BETAINE ANHYDROUS- betaine anhydrous powder, for solution
Eton Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BETAINE ANHYDROUS FOR ORAL SOLUTION safely and effectively. See full prescribing information for BETAINE ANHYDROUS FOR ORAL SOLUTION.

BETAINE ANHYDROUS FOR ORAL SOLUTION
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

(1)
(1)
Betaine Anhydrous for Oral Solution is a methylating agent indicated in pediatric and adult patients for the treatment of homocystinuria to decrease elevated homocysteine blood concentrations. Included within the category of homocystinuria are:
• Cystathionine beta-synthase (CBS) deficiency
• 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency
• Cobalamin cofactor metabolism (cbl) defect (1)

DOSAGE AND ADMINISTRATION

Adults and Pediatric Patients 3 Years of Age and Older
• The recommended dosage is 6 grams per day, administered orally in divided doses of 3 grams twice daily. (2.1)
Pediatric Patients Less than 3 Years of Age
• The recommended starting dosage is 100 mg/kg/day, administered orally in divided doses of 50 mg/kg twice daily, and then increased weekly by 50 mg/kg increments. (2.1)
• Monitor patient response by plasma homocysteine concentrations. (2.1)
• Increase the dosage gradually until the plasma total homocysteine concentration is undetectable or present only in small amounts. (2.1)
Preparation and Administration Instructions
• Prescribed amount of Betaine Anhydrous for Oral Solution should be measured with the measuring scoop provided and then dissolved in 4 to 6 ounces of water, juice, milk, or formula until completely dissolved, or mixed with food for immediate ingestion. (2.2) (2)

DOSAGE FORMS AND STRENGTHS

For oral solution: in bottles containing 180 grams of betaine anhydrous. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

Hypermethioninemia in Patients with CBS Deficiency:
Betaine Anhydrous for Oral Solution may worsen elevated plasma methionine concentrations and cerebral edema has been reported. Monitor plasma methionine concentrations in patients with CBS deficiency. Keep plasma methionine concentrations below 1,000 micromol/L through dietary modification and, if necessary, a reduction of Betaine Anhydrous for Oral Solution dosage. (5)

ADVERSE REACTIONS

Most common adverse reactions (> 2%) are: nausea and gastrointestinal distress, based on physician survey. (6)
(6)

To report SUSPECTED ADVERSE REACTIONS, contact Eton Pharmaceuticals, Inc. (6)
at 1-855-224-0233 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)
(6)
(6)

Revised: 4/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Betaine Anhydrous for Oral Solution is indicated for the treatment of homocystinuria to decrease
elevated homocysteine blood concentrations in pediatric and adult patients. Included within the
category of homocystinuria are:

- Cystathionine beta-synthase (CBS) deficiency
- 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency
- Cobalamin cofactor metabolism (cbl) defect

2. DOSAGE AND ADMINISTRATION

2.1 Dosage

Therapy with Betaine Anhydrous for Oral Solution should be directed by physicians knowledgeable in the management of patients with homocystinuria.

Adults and Pediatric Patients 3 Years of Age and Older

The recommended dosage is 6 grams per day, administered orally in divided doses of 3 grams
twice daily.

Pediatric Patients Less than 3 Years of Age
The recommended starting dosage is 100 mg/kg/day divided in twice daily doses, and then
increased weekly by 50 mg/kg increments.

Monitoring
Monitor patient response to Betaine Anhydrous for Oral Solution by homocysteine plasma
concentration. Increase the dosage in all patients gradually until the plasma total homocysteine
concentration is undetectable or present only in small amounts. An initial response in homocysteine plasma concentrations usually occurs within several days and steady state plasma
concentrations occur within a month.

Monitor plasma methionine concentrations in patients with CBS deficiency [*see Warnings and
Precautions (5.1)*].

Maximum Dosage
Dosages of up to 20 grams/day have been necessary to control homocysteine concentrations in
some patients. However, one pharmacokinetic and pharmacodynamic in vitro simulation study
indicated minimal benefit from exceeding a twice-daily dosing schedule and a 150 mg/kg/day
dosage for Betaine Anhydrous for Oral Solution.

2.2 Preparation and Administration Instructions

- Shake bottle lightly before removing cap.
- Measure the number of scoops for the patient's dose with the scoop provided. One level

scoop (1.5 cc) is equivalent to 1 gram of betaine anhydrous powder.

- Mix powder with 4 to 6 ounces (120 to 180 mL) of water, juice, milk, or formula until

completely dissolved, or mix with food, then ingest mixture immediately.

- Always replace the cap tightly after using and protect the bottle from moisture.

3. DOSAGE FORMS AND STRENGTHS

Betaine Anhydrous for Oral Solution is a white, granular, hygroscopic powder for oral

solution
available in bottles containing 180 grams of betaine anhydrous.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Hypermethioninemia in Patients with CBS Deficiency

Patients with homocystinuria due to cystathionine beta-synthase (CBS) deficiency may also have
elevated plasma methionine concentrations. Treatment with Betaine Anhydrous for Oral Solution
may further increase methionine concentrations due to the remethylation of homocysteine to
methionine. Cerebral edema has been reported in patients with hypermethioninemia, including
patients treated with Betaine Anhydrous for Oral Solution [see Adverse Reactions (6.2)]. Monitor
plasma methionine concentrations in patients with CBS deficiency. Plasma methionine
concentrations should be kept below 1,000 micromol/L through dietary modification and, if
necessary, a reduction of Betaine Anhydrous for Oral Solution dosage.

6. ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:
• Hypermethioninemia and cerebral edema in patients with CBS deficiency [see Warnings and
Precautions (5.1)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates
observed in 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 practice.

The assessment of clinical adverse reactions is based on a survey study of 41 physicians, who
treated a total of 111 homocystinuria patients with Betaine Anhydrous for Oral Solution. Adverse
reactions were retrospectively recalled and were not collected systematically in this open-label,
uncontrolled, physician survey. Thus, this list may not encompass all types of potential adverse

reactions, reliably estimate their frequency, or establish a causal relationship to drug exposure. The following adverse reactions were reported (Table 1):

Table 1: Number of Patients with Adverse Reactions to Betaine Anhydrous for Oral Solution by Physician Survey

Adverse Reactions	Number of Patients
Nausea	2
Gastrointestinal distress	2
Diarrhea	1
"Bad Taste"	1
"Caused Odor"	1
Questionable pyschological	1
"Aspirated the powder"	1

6.2 Post-marketing Experience

The following adverse reactions have been identified during post approval use of Betaine Anhydrous for Oral Solution. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Severe cerebral edema and hypermethioninemia have been reported within 2 weeks to 6 months of starting Betaine Anhydrous for Oral Solution therapy, with complete recovery after discontinuation of Betaine Anhydrous for Oral Solution. All patients who developed cerebral edema had homocystinuria due to CBS deficiency and had severe elevation in plasma methionine concentrations (range 1,000 to 3,000 microM). As cerebral edema has also been reported in patients with hypermethioninemia, secondary hypermethioninemia due to betaine therapy has been postulated as a possible mechanism of action [see Warnings and Precautions (5.1)].

Other adverse reactions include: anorexia, agitation, depression, irritability, personality disorder, sleep disturbed, dental disorders, diarrhea, glossitis, nausea, stomach discomfort, vomiting, hair loss, hives, skin odor abnormalities, and urinary incontinence.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from a limited number of published case reports and post-marketing experience with Betaine Anhydrous for Oral Solution use in pregnancy have not identified any drug associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with betaine.

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

8.2 Lactation

Risk Summary

There are no data on the presence of betaine in human or animal milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Betaine Anhydrous for Oral Solution and any potential adverse effects on the breastfed child from Betaine Anhydrous for Oral Solution or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of Betaine Anhydrous for Oral Solution have been established in

pediatric patients. The majority of case studies of homocystinuria patients treated with Betaine Anhydrous for Oral Solution have been pediatric patients, including patients ranging in age from 24 days to 17 years [see Clinical Studies (14)]. Children younger than 3 years of age may benefit from dose titration [*see Dosage and Administration (2.1)*].

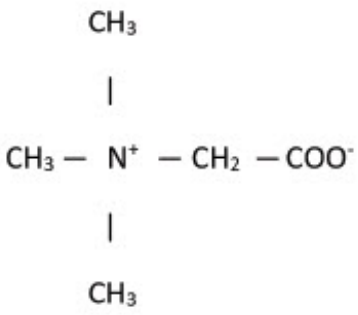
10. OVERDOSAGE

There is no information on Betaine Anhydrous for Oral Solution overdose in humans. In an acute toxicology study in rats, death occurred frequently at doses equal to or greater than 10 g/kg.

11. DESCRIPTION

Betaine Anhydrous for Oral Solution is an agent for the treatment of homocystinuria. It contains

no ingredients other than anhydrous betaine. Betaine Anhydrous for Oral Solution is a white,
granular, hygroscopic powder, which is diluted in water and administered orally. The chemical
name of betaine anhydrous powder is trimethylglycine. It has a molecular weight of 117.15. The
structural formula is:



12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Betaine Anhydrous for Oral Solution acts as a methyl group donor in the remethylation of
homocysteine to methionine in patients with homocystinuria. Betaine occurs naturally in the body.
It is a metabolite of choline and is present in small amounts in foods such as beets, spinach, cereals,
and seafood.

12.2 Pharmacodynamics

Betaine Anhydrous for Oral Solution was observed to lower plasma homocysteine concentration
in three types of homocystinuria, including CBS deficiency; MTHFR deficiency; and cbl defect.
Patients have taken Betaine Anhydrous for Oral Solution for many years without evidence of
tolerance. There has been no demonstrated correlation between Betaine concentration and
homocysteine concentration.

In CBS-deficient patients, large increases in methionine concentration over baseline have been
observed. Betaine Anhydrous for Oral Solution has also been demonstrated to increase low plasma
methionine and S-adenosylmethionine (SAM) concentration in patients with MTHFR

deficiency
and cbl defect.

12.3 Pharmacokinetics

Pharmacokinetic studies of Betaine Anhydrous for Oral Solution are not available. Plasma betaine
concentrations following administration of Betaine Anhydrous for Oral Solution have not been
measured in patients and have not been correlated to homocysteine concentration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity and fertility studies have not been conducted with Betaine Anhydrous
for Oral Solution. No evidence of genotoxicity was demonstrated in the following tests: metaphase
analysis of human lymphocytes; bacterial reverse mutation assay; and mouse micronucleus test.

14. CLINICAL STUDIES

Betaine Anhydrous for Oral Solution was studied in a double-blind, placebo-controlled, crossover
study in 6 patients (3 males and 3 females) with CBS deficiency, ages 7 to 32 years at enrollment.
Betaine Anhydrous for Oral Solution was administered at a dosage of 3 grams twice daily, for 12
months. Plasma homocystine concentration were significantly reduced ($p<0.01$) compared to
placebo. Plasma methionine concentrations were variable and not significantly different compared
to placebo.

Betaine Anhydrous for Oral Solution has also been evaluated in observational studies without
concurrent controls in patients with homocystinuria due to CBS deficiency, MTHFR deficiency,
or cbl defect. A review of 16 case studies and the randomized controlled trial previously described
was also conducted, and the data available for each study were summarized; however, no formal
statistical analyses were performed. The studies included a total of 78 male and female patients
with homocystinuria who were treated with Betaine Anhydrous for Oral Solution. This included
48 patients with CBS deficiency, 13 with MTHFR deficiency, and 11 with cbl defect,

ranging in
age from 24 days to 53 years. The majority of patients (n=48) received 6 gm/day, 3 patients
received less than 6 gm/day, 12 patients received doses from 6 to 15 gm/day, and 5 patients
received doses over 15 gm/day. Most patients were treated for more than 3 months (n=57) and 30
patients were treated for 1 year or longer (range 1 month to 11 years). Homocystine is formed
nonenzymatically from two molecules of homocysteine, and both have been used to evaluate the
effect of Betaine Anhydrous for Oral Solution in patients with homocystinuria. Plasma
homocystine or homocysteine concentrations were reported numerically for 62 patients, and 61 of
these patients showed decreases with Betaine Anhydrous for Oral Solution treatment.
Homocystine decreased by 83 to 88% regardless of the pre-treatment concentration, and
homocysteine decreased by 71 to 83%, regardless of the pre-treatment concentration. Clinical
improvement, such as improvement in seizures, or behavioral and cognitive functioning, was
reported by the treating physicians in about three-fourths of patients. Many of these patients were
also taking other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), and folate
with variable biochemical responses. In most cases, adding Betaine Anhydrous for Oral Solution
resulted in a further reduction of either homocystine or homocysteine concentrations.

16. HOW SUPPLIED/STORAGE AND HANDLING

Betaine Anhydrous for Oral Solution is available in plastic bottles containing 180 grams of betaine
anhydrous as a white, granular, hygroscopic powder. Each bottle is equipped with a plastic childresistant
cap and is supplied with a polypropylene measuring scoop. One level scoop (1.5 cc) is equal to 1 gram of betaine anhydrous powder.

NDC 71863-115-18 (180 g/bottle)

Storage
Store at 20° to 25°C (68° to 77°F), excursions permitted to 15° to 30°C (59° to 86°F) [*See USP
Controlled Room Temperature*].

Protect from moisture.

17. PATIENT COUNSELING INFORMATION

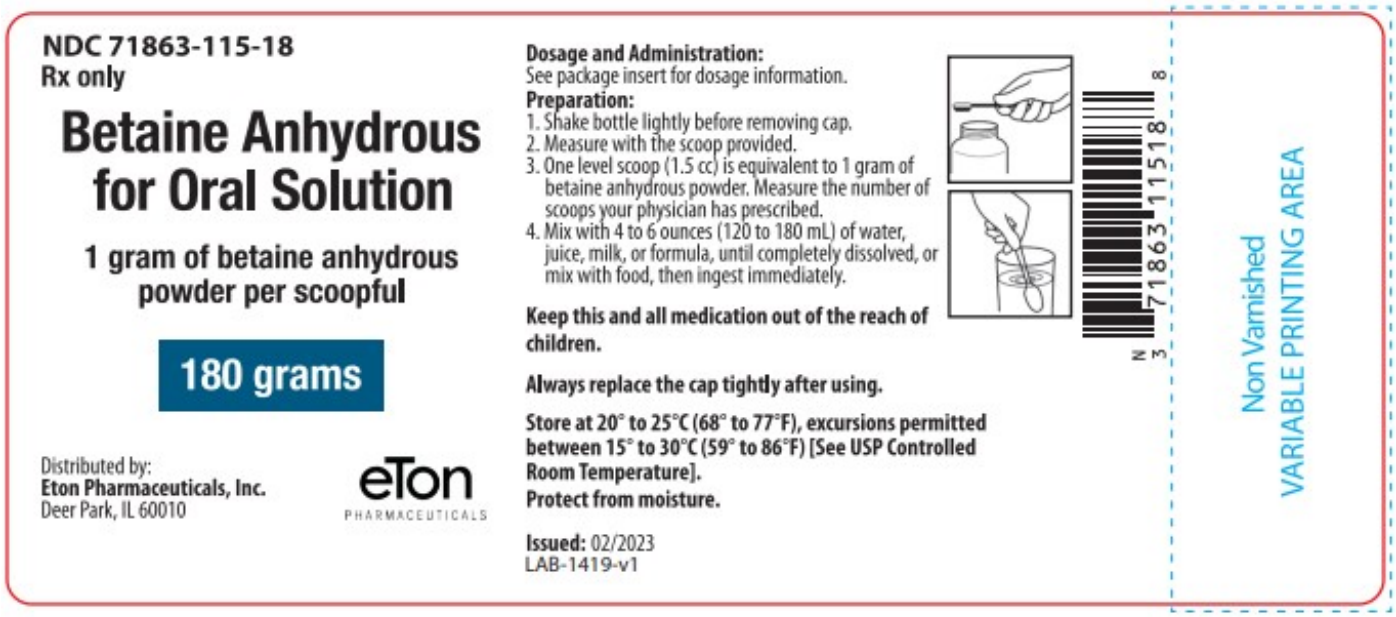
Preparation and Administration Instructions

Instruct patients and caregivers to administer Betaine Anhydrous for Oral Solution as follows:
• Shake bottle lightly before removing cap.
• Measure the number of scoops for the patient's dose with the scoop provided. One level
scoop (1.5 cc) is equivalent to 1 gram of betaine anhydrous powder.
• Mix powder with 4 to 6 ounces (120 to 180 mL) of water, juice, milk, or formula until completely dissolved, or mix with food, then ingest mixture immediately.
• Always replace the cap tightly after using and protect the bottle from moisture.

Distributed by:
Eton Pharmaceuticals, Inc.
Deer Park, IL 60010

Issued: 02/2023

Betaine Anhydrous Label:



BETAINE ANHYDROUS

betaine anhydrous powder, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:71863-115
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BETAINE (UNII: 3SCV180C9W) (BETAINE - UNII:3SCV180C9W)	BETAINE	1 g in 1 g

Product Characteristics

Color	white	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:71863-115-18	180 g in 1 BOTTLE; Type 0: Not a Combination Product	02/01/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210508	02/01/2023	

Labeler - Eton Pharmaceuticals, Inc. (080870465)

Registrant - Eton Pharmaceuticals, Inc. (080870465)

Establishment

Name	Address	ID/FEI	Business Operations
Amino GmbH		507524424	api manufacture(71863-115)

Establishment

Name	Address	ID/FEI	Business Operations
University of Iowa Pharmaceuticals		968854286	manufacture(71863-115) , pack(71863-115)

Revised: 12/2023 Eton Pharmaceuticals, Inc.