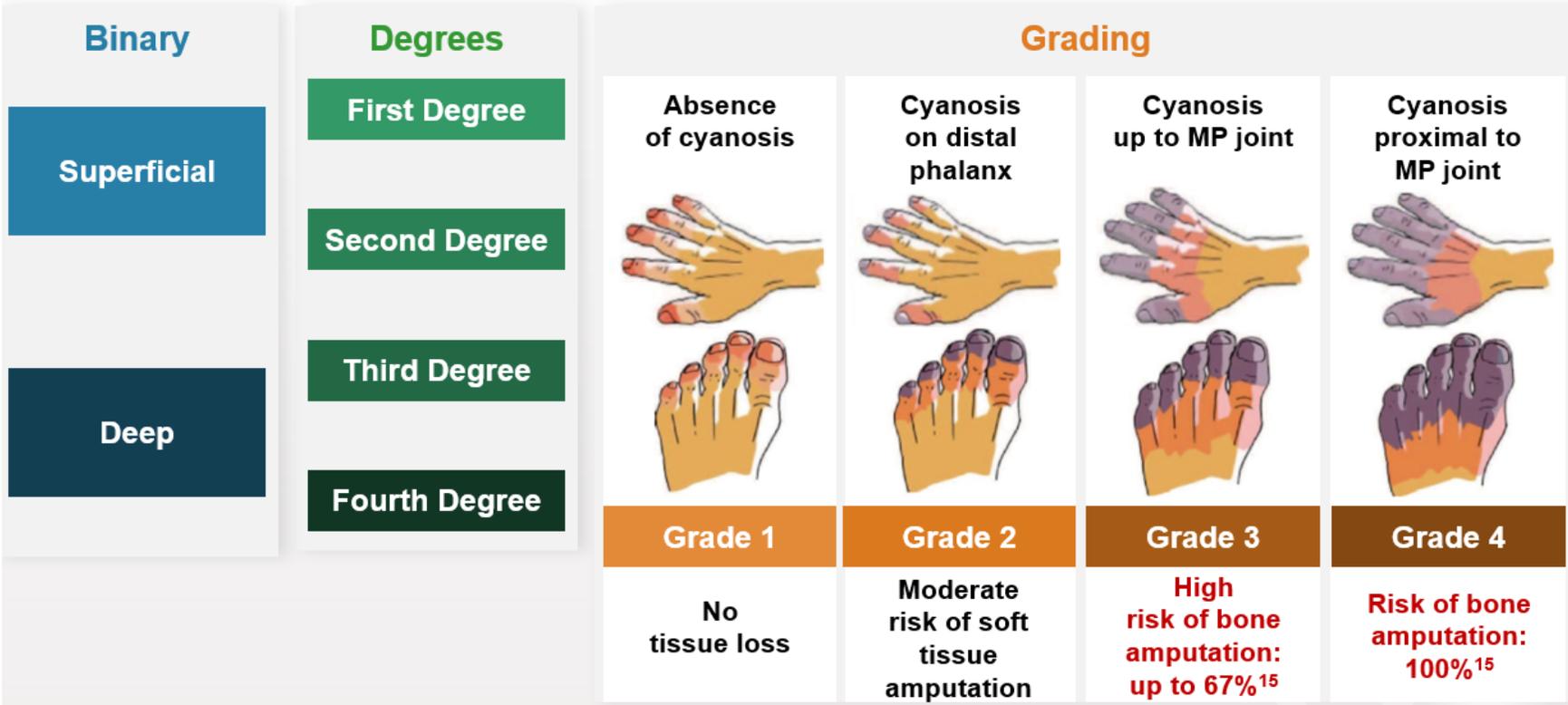
Medical comorbidities & conditions heighten risks of frostbite⁹⁻¹²

Peripheral vascular disease
Diabetes
Neuropathies
Dementia
Mental illness
Routine medication use (e.g., beta-blockers)
Alcohol and substance use disorders

The overall incidence of frostbite injury in the U.S. is extremely low at 0.83 cases per 100,000 people⁹.
FY 2023 Medicare claims for severe frostbite (N=62) involved patients <65 years of age (63%) and ≥65 years of age (37%)¹³.

The higher the grade of frostbite, the higher the amputation rate; most often fingers and toes^{14,15}

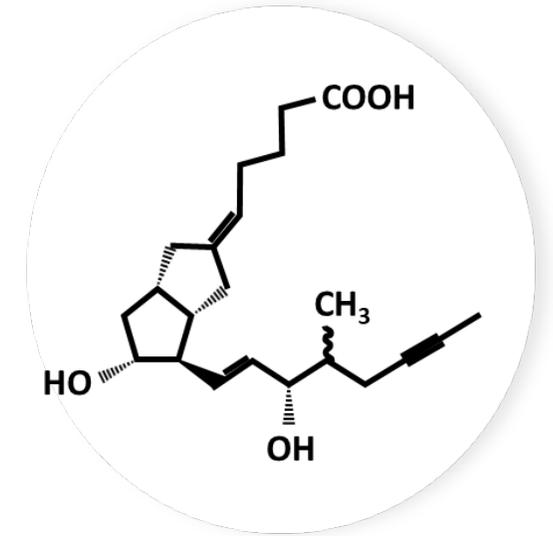
The significant, debilitating, lifelong consequences of amputation of digits lead to long-term disability, inability to perform activities of daily living, and often inhibit the ability to work^{9,10,16}



MP: metacarpophalangeal.
Sources: Norheim AJ, et al. *Int J Circumpolar Health*. 2023;82:2203923²¹; Cauchy E, et al. *Wilderness Environ Med*. 2016;27:92-99²²

AURLUMYN™ is a prostacyclin mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations²

- AURLUMYN™ (iloprost) injection is a clear, colorless sterile solution formulated for intravenous use supplied in single-use glass vials
- Potent synthetic analog of prostacyclin
- Half-life is 20-30 minutes
- May improve outcomes and reduce the risk of amputations by enhancing cutaneous blood flow and inhibiting platelet aggregation



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- Iloprost has long been recognized for its potent therapeutic value in treating severe frostbite, and its use has been published in the medical and scientific literature dating back to 1994³.
 - *“By acting at all stages of the warming and progressive necrosis phase, it appears to be the ideal molecule”* (Cheguillaume 2011)¹⁷
 - *“These characteristics [potent vasodilator, inhibits platelet aggregation, and enhances fibrinolytic activity] make it a drug of choice to reverse the marked vasoconstriction and microthrombosis occurring in frostbite”* (Poole and Gauthier 2016)¹⁸

AURLUMYN™ is an acute treatment for severe frostbite and is administered as a continuous intravenous infusion over 6 hours each day for up to a maximum of 8 consecutive days²

Recommended dosing²

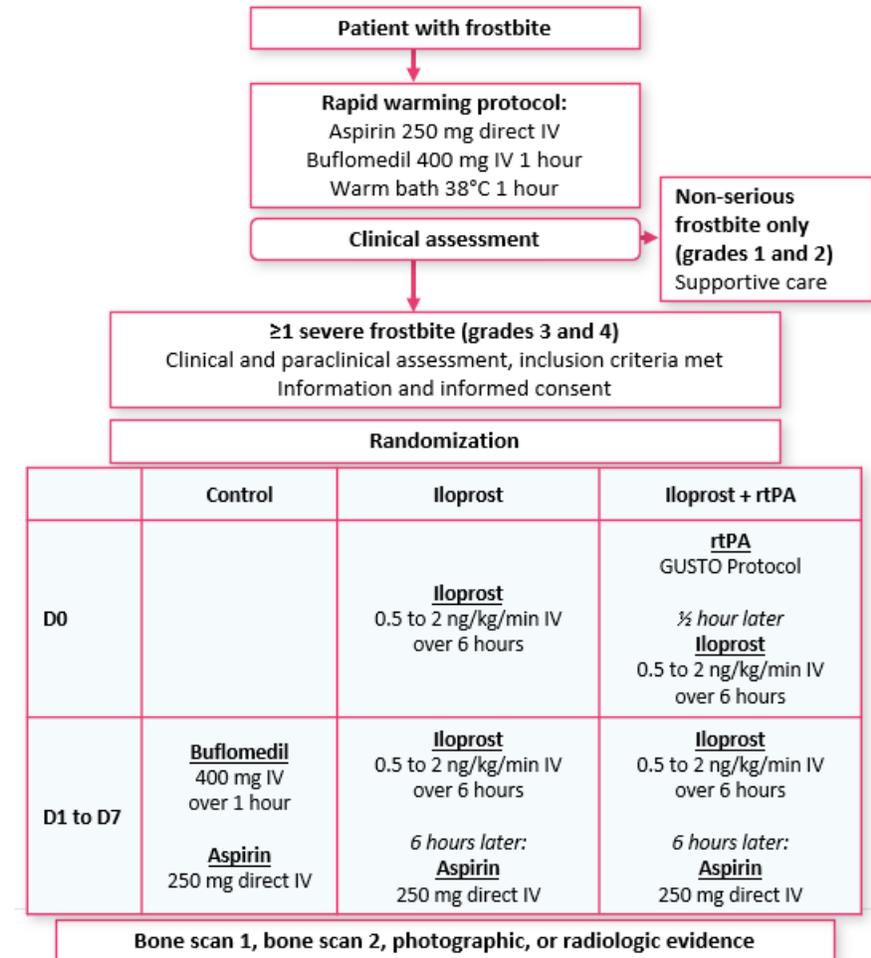
Titration and Maintenance	Time Point	Dose	Instructions
Starting dose Days 1-3		0.5 ng/kg/min	
Titration Days 1-3	30 min	1.0 ng/kg/min	↓ dose to 0.5 ng/kg/min if not tolerated
	60 min	1.5 ng/kg/min	↓ dose to 1.0 ng/kg/min if not tolerated
	90 min	2.0 ng/kg/min	↓ dose to 1.5 ng/kg/min if not tolerated
	Hours 2-6	Highest tolerated dose	Highest tolerated dose will be administered for remainder of infusion
Starting dose Maintenance Days 4-8		Highest tolerated dose or 2.0 ng/kg/min	Highest tolerated dose from previous day will be administered

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

- AURLUMYN™ is supplied in a carton containing one 100 mcg per mL single-dose glass vial (NDC 83226-2001-1).
- The AURLUMYN™ infusion procedure will be documented in the medical record in the same manner as other therapies that are administered via IV infusion, including within the medication records, physician orders, and progress notes.

FDA approval based on the only randomized study ever completed in frostbite^{17,19}

- Pivotal randomized, controlled, open-label study (1996-2008)
 - 47 patients with severe frostbite (grades 3 or 4)
 - Mean age 33.1 years (18, 55)
- Treatment arms
 - Control: buflomedil (vasodilator)
 - Iloprost
 - Iloprost + rtPA
- 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



D: day; IV: intravenous; rtPA: recombinant tissue plasminogen activator.

AURLUMYN™ significantly reduces the risk of amputation of fingers and toes in adults with severe frostbite^{17,19}

Pivotal randomized, controlled, open-label study: likelihood of amputation (Primary Endpoint)^{17,19}

Treatment Group	All Frostbite		Grade 3		Grade 4	
	Patients with Frostbite n	Patients Likely ^b to Receive Amputation n (%)	Patients with Frostbite n	Patients Likely ^b to Receive Amputation n (%)	Patients with Frostbite n	Patients Likely ^b to Receive Amputation n (%)
Control (n=15) ^a	15	9 (60.0)	12	7 (58.3)	2	2 (100)
Iloprost (n=16)	16	0	14	0	2	0
Iloprost + rtPA (n=16)	16	3 (18.7)	10	2 (20.0)	6	1 (16.7)
Combined iloprost (± rtPA) (n=32)	32	3 (9.4)	24	2 (8.3)	8	1 (12.5)

Prognostic risk of amputation: control (buflomedil), 60.0%, iloprost alone: 0.0%, and iloprost + rtPA, 18.7%

Follow-up at 3 months post-treatment confirmed the predicted amputation outcome in 40 of the 47 participants with follow-up evidence

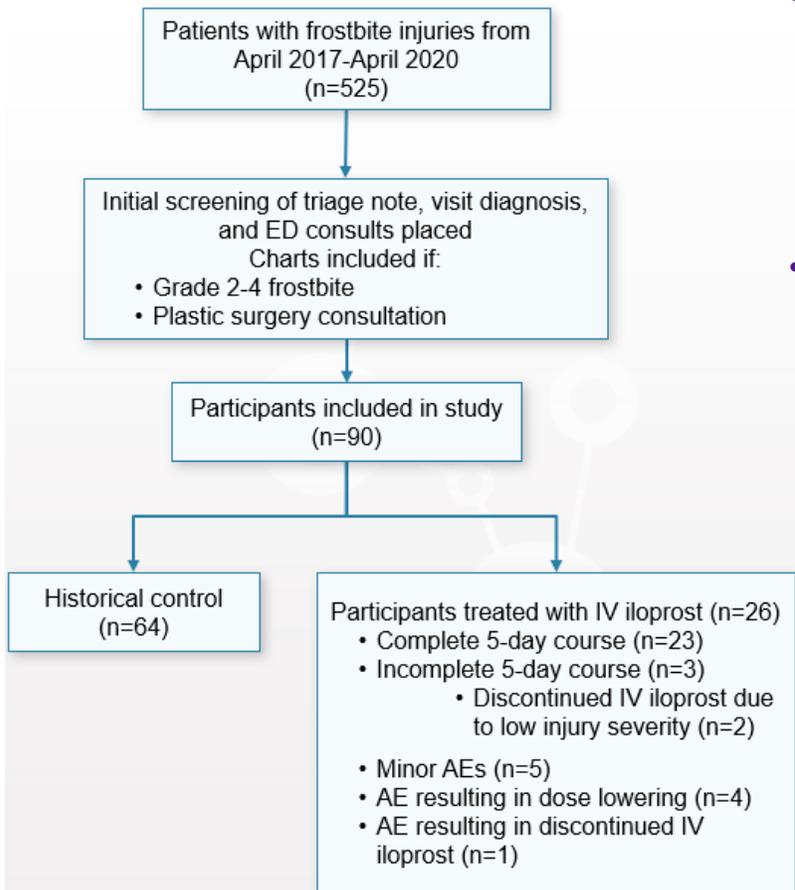
- AEs were minor: flushing (55%), nausea (25%), palpitations (15%), vomiting (5%)
- No discontinuations due to AEs

All combined (n=47), iloprost vs control $P < 0.001$, iloprost + rtPA vs control $P < 0.03$, iloprost + rtPA vs iloprost $P > 0.11$, (Fisher's exact test); all stages combined (n=47), iloprost ± rtPA vs control $P < 0.0001$.

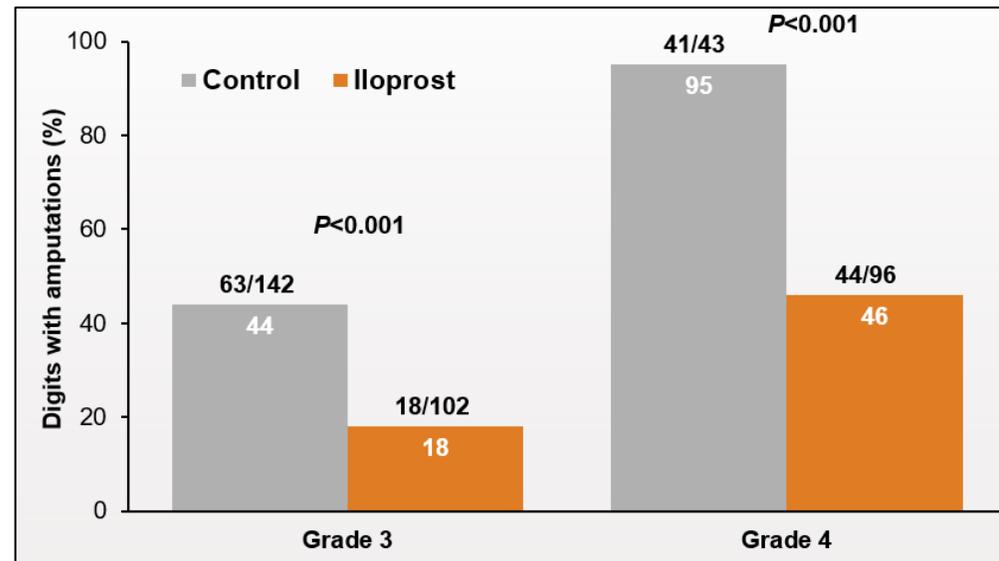
^aOne patient enrolled in the control group was found to have only stage 2 frostbite. ^bLikelihood of amputation was determined by the presence of a radiotracer anomaly in at ≥1 digit in the bone phase of technetium scintigraphy after 8 days of treatment.

rtPA, recombinant tissue plasminogen activator.

Supportive evidence from urban, multicenter, retrospective, observational study confirms highly favorable results for patients with frostbite treated with intravenous iloprost compared to standard care²⁰



- Multicenter, retrospective, observational study of consecutive patients who presented to Calgary EDs with Grade 2-4 frostbite injuries (April 2017-April 2020)²⁰
 - Historical control: patients prior to February 2019 who were managed with standard care (local best practice without iloprost) (n=64)
 - IV iloprost group: patients from February 2019 onward managed with 5-day iloprost infusion protocol (n=26)
- Primary effectiveness outcome: rate of affected digits amputated, stratified by frostbite severity²⁰



AE: adverse event; ED: emergency department; EMR: electronic medical record; IV: intravenous

AURLUMYN™ fulfills the significant and clear unmet medical need for an FDA-approved therapy to prevent amputation in patients with severe frostbite in the U.S.

- Severe frostbite injury results in significant lifelong disability from amputation of limbs and digits, causing extensive morbidity, reducing the ability to perform activities of daily living, severely decreasing health-related and functional quality of life, and often leading to inability to work.
 - Intravenous iloprost has been used safely and has been widely adopted for the treatment of frostbite outside the U.S., dating back to 1994, with significant improvements in the rate of digit amputation over historical controls.
 - Intravenous iloprost is recommended as the first-line therapy for severe (grades 3 and 4) frostbite cases, based on consensus guidelines from leaders in the field of frostbite treatment.
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- With the FDA approval of AURLUMYN™, the internationally recognized first-line treatment for severe frostbite is available in the U.S. and will aid physicians when making difficult, time-sensitive treatment decisions and amputation risk assessments.
 - Reduction in the risk of amputation of fingers and toes, without increasing harm, will significantly benefit Medicare beneficiaries' (eligible by age and by disability) long-term health and functional quality of life, with avoidance of debilitating, lifelong consequences of digit amputation.

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