

IMPORTANT PRESCRIBING INFORMATION

22 December 2017

Subject: Temporary importation of CYSTADANE® (betaine anhydrous for oral solution) to address impending shortage

Dear Health Care Provider,

There has been a manufacturing issue with the CYSTADANE® (betaine anhydrous for oral solution) approved for use and distribution in the United States (“U.S.-labeled CYSTADANE”), which has resulted in an interim shortage of this product in the U.S. market.

In order to alleviate the shortage of CYSTADANE in the U.S., Recordati Rare Diseases Inc. (Recordati) is coordinating with the U.S. Food and Drug Administration (FDA) to increase the availability of CYSTADANE. Recordati has initiated temporary importation of its CYSTADANE product approved for use in the United Kingdom into the U.S. market. This product is manufactured by Orphan Europe SARL in France. At this time, no other entity except Recordati, as the U.S. agent of Orphan Europe SARL, is authorized to import or distribute these products in the United States. FDA has not approved the product manufactured by Orphan Europe SARL’s manufacturing facility in France. The imported CYSTADANE is lot CYP1705. It will be dispensed by the U.S. specialty pharmacy, AnovoRx Group LLC.

There are some key differences between the FDA-approved CYSTADANE and the imported CYSTADANE.

- **Measuring scoops:** FDA-approved CYSTADANE is packaged with one scoop (white) that dispenses 1g of betaine anhydrous. Imported CYSTADANE is packaged with 3 measuring scoops (green, blue, and pink) that dispense 100mg, 150mg, or 1g of betaine anhydrous. The large 1g pink scoop in the imported CYSTADANE is equivalent to the white 1g scoop in the FDA-approved CYSTADANE. Patients should pay careful attention to use the appropriate scoop to take their prescribed dose. **Please pass this information along to the patients. If the incorrect scoop is utilized, improper dosing may result, and the CYSTADANE treatment can be ineffective. This may result in an increased risk for cognitive disability and/or stroke due to the progression of the underlying disease.**
- **Dosing:** The labeled dosing in the FDA-approved CYSTADANE is 6 grams/day in divided doses of 3 grams twice daily, and, for pediatric patients less than 3 years of age, dosage may be started at 100 mg/kg/day divided in twice daily doses and increased weekly by 50 mg/kg increments. The labeled dosing in the imported CYSTADANE is 100 mg/kg/day divided into 2 doses per day. **Practitioners should be aware of these differences when prescribing and monitoring CYSTADANE.**

A copy of the FDA-approved full prescribing information is being distributed with the imported CYSTADANE. Please refer to the FDA-approved package insert for full prescribing

information. Storage conditions are the same as that of the FDA-approved product. Store at room temperature, 15° – 30°C (59° – 86°F). CYSTADANE is for oral use only. Protect from moisture. Keep this and all medications out of the reach of children.

U.S. FDA-approved Indication

CYSTADANE (betaine anhydrous for oral solution) is a methylating agent indicated for the treatment of homocystinuria to decrease elevated homocysteine blood levels. Included within the category of homocystinuria are:

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

For reporting of adverse events and more information

Any adverse effects or medication issues resulting from the use of this drug or quality issues should be reported to Recordati Rare Diseases Inc. at 1-888-575-8344.

Adverse events or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax:

- Complete and submit the report **Online**: www.fda.gov/medwatch/report.htm
- **Regular mail or Fax**: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178.

Important Safety Information

- **Hypermethioninemia**: CYSTADANE may worsen elevated plasma methionine concentrations in patients with CBS deficiency. Cerebral edema has been reported in patients receiving CYSTADANE.
- **Monitoring**: Monitor plasma methionine concentrations in patients with CBS deficiency. Keep plasma methionine concentrations below 1,000 µmol/L through dietary modification and, if necessary, a reduction of CYSTADANE dose.
- **Most common adverse reactions** (incidence > 2%) were nausea and gastrointestinal distress, based on physician survey.
- **Pregnancy**: Animal reproduction studies have not been conducted with CYSTADANE. Use only if clearly needed.
- **Nursing women**: It is not known whether CYSTADANE is excreted in human milk. Use only if clearly needed.
- **Pediatrics**: Pediatric patients ranging in age from 24 days to 17 years have been treated with CYSTADANE. Children younger than 3 years of age may benefit from dose titration.



We are committed to helping address patients' unmet needs through our corporate mission. If you have questions or concerns regarding this product, please call AnovoRx Group, the specialty pharmacy that dispenses CYSTADANE, at 1-888-487-4703 or Recordati Rare Diseases Medical Information at 1-888-575-8344.

A handwritten signature in black ink, appearing to read "Steven R. Peltier".

Steven R. Peltier

Vice President, Regulatory & Quality Compliance
Chief Compliance Officer
Recordati Rare Diseases Inc.

Product Comparison

FDA Approved (U.S.) Dosing and How Supplied Section	Imported (UK) Dosing and How Supplied Section
2 DOSAGE AND ADMINISTRATION 2.1 Dosage The usual dosage in adult and pediatric patients is 6 grams per day administered orally in divided doses of 3 grams twice daily. In pediatric patients less than 3 years of age, dosage may be started at 100 mg/kg/day divided in twice daily doses, and then increased weekly by 50 mg/kg increments. Therapy with Cystadane should be directed by physicians knowledgeable in the management of patients with homocystinuria. Patient response to Cystadane can be monitored by homocysteine plasma levels. Dosage in all patients can be gradually increased until plasma total homocysteine is undetectable or present only in small amounts. Response (by homocysteine plasma levels) usually occurs within several days and steady state within a month. Plasma methionine concentrations should be monitored in patients with CBS deficiency [See <i>Warnings and Precautions (5.1)</i>]. Dosages of up to 20 grams per day have been necessary to control homocysteine levels in some patients. However, one pharmacokinetic and pharmacodynamic <i>in vitro</i> simulation study indicated minimal benefit from exceeding a twice-daily dosing schedule and a 150 mg/kg/day dosage for Cystadane. 2.2 Administration The prescribed amount of Cystadane should be measured with the measuring scoop provided (one level 1.7 mL scoop is equal to 1 gram of betaine anhydrous powder) and then dissolved in 4 to 6 ounces (120 to 180 mL) of water, juice, milk, or formula, or mixed with food for immediate ingestion.	<u>3. How to take Cystadane</u> The use of this medicine will be supervised by a doctor experienced in the treatment of patients with homocystinuria. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose in children and adults is 100mg/kg/day divided in 2 doses per day. In some patients doses above 200 mg/ kg/day were needed to reach therapeutic goals. Your doctor may adapt the dose depending on your laboratory values. You will therefore need regular blood tests to determine the correct daily dose. You should take Cystadane orally (by mouth). To measure the dose: • shake the bottle lightly before opening • take the correct measuring spoon: – the small green spoon measures 100 mg of betaine anhydrous powder; – the middle size blue spoon measures 150 mg of betaine anhydrous powder; – the large pink spoon measures 1 g of betaine anhydrous powder. • take a heaped spoonful of powder out of the bottle • pass the flat back of a knife over the top of the spoon • the powder left in the spoon is one spoonful • take the correct number of spoonfuls of powder from the bottle Mix the measured dose of powder with water, juice, milk, formula or food until completely dissolved and ingest immediately after mixing.
16 HOW SUPPLIED/STORAGE AND HANDLING Cystadane is available in plastic bottles containing 180 grams of betaine anhydrous. Each bottle is equipped with a plastic child-resistant cap and is supplied with a polystyrene measuring scoop. One level scoop (1.7 mL) is equal to 1 gram of betaine anhydrous powder. NDC 52276-400-01 180 g/bottle	<u>6. Contents of the pack and other information</u> What Cystadane contains • The active substance is betaine anhydrous. 1 g of oral powder contains 1 g of betaine anhydrous. • There is no other ingredient. What Cystadane looks like and contents of the pack Cystadane is a white crystalline free flowing powder. It is presented in bottles with child resistant closures. Each bottle contains 180 g of powder. Each carton contains one bottle and three measuring spoons.

FDA-approved (U.S.) Bottle Label:

Supplied by:
Orphan Europe SARL
Puteaux, France

Licensed to and Distributed by:
Recordati Rare Diseases Inc.
Lebanon, NJ 08833 U.S.A.

Lot #:
EXP:

Rev Date: April 2017
OEP999



N 3 52276-400-01 6

NDC 52276-400-01

CYSTADANE®
betaine anhydrous for oral solution

1 gram of betaine anhydrous
powder per scoopful

180 grams

Dosage and Administration:
See package insert for dosage information.

Preparation:

1. Shake bottle lightly before removing cap.
2. Measure with the scoop provided.
3. One level scoop (1.7 cc) is equivalent to 1 gram of betaine anhydrous powder. Measure the number of scoops your physician has prescribed.
4. Mix with 4 to 6 ounces (120 to 180 mL) of water, juice, milk, or formula, until completely dissolved, or mix with food, then ingest immediately.

Keep this and all medication out of the reach of children.
Always replace the cap tightly after using.
Store at room temperature, 15° – 30°C (59° – 86°F). Protect from moisture.

Imported (U.K.) Bottle Label:

Lot / Lote / Serial / Ser / Ch.-B. /
Identifiant / Identifik / No. Séri / C. Séri-
EXP / CAD / Utilization / Takas /
Dét. / Date / Avt. / Inden. / Stock /
Avertissement / Avis /
Avertissement / Avis

CYSTADANE®
1g

Cystadane 1 g nepopanous npax	Бетанум, безводен (BG)	Cystadane 1 g polvere orale	Betaina anidra (IT)
Cystadane 1 g peroralni prašek	Betainum anhydricum (CS)	Cystadane 1 g geriamieji milteliai	Bervandenis betainas (LT)
Cystadane 1 g oralni pulver	Betain, vandfri (DA)	Cystadane 1 g pulveris iekšējai lietošanai	Betaine anhydrous (LV)
Cystadane 1 g Pulver zum Einnehmen	Wasserfreies Betain (DE)	Cystadane 1 g trab għall-baliq	Betaine anidru (MT)
Cystadane 1 g πόσιν κόνις	Ανυδρή βηταίνη (EL)	Cystadane, 1 g poeder voor oraal gebruik	Watervrij betaine (NL)
Cystadane 1 g oral powder	Betaine anhydrous (EN)	Cystadane 1 g pulver	Betain, vannfritt (NO)
Cystadane 1 g polvo oral	Betaina anhidra (ES)	Cystadane 1 g proszek doustny	Betaina bezwodna (PL)
Cystadane 1 g suukaudne pulber	Veevaba betaiin (ET)	Cystadane 1 g pó oral	Betaina anidra (PT)
Cystadane 1 g jauhe	Betaiini, vedetön (FI)	Cystadane 1 g pulbere orală	Betaină anhidră (RO)
Cystadane 1 g poudre orale	Béitainé anhydre (FR)	Cystadane 1 g peroralniho prášku	Bezvodný betain (SK)
Cystadane 1 g oralni prašek	Bezvodni betain (HR)	Cystadane 1 g peroralni prašek	Brezvodni betain (SL)
Cystadane 1 g beśledzięs por	Vízmentes betain (HU)	Cystadane 1 g oralt pulver	Betain vattenfritt (SV)
Cystadane 1 g duft til inntøku	Vatnfritt betain (IS)		

EU/1/06/379/001



ORPHAN EUROPE

RECORDATI GROUP

Orphan Europe SARL - Immeuble "Le Wilson" - 70 avenue du Général de Gaulle F-92800 Puteaux - France

Imported (U.K.) Carton:



EU/1/06/373/001
F-92 800 Puteaux
70 Avenue du Général de Gaulle
Immeuble de la Wilson
RECORDATI GROUP
EUROPE

EN - MT - ES - PT - LV - LT
FI - SV - DA - NO - ET - IS

Cystadane 1 g oral powder.
Betaine anhydrous.
1 g of powder contains 1 g of betaine anhydrous. 180 g of oral powder and three measuring spoons.
Three measuring spoons (green, blue, pink) dispense 100mg, 150mg or 1g of betaine anhydrous. Lightly shake the bottle before opening. Read the package leaflet before use. **ORAL USE.**
Keep out of the sight and reach of children. Do not store above 25°C. Keep the bottle tightly closed in order to protect from moisture. Medicinal product subject to medical prescription.

Cystadane 1 g oral powder.
Betaine anhydrous.
1 g of powder contains 1 g of betaine anhydrous. 180 g of oral powder and three measuring spoons.
Three measuring spoons (green, blue, pink) dispense 100mg, 150mg or 1g of betaine anhydrous. Lightly shake the bottle before opening. Read the package leaflet before use. **ORAL USE.**
Keep out of the sight and reach of children. Do not store above 25°C. Keep the bottle tightly closed in order to protect from moisture. Medicinal product subject to medical prescription.

Cystadane 1 g polvo oral. Betaina anhidra.
1 g de polvo contiene 1 g de betaina anhidra. 180 g de polvo oral y tres cucharas graduadas. Tres cucharas graduadas (verde, azul, rosa) dispensan 100 mg, 150 mg o 1 g de betaina anhidra. Antes de abrir, agitar ligeramente el frasco. Leer el prospecto antes de utilizar este medicamento. **VÍA ORAL.** Mantener fuera de la vista y del alcance de los niños. No conservar a temperatura superior a 25°C. Mantener el frasco perfectamente cerrado para protegerlo de la humedad. Medicamento sujeto a prescripción médica.

Cystadane 1 g pó oral. Betaina anidra.
1 g de pó contém 1 g de betaina anidra. 180 g de pó oral e três colheres-medida. As três colheres-medida (verde, azul, rosa) dispensam 100 mg, 150 mg ou 1 g de betaina anidra. Agite ligeiramente o frasco antes de o abrir. Consultar o folheto informativo. **VIA ORAL.** Manter fora da vista e do alcance das crianças. Não conservar acima de 25°C. Manter o frasco bem fechado para proteger da humidade. Medicamento sujeito a receita médica.

Cystadane 1 g pulveris iekšīgai lietošanai. Betaine anhydrous.
1 g pulvera satur 1 g bezūdens betaina. 180 g pulvera iekšīgai lietošanai un trīs mērkarotes. Pievienotas trīs mērkarotes (zaļa, zila, rozā brāzā) 100 mg, 150 mg vai 1 g bezūdens betaina dozēšanai. Pudēl pirms atvēršanas viegli sakratiet. Pirms lietšanas izlasiet lietošanas instrukciju. **IEKŠĪGAI LIETOŠANAI.** Uzglabāt bērniem neredzamā un nepieejamā vietā. Uzglabāt temperatūrā līdz 25°C. Pudēl uzglabāt cieši noslēgtu, lai pasargātu no mitruma. Receptu zāles.

Cystadane 1 g geriamieji milteliai.
Bevandenis betainas.
1 g miltelių yra 1 g bevandenis betainos. 180 g geriamųjų miltelių ir tryš matavimo šaukšteliai. Tėmės matavimo šaukštai (žaliu, mėlynu, rausvu) atmatuojama 100 mg, 150 mg arba 1 g bevandenis betainos. Prieš atidarydami buteliuką nesmarkinkite jį pakutytėje. **VAIRTOTI PER BURNĄ.** Laikyti vaikams nepasiekiamoje ir nepasiekiamoje vietoje. Laikyti ne aukštesnėje kaip 25 °C temperatūroje. Buteliuką laikyti sandary, kad preparatas būtų apsaugotas nuo drėgmės. Receptinis vaistinis preparatas.

Cystadane 1 g jauhe. Betaini, vedetön.
1 g jauhetta sisältää 1 g vedetöntä betaiinia. 180 g jauhetta ja kolme mittalusikkaa. Kolmella mittalusikalla (vihreä, sininen, vaaleanpunainen,) annostellaan 100 mg, 150 mg tai 1 g vedetöntä betaiinia. Seisota pulloa kevyesti ennen avaamista. Lue pakkausseloste ennen käyttöä. **SUUN KAUTTA.** Ei lasten ulottuvilla eikä näkyville. Säilytä alle 25°C. Pidä pullo tiiviisti suljettuna. Hoida kosteudelle. Reseptilääke.

Cystadane 1 g oralt pulver. Betain vattenfritt.
1 g pulver innehåller 1 g betain vattenfritt. 180 g oralt pulver och tre doseringskedor. Tre doseringskedor (grön, blå, rosa) mäter upp 100 mg, 150 mg eller 1 g av betain vattenfritt. Skaka burken lätt innan du öppnar den. Läs baksidens del före användning. **ORALT BRUK.** Öppnarens utgångspunkt för barn. Förvaras vid högst 25 °C. Tillslut burken väl. Fukt känsligt. Receptbelagt läkemedel.

Cystadane, 1 g oralt pulver. Betain, vandfritt.
1 g pulver indeholder 1 g betain, vandfritt. 180 g pulver og tre måleskeer. Tre måleskeer (grøn, blå, rosa) til måling af 100 mg, 150 mg eller 1 g betain, vandfritt. Rist flasken forsigtigt før den åbnes. Læs pakningsvedlegget før brug. **ORAL BRUK.** Opbevares utilgængelig for børn. Opbevares ved højst 25 °C. Hold flasken godt lukket for at beskytte mod fugtighed. Receptpligtigt lægemiddel.

Cystadane 1 g pulver. Betain, vannfritt.
1 g pulver inneholder 1 g betain, vannfritt. 180 g pulver og tre måleskeer. Tre måleskeer (grønn, blå, rosa) til måling av 100 mg, 150 mg eller 1 g betain, vannfritt. Rist flasken forsiktig før den åpnes. Les pakningsvedlegget før bruk. **ORAL BRUK.** Oppbevares utilgjengelig for barn. Oppbevares ved høyst 25 °C. Hold flasken tett lukket for å beskytte mot fuktighet. Receptpliktig legemiddel.

Cystadane 1 g suukaudne pulber. Veevaba betaiini.
1 g pulbrit sisaldab 1 g veevaba betaiini. 180 g suukaudset pulbrit ja kolm mõõtelusikat. Kolm mõõtelusikat (roheline, sinine, roosa) 100 mg, 150 mg, või 1 g veevaba betaiini mõõtmiseks. Enne avamist pudelit veidi loksutada. Enne ravimi kasutamist lugege pakendi infolehti. **SUUKAUDNE.** Hoida laste eest varjatult ja kättesaamatus kohas. Hoida temperatuuril kuni 25 °C. Hoida pudelit tihedalt suletuna. Hoida niiskuse eest kaitsvalt. Retseptiravim.

Cystadane 1 g duft til inntøku.
Vatnsfritt betain.
1 g af duft til inntøku og þrjár mæliskleifar. 180 g af duft til inntøku og þrjár mæliskleifar. Þrjár mæliskleifar (græn, blá, bleik) fyrir 100 mg, 150 mg eða 1 g af vatnsfria betaini. Hristið glasið lauslega áður en það er opnað. **TIL INNTÖKU.** Geymið þar sem börn hvorki ná til né sjá. Geymið glasið vel lokað til vagnar gegn raka. Lyfið er lyfseðilskykt.

ESPAÑA C.N. 658697.6 **IX**
Uso hospitalario
8 47 0006 586976

Portugal
Nº de código nacional: 5022728
Medicamento sujeito a receita médica
5022728

United Kingdom & Ireland
[POM]

Latvia
Receptu zāles

Finland/Suomi, Sverige, Danmark, Norge, Island
Vnr 10 86 97
7 046261 086974

Finland/Suomi, Sverige, Danmark, Norge, Island
Vnr 10 86 97
7 046261 086974

Finland/Suomi, Sverige, Danmark, Norge, Island
Vnr 10 86 97
7 046261 086974

Shelf life after the first opening: 3 months /
Vara il jndetah 1-errevet darba: Jskodi 3 mēnes /
3 mēnes / Período de validade uma vez aberto: 3 meses /
Prazo de validade após a primeira abertura: 3 meses /
Uzglabāšanas laiks pēc pudeles pirmas atvēršanas: 3 mēneši /
Tilnamumo laikas po pirmojo atidarymo: 3 mėnesiai / Kestoaika avaamisen jälkeen: 3 kuukautta / Hållbarhet av öppnad burk: 3 månader /
Holdsbarhet efter første åbning: 3 måneder / Holdbarhetstid etter åpning: 3 måneder / Kållhållstiden pårast: esmalardset avastis: 3 kuus / Geymskapstid etfr ab glasið hefur verið opnað: 3 mánuðir.

Lot / Lots / Séri / Serija /
Sats / Ench / Runch /
Parti nr:
EXP / CAD / Utgångsdatum /
Der. Lids / Tila / M /
Käyt.Vim / Utg.dat:

OEP 1051