RECORDATI RARE DISEASES GROUP
Focused on the Few™

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, 15º – 30ºC (59º – 86ºF). 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.

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

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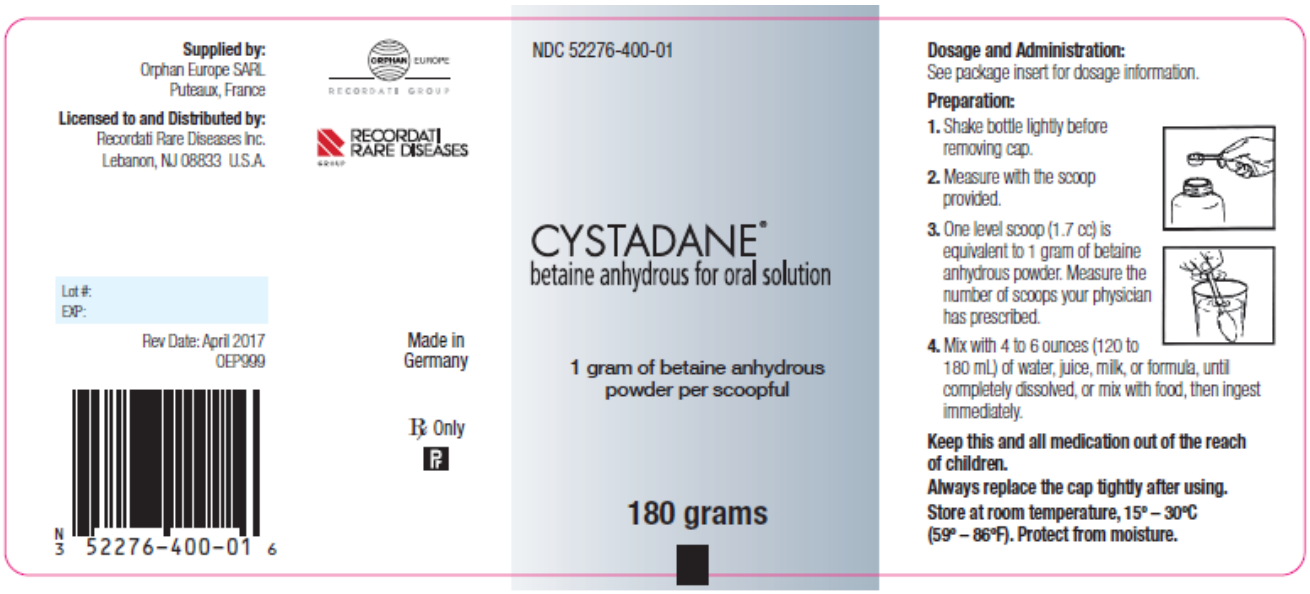
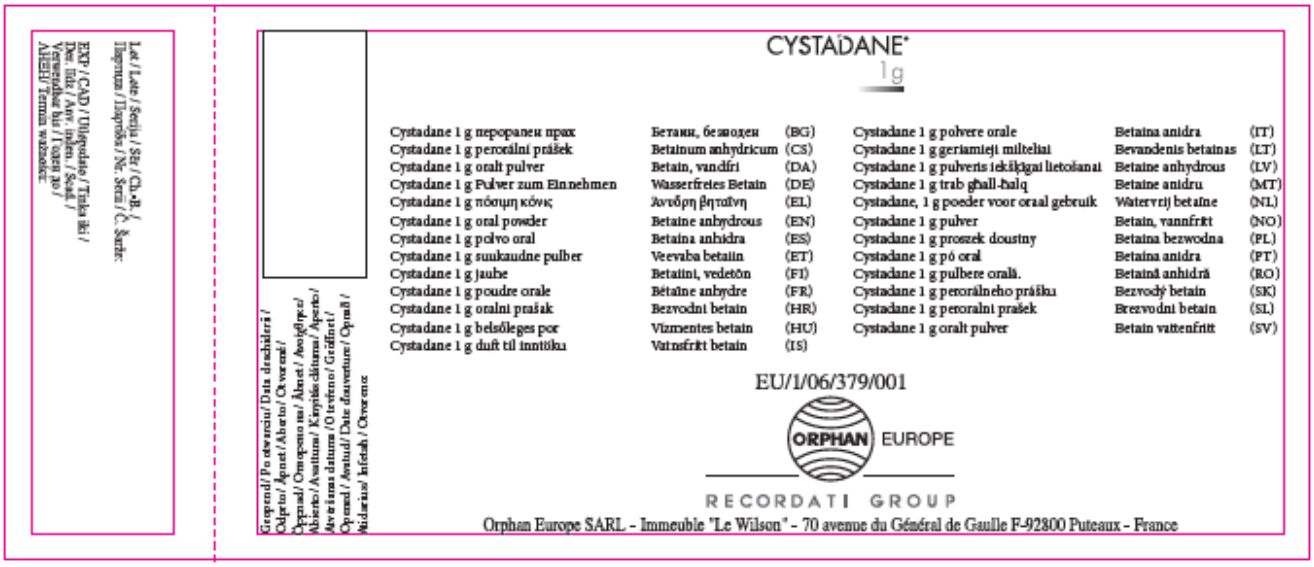
Product Comparison

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 Warnings and Precautions (5.1)]*. Dosages of up to 20 grams per day have been necessary to control homocysteine levels 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 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.	**3. How to take Cystadane** 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	**6. Contents of the pack and other information** **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:



Imported (U.K.) Bottle Label:



Imported (U.K.) Carton: