Loargys®
(pegzilarginase-nbln)

Get to the root of Arginase 1 Deficiency (ARG1-D)[1]

LOARGYS is the first and only therapy proven to lower arginine[1]

IMPORTANT SAFETY INFORMATION

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

See full prescribing information for complete boxed warning

Initiate LOARGYS in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue LOARGYS, and immediately initiate appropriate medical treatment, including use of epinephrine.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions Including Anaphylaxis: Life-threatening hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with enzyme replacement therapies, including LOARGYS. Hypersensitivity reactions that were mild to moderate in severity occurred in 13% (6/48) of LOARGYS-treated subjects in clinical trials. Hypersensitivity reactions have included facial swelling, rash, flushing and dyspnea. The reactions generally occurred with the first few doses but may occur later in treatment.

Please see additional Important Safety Information on following pages and full Prescribing Information.

ARG1-D is a debilitating and progressive inherited metabolic disease[2]

ARG1-D is caused by variants in the *ARG1* gene that results in impaired or absent arginase 1 enzyme activity[2,3]

Persistently elevated levels of arginine in patients with ARG1-D are key drivers of disease manifestations, including progressive spasticity, developmental delay, and seizures.[2]

Current treatment guidelines for ARG1-D recommend **lowering plasma arginine levels** to reduce disease burden.[2,4]

The clinical presentation of ARG1-D is heterogeneous[3]

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

Administration of LOARGYS should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis in a healthcare setting with appropriate medical monitoring and support measures. Premedication with an antihistamine and/or corticosteroid should be considered in patients who previously have developed a hypersensitivity reaction. If a *severe* hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue LOARGYS and immediately initiate appropriate medical treatment, including use of epinephrine. Consider the risks and benefits of re-administering LOARGYS in patients who have experienced a severe hypersensitivity reaction. Caution should be exercised upon rechallenge. Inform patients of the symptoms of life-threatening hypersensitivity reactions and to seek immediate medical attention should symptoms occur. If a mild or moderate reaction occurs, consider treatment with antihistamines and/or corticosteroids.

Please see additional Important Safety Information on following pages and full Prescribing Information.

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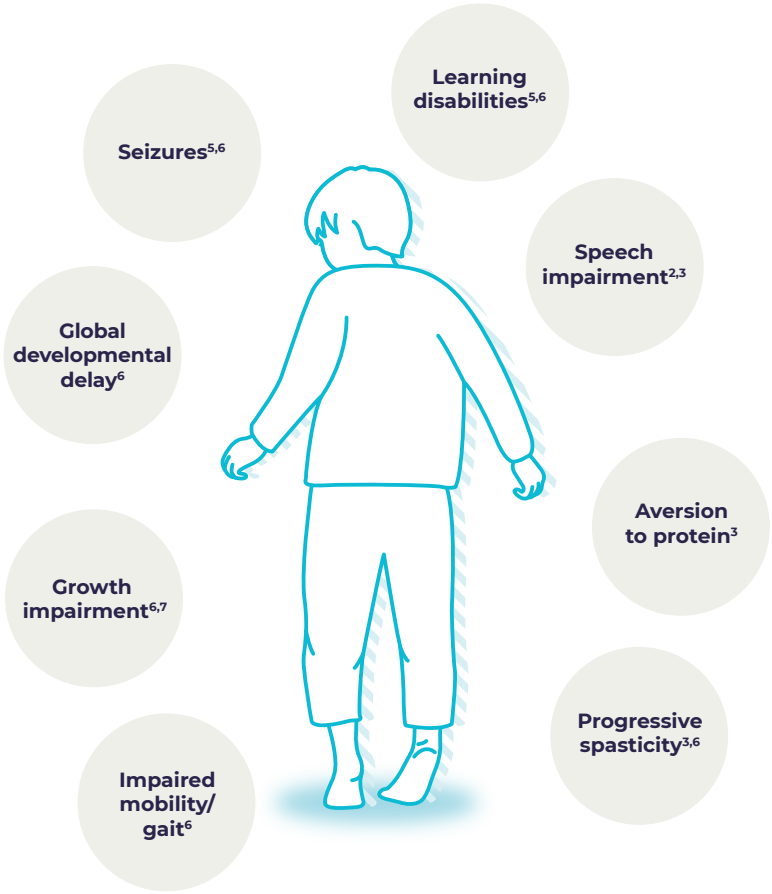
Manifestations typically start in childhood, although symptoms can appear later in life due to accumulating levels of plasma arginine[3]

Initial onset is typically confined to the lower limbs; however, as spasticity worsens, the upper limbs can also become affected.[3]

Persistently high plasma levels of arginine and arginine-related metabolites increase the risk of significant morbidity and early mortality.[2]*



Symptoms often mimic other neurologic and neurometabolic disorders. A genetic test may confirm a diagnosis[2,3]

*The associated clinical response of this product is not yet confirmed.

IMPORTANT SAFETY INFORMATION (CONTINUED)

ADVERSE REACTIONS

The most common adverse reactions are vomiting, pyrexia, infusion associated reactions and constipation.

Please see additional Important Safety Information on following pages and full Prescribing Information.

Loargys® (pegzilarginase-nbln)

ARG1-D can be verified in routine testing

For newborns with a positive screen or people with a medical history, symptoms, and physical findings suggestive of ARG1-D, plasma arginine levels should be measured in a routine plasma quantitative amino acid analysis.[8-10]

If hyperargininemia is present, the ARG1-D diagnosis may be confirmed by a genetic test.[8]*

*Due to the genetic heterogeneity of *ARG1* genotypes, not all variants causing ARG1-D have been identified.

BIOCHEMICAL[4,8]

Elevations in plasma arginine detected via plasma amino acid assay

Reduced red blood cell arginase activity

GENETIC[4,8]

ARG1 variant analysis

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no available data on LOARGYS use in pregnant females to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

Please see additional Important Safety Information on following pages and full Prescribing Information.

Loargys® (pegzilarginase-nbln)

Management of ARG1-D requires an integrated approach

ARG1-D is a lifelong, chronic disease requiring a multidisciplinary care team. This care team could include[11,12]:

- Metabolic geneticist
- Dietician
- Neurologist
- Physical therapist
- Other healthcare professionals recommended by the team

The current standard of care for ARG1-D primarily focuses on symptom management.[2,4] LOARGYS is the first and only therapy proven to lower arginine[1]

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS (CONTINUED)

Lactation: There is no data on the presence of LOARGYS in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LOARGYS and any potential adverse effects on the breast-fed infant from LOARGYS or from the underlying maternal condition.

Please see additional Important Safety Information on following pages and full Prescribing Information.

Loargys® (pegzilarginase-nbln)

LOARGYS is a novel, pegylated, cobalt-substituted recombinant human arginase 1 enzyme[1]

LOARGYS has been engineered to deliver enhanced degradation of arginine[1,13]

Compared to the endogenous arginase, LOARGYS achieves higher catalytic activity and longer half-life.[1,13]

LOARGYS acts by reducing plasma levels of arginine, with corresponding increases in plasma ornithine levels and decreases in plasma guanidino compound levels.[13]

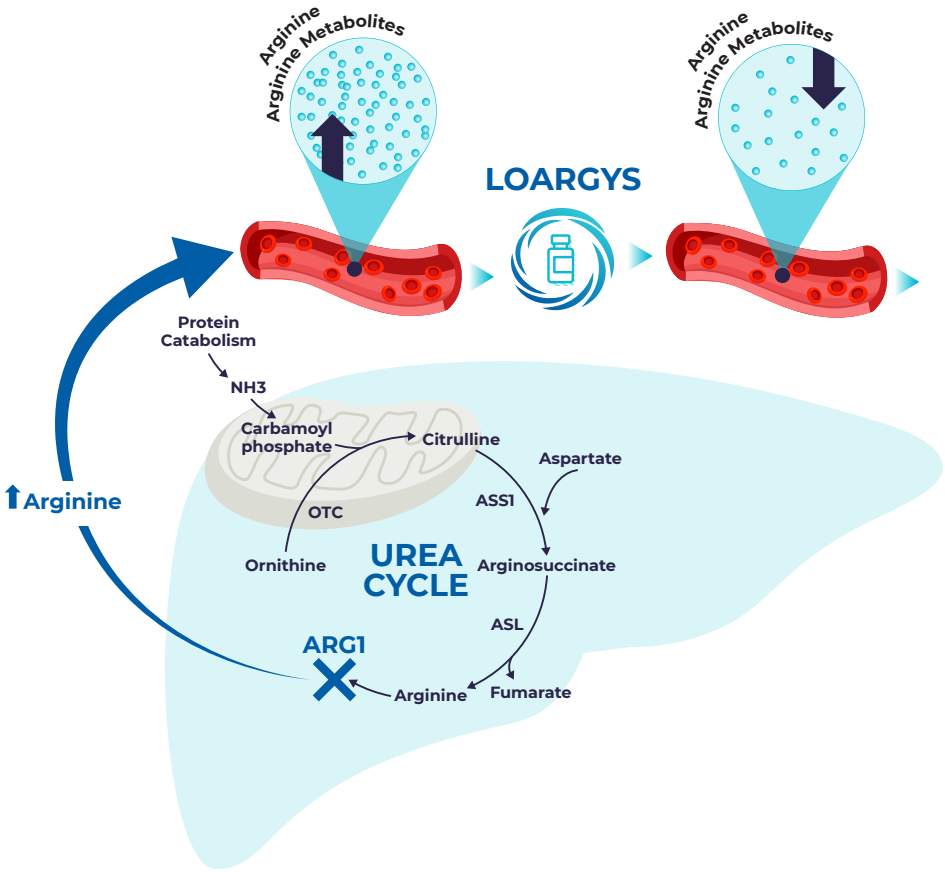


Image adapted from Diaz, 2023 and the Loargys Prescribing Information.[2,13]

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS (CONTINUED)

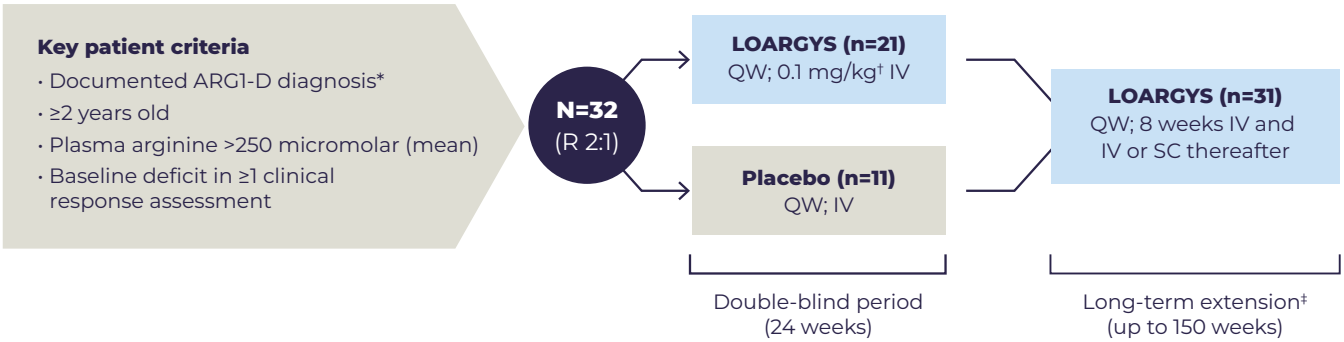
Pediatric: The safety and effectiveness of LOARGYS have been established for the reduction of plasma arginine in pediatric patients 2 years and older with ARG-1 D, in conjunction with dietary protein restriction. The safety and effectiveness of LOARGYS have not been established for the reduction of plasma arginine in pediatric patients aged less than 2 years with ARG-1 D.

Please see additional Important Safety Information on following pages and full Prescribing Information.

Loargys® (pegzilarginase-nbln)

LOARGYS was studied in PEACE, a phase 3 study with 32 patients aged 2-29 years with a confirmed ARG1-D diagnosis[1,13]

Pegzilarginase Effect on Arginase 1 Clinical Endpoints (PEACE) was a pivotal phase 3, randomized, double-blind, placebo-controlled, international study that evaluated the efficacy and safety of weekly LOARGYS added to standard of care management.[1]



Efficacy outcomes[1]

Primary: Change from baseline in plasma arginine at week 24

Patients included in the PEACE trial received LOARGYS for up to 152 weeks.

IV, intravenous; LTE, long-term extension; SC, subcutaneous; QW, once weekly.
The associated clinical response of this product is not yet confirmed.
*ARG1-D diagnosis was based on elevated plasma arginine, pathogenic *ARG1* variant, and/or diminished erythrocyte arginase activity.
†Weekly dosing; if needed, dose modifications permitted based on plasma arginine levels with maintenance of blinding.
‡Blinding maintained through the first 8 weeks of the long-term extension.

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS (CONTINUED)

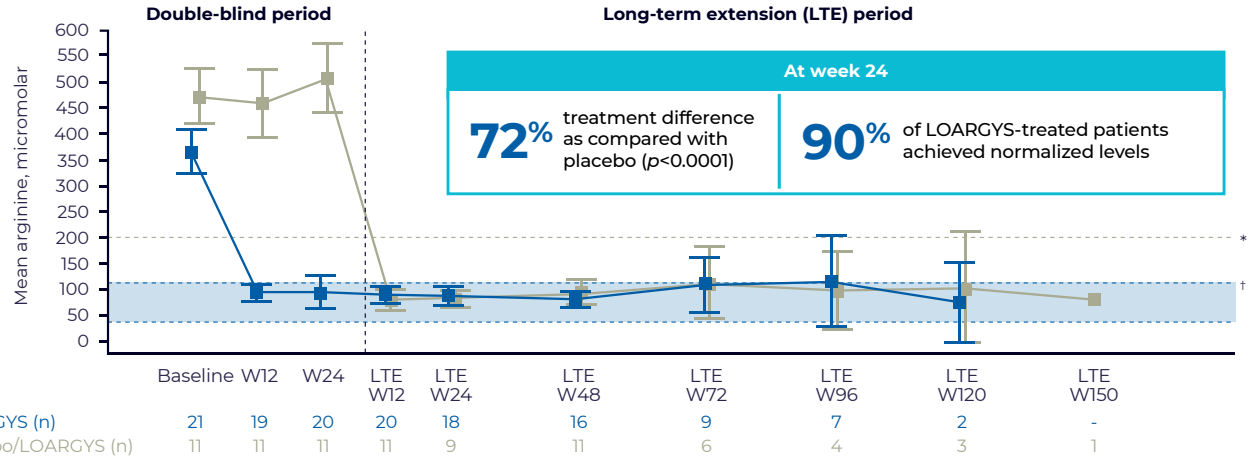
Geriatric: Clinical studies of LOARGYS did not include subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

Please see additional Important Safety Information on following pages and full Prescribing Information.

Loargys® (pegzilarginase-nbln)

LOARGYS sustained normal plasma arginine levels for up to 152 weeks[13]

- The median duration of LOARGYS exposure in the LTE, excluding the double-blind period of 24 weeks, was 94 weeks (range, 62-152 weeks)[13]



*The guideline-recommended target level for plasma arginine was <200 micromolar.
†The normal range for plasma arginine (as defined in the PEACE study) was 40-115 micromolar.

IMPORTANT SAFETY INFORMATION (CONTINUED)

INDICATION

LOARGYS is an arginine specific enzyme indicated for the treatment of hyperargininemia in adult and pediatric patients 2 years of age and older with Arginase 1 Deficiency (ARG1-D), in conjunction with dietary protein restriction.

This indication is approved under accelerated approval based on reduction of plasma arginine. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Please see additional Important Safety Information on following pages and full Prescribing Information.

Loargys® (pegzilarginase-nbln)

LOARGYS is well tolerated with demonstrated safety[1,13‡]

- The safety of LOARGYS was evaluated in a phase 3 study (Trial 1, PEACE). Additional safety information was derived from Trial 2, a phase 1 open-label trial, and Trial 3, an open-label extension of Trial 2 [1,13]
- The most common adverse reactions are vomiting, pyrexia, infusion associated reactions, and constipation[13]

13% (Trials 1, 2 & 3; N=48)

Hypersensitivity reactions (HSRs)

Hypersensitivity reactions such as facial swelling, rash, flushing, and dyspnea were reported in 13% (6/48) of LOARGYS-treated patients during clinical trials.[13]

14% (Trials 1 & 3, N=44)

Injection site reactions (ISRs)

Injection site reactions were reported in 14% (6/44) of LOARGYS-treated patients after subcutaneous administration during the open-label extension periods in Trial 1 and Trial 3. Symptoms include pain, erythema, swelling, irritation, and rash at the injection site.[13]

13% (Trial 1, N=32)

50% (Trials 2 & 3, N=16)

Immunogenicity

In Trial 1 (N=32), 13% of LOARGYS-treated patients tested positive for anti-drug antibodies (ADAs). In pooled data from Trials 2 and 3 (N=16), 50% tested positive. ADAs decreased during continued treatment.[13]

- There were no discontinuations due to adverse events across all clinical trials[1,14,15]
- HSRs were mild to moderate in severity[13]
- Across all 3 trials, the incidence of HSRs was 42% (5/12) in LOARGYS-treated patients who developed ADAs and 3% (1/36) in those who were ADA negative[13]

‡See full Prescribing Information for additional Safety Information.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions Including Anaphylaxis: Life-threatening hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with enzyme replacement therapies, including LOARGYS. Hypersensitivity reactions that were mild to moderate in severity occurred in 13% (6/48) of LOARGYS-treated subjects in clinical trials. Hypersensitivity reactions have included facial swelling, rash, flushing and dyspnea. The reactions generally occurred with the first few doses but may occur later in treatment.

Please see additional Important Safety Information on following pages and full Prescribing Information.

Loargys® (pegzilarginase-nbln)

Recommended LOARGYS dosing and administration[13]

Prior to LOARGYS treatment

- Administer LOARGYS under the supervision of a healthcare provider knowledgeable in the management of hypersensitivity reactions, including anaphylaxis
- Initiate LOARGYS in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment
- Consider pre-medication with antihistamines
- Obtain a baseline plasma arginine concentration

How to initiate LOARGYS

1. LOARGYS is supplied in 2 mg/0.4 mL single-dose vials
2. The recommended starting dosage of LOARGYS is 0.1 mg/kg (actual body weight) administered via intravenous infusion once weekly
3. Store LOARGYS refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake

Please see full Prescribing Information for more directions on proper dosing and administration.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

Administration of LOARGYS should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis in a healthcare setting with appropriate medical monitoring and support measures. Premedication with an antihistamine and/or corticosteroid should be considered in patients who previously have developed a hypersensitivity reaction. If a *severe* hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue LOARGYS and immediately initiate appropriate medical treatment, including use of epinephrine. Consider the risks and benefits of re-administering LOARGYS in patients who have experienced a severe hypersensitivity reaction. Caution should be exercised upon rechallenge. Inform patients of the symptoms of life-threatening hypersensitivity reactions and to seek immediate medical attention should symptoms occur. If a mild or moderate reaction occurs, consider treatment with antihistamines and/or corticosteroids.

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Loargys® (pegzilarginase-nbln)

Monitoring of plasma arginine for patients treated with LOARGYS[13]

LOARGYS is available only to patients who are enrolled in Study IMM-PEG-005 for purposes of obtaining Immedica Pharma's Nor-NOHA Blood Collection Tubes and the LOARGYS Arginine Assay. For additional information, please contact Immedica Pharma at 1-(844)-627-4687 and dial 1 to speak to a Medical Information representative.

- For patients treated with LOARGYS, plasma arginine samples must be collected into Immedica Pharma's Nor-NOHA Blood Collection Tubes, which contain Nω-hydroxy-nor-Arginine (nor-NOHA), an enzyme inhibitor used to inhibit post-sampling degradation of arginine by LOARGYS
- Plasma arginine concentration is then measured using Immedica Pharma's LOARGYS Arginine Assay

Recommended dosage adjustment and monitoring

After four weeks of LOARGYS administration, measure pre-dose (168 hours after prior dose) plasma arginine to determine the need for dosage adjustment. If two consecutive weekly pre-dose measurements of plasma arginine are not in the desired therapeutic range, increase or decrease the weekly LOARGYS dosage as follows:

- If the pre-dose plasma arginine concentration is below 50 micromolar, reduce the weekly LOARGYS dosage by 0.05 mg/kg
- If the pre-dose plasma arginine concentration is above 150 micromolar, increase the weekly LOARGYS dosage by 0.05 mg/kg

The maximum recommended LOARGYS dosage is 0.2 mg/kg once weekly. If a dose is missed, administer LOARGYS as soon as possible. Do not administer two LOARGYS doses on the same day or within four days of another dose to make up for a missed dose. Ensure there is a minimum of 4 days between doses.

IMPORTANT SAFETY INFORMATION (CONTINUED)

ADVERSE REACTIONS

The most common adverse reactions are vomiting, pyrexia, infusion associated reactions and constipation.

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Loargys® (pegzilarginase-nbln)

The table below provides examples to determine the total LOARGYS dose required for 3 different patient cases

Determine the number of LOARGYS vials needed based on actual body weight in kg and the recommended dose. Round the calculated volume of LOARGYS to nearest 0.1 mL.[13]

	Body Weight (kg and lbs)	**LOARGYS Weekly Dosage** (mg/kg)	**Total Dose Required** (mg) [Body weight (kg) x dose (mg/kg)]	**Total Dose Required** (mL) [Total dose required (mg) x (0.4 mL/2 mg)]
Patient example 1	11.33 kg (25 lbs)	0.1 mg/kg	1.133 mg	0.2 mL
Patient example 2 (titration)	22.68 kg (50 lbs)	0.15 mg/kg	3.402 mg	0.7 mL
Patient example 3 (titration)	68.04 kg (150 lbs)	0.2 mg/kg	13.608 mg	2.7 mL

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no available data on LOARGYS use in pregnant females to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

Please see additional Important Safety Information on following pages and full Prescribing Information.

Loargys® (pegzilarginase-nbln)

LOARGYS preparation instructions[13]

Use aseptic technique when preparing and administering LOARGYS

1. Remove the vial(s) from the refrigerator and allow the vial(s) to reach room temperature
2. Visually inspect the solution in the vials for particulate matter and discoloration. The solution should be clear to slightly opalescent, colorless to slightly yellow or slightly pink. Discard the vial(s) if the solution is not consistent with this appearance or if visible particulate matter is present
3. Use a syringe to withdraw the calculated volume from the vial(s) and round the calculated volume of LOARGYS to nearest 0.1 mL
4. Discard unused portion

For intravenous administration

1. Dilute the withdrawn volume of LOARGYS solution in 0.9% Sodium Chloride Injection to a maximum concentration of 0.5 mg/mL
2. Gently invert the infusion bag to mix the solution. Avoid vigorous shaking or agitation
3. Administer the intravenous infusion over at least 30 minutes
4. After LOARGYS infusion, use 0.9% Sodium Chloride to flush the line
   a. Do not mix other medications with LOARGYS or co-administer other drugs through the same intravenous line
5. After 8 weeks of once weekly intravenous LOARGYS, patients may be switched to once weekly subcutaneous LOARGYS at the same dosage of intravenous therapy

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS (CONTINUED)

Lactation: There is no data on the presence of LOARGYS in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LOARGYS and any potential adverse effects on the breast-fed infant from LOARGYS or from the underlying maternal condition.

Please see additional Important Safety Information on following pages and full Prescribing Information.

Loargys® (pegzilarginase-nbln)

For subcutaneous administration[13]

1. Administer the undiluted solution subcutaneously into the abdomen, lateral part of the thigh, or the side or back of the upper arms
   a. If more than 1 injection is needed for a single dose of LOARGYS, the injection sites should be at least 1 inch apart
   b. Do not inject into scar tissue or areas that are reddened, inflamed, or swollen. If injecting into the abdomen, avoid the area directly surrounding the navel
   c. Rotate injection sites between doses
2. Patients treated subcutaneously may experience shorter periods of hypoargininemia than patients treated with LOARGYS intravenously
3. If patients tolerate maintenance subcutaneous administration of LOARGYS, they may receive subcutaneous administration at home under the supervision of a healthcare provider

Home Administration
When switching patients from subcutaneous administration in a supervised clinical setting to at home administration under the supervision of a healthcare provider, initially use the same dose

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS (CONTINUED)

Pediatric: The safety and effectiveness of LOARGYS have been established for the reduction of plasma arginine in pediatric patients 2 years and older with ARG-1 D, in conjunction with dietary protein restriction. The safety and effectiveness of LOARGYS have not been established for the reduction of plasma arginine in pediatric patients aged less than 2 years with ARG-1 D.

Please see additional Important Safety Information on following pages and full Prescribing Information.

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Storage of the solution after preparation[13]

- Use LOARGYS immediately after preparation. If not used immediately, store the diluted solution for intravenous use in the infusion container and the undiluted solution for subcutaneous use in the syringe for up to:
  - 2 hours at room temperature at 20°C to 25°C (68°F to 77°F) or
  - 4 hours if stored refrigerated at 2°C to 8°C (36°F to 46°F)
- Discard LOARGYS if not administered within these time frames, including total infusion time, if administered intravenously.

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS (CONTINUED)

Geriatric: Clinical studies of LOARGYS did not include subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

INDICATION

LOARGYS is an arginine specific enzyme indicated for the treatment of hyperargininemia in adult and pediatric patients 2 years of age and older with Arginase 1 Deficiency (ARG1-D), in conjunction with dietary protein restriction.

This indication is approved under accelerated approval based on reduction of plasma arginine. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Please see additional Important Safety Information on following pages and full Prescribing Information.

Loargys® (pegzilarginase-nbln)

Choose LOARGYS for your ARG1-D patients

LOARGYS is the first and only therapy proven to lower arginine[1]

- LOARGYS rapidly normalizes plasma arginine levels in patients with ARG1-D and reduces toxic arginine-related metabolites[1]
- LOARGYS is well tolerated with demonstrated safety[1]*
- LOARGYS has the potential to impact the management of ARG1-D in patients with few clinical options[1]

*See full Prescribing Information for additional Safety Information.

Learn more about ARG1-D and how treatment with LOARGYS can benefit your patients

Please see additional Important Safety Information on previous pages and full Prescribing Information.

References: 1. Russo RS, et al. Efficacy and safety of pegzilarginase in arginase 1 deficiency (PEACE): a phase 3, randomized, double-blind, placebo-controlled, multi-centre trial. *EClinicalMedicine*. 2024;68:102405. **2.** Diaz GA, et al. The role and control of arginine levels in arginase 1 deficiency. *J Inherit Metab Dis*. 2023;46(1):3-14. **3.** Carvalho DR, et al. Clinical features and neurologic progression of hyperargininemia. *Pediatr Neurol*. 2012;46:369-374. **4.** Häberle J, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. *J Inherit Metab Dis*. 2019;1-39. **5.** Catsburg C, et al. Arginase 1 deficiency: using genetic databases as a tool to establish global prevalence. *Orphanet J Rare Dis*. 2022;17(1):94. **6.** McNutt MC, et al. Arginase 1 deficiency in patients initially diagnosed with hereditary spastic paraplegia. *Mov Discord Clin Pract*. 2022;10(1):109-114. **7.** Schlune A, et al. Hyperargininemia due to arginase I deficiency: the original patients and their natural history, and a review of the literature. *Amino Acids*. 2015;47:1751-1762. **8.** Sun A, et al. Arginase deficiency. In: Adams MP, et al, eds. GeneReviews®. Seattle, WA: University of Washington, Seattle; 2020. **9.** Ah Mew N, et al. Urea Cycle Disorders Overview. 2003. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1217/. Accessed May 31, 2025. **10.** Therrell BL, et al. Newborn screening for hyperargininemia due to arginase 1 deficiency. *Mol Gen Metab*. 2017;121:308-313. **11.** NORD Guides for Physicians. The Physician's Guide to Urea Cycle Disorders. 2012. Available at https://nucdforg.presencehost.net/file_download/79b6b024-9942-4e78-bcb7-24d6a77eeeeb. Accessed May 31, 2025. **12.** Amayreh W, et al. Treatment of arginase deficiency revisited: guanidinoacetate as a therapeutic target and biomarker for therapeutic monitoring. *Dev Med Child Neurol*. 2014;56:1021-1024. **13.** LOARGYS (pegzilarginase-nbln) Prescribing Information. Immedica Pharma. **14.** Diaz GA, et al. Clinical effect and safety profile of pegzilarginase in patients with arginase 1 deficiency. *J Inherit Metab Dis*. 2021;44(4):847-856. **15.** McNutt M, et al. Long-term efficacy and tolerability of pegzilarginase in arginase 1 deficiency: results of two international multicentre open-label extension studies. *J Inherit Metab Dis*. 2025;48(4):e70066. doi:10.1002/jimd.70066.

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