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pariglasgene
brecaparvovec-opnr
suspension for IV infusion

The **First and Only** FDA-Approved Therapy for GSDIa
in patients aged 8 years and older[1]

Help *reduce daily intake*[a] of



[a]Based on reduction in total daily cornstarch intake in GENGLYCOS patients compared with placebo patients at Week 48.[1] **See data inside**.

Indication

GENGLYCOS (pariglasgene brecaparvovec-opnr) is indicated to reduce daily cornstarch intake as an adjunct to nutritional management in adult and pediatric patients 8 years of age and older with glycogen storage disease type Ia (GSDIa).

This indication is approved under accelerated approval based on reduction in daily cornstarch intake. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

Important Safety Information

CONTRAINDICATIONS

GENGLYCOS is contraindicated in patients with known severe hepatic fibrosis or cirrhosis.

WARNINGS AND PRECAUTIONS

Hypersensitivity and Infusion Reactions (IRs)

- Hypersensitivity reactions including anaphylaxis and IRs have occurred with GENGLYCOS treatment. Severe reactions have been reported. Monitor for signs and symptoms of hypersensitivity and IRs, including urticaria, flushing, hypotension, bronchospasm, dyspnea, chest tightness, nausea, vomiting, headache, abdominal pain, lightheadedness, flu-like symptoms, shivering, rash, and hypertension.

Please see additional Important Safety Information throughout and the full Prescribing Information.

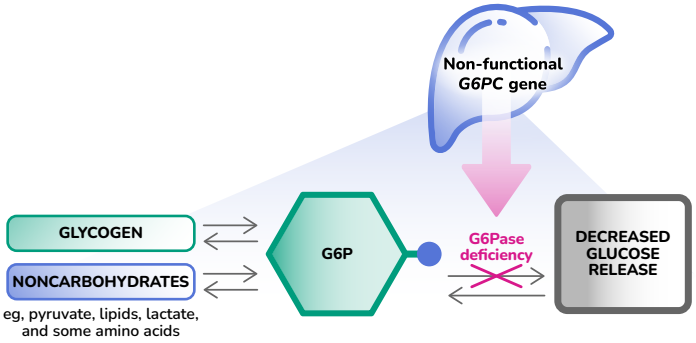
Proposed mechanism of action

GENGLYCOS is the first and only FDA-approved therapy designed to address GSDIa at the genetic level[1]

GSDIa Pathophysiology

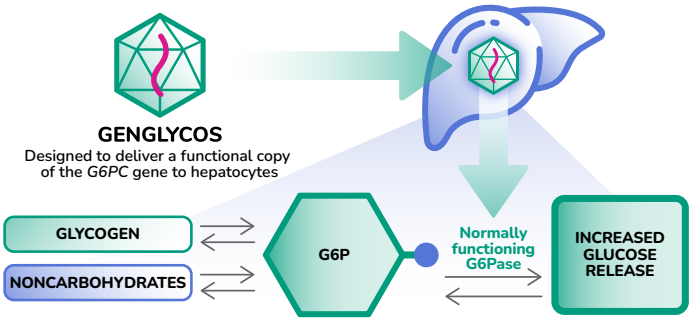
Glycogen storage disease type Ia (GSDIa) is caused by pathogenic variants in the *G6PC* (*G6PC1*) gene, resulting in a deficiency of glucose-6-phosphatase (G6Pase), the enzyme that catalyzes the final step in the production of glucose via both the glycogenolysis and gluconeogenesis pathways.[2]

Without G6Pase, patients with GSDIa are unable to release glucose during periods of fasting or high energy demands.[2]



Proposed GENGLYCOS Mechanism of Action

GENGLYCOS is an adeno-associated virus serotype 8 (AAV8) based gene therapy designed to deliver a copy of the glucose-6-phosphatase (*G6PC*) gene with native human *G6PC* promoter and enhancer elements to hepatocytes, resulting in the production of normally functioning G6Pase.[1]



FDA, US Food and Drug Administration; G6P, glucose-6-phosphate; GSDIa, glycogen storage disease type Ia.

Important Safety Information (cont.)

WARNINGS AND PRECAUTIONS (CONT.)

Hypersensitivity and Infusion Reactions (IRs)(cont.)

- Premedicate with acetaminophen and non-sedating antihistamines and administer GENGLYCOS according to recommended infusion rates. Monitor patients during and after completion of GENGLYCOS infusion as clinically indicated. If anaphylaxis or severe IR occurs, pause GENGLYCOS infusion immediately and initiate medical treatment as clinically indicated, monitoring as needed. For mild to moderate IRs, consider slowing or temporarily interrupting the infusion, and administer symptomatic treatment as clinically indicated. The infusion may be restarted at half the prior rate upon resolution of symptoms.
- Medical support measures, including cardiopulmonary resuscitation equipment and medications for the treatment of anaphylaxis (e.g., epinephrine, antihistamines, corticosteroids), should be available during GENGLYCOS administration.

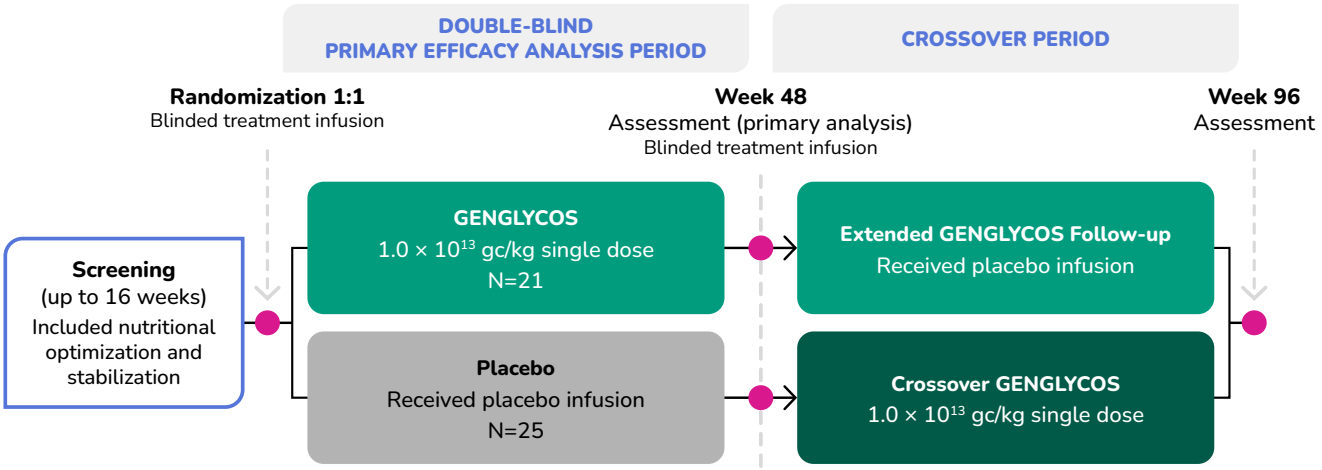
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The efficacy of GENGLYCOS was evaluated in a pivotal phase 3 study[1]

The pivotal phase 3 study (NCT05139316) was a multicenter, randomized, double-blind, placebo-controlled, crossover trial that included 46 patients aged 8 years and older with confirmed GSDIa.[1]

Study Design[1]



Patients with detectable baseline anti-AAV8 total antibodies were excluded.[1]

Endpoints evaluated in the pivotal phase 3 study[1]

Endpoints reflect comparisons between GENGLYCOS and placebo arms. Additional Week 96 analyses were performed for these endpoints during the crossover period.

PRIMARY ENDPOINT

- Percent change from baseline to Week 48 in daily cornstarch intake[a] (g)

KEY SECONDARY ENDPOINTS

- Change from baseline to Week 48 in number of daily cornstarch doses
- Change from baseline to Week 48 in the percent of glucose values within hypoglycemic range (<70 mg/dL) averaged over a 4-week period

[a]Daily cornstarch intake was recorded by patients and caregivers in an electronic diary and was prescribed and adjusted by the principal investigator based on blinded weekly assessments of continuous glucose monitoring data.

AAV8, adeno-associated virus serotype 8; gc/kg, genome copies per kilogram; GSDIa, glycogen storage disease type Ia.

Important Safety Information (cont.)

WARNINGS AND PRECAUTIONS (CONT.)

Hepatotoxicity

- Immune-mediated hepatotoxicity, with elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels, has occurred with GENGLYCOS. Avoid use in patients with preexisting hepatic impairment or acute hepatic viral infection.

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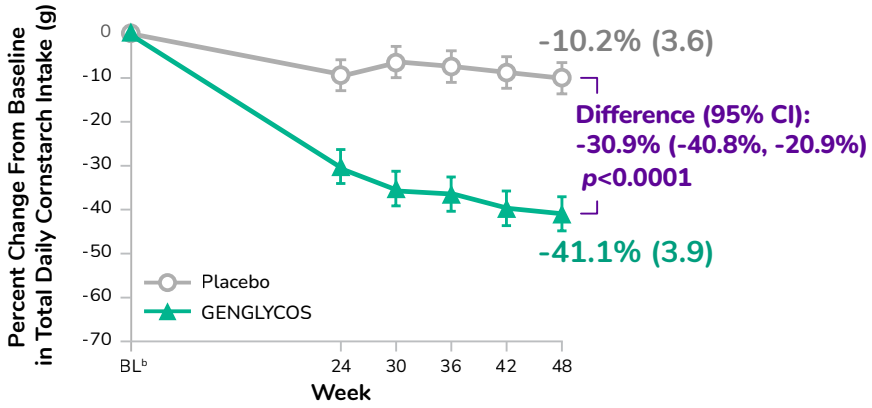
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Significant reduction in total daily cornstarch intake vs placebo at Week 48[1,3]

PRIMARY ENDPOINT

GENGLYCOS treatment resulted in a significant reduction in total daily cornstarch intake compared with placebo at Week 48[1,3]

Percent Change From Baseline to Week 48 in Total Daily Cornstarch Intake (LS Mean [SE][a])[1,3]



Placebo, n	25	24	23	22	22	23
GENGLYCOS, n	21	20	18	19	18	19

Reduction in total daily cornstarch intake observed from baseline to Week 96[1]:

-60.8% (19.7%)

Observed mean (SD) change across available data (15 of 21 patients) in the extended GENGLYCOS group

Continued reduction in total daily cornstarch intake observed in the GENGLYCOS group through Week 96[1]

[a]The LS mean, SE, and 95% CI were estimated using a mixed model for repeated measures (MMRM).
[b]Blinded investigational product infusion.

Percent Change From Baseline to Week 48 in Total Daily Cornstarch Intake (LS Mean [SE][a])[1,3]

	GENGLYCOS	Placebo
	(N=21)	(N=25)
Baseline (g), mean (SD)	293.9 (83.2)	271.7 (109.0)
Percent change from baseline, LS mean (SE)	-41.1% (3.9%)	-10.2% (3.6%)
Difference (95% CI)	-30.9% (-40.8%, -20.9%)	
p-value	<0.0001	

[a]The LS mean, SE, and 95% CI were estimated using a mixed model for repeated measures (MMRM).

BL, baseline; CI, confidence interval; LS, least square; SE, standard error; SD, standard deviation.

Important Safety Information (cont.)

WARNINGS AND PRECAUTIONS (CONT.)

Hepatotoxicity (cont.)

- Prior to GENGLYCOS infusion, evaluate liver-related medical history and assess liver function by clinical examination and laboratory testing. Advise patients to immediately report signs and symptoms of hepatotoxicity, including fatigue, jaundice, dark urine, nausea, vomiting, and right upper quadrant pain. Administer corticosteroids to all patients after GENGLYCOS infusion in order to mitigate hepatic reactions. Elevated transaminases may require adjustment of the corticosteroid treatment regimen, including increased dose or prolongation of the corticosteroid taper.

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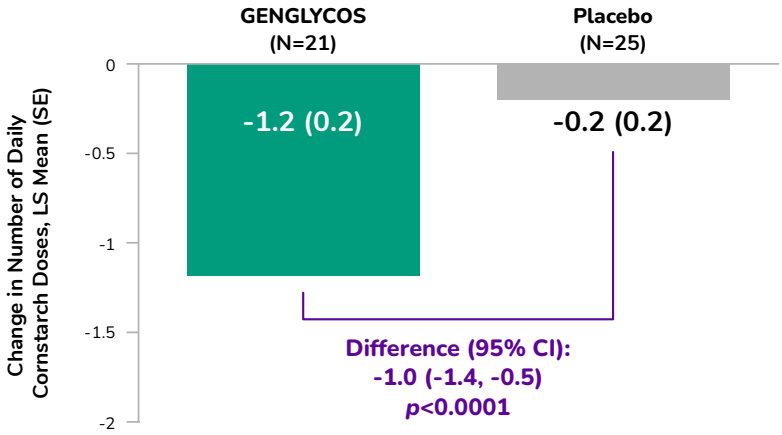
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Reduction in number of daily cornstarch doses[1,3]

SECONDARY ENDPOINT

GENGLYCOS-treated patients experienced a significant reduction in the number of daily cornstarch doses at Week 48[1,3]

Change From Baseline to Week 48 in Number of Daily Cornstarch Doses (LS Mean [SE][a])[1,3]



Reduction in the number of daily cornstarch doses observed from baseline to Week 96[1]:

-2.0 (1.3)

Observed mean (SD) change across available data (15 of 21 patients) in the extended GENGLYCOS group

Continued reduction in daily cornstarch doses observed in the GENGLYCOS group through Week 96[1]

[a]The LS mean, SE, and 95% CI were estimated using a mixed model for repeated measures (MMRM).

Change from Baseline to Week 48 in Number of Daily Cornstarch Doses (LS Mean [SE][a])[1,3]

	GENGLYCOS	Placebo
	(N=21)	(N=25)
Baseline, mean (SD)	5.8 (1.3)	5.1 (1.4)
Change from baseline, LS mean (SE)	-1.2 (0.2)	-0.2 (0.2)
Difference (95% CI)	-1.0 (-1.4, -0.5)	
p-value	<0.0001	

[a]The LS mean, SE, and 95% CI were estimated using a mixed model for repeated measures (MMRM).

BL, baseline; CI, confidence interval; LS, least square; SE, standard error; SD, standard deviation.

Important Safety Information (cont.)

WARNINGS AND PRECAUTIONS (CONT.)

Hepatotoxicity (cont.)

- Monitor transaminase levels for the first 6 months after GENGLYCOS administration. Continue to monitor transaminases in all patients who develop transaminase elevations, until transaminases return to baseline or as clinically indicated.

Adrenal Insufficiency

- Adrenal insufficiency, including serious events, has been reported in patients receiving GENGLYCOS during corticosteroid use and tapering.

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Glucose values in hypoglycemic range remained low in both groups[1]

SECONDARY ENDPOINT

Glucose values in hypoglycemic range (<70 mg/dL) remained low in both groups at Week 48[1]

Change in Percent of Glucose Values in the Hypoglycemic Range (<70 mg/dL) From Baseline to Week 48 (LS Mean [SE][a])[1]

	GENGLYCOS	Placebo
	(N=21)	(N=25)
Baseline, mean (SD)	2.5% (2.5%)	1.9% (2.2%)
Change from baseline, LS mean (SE)	3.1% (0.8%)	0.1% (0.8%)
Difference (95% CI)	3.1% (0.9%, 5.2%)	

Change in percent of glucose values in the hypoglycemic range (<70 mg/dL) from baseline to Week 96:

5.2% (6.3%)

Observed mean (SD) change across available data (19 of 21 patients) in the extended GENGLYCOS group

[a]The LS mean, SE, and 95% CI were estimated using a mixed model for repeated measures (MMRM).

CI, confidence interval; LS, least square; SE, standard error; SD, standard deviation.

Important Safety Information (cont.)

WARNINGS AND PRECAUTIONS (CONT.)

Adrenal Insufficiency (cont.)

- Signs and symptoms of adrenal insufficiency include fatigue, weakness, anorexia, nausea, vomiting, hypotension, hyponatremia, and hypoglycemia. Adrenal crisis may present as severe hypotension, acute abdominal pain, or loss of consciousness.
- Monitor patients for signs and symptoms of adrenal insufficiency and adrenal crisis after GENGLYCOS administration during and after corticosteroid therapy and tapering. Taper corticosteroid therapy gradually. Do not abruptly discontinue corticosteroid therapy.

AAV Vector Integration and Risk of Tumorigenicity

- There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome.
- GENGLYCOS is composed of a recombinant, non-replicating AAV8 vector whose DNA persists largely in episomal form. Random integration of recombinant AAV-vector DNA into human DNA has been reported with AAV gene therapies. The clinical relevance of individual integration events is unknown, but it is acknowledged that individual integration events could potentially contribute to a risk of tumorigenicity. If a tumor develops in a patient receiving GENGLYCOS, health care providers should contact and report the tumor to Ultragenyx Pharmaceutical Inc. at 1-888-756-8657.

ADVERSE REACTIONS

- Seven serious adverse events were observed in the Primary Efficacy Analysis Period (PEAP) of Study 1 (Weeks 1-48), including anaphylaxis/infusion reaction (2), adrenal insufficiency (2), high lactate level (2) and hypoglycemia (1).
- The most common adverse reactions during the PEAP of Study 1 (occurring in ≥10% of patients) with higher frequency in GENGLYCOS compared to placebo were ALT/AST enzyme elevated (71%), nausea (38%), headache (24%), hypertriglyceridemia (29%), adrenal insufficiency (24%), constipation (19%), hyperglycemia (14%), acne/dermatitis acneiform (19%), Cushingoid features (14%), and anaphylaxis (10%).

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Safety of GENGLYCOS[1]

Safety of GENGLYCOS was evaluated in 2 clinical studies[1]

- The phase 3 pivotal trial included 46 patients aged 8 years and older with GSDIa. During the Primary Efficacy Analysis Period (PEAP, Weeks 1-48), 21 patients received GENGLYCOS at the recommended dose of 1.0×10^{13} gc/kg and 25 received placebo. After Week 48, 19 placebo-treated patients subsequently received GENGLYCOS and were followed to Week 96
- The dose-finding phase 1/2 study included 12 adult patients with GSDIa with a follow up duration of 52 weeks
- Seven serious adverse events (SAEs) were observed in the PEAP of the pivotal phase 3 study, including anaphylaxis/infusion reaction (2), adrenal insufficiency (2), high lactate level (2), and hypoglycemia (1)

Most Common Adverse Reactions in the PEAP (Occurring in ≥10% of Patients) of the Pivotal Phase 3 Study With Higher Frequency in GENGLYCOS vs Placebo[1]

Adverse reaction	GENGLYCOS	Placebo
Events n | Subjects N (%)	**(N=21)**	**(N=25)**
ALT/AST enzyme elevated[a]	29 | 15 (71)	6 | 3 (12)
Nausea	12 | 8 (38)	10 | 4 (16)
Headache	11 | 5 (24)	9 | 3 (12)
Hypertriglyceridemia[b]	10 | 6 (29)	2 | 2 (8)
Adrenal insufficiency[c]	7 | 5 (24)	0 | 0
Constipation	5 | 4 (19)	0 | 0
Hyperglycemia[d]	5 | 3 (14)	0 | 0
Acne/dermatitis acneiform	4 | 4 (19)	0 | 0
Cushingoid features	3 | 3 (14)	0 | 0
Anaphylaxis[e]	2 | 2 (10)	0 | 0

[a]All events were mild to moderate (<5.0x ULN), except one severe (Grade 3) asymptomatic event (peak ALT: 253 U/L). ALT/AST elevations peaked between 4 and 12 weeks post-GENGLYCOS administration and resolved within 15 weeks. [b]All adverse events were mild to moderate. [c]Two SAEs were reported. [d]All adverse events were mild. [e]Two serious adverse reactions with onset within minutes of GENGLYCOS administration.

- Safety evaluations during the Crossover Period of the pivotal phase 3 study and the dose-finding phase 1/2 study did not identify any additional adverse reactions

ALT, alanine aminotransferase; AST, aspartate aminotransferase; gc/kg, genome copies per kilogram; GSDIa, glycogen storage disease type Ia; ULN, upper limit of normal.

Important Safety Information (cont.)

DRUG INTERACTIONS

Vaccinations

- Vaccine schedules may need to be adjusted for immunosuppressive therapy, and vaccines should be avoided 1 month prior to GENGLYCOS administration.

USE IN SPECIFIC POPULATIONS

Pregnancy

- GENGLYCOS should not be used during pregnancy. There are no data on the use of GENGLYCOS in pregnant women. It is unknown whether GENGLYCOS can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

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Administered as a single-dose intravenous infusion[1]

GENGLYCOS is provided as a kit to meet the dosing requirements for each patient[1]



The recommended dosage of GENGLYCOS is 1.0 x 10^{13} gc/kg body weight, administered as a single-dose intravenous infusion.[1]

GENGLYCOS is provided as a customized kit based on body weight.[1]

GENGLYCOS can only be administered at a Qualified Treatment Center (QTC); our UltraCare® team can work with you to find a QTC.

Scan or click for recommended dosing in Prescribing Information.

gc/kg, genome copies per kilogram.

Important Safety Information (cont.)

USE IN SPECIFIC POPULATIONS (CONT.)

Contraception

- Women of childbearing potential should use effective contraception for at least 12 months after administration of GENGLYCOS.
- For 6 months after administration of GENGLYCOS, men must not donate semen, and men of reproductive potential and their female partners must prevent or postpone pregnancy using an effective form of contraception.

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Getting started with GENGLYCOS

The following tests and assessments should be performed prior to GENGLYCOS administration[1]

Select patients without detectable anti-AAV8 antibodies for treatment with GENGLYCOS. Do not administer GENGLYCOS to patients with a detected result for antibodies to AAV8[a]

Assess adrenal function (perform clinical examination and laboratory testing including morning serum cortisol and ACTH)

Assess liver function (perform clinical examination and laboratory testing including ALT, AST, and total bilirubin)

The GENGLYCOS Treatment Brochure is available through your Sales Representative.

[a]An FDA authorized test for detection of anti-AAV8 total binding antibodies is not currently available. For information regarding anti-AAV8 antibody testing, contact Ultragenyx Pharmaceutical Inc. at 1-888-756-8657. Currently available tests may vary in accuracy and design.

AAV8, adeno-associated virus serotype 8; ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; AST; aspartate aminotransferase; FDA, US Food and Drug Administration.

Important Safety Information (cont.)

ADDITIONAL PATIENT COUNSELING INFORMATION

Vector Shedding

- Inform patients/caregivers that vector distribution in blood and vector shedding in urine, stool, and saliva can occur after GENGLYCOS infusion. Advise patients/caregivers on proper hygiene when handling patient body waste. These precautions should be followed for 3 months after GENGLYCOS infusion.

Report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. You may also report side effects to Ultragenyx Pharmaceutical Inc. at 1-888-756-8657.

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The first and only FDA-approved therapy for GSDIa in patients aged 8 years and older[1]

UltraCare® Gene Therapy Guides are available to help support your patient along their GENGLYCOS treatment journey

Scan or click to access resources

Scan or click to learn more about GENGLYCOS

FDA, US Food and Drug Administration; GSDIa, glycogen storage disease type Ia.

Indication

GENGLYCOS (pariglasgene brecaparvovec-opnr) is indicated to reduce daily cornstarch intake as an adjunct to nutritional management in adult and pediatric patients 8 years of age and older with glycogen storage disease type Ia (GSDIa).

This indication is approved under accelerated approval based on reduction in daily cornstarch intake. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

Important Safety Information

CONTRAINDICATIONS

GENGLYCOS is contraindicated in patients with known severe hepatic fibrosis or cirrhosis.

Please see the full Prescribing Information for GENGLYCOS.

References: 1. GENGLYCOS [Prescribing Information]. Novato, CA: Ultragenyx Pharmaceutical Inc; August 2026. **2.** Derks TGJ, Rodriguez-Buritica DF, Ahmad A, et al. Glycogen storage disease type Ia: current management options, burden and unmet need. *Nutrients.* 2021;13(11):3828. **3.** Ultragenyx Pharmaceutical Inc. Data on file.

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