



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GLYCEROL PHENYLBUTYRATE ORAL LIQUID safely and effectively. See full prescribing information for GLYCEROL PHENYLBUTYRATE ORAL LIQUID.

GLYCEROL PHENYLBUTYRATE oral liquid
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

Glycerol phenylbutyrate is a nitrogen-binding agent indicated for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Glycerol phenylbutyrate oral liquid must be used with dietary protein restriction and, in some cases, dietary supplements (1).

- Glycerol phenylbutyrate oral liquid is not indicated for treatment of acute hyperammonemia in patients with UCDs. (1)
- Safety and efficacy for treatment of *N*-acetylglutamate synthase (NAGS) deficiency has not been established. (1)

DOSE AND ADMINISTRATION

Glycerol phenylbutyrate oral liquid should be prescribed by a physician experienced in management of UCDs. For administration and preparation, see full prescribing information. (2.1, 2.8)

Switching From Sodium Phenylbutyrate Tablets or Powder to Glycerol Phenylbutyrate Oral Liquid

- Patients should receive the dosage of glycerol phenylbutyrate that contains the same amount of phenylbutyric acid, see full prescribing information for conversion. (2.3)

Initial Dosage in Phenylbutyrate-Naïve Patients (2.3)

- Recommended dosage range is 4.5 to 11.2 mL/mL/day (5 to 12.4 g/mL/day).
- For patients with some residual enzyme activity not adequately controlled with dietary restriction, the recommended starting dose is 4.5 mL/mL/day.
- Take into account patient's estimated urea synthetic capacity, dietary protein intake, and diet adherence.

Dosage Adjustment and Monitoring

- Follow plasma ammonia levels to determine the need for dosage adjustment. (2.4)

Dosage Modifications in Patients with Hepatic Impairment

- Start dosage at lower end of range. (2.5, 6, 7)

DOSE FORMS AND STRENGTHS

Oral liquid: 1.1 g/mL (3)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Glycerol phenylbutyrate oral liquid is indicated for use as a nitrogen-binding agent for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Glycerol phenylbutyrate oral liquid must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

Limitations of Use

- Glycerol phenylbutyrate oral liquid is not indicated for the treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels.
- The safety and efficacy of glycerol phenylbutyrate oral liquid for the treatment of *N*-acetylglutamate synthase (NAGS) deficiency has not been established.

2 DOSE AND ADMINISTRATION

2.1 Important Administration Instructions

Glycerol phenylbutyrate oral liquid should be prescribed by a physician experienced in the management of UCDs.

- Instruct patients to take glycerol phenylbutyrate oral liquid with food or formula and to administer it directly into the mouth via oral syringe.
- Instruct patients to use the glycerol phenylbutyrate oral liquid bottle and oral syringe as follows:
 - Use a new reclosable bottle cap adapter with each new bottle that is opened.
 - Open the glycerol phenylbutyrate oral liquid bottle and twist on the new reclosable bottle cap adapter.
 - Use a new and dry oral syringe to withdraw each prescribed dose of glycerol phenylbutyrate oral liquid.
 - Discard the oral syringe after each dose.
 - Tightly close the tethered tab on the reclosable bottle cap adapter after each dose.
 - Do not reuse the reclosable bottle cap adapter.
 - Discard bottle and any remaining contents 28 days after opening.
 - If water or moisture enters the glycerol phenylbutyrate oral liquid bottle, the contents will become cloudy in appearance. If the contents of the bottle appear cloudy at any time, do not use the remaining glycerol phenylbutyrate oral liquid in the bottle and return it to the pharmacy to be discarded.

- Instruct that glycerol phenylbutyrate oral liquid should be administered just prior to breastfeeding in infants who are breastfeeding.
- For patients who cannot swallow, see the instructions on administration of glycerol phenylbutyrate oral liquid by nasogastric tube or gastrostomy tube *Use Dosage and Administration (2.6)*.

For patients who require a volume of less than 1 mL per dose via nasogastric or gastrostomy tube, the delivered dose may be less than anticipated. Clearly monitor these patients using ammonia levels. *Use Dosage and Administration (2.6)*.

The recommended dosages for patients switching from sodium phenylbutyrate to glycerol phenylbutyrate oral liquid and patients naïve to phenylbutyric acid are different. *Use Dosage and Administration (2.2, 2.3)*. For both subpopulations:

- Patients 2 years of age and older: Give glycerol phenylbutyrate oral liquid in equally divided dosages, each rounded up to the nearest 0.5 mL.
- Patients less than 2 years: Give glycerol phenylbutyrate oral liquid in 3 or more equally divided dosages, each rounded up to the nearest 0.1 mL.
- The maximum total daily dosage is 17.5 mL (18 g).
- Glycerol phenylbutyrate oral liquid must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

2.2 Switching From Sodium Phenylbutyrate to Glycerol Phenylbutyrate Oral Liquid

Patients switching from sodium phenylbutyrate to glycerol phenylbutyrate oral liquid should receive the dosage of glycerol phenylbutyrate oral liquid that contains the same amount of phenylbutyric acid. The conversion table for glycerol phenylbutyrate tablets (g) is as follows:

Total daily dosage of glycerol phenylbutyrate (mL) = total daily dosage of sodium phenylbutyrate tablets (g) x 0.88

Total daily dosage of glycerol phenylbutyrate (mL) = total daily dosage of sodium phenylbutyrate powder (g) x 0.81

2.3 Initial Dosage in Phenylbutyrate-Naïve Patients

The recommended dosage range, based upon body surface area, in patients naïve to phenylbutyrate (PBA) is 4.5 to 11.2 mL/mL/day (5 to 12.4 g/mL/day). For patients with some residual enzyme activity not adequately controlled with protein restriction, the recommended starting dosage is 4.5 mL/mL/day. In determining the starting dosage of glycerol phenylbutyrate oral liquid in treatment naïve patients, consider the patient's residual urea synthetic capacity, dietary protein requirements, and diet adherence. Dietary protein is approximately 10% nitrogen by weight. Given that approximately 47% of dietary nitrogen is excreted in waste and approximately 70% of administered PBA does not get converted to urinary phenylacetylglutamine (PACG), an initial estimated glycerol phenylbutyrate oral liquid dose for a 24-hour period is 0.5 mL glycerol phenylbutyrate oral liquid per gram of dietary protein ingested per 24-hour period. The total daily dosage should not exceed 17.5 mL.

2.4 Dosage Adjustment and Monitoring

During treatment with glycerol phenylbutyrate oral liquid, patients should be followed clinically and with plasma ammonia levels to determine the need for dosage stratification. Closely monitor plasma ammonia levels during treatment with glycerol phenylbutyrate oral liquid and when changing the dosage of glycerol phenylbutyrate oral liquid.

The methods used for measuring plasma ammonia levels vary among individual laboratories and values obtained using different assay methods may not be interchangeable. Normal ranges and therapeutic target levels for plasma ammonia depend upon the assay method used by the individual laboratory. During treatment with glycerol phenylbutyrate oral liquid, refer to the assay-specific normal ranges and the therapeutic target ranges for plasma ammonia.

Normal Plasma Ammonia

In patients treated with glycerol phenylbutyrate oral liquid who experience neurologic symptoms (e.g., nausea, vomiting, headache, somnolence or confusion) in the absence of high plasma ammonia or other intercurrent illness to explain these symptoms, consider the glycerol phenylbutyrate oral liquid dosage and clinically monitor patients for potential neurotoxicity from high glycerol phenylbutyrate (PBA) concentrations. If available, obtain measurements of plasma PAA concentrations and plasma phenylacetylglutamine (PACG) to calculate the ratio of plasma PAA to PACG which may help to guide glycerol phenylbutyrate oral liquid dosage. The PAA to PACG ratio has generally been less than 1 in patients with UCDs who did not have significant plasma PAA accumulation. In general, a high PAA to PACG ratio may indicate a slower or less efficient conjugation reaction to form PACG, which may lead to increases in PAA without further conversion to PACG. *Use Warnings and Precautions (5.1, Clinical Pharmacology (12.3))*.

Dosage in Ammonia

In patients 6 years and older, when plasma ammonia is elevated, increase the glycerol phenylbutyrate oral liquid dosage to maintain fasting plasma ammonia to less than half the upper limit of normal (ULN). In infants and pediatric patients below 6 years of age, if obtaining fasting ammonia is problematic due to frequent feedings, adjust the glycerol phenylbutyrate oral liquid dosage to keep the first ammonia reading below the ULN for age. If available, the ratio of PAA to PACG in the same plasma sample may provide additional information to assist in dosage adjustment decisions. *Use Use in Specific Populations (8.7, Clinical Pharmacology (12.3))*.

Dosage in Protein Intake

If available, urinary phenylacetylglutamine (PACG) measurements may be used to help guide glycerol phenylbutyrate oral liquid dosage adjustment. Each day of UPAGN excreted over 24 hours covers waste nitrogen generated from 1.4 grams of dietary protein. If UPAGN excretion is insufficient to cover daily dietary protein intake and the fasting ammonia is greater than half the ULN, the glycerol phenylbutyrate oral liquid dosage should be increased. The amount of dosage adjustment needed factor in the amount of dietary protein that has not been covered, as indicated by the 24-hour UPAGN output, and the estimated glycerol phenylbutyrate oral liquid dose needed per gram of dietary protein ingested and the maximum total daily dosage (i.e., 17.5 mL).

Consider a patient's use of concomitant medications, such as probenecid, when making dosage adjustment decisions based on UPAGN. Probenecid may result in a decrease of the urinary excretion of PACG. *Use Drug Interactions (7.2)*.

2.5 Dosage Modifications in Patients with Hepatic Impairment

For patients with moderate to severe hepatic impairment, the recommended starting dosage is at the lower end of the recommended dosage range (4.5 mL/mL/day) and the dosage should be kept at the lowest necessary to control their plasma ammonia. *Use Use in Specific Populations (8.7)*.

2.6 Preparation for Nasogastric Tube or Gastrostomy Tube Administration

It is recommended that all patients who can swallow take glycerol phenylbutyrate oral liquid orally, even those with nasogastric and/or gastrostomy tubes. For patients who cannot swallow, a nasogastric tube or gastrostomy tube may be used to administer glycerol phenylbutyrate oral liquid as follows:

- Place a new dry oral syringe to withdraw each prescribed dosage of glycerol phenylbutyrate oral liquid from the bottle.
- Place the tip of the syringe into the nasogastric/gastrostomy tube.
- Utilize the plunger of the syringe, administer glycerol phenylbutyrate oral liquid into the tube.
- Use a separate syringe to flush the nasogastric/gastrostomy tube. Flush once with 10 mL of water or formula and allow the flush to drain.
- If needed, flush a second time with an additional 10 mL of water or formula to clear the tube.

For patients who require a volume of less than 1 mL per dose via nasogastric or gastrostomy tube, the delivered dosage may be less than anticipated due to incomplete delivery of glycerol phenylbutyrate oral liquid to the gastric lumen. Therefore, these patients should be closely monitored using ammonia levels following initiation of glycerol phenylbutyrate oral liquid dosing or dosage adjustment.

3 DOSE FORMS AND STRENGTHS

Oral liquid: clear, colorless to pale yellow, 1.1 g/mL of glycerol phenylbutyrate (delivers 1.02 g/mL phenylbutyrate).

4 CONTRAINDICATIONS

Glycerol phenylbutyrate oral liquid is contraindicated in patients with known hypersensitivity to phenylbutyrate. Signs of hypersensitivity include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

5 WARNINGS AND PRECAUTIONS

5.1 Neurotoxicity

Increased exposure to PAA, the major metabolite of glycerol phenylbutyrate, may be associated with neurotoxicity in patients with UCDs. In a study of adult cancer patients, subjects received sodium phenylbutyrate administered as a 1-hour infusion twice daily at two dose levels of 125 and 150 mg/kg for a 2-week period. Of 18 subjects enrolled, 7 had a history of primary central nervous system tumor. Signs and symptoms of potential PAA neurotoxicity, which were reversible, were reported at plasma PAA concentrations above 500 micrograms/mL and included somnolence, fatigue, lightheadedness, headache, dyspnea, hypoxia, disorientation, impaired memory, and exacerbation of preexisting neuropathy. PAA concentrations were not measured when symptoms resolved.

In healthy subjects, after administration of 4 mL and 6 mL glycerol phenylbutyrate 3 times daily (3.2 g/day and 10.8 g/day, respectively) for 3 days, a dose-dependent increase in non-serious nervous system adverse reactions were observed. In subjects who had nervous system adverse reactions, plasma PAA concentrations, which were measured on Day 3 per protocol and not always at end of symptoms, ranged from 1 to 56 micrograms/mL, with 4 mL glycerol phenylbutyrate 3 times daily and from 5.7 to 24.2 micrograms/mL, with 6 mL glycerol phenylbutyrate 3 times daily.

In clinical trials in patients with UCDs who had been on sodium phenylbutyrate prior to administration of glycerol phenylbutyrate, adverse reactions of headache, fatigue, symptoms of peripheral neuropathy, seizures, tremor and/or dizziness were reported. No correlation between plasma PAA concentration and neurologic symptoms was identified but plasma PAA concentrations were generally not consistently measured at the time of neurologic symptom occurrence. *Use Clinical Pharmacology (12.3)*.

If symptoms of vomiting, nausea, headache, somnolence or confusion are present in the absence of high ammonia or other intercurrent illness which explains these symptoms, consider the potential for PAA neurotoxicity which may need reduction in the glycerol phenylbutyrate dosage. *Use Dosage and Administration (2.4)*.

5.2 Pancreatic Insufficiency or Intestinal Malabsorption

Exocrine pancreatic enzymes hydrolyze glycerol phenylbutyrate in the small intestine, separating the active moiety, phenylbutyrate, from glycerol. This process allows phenylbutyrate to be absorbed into the circulation. Low or absent pancreatic enzymes or intestinal disease resulting in fat malabsorption may result in reduced or absent digestion of glycerol phenylbutyrate and/or absorption of phenylbutyrate and reduced control of plasma ammonia. Monitor ammonia levels closely in patients with pancreatic insufficiency or intestinal malabsorption.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Neurotoxicity *Use Warnings and Precautions (5.1)*
- Pancreatic insufficiency or intestinal malabsorption *Use Warnings and Precautions (5.2)*
- Clinical Trials Experience

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

Assessment of adverse reactions was based on exposure of 45 adult patients (31 female and 14 male) with UCD subtype deficiencies of ornithine transcarbamoylase (OTC, n=40), carbonyl phosphate synthetase (CPS, n=2), and argininosuccinate lyase (ASL, n=1) in a randomized, double-blind, active-controlled glycerol phenylbutyrate vs sodium phenylbutyrate, crossover, 4-week study (Study 1) that enrolled patients 10 years of age and older. *Use Clinical Studies (14.1)*. One of the 45 patients receiving only sodium phenylbutyrate prior to withdrawing day 1 of the study due to adverse reactions.

The most common adverse reactions occurring in at least 10% of patients reported during short-term treatment with glycerol phenylbutyrate were diarrhea, flatulence, and headache. Table 1 summarizes adverse reactions occurring in 2 or more patients treated with glycerol phenylbutyrate or sodium phenylbutyrate (incidence of at least 4% in either treatment arm).

Table 1: Adverse Reactions Reported in 2 or More Adult Patients with UCDs (at least 4% in Either Treatment Arm) in Study 1

	Number (%) of Patients in Study 1 (N = 45)	Number (%) of Patients in Study 1 (N = 44)
Diarrhea	3 (7)	7 (16)
Headache	4 (8)	6 (14)
Flatulence	1 (2)	6 (14)
Abdominal pain	2 (4)	3 (7)
Vomiting	2 (4)	3 (7)
Decreased appetite	2 (4)	3 (7)
Fatigue	1 (2)	3 (7)
Dyspepsia	3 (7)	2 (5)
Nausea	3 (7)	1 (2)
Dizziness	4 (8)	0
Abdominal discomfort	3 (7)	0

Other Adverse Reactions

Glycerol phenylbutyrate has been evaluated in 77 patients with UCDs (51 adult and 26 pediatric patients ages 2 years to 17 years) in 2 open-label long-term studies, in which 69 patients completed 12 months of treatment with glycerol phenylbutyrate (median exposure = 51 weeks). During these studies there were no deaths.

Adverse reactions reported in at least 10% of adult patients were nausea, vomiting, diarrhea, decreased appetite, dizziness, headache, and fatigue.

CONTRAINDICATIONS

Known hypersensitivity to phenylbutyrate. (4)

WARNINGS AND PRECAUTIONS

- Neurotoxicity: Phenylacetate (PAA), the active moiety of glycerol phenylbutyrate, may be toxic; reduce dosage for symptoms of neurotoxicity. (5.1)
- Pancreatic Insufficiency or Intestinal Malabsorption: Monitor ammonia levels closely. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (>10%) in adults are diarrhea, flatulence, and headache. (5.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cambiar Pharmaceuticals, Inc. at 1-866-455-1395 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Carbocisteine, valproic acid, or haloperidol: May increase plasma ammonia level; monitor ammonia levels closely. (7.1)
- Probenecid: May affect renal excretion of metabolites of glycerol phenylbutyrate, including phenylacetylglutamine (PACG) and PAA. (7.2)
- CYP2A4 Substrates with narrow therapeutic index (e.g., aflentanil, quinidine, cyclosporine): Glycerol phenylbutyrate may decrease exposure; monitor for decreased efficacy of the narrow therapeutic index drug. (7.3)
- Midazolam: Decreased exposure; monitor for suboptimal effect of midazolam. (7.3)

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding is not recommended. (8.2)

See 17 for **PATIENT COUNSELING INFORMATION** and Medication Guide.

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8.4 Pediatric Use

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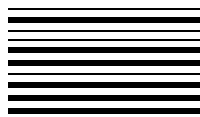
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These are not all of the possible side effects of glycerol phenylbutyrate oral liquid. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store glycerol phenylbutyrate oral liquid?

- Store glycerol phenylbutyrate oral liquid between 69°F to 77°F (20°C to 25°C).

Keep glycerol phenylbutyrate oral liquid and all medicines out of the reach of children.

General information about the safe and effective use of glycerol phenylbutyrate oral liquid.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use glycerol phenylbutyrate oral liquid for a condition for which it was not prescribed. Do not give glycerol phenylbutyrate oral liquid to other people, even if they have the same symptoms you have. It may harm them. You can ask your doctor or pharmacist for information about glycerol phenylbutyrate oral liquid that is written for health professionals.

What are the ingredients in glycerol phenylbutyrate oral liquid?

Active ingredient: glycerol phenylbutyrate

Medication Guide available at <http://camberpharma.com/medication-guides>



Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854.

By: Annora Pharma Pvt. Ltd.
Sangareddy - 502313, Telangana, India.

For more information, call 1-866-495-1995.

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Age Range	Glycerol Phenylbutyrate Dose	Mean Peak PAA Concentration* (SD)	Median Peak PAA Concentration* (Range)
Less than 2 months (n=16)	3.1 to 12.7 mL/mL/day (3.4 to 14 g/mL/day)	257 (162)	205 (96 to 707)
2 months to less than 2 years (n=17)	3.3 to 12.3 mL/mL/day (3.7 to 12.5 g/mL/day)	142 (288)	35 (1 to 1215)
2 years to 17 years (n=53)	1.4 to 13.7 mL/mL/day (1.5 to 15.1 g/mL/day)	70 (78)	50 (1 to 410)
Adults (n=43)	0.6 to 14 mL/mL/day (0.7 to 15.4 g/mL/day)	38 (40)	25 (1.6 to 178)

Distribution

In vitro, the extent of plasma protein binding for ¹⁴C labeled metabolites was 81% to 98% for PBA (over 1 to 250 microgram/mL), and 37% to 66% for PAA (over 5 to 500 microgram/mL). The protein binding for PAGN was 7% to 12% and no concentration effects were noted.

Elimination

Upon oral administration, pancreatic lipase hydrolyzes glycerol phenylbutyrate (i.e., glycerol phenylbutyrate), and release PBA. PBA undergoes β-oxidation to PAA, which is conjugated with glutamine in the liver and in the kidney through the enzyme phenylacetyl-CoA: L-glutamine-N acetyltransferase to form PAGN. PAGN is subsequently eliminated in the urine.

Saturation of conjugation of PAA and glutamine to form PAGN was suggested by increases in the ratio of plasma PAA to PAGN with increasing dose and with increasing severity of hepatic impairment.

In healthy subjects, after administration of 4 mL, 6 mL, and 9 mL 3 times daily for 3 days, the ratio of mean AUC₀₋₂₄ of PAA to PAGN was 1, 1.25, and 1.6, respectively. In a separate study, in patients with hepatic impairment (Child Pugh B and C), the ratios of mean C_{max} values for PAA to PAGN among all patients dosed with 6 mL and 9 mL, twice daily were 1 and 3.7.

In *in vitro* studies, the specific activity of lipases for glycerol phenylbutyrate was in the following decreasing order: pancreatic triglyceride lipase, carboxyl ester lipase, and pancreatic lipase-related protein 2. Further, glycerol phenylbutyrate was hydrolyzed *in vitro* by esterases in human plasma. In these *in vitro* studies, a complete disappearance of glycerol phenylbutyrate did not produce an equivalent PBA, suggesting the formation of mono- or bis ester metabolites. However, the formation of mono- or bis esters was not studied in humans.

Excretion

The mean (SD) percentage of administered PBA excreted as PAGN was approximately 69% (17) in adults and 66% (24) in pediatric patients with UCIDs at steady state. PAA and PBA represented minor urinary metabolites, each accounting for less than 1% of the administered dose of PBA.

Specific Populations

Age: Pediatric Population

Population pharmacokinetic modeling and dosing simulations suggest body surface area to be the most significant covariate explaining the variability of PAA clearance. PAA clearance was 10.0 L/h, 15.4 L/h, and 24.4 L/h, respectively, for patients ages 0 to 5, 6 to 11, and 12 to 17 years with UCIDs.

In pediatric patients with UCIDs (n = 14) aged 2 months to less than 2 years, PAA clearance was 8.8 L/h.

In pediatric patients with UCIDs (n = 16) ages less than 2 months, PAA clearance was 3.8 L/h. The mean peak ratio of PAA to PAGN in UCID patients aged birth to less than 2 months was higher (mean: 1.6; range 0.1 to 7.1) than that of UCID patients aged 2 months to less than 2 years (mean 0.5; range 0.1 to 1.2).

In healthy adult subjects, a gender effect was found for all metabolites, with women generally having higher plasma concentrations of all metabolites than men at a given dose level. In healthy female subjects, mean C_{max} for PAA was 51 and 120% higher than in male volunteers after administration of 4 mL and 6 mL 3 times daily for 3 days, respectively. The dose normalized mean AUC₀₋₂₄ for PAA was 108% higher in females than in males.

Renal Impairment

The pharmacokinetics of glycerol phenylbutyrate in patients with impaired renal function, including those with end stage renal disease (ESRD) or those on hemodialysis, have not been studied (see *Use in Specific Populations (8.6)*).

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of glycerol phenylbutyrate were studied in patients with mild, moderate and severe hepatic impairment of Child Pugh class A, B, and C, respectively receiving 100 mg/kg glycerol phenylbutyrate twice daily for 7 days.

Plasma glycerol phenylbutyrate was not measured in patients with hepatic impairment.

After multiple doses of glycerol phenylbutyrate in patients with hepatic impairment of Child Pugh A, B, and C, geometric mean AUC₀₋₂₄ of PBA was 42%, 84%, and 50% higher, respectively, while geometric mean AUC₀₋₂₄ of PAA was 22%, 53%, and 94% higher, respectively, than in healthy subjects.

In patients with hepatic impairment of Child Pugh A, B, and C, geometric mean AUC₀₋₂₄ of PAGN was 42%, 27%, and 22% lower, respectively, than that in healthy subjects.

The proportion of PBA excreted as PAGN in the urine in Child Pugh A, B, and C was 80%, 56%, and 85%, respectively, and, in healthy volunteers, was 67%.

In another study in patients with moderate and severe hepatic impairment (Child Pugh B and C), mean C_{max} of PAA was 144 microgram/mL (range: 14 to 358 microgram/mL) after daily dosing of 6 mL of glycerol phenylbutyrate twice daily, while mean C_{max} of PAA was 292 microgram/mL (range: 57 to 855 microgram/mL) after daily dosing of 9 mL of glycerol phenylbutyrate twice daily. The ratio of mean C_{max} values for PAA to PAGN among all patients dosed with 6 mL and 9 mL, twice daily were 3 and 3.7, respectively.

After multiple doses, a PAA concentration greater than 200 microgram/mL was associated with a ratio of plasma PAA to PAGN concentrations higher than 2.5 (see *Dosage and Administration (2.5)*).

Drug Interaction Studies

In vitro PBA or PAA did not induce CYP1A2, suggesting that *in vivo* drug interactions via induction of CYP1A2 is unlikely.

In vitro studies, PBA at a concentration of 800 microgram/mL caused greater than 80% reversible inhibition of cytochrome P450 isoenzymes CYP2C8, CYP2D6, and CYP3A4/5 (testosterone 6β-hydroxylase activity). The *in vitro* study suggested that *in vivo* drug interactions with substrates of CYP2D6 cannot be ruled out. The inhibition of CYP isoenzymes 1A2, 2C8, 2C19, and 2D6 by PBA at concentrations of 2.8 mg/mL was observed *in vitro*. Clinical implication of these results is unknown.

Effects of glycerol phenylbutyrate on other drugs

Midazolam

In healthy subjects, when oral midazolam was administered after multiple doses of glycerol phenylbutyrate (4 mL, three times a day for 3 days) under fed conditions, the mean C_{max} and AUC for midazolam were 25% and 32% lower, respectively, compared to administration of midazolam alone. In addition, the mean C_{max} and AUC for 1-hydroxy midazolam were 28% and 58% higher, respectively, compared to administration of midazolam alone (see *Drug Interactions (7.3)*).

Celecoxib

Concomitant administration of glycerol phenylbutyrate did not significantly affect the pharmacokinetics of celecoxib, a substrate of CYP2D6. When 200 mg of celecoxib was orally administered with glycerol phenylbutyrate (4 mL, three times a day for 6 days) under fed conditions, the mean C_{max} and AUC for celecoxib were 13% and 9% lower than after administration of celecoxib alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 2-year study in Sprague Dawley rats, glycerol phenylbutyrate caused a statistically significant increase in the incidence of pancreatic acinar cell adenoma, carcinoma, and combined adenoma or carcinoma at a dose of 850 mg/kg/day in males (4.7 times the dose of 6.3 mL/mL/day in adult patients, based on combined AUCs for PBA and PAA). The incidence of the following tumors was also increased in female rats at a dose of 800 mg/kg/day: thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, uterine endometrial stromal polyp, and combined polyp or carcinoma. The dose of 850 mg/kg/day in male rats is 9 times the dose of 7.5 mL/mL/day in pediatric patients, based on combined AUCs for PBA and PAA. The dose of 800 mg/kg/day in female rats is 5.5 times the dose of 7.5 mL/mL/day in pediatric patients, based on combined AUCs for PBA and PAA. In a 26-week study in transgenic Tg.ras26 mice, glycerol phenylbutyrate was not tumorigenic at doses up to 1000 mg/kg/day.

Mutagenesis

Glycerol phenylbutyrate was not genotoxic in the Ames test, the *in vitro* chromosomal aberration test in human peripheral blood lymphocytes, or the *in vivo* rat micronucleus test. The metabolites PBA, PAA, PAGN, and phenylacetylglutamine were not genotoxic in the Ames test or *in vitro* chromosome aberration test in Chinese hamster ovary cells.

Impairment of Fertility

Glycerol phenylbutyrate had no effect on fertility or reproductive function in male and female rats at oral doses up to 900 mg/kg/day. At doses of 1200 mg/kg/day (approximately 7 times the dose of 8.9 mL/mL/day in adult patients, based on combined AUCs for PBA and PAA), maternal toxicity was observed and the number of viable embryos was increased.

14 CLINICAL STUDIES

14.1 Clinical Studies in Adult Patients with UCIDs

Active Controlled, 4-Week, Noninferiority Study (Study 1)

A randomized, double-blind, active-controlled, crossover, noninferiority study (Study 1) compared glycerol phenylbutyrate to sodium phenylbutyrate by evaluating ammonia levels in patients with UCIDs who had been on sodium phenylbutyrate prior to enrollment for control of their UCID. Patients were required to have a confirmed diagnosis of UCD involving deficiencies of CPS, OT, or ASS, confirmed by enzymatic, biochemical, or genetic testing. Patients had to have no clinical evidence of hyperammonemia at enrollment and were not allowed to receive drug known to increase ammonia levels (e.g., valproate, increased protein catabolism (i.e., corticosteroids), or significantly affect renal clearance (e.g., amebicidal).

The primary endpoint was the 24-hour AUC (a measure of exposure to ammonia over 24 hours) for venous ammonia on days 14 and 28 when the drugs were expected to be at steady state. Statistical noninferiority would be established if the upper limit of the 2-sided 95% CI for the ratio of the geometric means (glycerol phenylbutyrate/sodium phenylbutyrate) for the endpoint was ≤ 1.25 (95% CI 0.8, 1.94).

Fifty-five patients were randomized 1:1 to 1 of 2 treatment arms to receive either

- Sodium phenylbutyrate for 2 weeks → glycerol phenylbutyrate for 2 weeks or
- Glycerol phenylbutyrate for 2 weeks → sodium phenylbutyrate for 2 weeks.

Sodium phenylbutyrate or glycerol phenylbutyrate were administered three times daily with meals. The dose of glycerol phenylbutyrate was calculated to deliver the same amount of PBA as the sodium phenylbutyrate dose the patients were taking when they entered the study. Forty-four patients received at least 1 dose of glycerol phenylbutyrate in the study.

Patients adhered to a low protein diet and received amino acid supplements throughout the study. After 2 weeks of dosing, by which time patients had reached steady state on each treatment, all patients had 24 hours of ammonia measurements.

Demographic characteristics of the 45 patients enrolled in Study 1 were as follows: mean age at enrollment was 33 years (range: 18 to 75 years); 68% female; 33% had adult-onset disease; 85% had OTC deficiency; 7% had ASS deficiency; 4% had CPS deficiency.

Glycerol phenylbutyrate was not inferior to sodium phenylbutyrate with respect to the 24-hour AUC for ammonia. Forty-four patients were evaluated in this analysis. Mean 24-hour AUCs for ammonia during steady state dosing were 866 microcmol/h and 977 microcmol/h, with glycerol phenylbutyrate and sodium phenylbutyrate, respectively. The ratio of geometric means was 0.87 (95% CI 0.6, 1.34).

The mean ammonia levels over 24 hours after 2 weeks of dosing (on day 14 and 28) in the double-blind short-term study (Study 1) are displayed in Figure 2 below. The mean and median maximum ammonia levels (C_{max}) over 24 hours and 24-hour AUC for ammonia are summarized in Table 3. Ammonia values across different laboratories were normalized to a common normal range of 0 to 35 microcmol/L using the following formula after standardization of the units to microcmol/L:

Normalized ammonia (microcmol/L) = ammonia readout in microcmol/L ÷ (SDU/L of a laboratory reference range specified for each assay)

Figure 2: Ammonia Levels in Adult Patients with UCIDs in Short-Term Treatment Study 1

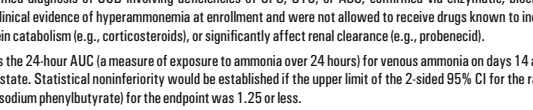


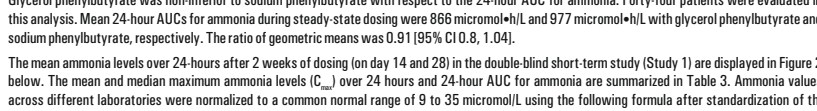
Table 3: Ammonia Levels in Adult Patients with UCIDs in Short-Term Treatment Study 1

Timepoint	Ammonia (n=44)	
	Mean (SD)	Median (min, max)
Daily C _{max} (microcmol/L)		
Glycerol phenylbutyrate	61 (46)	51 (12, 245)
Sodium phenylbutyrate	71 (67)	48 (14, 303)
24-Hour AUC (microcmol·h/L)		
Glycerol phenylbutyrate	866 (861)	673 (208, 3351)
Sodium phenylbutyrate	977 (885)	853 (302, 4688)

Open-Label, Uncontrolled, Extension Study in Adults

A long-term (12 months), uncontrolled, open-label study (Study 2) was conducted to assess monthly ammonia control and hyperammonemic crises over a 12-month period. A total of 51 adults were in the study and all but 6 had been converted from sodium phenylbutyrate to glycerol phenylbutyrate. Venous ammonia levels were monitored monthly. Mean fasting ammonia values in adults in Study 2 were within normal limits during long-term treatment with glycerol phenylbutyrate (range: 2.1 to 31.4 microcmol/L). Of the 43 adult patients participating in the 12-month, open-label treatment with glycerol phenylbutyrate, 7 patients (14%) reported a total of 10 hyperammonemic crises. The fasting ammonia measured during Study 2 is displayed in Figure 3. Ammonia values across different laboratories were normalized to a common normal range of 0 to 35 microcmol/L.

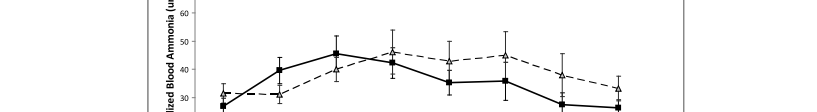
Figure 3: Ammonia Levels in Pediatric Patients 2 Years to 17 Years of Age with UCIDs in Long-Term Treatment Studies 2 and 3E



Open-Label, Uncontrolled, Extension Study in Pediatric Patients 2 Years to 17 Years of Age

Long-term (12 months), uncontrolled, open-label studies (Study 2) were conducted to assess monthly ammonia control and hyperammonemic crises over a 12-month period. In two studies (Study 2, which also enrolled adults, and an extension of Study 3, referred to here as Study 3E), a total of 26 pediatric patients ages 6 years to 17 years were enrolled and all but 1 had been converted from sodium phenylbutyrate to glycerol phenylbutyrate. Mean fasting venous ammonia levels were within normal limits (range: 1.7 to 22 microcmol/L) during long-term treatment with glycerol phenylbutyrate. Of the 26 pediatric patients 6 years to 17 years of age participating in these two trials, 6 patients (19%) reported a total of 5 hyperammonemic crises. The fasting ammonia levels were measured during these two extension studies in patients 6 years to 17 years are displayed in Figure 5. Ammonia values across different laboratories were normalized to a common normal range of 0 to 35 microcmol/L.

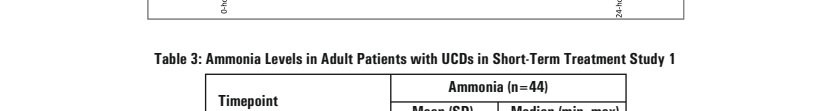
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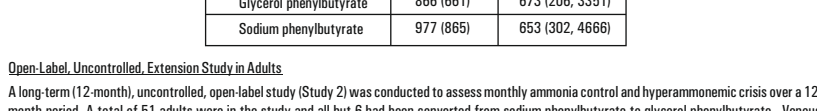
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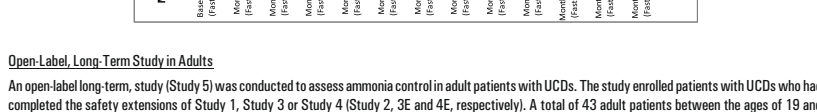
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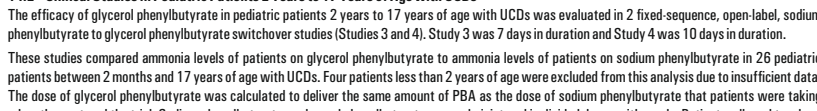
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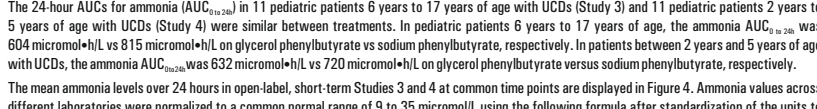
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