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NDA 020576

FIRM: ORPHAN MEDCL

1 OF 1

TRADE NAME: CYSTADANE

GENERIC NAME: BETAINE ANHYDROUS POWDER

Summary Basis of Approval  
Cover Form

Appl #: 020576

Firm: ORPHAN MEDCL

Reviewing Div: 510

Trade Name: CYSTADANE (BETAINE ANHYDROUS POWDER)

Generic Name:

BETAINE ANHYDROUS POWDER

Approval Letter: Y

Statistician Review: N

SBA Form: N

Bio/Dissolution Review: Y

Final Printed Labeling: N

Microbiologist Review: N

Medical Officer Review: Y

NAS/NRC Review: N

Chemist Review: Y

Pharmacologist Review: Y

Federal Register Notice: N

Completion Date: 15-MAY-97

NDAA 20576

Approval Letter  
And Related  
Correspondence



NDA 20-576

Orphan Medical Inc.  
Attention: Ms. Marie Kuker  
Director, Regulatory Affairs  
13911 Ridgedale Drive  
Suite 475  
MINNETONKA, MN 55305

OCT 25 1996

Dear Ms. Kuker:

Please refer to your new drug application dated October 20, 1995, received October 25, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cystadane® (betaine anhydrous for oral solution).

We acknowledge receipt of your amendments dated January 26, May 22, July 9, 19, and 29, August 1 and 7, September 4, 12, and 23, and October 25, 1996.

This new drug application provides for the use of Cystadane for the treatment of homocystinuria to decrease elevated homocysteine blood levels. Included within the category of homocystinuria are deficiencies or defects in:

1. cystathionine beta-synthase (CBS),
2. 5,10-methylenetetrahydrofolate reductase (MTHFR),
3. cobalamin cofactor metabolism (cbl).

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated October 25, 1996. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted by facsimile on October 25, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 16 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-576. Approval of this submission by FDA is not required before the labeling is used.

**NDA 20-576**

**Page 2**

**Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.**

**Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.**

**Please submit one market package of the drug product when it is available.**

**We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.**

**If you have any questions, please contact:**

**Steve McCort  
Consumer Safety Officer  
(301) 443-3510**

**Sincerely yours,**



**James Bilstad, M.D.  
Director  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research**

EXCLUSIVITY SUMMARY for NDA # 20-576 SUPPL # \_\_\_\_\_

Trade Name Cystadane Generic Name betaine anhydrous for oral solution

Applicant Name Orphan Medical Inc. HFD- 510

Approval Date \_\_\_\_\_

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?  
YES /x\_/ NO /\_\_\_/

b) Is it an effectiveness supplement?

YES /\_\_\_/ NO /x\_/

If yes, what type? (SE1, SE2, etc.)  
\_\_\_\_\_

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /x\_/ NO /\_\_\_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:  
\_\_\_\_\_  
\_\_\_\_\_

l) the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

\_\_\_\_\_

is FDA  
active  
before-  
." (An  
proved

**I HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO TO THE SIGNATURE BLOCKS ON PAGE 8.**

and, if

is a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /  / NO /  /

NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE ON PAGE 8.**

LY TO

drug product or indication a DESI upgrade?

YES /  / NO /  /

**ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE ON PAGE 8 (even if a study was required for the upgrade).**

**FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
her #1 or #2, as appropriate)

the active ingredient product.

FDA previously approved under section 505 of the Act any drug product containing same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular or salt (including salts with hydrogen or coordination bonding) or other non-covalent active (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /  / NO /  /

es," identify the approved drug product(s) containing the active moiety, and, if applicable, the NDA #(s).

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

### **PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

\_\_\_\_\_  
\_\_\_\_\_

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /  /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /  / NO /  /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # \_\_\_\_\_

Investigation #2, Study # \_\_\_\_\_

Investigation #3, Study # \_\_\_\_\_

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES / ___ /	NO / ___ /
Investigation #2	YES / ___ /	NO / ___ /
Investigation #3	YES / ___ /	NO / ___ /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES / ___ /	NO / ___ /
Investigation #2	YES / ___ /	NO / ___ /
Investigation #3	YES / ___ /	NO / ___ /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #\_\_, Study # \_\_\_\_\_

Investigation #\_\_, Study # \_\_\_\_\_

Investigation #\_\_, Study # \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # \_\_\_\_ YES / \_\_ / ! NO / \_\_ / Explain: \_\_\_\_

Investigation #2

IND # \_\_\_\_ YES / \_\_ / ! NO / \_\_ / Explain: \_\_\_\_

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / \_\_ / Explain \_\_\_\_ ! NO / \_\_ / Explain \_\_\_\_





October 16, 1995

Section 14

**PATENT CERTIFICATION/INFORMATION**

There is no applicable patent which claims the use, method of using, or method of manufacturing of Cystadane™ (betaine anhydrous powder) for the treatment of patients with homocystinuria, as provided for under this NDA 20,576.

A handwritten signature in black ink, appearing to read "Bert Spilker". The signature is fluid and cursive, with a large initial "B" and "S".

Bert Spilker, PhD, MD  
President

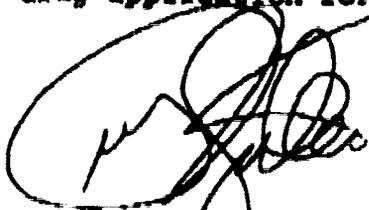


October 16, 1995

**GENERIC DRUG ENFORCEMENT ACT OF 1992 CERTIFICATION**

This information is submitted in accordance with Section 306(k) (1) of the Act (21 U.S.C. 335a (k) (1)).

I certify that Orphan Medical, Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with this new drug application for bupropion anhydrous powder.



Bert Spilker PhD, MD  
President

Date: October 3, 1996  
To: NDA 20-576 Cystadane  
(betaine anhydrous powder for oral solution)  
From: Solomon Sobel M.D. *Solomon Sobel*  
Subject: Approval of NDA; Division Director's Memo

This NDA relies entirely on published literature for approval. The observations in the case reports lack concurrent controls (except for one small study by Dr. Gahl) and rely on changes from baseline measurements and the historic expectation of the lack of spontaneous improvement.

The most useful endpoint in establishing efficacy is biochemical, i.e., the reduction of serum levels of homocysteine. There are also a variety of clinical endpoints which show improvement such as increase in bone density, behavioral improvement etc. The individual literature reports usually contain less than 5 patients. There are 2 somewhat larger reports.

Dr. Troendle has summarized these findings in a tabular form. (see Team Leaders Review).

This is an orphan drug application. There are probably less than 1000 patients with homocystinuria in the United States. There is heterogeneity of the patient population which includes 3 forms of the disease (cystathionine beta-synthase deficiency, methylene tetrahydrofolate reductase deficiency, and cobalamin defect) and a variability of response to other modalities.

Labeling recommendations for the sequence of use of other therapies which include pyridoxine, folic acid, and vitamin B12 or their use in combination with betaine are difficult to make. The wording in the INDICATIONS AND USAGE section allows that these therapies may be used concomitantly with betaine. The approach to therapy varies significantly and depends on an evaluation of the cause of the homocystinuria and empiric responses to the various modalities of treatment.

Betaine adds to the range of available therapies.

The Division has made an independent attempt to ascertain the validity of the data through interview by the reviewing medical officer of the principal investigator of the study considered most significant (Dr. William G. Gahl of NIH).

Recommendation: The Division recommends approval of betaine for use in the treatment of homocystinuria. This will add to the available modalities for the treatment of this rare disease.

cc: Orig. NDA  
HFD-510/div. file  
HFD-510/CSO McCort

DRUG STUDIES IN PEDIATRIC PATIENTS  
(To be completed for all NME's recommended for approval)

NDA # 20-576

Trade (generic) name CYSTADANE (betaine anhydrous)  
for oral solution

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.98 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for AWC studies in children.

a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

a. The applicant has committed to doing such studies as will be required.

(1) Studies are ongoing.

(2) Protocols have been submitted and approved.

(3) Protocols have been submitted and are under review.

(4) If no protocol has been submitted, on the next page explain the status of discussions.

b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

Page 2 -- Drug Studies in Pediatric Patients

5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

[A large area of the page is filled with horizontal lines, indicating a space for handwritten explanation or notes.]

*[Handwritten Signature]*  
\_\_\_\_\_  
Signature of Preparer

*[Handwritten Date]*  
\_\_\_\_\_  
Date

cc: Orig NUA  
MFD-5/C/Div File  
NUA Action Package

**An advisory meeting for this drug was not scheduled.**

**There were no Federal Register notices for this product.**

# Final Printed Labeling

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE  
ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE  
PUBLIC.

# Medical Officers Review

JUN 19 1996

Medical Officer Review

NDA #20,576

M. O. Review #1

Submission: October 25, 1995

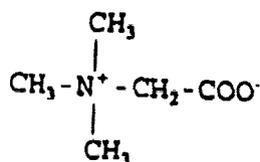
Review completed: May 21, 1996

Drug name: Cystadane

Generic name: betaine anhydrous powder

Proposed trade name: Cystadane

Chemical name: trimethylglycine



Sponsor: Orphan Medical, Inc.

13911 Ridgedale Drive, Suite 475

Minnetonka, MN 55305

phone: (612) 513-6900

Pharmacologic Category: amino acid

Proposed Indication: to decrease elevated homocysteine blood levels in patients of all age groups with:

1. cystathionine beta-synthase (CSD) type of homocystinuria, or
2. methylene tetrahydrofolate reductase deficiency (MTHRD), or
3. cobalamin defect (Cobal)

types of homocystinuria.

In the draft labeling as originally submitted it is stated that Cystadane is indicated also to increase methionine and S-adenosylmethionine blood levels in pts with MTHRD and cobalamin defect (Cobal) types of homocystinuria.

Furthermore, it is claimed, Cystadane can be administered along with folate, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> (cobalamin).

Dosage Form and Route of Administration: a white granular powder that is to be dissolved in water and then taken orally. A scoop is provided with the drug; one level scoop (1.7 cc) is equivalent to 1.0 gm of betaine anhydrous powder. The pt or caregiver is to measure out the number of scoops prescribed by the physician, and the total amount of powder is then to be mixed with 4 to 6 ounces of water and drunk immediately.

NDA Drug Classification: 1 S (or P?)

Related Drugs: choline; betaine is a metabolite of the former.  
all amino acids

Related Reviews: MOR of individually sponsored IND's for this drug, numbers of which are listed in the chemist's review.

2	Table of Contents	
		Page
	General Information	1
	Material Reviewed	2
	Clinical Background	2
	Clinical Studies	8
	Labeling Review	12
	Discussion and Conclusions	14
	Recommendations	16

3 Material Reviewed

All volumes of the NDA, which itself consists entirely of published articles. 16 of these publications describe either completely uncontrolled trials or else are reviews of the subject; another recounts a clinicopharmacologic study in normals, and the final article describes the only controlled study, which was conducted by William Gahl, M. D., at NIH. However, Dr. Gahl's trial was carried out under his own IND, and had no connection with, backing by, and/or financial support from or input by Orphan Medical; the company merely requested Gahl's case reports after he had finished his trial in 5 pts (trial initiated in 6 but only completed in 5), and he supplied these to the company.

4 Chemistry/Manufacturing Controls

See chemist's review.

5 Animal Pharmacology/Toxicology

See pharmacologist's review, as well as some further information below in this review.

6 Clinical Background

6.1 Relevant human experience. Homocystinuria is an inborn error of metabolism and is manifested by the excretion of homocystine in the urine; it is associated with systemic abnormalities of connective tissue. The condition is inherited as an autosomal recessive; in the great majority of cases, the clinical picture is due to deficient activity of the enzyme cystathionine synthetase. Homocystinuria has also been observed to occur in the setting of 3 other rare genetic disorders;

1. deficiency of N<sup>5,10</sup>-methylenetetrahydrofolate reductase, or
2. a defect in vitamin B<sub>12</sub> metabolism, or

3. a selective defect in intestinal absorption of vitamin B<sub>12</sub>.

In all 3 of these latter disorders, a lack of elevation of serum methionine distinguishes from cystathionine synthase deficiency. "Low methionine diet might be disastrous" in cases due to these 3 causes.

Betaine has also been demonstrated to increase plasma levels of methionine and S-adenosylmethionine (SAM) in MTHRD and Cobal pts who have low levels of methionine and SAM; these latter are "thought to be the cause of demyelination and other neurologic problems."

Cystadane is indicated to decrease elevated homocyst(e)ine blood levels in pts of all age groups with:

1. cystathionine beta-synthase (CSD), or
2. methylene tetrahydrofolate reductase deficiency (MTHRD), or
3. cobalamin defect (Cobal).

types of homocystinuria.

Cystadane is also indicated to increase methionine and S-adenosylmethionine blood levels in pts with methylene-tetrahydrofolate reductase deficiency (MTHRD) and cobalamin defect (Cobal) types of homocystinuria.

Response of the individual pt to Cystadane "can be monitored by homocysteine plasma levels." Response "usually occurs within a week and steady state within a month."

In CSD type pts, increases in methionine blood levels "may become greatly elevated." However, monitoring of pts "with high methionine blood levels for many years has not revealed any toxicities or other clinical problems." The package insert claims that Cystadane "can be administered along with folate, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> (cobalamin)."

Betaine does occur naturally in the body. It is a "metabolite of choline," which is a normal dietary component found in many foods. Betaine itself is present in small amounts in foods such as beets, spinach, cereals, beans, citrus fruits, and seafood.

Current specific therapy for the metabolic defect of homocystinuria consists principally of administration to the patient of low methionine diet plus supplementation with pyridoxine (vitamin B<sub>6</sub>); the latter is a cofactor for cystathionine synthetase. Rationale for the low methionine diet: the accumulated metabolites proximal to the site of enzyme block are toxic but can be reduced by restriction of input to the relevant metabolic pathway. Furthermore, since

cystine becomes an essential AA in the homocystinuric, supplementation of the low methionine diet by cystine seems logical. Some investigators have also used a methyl donor, choline, for treatment, in combination with the low methionine diet; choline assists in the remethylation of homocysteine to methionine. Others have used betaine "on the basis of a similar rationale."

Investigation has also "shown that the homocystinuric can synthesize cystathionine from homoserine and cysteine." At least one group has reasoned "that deficiency of cystathionine may be an important factor in the mental retardation" and has therefore "suggested treatment with homoserine and cysteine."

Folic acid "is involved in the salvage pathway by which homocystine is remethylated to methionine," so it "has also been recommended. With folic acid administration, homocystine in the urine is reduced and methionine increased." Any response, in fact, to B<sub>12</sub> may be blunted or abolished by depletion of folate, so it should be ascertained that folate is adequate before any conclusion is reached about vitamin B<sub>12</sub> response or lack of same.

"The simplest and in some patients the most effective therapy for homocystinuria is vitamin B<sub>12</sub> in pharmacologic dosage" [my underlining] (50 to 300 mg/day). Homocystinuria is "a vitamin-dependent inborn error of metabolism, one of a group that also includes methylmalonic aciduria, cystathioninuria, pyridoxine-responsive anemia, and xanthurenic aciduria. Like some of the others, homocystinuria exists in both vitamin B<sub>12</sub>-responsive forms and in nonresponsive forms." It is said that most of the clinically mildly affected cases have the B<sub>12</sub>-responsive type. Either responsiveness or its lack is difficult to predict in more severely affected pts, but responsiveness to B<sub>12</sub> appears to be "rare" in "very" severely affected pts.

Enhanced platelet aggregation "may be the leading factor in thrombosis in homocystinuria," so that a rational approach to therapy would appear to be addition to a therapeutic regimen of such agents as phenylbutazone, sulfinpyrazone, dipyridamole, and chloroquine, "which inhibit platelet aggregation and/or release of platelet constituents when the agent is given in doses without major side effects."

The package insert claims that there are no known contraindications. The same draft labeling states that there also are no Warnings; "no serious risks are known regarding the use of Cystadane in prescribed dosage."

The majority of case studies of homocystinuria pts who have been treated with betaine have been conducted in pediatric pts. In its most severe form, the disorder can be manifested within the first months or years of life by "lethargy, failure to thrive, developmental delays, seizures or eye lens displacement." Pts have "been treated successfully without adverse effects within the first months or years of life with dosages of 6 gm per day or more of betaine with resultant biochemical and clinical improvement. However, dosage titration may be preferable in pediatric" pts.

The PI says that adverse reactions to this drug "have been minimal." In a survey study of physicians who had treated a total of 111 homocystinuria patients with betaine, the types of adverse effects and the number of pts experiencing them were:

9 reactions, including nausea, GI distress, diarrhea, "caused odor," aspirated the powder, questionable psychological changes, and "unspecified problem."

These reactions all appeared to be relatively minor in degree.

6.2 Important information from related INDs and NDAs. There have been 12 individual INDs for this compound, all but 2 of which deal with therapy of homocystinuria; the 2 exceptions cover the treatment of molybdenum cofactor deficiency and usage of the drug to effect a decrease in sulfite levels in pts with molybdenum cofactor deficiency. There have been no approved NDAs for betaine or related drugs. When I called Dr. William G. Gahl at NIH (more below), he said, during the course of our conversation, that rats that are fed high doses of betaine will die, but exact cause of demise is unknown and death may even be due to one of the metabolic products of that substance, namely the homocystine that is produced.

6.3 Foreign experience. Betaine is marketed in several other countries, mostly in Europe, South Africa, and Australia, but it is sold there as an aid in digestion, and for hepatic disorders, hypokalemia, pancreatic secretory disorders, and as a tonic. Betaine anhydrous, betaine monohydrate, and betaine HCl have "widespread use in the animal feed industry, where tons per annum are used as an additive to cattle, fish and poultry feed." In fact, it is even now available in "health food stores" in the US, where it was marketed as a "digestive aid" or "stomach acidifier" until the early 1990s, "usually in preparations of 5 grains of betaine hydrochloride mixed with 135 mg of pepsin." In the preparations provided through health food stores in this country, the amount contained in available tablets is only a fraction of the dosage recommended to be employed in

treatment of homocystinuria in this present NDA.

6.4 Human pharmacology, pharmacokinetics, pharmacodynamics. None of these cited and described trials were conducted by, funded by, or had any assistance or input from Orphan Medical. PK studies are not available. However, PD measurements (ie, monitoring of plasma homocysteine levels) have demonstrated that the "onset of action of betaine is within several days and that steady state in response to dosage is achieved within several weeks. Patients have taken betaine for many years without evidence of tolerance."

When Cystadane is administered in recommended oral dosage to children or adults, it acts as a methyl group donor in the remethylation of homocysteine to methionine in pts with homocystinuria. "As a result, toxic blood levels of homocysteine are reduced in these patients, usually to 20-30 percent or less of pre-treatment levels."

The publication which is described as a clinicopharmacologic study of methionine kinetics in 8 healthy adult men, and effect of dietary betaine on this parameter, assessed effects of a 3 gm daily supplement given for 5 days. All 8 subjects were included one or more times in 4 groups of 4 subjects; all received a control diet based on an L AA mixture. Estimates were able to be made of transmethylation rate (TM) of methionine, remethylation (RM) of homocysteine, and oxidation of methionine. RM "tended to increase. . .but the TM and methionine oxidation were significantly. . .higher after betaine supplementation when estimated with the oral tracer. No differences were detected with the IV tracer. Methionine concentration in plasma obtained from blood taken from subjects in the fed state was higher. . .with betaine supplementation suggesting that excess methyl-group intake may increase the dietary requirement for methionine."

6.5 Other relevant background information. Orphan Medical and DMEDP met on February 14, 1995, to discuss the format and content of a projected NDA submission by the former for betaine anhydrous powder for treatment of homocystinuria. Several comments and questions were brought up, and a response has been prepared by the company. Separate minutes of the meeting prepared individually by both FDA and Orphan Medical are contained in Vol 9.9, which also includes responses by the company to questions from FDA.

6.6 Directions for Use. The package insert instructs the patient or caregiver to measure drug with a scoop that is provided. One level scoop (1.7 cc) is equivalent to 1.0 grams of betaine anhydrous powder. The pt is to measure out the number of scoops prescribed by the physician, mix these

with 4 to 6 ounces of water, and drink the mixture immediately. Pts have been treated successfully "without adverse effects" within the first months or years of life with dosages of 6 gm per day or more. "However, dosage titration may be preferable in pediatric patients."

Usual dosage used in adult and pediatric pts is 6 grams per day, administered orally and in divided doses of 3 grams BID. However, dosages of up to 20 grams per day have been necessary to control homocysteine levels in some patients. In pediatric pts less than 3 years of age, dosage may be started at 100 mg/kg/day and then increased weekly by 100 mg/kg increments. Dosage in all pts can be gradually increased until plasma homocysteine is undetectable or present only in small amounts.

#### 7 Description of Clinical Data Sources

In addition to the placebo-controlled, crossover study conducted by Gahl and then published, the sponsor offers two other presentations as primary support for this NDA approval.

1. The first is a meta-analysis "of all of the clinical studies that have been carried out regarding this therapeutic use of betaine." This includes material extracted from 17 publications that described a total of 78 cases. The quality and thoroughness of these case reports varied greatly, and few of the articles are truly comparable.

2. A second primary support element is "a survey study to determine the current (as of 1993) use of betaine in the treatment of homocystinuria." Orphan Medical contracted in August 1993 with the Metabolic Information Network (MIN) in Dallas, Texas, to "conduct an independent study of the current use of betaine by primarily metabolic/genetic specialists in the treatment of patients with homocystinuria."

The MIN mailed out a one-page report form and mail-in post card in early August 1993 to 110 physicians who had either: 1) submitted cases for any type of homocystinuria to the MIN, or 2) "indicated for the MIN Physician Directory that they had diagnosed or followed cases of homocystinuria, but had not submitted cases to the MIN." Later during that same month similar report forms and post cards were sent to another 84 physicians "of a slightly different category. These were specialists at major US and Canadian metabolic centers who had reported other types of metabolic disorder cases to the MIN but not homocystinuria."

The questions posed on the form and post cards were designed primarily to ascertain safety information: physicians were asked whether they had used betaine and whether any AR had occurred. No specific questions were asked regarding efficacy, although space was provided for comments.

There were thus mailings to 194 physicians; report forms and/or post cards were returned by 103, but one was blank. Of the resultant 102 responses,

- a) 37 reported they had never treated homocystinuria.
- b) 23 reported treatment of 64 pts with homocystinuria, but none of these used betaine.
- c) 41 physicians reported treating a further 190 homocystinurics, and 111 of these had been given betaine.

Although, as stated, comments specifically regarding efficacy had not been requested, 30 such entries were received.

3. Additional information was sought personally by this reviewer, and the evaluation of value of this drug, its place in therapy, and comments have been used throughout this MOR as well as in conclusions and recommendations reached. This additional information consisted of a phone call placed to the Metabolic Information Network and a resultant fax transmittal from MIN, as well as phone conversations with Drs. William Gahl, Harvey Levy, and Harvey Mudd; these are described later.

## 8 Clinical Studies

A) The double-blind, placebo-controlled, randomized, crossover study describing effect of oral betaine on vertebral body bone density in pyridoxine-non-responsive homocystinuria (CSD type) was conducted by Gahl et al at NIH and Georgetown. Purpose of study: to determine effects of betaine that is used to treat pts with decreased bone density due to homocystinuria. Each of the treatment periods was one year in duration. There were 6 pts (3M, 3F) aged 7-32. One F was later eliminated from analysis because she had a compression Fx of T10, was wheelchair-bound due to previous CVA, and did not give reproducible measurements of bone density.

Specific drug used was betaine HCl (from Sigma Chemical Co.) as a liquid solution of 1.5 gm/5 mL; it was administered at dosage of 3 gm BID in orange juice or similar beverage.

Primary efficacy assessments were single energy quantitative computed tomography (QCT) densitometry using a CT scanner at pre-Rx time and then Q6 months; plasma levels of homocystine and methionine were also measured on average x3 during each

treatment period. Results showed that bone density measurements determined after 6 and 12 months betaine Rx did not differ from those after 6 and 12 months of placebo. Betaine did significantly reduce plasma homocystine levels; methionine levels were altered variably and any changes in this were not significant. There were no SE or intolerance to meds in any pt.

B) A table in Vol 1.6, pages 1723 through 1728, lists all publications, titles of articles, location, authors, design of trial, betaine dosage, and results. The meta-analysis, which consists mainly of descriptive statistics, summarizes these 17 trials and/or reviews. There were a total of 78 pts, ranging in age from 24 days to 53 years; all except one had "severe clinical manifestations."

Dosage was reported in terms of gms/day for 68 pts; 48 of these received 6 gm/day, 3 took 3 to < 6 gm/day, and 17 took dosages of 6 to as much as 20 gm/day. Ten had dosage reported in terms of mg/kg/day; this ranged from 113 to 1000 mg/kg/day. In conclusion, "several" pts (total of 5) "received chronic dosages of 15 or more grams per day." "Few patients" received less than 6 gm/day.

Durations of therapy with betaine were reported for 71 of the group of 78 pts; 14 were treated for less than 3 months and 57 for 3 months or more. A total of 30/71 had been treated for 1 year or longer.

Primary criterion of efficacy in these publications was a decrease in plasma level of homocystine and/or homocysteine. These levels were reported "by the direction of change or numerically" for 69/78. Of the 69 pts, 68 (99%) reported or demonstrated decreased plasma level; values did not change in one, but his baseline value was reported to be "trace to 10 units. A value of 10 is very low compared to most patients' pre-treatment levels." Homocystine or homocysteine levels were reported numerically for 62 pts, of whom 61 (98%) demonstrated decreases. Dosage in terms of grams per day was reported at a level of 6 gms/day or more for 52 of these pts; plasma level of homocyst(e)ine decreased by 47 to 100% (patient average), depending on the specific enzyme or co-factor defect. The sponsor concludes that "regardless of whether homocysteine or homocystine was measured and regardless of the type of homocystinuria, the response to betaine treatment was consistent across studies."

Clinical response was reported for 48/78 pts, although "some studies were directed at assessing only biochemical response." Among these 48, 37 (77%) are said to have improved, 10 (21%) remained the same, and 1 (2%) showed a

worsening of seizures, behavior, and/or mental retardation. The sponsor thus concludes that, regardless of the type of homocystinuria, the "majority of patients experienced clinical improvement in response to betaine therapy." Response rate of CSD-type pts appeared to be less than that for the other types (66% improved among CSD vs 88-100% for other types) because of Gahl's study, in which only bone density was assessed clinically; treatment in these patients for this duration resulted in no improvement in this parameter. "Without including this study the CSD improvement rate is 79% (19 of 24)." In addition, it is not known if a longer duration of therapy or a higher dosage or some other change might or might not lead to improvement in the osteoporosis of homocystinuria.

Response by age reveals report of age at time of betaine treatment for 49/78. Table 5 (page 1772) appears to show that there was decreasing magnitude of biochemical response with increased age, but "this cannot be concluded because of the small numbers of patients in each group, and the fact that percentages can give misleading impressions in some cases (e.g. if baselines vary)." Cells of the table classified by age, cause of homocystinuria, and average percentage of biochemical decrease from baseline contain only 5 to 11 pts each. "Also, the clinical response does not show this trend," but each cell in this categorization contains only from as few as 1 to as many as 8 subjects.

Biochemical response and clinical response are categorized by gender of subjects and type of homocystinuria for 43/78.. There was "no apparent difference regarding biochemical response rates between males and females." Both genders showed mean percentage decrease of 80 in homocystine or homocysteine. "Regarding clinical response the numbers of patients reported upon is too small to allow assessment of the apparent difference." Only 23/43 had entries for clinical response, and although initially it appears that a larger percentage of females improved, the difference was only 5/9 males vs 12/14 females.

Responses categorized by pre-Rx plasma levels of homocystine or homocysteine and type of homocystinuria showed "no apparent differences in biochemical responses." Mean percentage of biochemical decreases varied from 71 to 88 in various cells. "Clinical response reports are too few to allow assessment of apparent differences." Clinical response was reported for 26/35 in those from publications in which homocystine was measured and in only 2/29 of those from articles in which homocysteine was the parameter that was measured.

The sponsor concludes that betaine "has been demonstrated to

be biochemically and clinically effective in the hands of independent physicians working around the world in the treatment of homocystinuria." In addition, the sponsor states that the drug "is equally effective in the treatment of all three basic types of homocystinuria." The company says that the drug "has remained effective in patients treated for many years." The recommended daily dosage is 6 gm, and "it is apparent that dosage can be safely raised if desired to lower blood levels of homocystine or homocysteine and to possibly improve a patient's clinical response."

Further conclusions are that betaine "has been effective in improving or preventing the progression (i.e. stayed the same) of the clinical manifestations of homocystinuria in 98% of the 48 patients reported (77% improved, 21% same). It has also been biochemically effective in 98% of patients." Finally, "in spite of the relatively small number of patients with this rare disorder studied, the beneficial results of betaine therapy and its safety are both evident and conclusive."

#### 9 Overview of Efficacy

The publications in this NDA differ considerably in quality, format of presentation, amount and types of information gathered, etc. No two of the articles are directly comparable, but this result follows because all these investigations were planned individually, conducted at different centers, used drug from different manufacturers, used dosages felt to be adequate and proper by the individual investigators, etc, and there was no unifying force behind the studies. Besides, as said previously, there is still considerable controversy about some of the medical knowledge related to this disorder or some aspects still unknown. However, each article individually appears to prove the limited claims and indications in the PI, as amended on May 22, 1996. Betaine either alone or more usually added to a regimen of other agents for this disorder does result in biochemical improvement when used in therapy of homocystinuria.

#### 10 Overview of Safety

The 17 publications that form the database from which the company extracted individual case summaries do not contain any reports of adverse events that could possibly be related to this drug. Any adverse experiences were either so "minor" and "nonconsequential" that the authors of articles did not mention them or else they were attributable to the underlying disorder itself, which is, of course, heterogeneous in presentation and can range from a devastating disorder to one recognized only by biochemical

abnormalities accompanied by no clinical S/Sx.

The survey by Metabolic Information Network covered treatment of 111 patients, with reports of "minor" AR in 9 patients; these are cited and listed above under Clinical Background and are included in the draft PI.

#### 10.1 Significant/Potentially Significant Events

10.1.1 Deaths: none reported among those placed on the drug. Again, the condition is rare, and any deaths would have been due to the disorder itself.

10.1.2 Other Significant/Potentially Significant Events: none.

The only possible and theoretical adverse effects from drug would result from any possible elevation of methionine (especially in the CSD type), and experts differ on toxicity from that source. Those whom I consulted uniformly claimed that there were no adverse sequelae of hypermethioninemia. Isolated hypermethioninemia, in fact, has been reported, with no clinical manifestations. A few of the publications cite a "well known toxicity of methionine" or a "rather marked toxicity of methionine," but what this toxicity manifests as is not identified (also see below for results of phone conversations placed by me). The PI discusses increased plasma methionine under both Clinical Pharmacology and Indications and Usage.

10.1.3 Overdose Experience: none reported.

#### 10.2 Other Safety Findings

There is no significant or relevant information under any of the subheadings of this part of outline of MOR, and, additionally, any pertinent information is covered in the draft insert.

Safety Update report dated Jan. 26, 1996: No clinical trials are in progress, so there is no new safety information that could impinge upon labeling.

### 11 Labeling Review

The proposed package insert contains headings and sections

that follow the order and titles recommended for all marketed drugs. The following changes in PI are recommended:

- a) Clinical Pharmacology, pg 2 (pg 730), paragraph 2: omit the last part of sentence, "which are thought to be. . .neurologic problems." There is not agreement on this, and some, in fact, have said that cystathionine deficiency in brain may cause the neurologic manifestations or there may even be other factors involved in neurologic findings. It is unknown as to which specific biochemical abnormalities cause which specific manifestations, and most feel that all S/Sx may be due entirely to the elevation of homocyst(e)ine. Besides, as it now reads, this might be interpreted to be an implied indication to employ this agent in neurologic problems alone that are unaccompanied by homocystinuria. It is probably true that unusual presentations of or some problems that present as neurologic disorders should be investigated for the presence of homocystinuria.

During the course of my telephone conversation with Ms. M. Kuker (see below), I told her that if the company intended to issue an accompanying educational brochure or publication (because of the rarity of homocystinuria and resulting lack of recognition of the disorder) for physicians, such hypotheses would probably be satisfactory for inclusion and discussion.

- b) Indications and Usage, pg 2 (pg 730), paragraph 1: there is a redundancy "type of homocystinuria" under #1 that is repeated in the last line of that paragraph.

c) Indications and Usage, pg 2 (pg 730), paragraph 2: omit entire paragraph. It seems in its present form to recommend this drug for patients with homocystinuria that is manifested only by hypomethioninemia and/or hypoSAM (without homocystinemia and elevated urinary homocyst(e)ine); whether such an entity even exists or has ever been described is unknown at present, and it is unknown if this drug might then be the treatment for such a disorder. In addition, no publication in this NDA and no authority that I have consulted feels that the drug is valued solely to increase methionine and SAM levels; function of the drug is to dispose of the excess homocyst(e)ine.

- d) Precautions, pg 3 (pg 731), General: add a statement, as is already and similarly true for the approved drugs Ceredase and Cerezyme, that therapy with Cystadane should be directed by physicians

knowledgeable in the management of patients with homocystinuria.

On May 21, 1996, I called Ms. Marie D. Kuker, Director of Regulatory Affairs of Orphan Medical, Inc., and requested that the above changes be made in the draft labeling. On May 22, Ms. Kuker called me back and told me that the company would agree to all these changes. I asked her therefore to put that agreement in a fax to me today, and to follow that up with the 3 official copies of such a submission.

## 12 Discussion and Conclusions:

1) This NDA is generally in poor condition, and the sponsor has made relatively poor use even of the published articles and has availed himself of only a small fraction of other information and sources that could have added considerably to the value of the NDA and imparted more knowledge about this disorder and its management. There are several reasons for such limited exertion. First, the company is a relatively newer entity and has had little previous experience with drug development; this is in fact the first NDA it has ever submitted to FDA. Other and larger companies showed little or no interest in submission of an NDA for this drug in this disorder after FDA Orphan Drugs inquired after a sponsor for the product. Additionally, the disorder for which this new treatment is to be indicated was described only within the past four decades, and it is rare. Homocystinuria differs in incidence in different populations, but it has been estimated that only approximately 800-1000 cases in total have been found and reported in the United States. It is obvious that this company was not willing and/or able to spend much on original work in homocystinuria; it has depended entirely upon knowledge already in the medical literature.

Although all publications contained in this NDA have been read and digested thoroughly for this MOR, and although as much information has been extracted from them as possible, and although further personal tabulations have been made and whatever additional conclusions have been drawn from the articles for use in this present review, I therefore checked with and/or called several sources of already existent information.

2) On May 15, 1996, a call was placed to the Metabolic Information Network, Dallas, TX, which responded with a fax that is included in this MOR. There is an information sheet "about the purpose and initiatives" of the MIN. Since approximately 1989 or 1990, I was told, the MIN has had reported to it from the U. S., Canada, and Mexico (mostly

the area around Mexico City) 160 cases of homocystinuria, and these are categorized as to type in the accompanying table. These reports from physicians to MIN are submitted strictly on a voluntary basis.

3) On April 3, 1996, I called Dr. William G. Gahl at NIH. Among the information that he imparted to me during the course of a rather lengthy conversation was the fact that as of the present only about a total of 750 cases have been recognized and reported from the entire U. S. since the original description of the disorder. Rats that are fed high doses of betaine will die suddenly, but the cause is unknown and demise may even be due to the metabolic product of homocysteine. Present clinical treatment of this clinical disorder does sometimes and under some circumstances include administration of methionine, since there are no known and unrecognized ADR to this AA. The rhetorical question was posed as to how proof could even be gathered that lesions were due to the excess in homocystinemia.

Dr. Gahl referred me to Drs. Harvey Mudd and Harvey Levy.

4) On May 7, 1996, I placed a call to Harvey Mudd, M. D., NIH, who is one of the co-authors in 1985 of a definitive publication and review of all previously known cases of this disorder. Again in a rather lengthy and completely informal conversation, Dr. Mudd was very informative about this disorder and this drug, and he was very generous with his time and knowledge. He told me, among other facts, that isolated hypermethioninemia has been reported in humans; methionine levels up to 20x normal have occurred with no resultant abnormality or possibly demyelination in the CNS. He felt that the vascular disease that occurs in homocystinurics is especially related to the elevation of homocyst(e)ine.

5) On May 15, 1996, I placed a call to Harvey Levy, M. D., Newborn Screening Lab, Massachusetts. A relatively lengthy and informal consultation ensued; Dr. Levy, just as the other physicians whom I called, also proved to be very generous with his time. During our conversation he used such modifiers as invaluable and proved beyond any shadow of a doubt in describing the efficacy and value of betaine in the treatment of homocystinuria. He also said that he felt that the drug was especially valuable for prevention of the vascular incidents that occur in this disorder. All types of homocystinuria do respond, because any resultant rise in methionine (in the most common type) is not the problem; the clinical S/Sx that occur during the course of this disorder are secondary to the elevation of homocyst(e)ine in plasma and tissues. When we spoke about toxicity of methionine, it

was claimed that actually there had been one report from back in the 20's or 30's that methionine excess was harmful in humans, but that there had been no reports since. Incidentally and parenthetically, the higher methionine levels that result from administration of betaine could even be protective in those afflicted with homocystinemia, although this opinion is only anecdotal thus far.

### 13 Recommendations:

It is therefore recommended that this NDA be approved for the specific indications given in the present amended draft labeling. There seems little question that some definite subset of this population, if indeed it is not the entire population of homocystinurics, will and do benefit from this drug; indeed, for some patients the drug is very important and possibly even highly necessary, because a low methionine diet (for CSD patients with high methionine levels) is difficult or impossible to follow and (for MTHRD and Cobal patients with low or normal methionine levels) low methionine diet may possibly even be harmful and the drug will help to raise methionine levels to normal.

Any further delimitation and/or expansion of usage actually awaits a furthering of basic medical knowledge about and investigation concerning the disorder(s) described under the title of homocystinuria. Experts in the field of inherited disorders of metabolism have testified to and proved the value of the drug in this specific disorder. Usage of the drug should be relatively limited for the foreseeable future. Although no two of the submitted publications are directly comparable, this results from the rarity of the disorder and because most published articles deal with one, two, or a few cases. For the same reasons, no controlled studies will ever be possible, unless a referral center undertakes such a trial; it can be confidently predicted, however, that if such a trial were to be contemplated it would be claimed to be unethical because no treatment in this disorder can be devastating to the patient. Comparison of treated cases to findings in patients who follow the natural course of homocystinuria leaves little doubt as to efficacy of this drug in decreasing elevated homocyst(e)ine blood levels in all 3 specified types of homocystinuria.

If a broadening of indications is ever to be sought, an attempt should be made to plan prospective trials that are controlled. However, even then it may not be possible to conduct adequate and well-controlled clinical trials, because no company may be interested in developing such an agent which it could not patent. Eventual goal in homocystinuria obviously is an attempt to correct the genetic disorder in heterozygotes as well as in those with clinical and/or biochemical homocystinuria or to treat patients pre-natally (which has been recently reported to be successful in extremely limited trials) or after detection

through screening programs after birth; for the approximately 50% or more (so far) reported cases with findings of mental retardation, seizures, or psychiatric disorders, appearance of Sx is too late for any substantive value from any type of treatment.

See the entry under 11 Labeling Review above for requested changes in the draft package insert and the results of my phone conversations with Ms. Marie Kuker of the company.

*Elton Herman*

Elton Herman

*Gloria Trumble*

6-19-96

cc: Orig NDA 20,576  
HFD-510  
HFD-510/EHerman/05-22-96

The Safety Update Report is included on page 12 of Dr. Herman's Medical Review.

# Statistical Review

**NDA 20-576**  
**Cystadane™ (betaine anhydrous for oral solution)**

**Statistical Review**

No statistical review was performed. The NDA for the most part rested on uncontrolled observation. The criteria for improvement varied. There was one small double blind, placebo controlled, randomized, crossover trial involving 6 patients. This study was not amenable to statistical evaluation.

# BIO Review

JUN 18 1996

***Clinical Pharmacology & Biopharmaceutics Review***

**NDA: 20-576**

**SUBMISSION DATE: October 21, 1995**

**BRAND NAME: CYSTADANE®**

**GENERIC NAME: Betaine anhydrous powder**

**REVIEWER: Carolyn D. Jones, Ph.D.**

**SPONSOR:**

Orphan Medical, Inc.  
Minnetonka, MN

**Type of Submission:**

Original NDA (NME)

Code: 1P

**SYNOPSIS:**

Betaine (trimethylglycine), a natural product extracted from the molasses of sugar beets, is intended for the treatment of elevated homocysteine levels in the condition homocystinuria (also known as homocystinemia). Homocystinuria is a very serious disorder caused by inborn errors in metabolism of methionine which result in high blood levels of homocysteine that are thought to interfere with the normal cross binding of collagen. It is these elevated levels that are believed to be responsible for the clinical manifestation of homocystinuria which includes thrombotic vascular disease, resulting in death before age 30, mental retardation, seizure disorders, optic lens dislocation, osteoporosis, skeletal abnormalities, psychiatric disorders and demyelination problems.

Betaine's primary pharmacological action is to lower elevated blood levels of homocysteine. According to the sponsor, betaine is the only agent available which is effective in correcting the biochemical abnormalities associated with all types of homocystinuria. The prognosis of patients left untreated is poor, however patients responding to treatment can have an improved quality of life and a normal lifespan.

Betaine occurs normally in the body either as a natural food source (e.g., spinach, beans, cereals, citrus fruits, vegetable and animal fats, seafood and egg yolks) or as a metabolite of choline. It is a component of the metabolic cycle of the essential amino acid methionine wherein it acts as a methyl group donor to convert homocysteine ( a metabolite of methionine) back to methionine. The usual dosage used in adult and pediatric patients is 6 gms/day administered orally in divided doses of 3 grams two times per day. In pediatric patients less than 3 years of age, dosage may be started at 100 mg/kg/day and then increased weekly by 100 mg/kg increments. Dosages of up to

20 grams/day have been necessary to control homocysteine levels in some patients. Some patients have received dosages up to 30 gm/day for up to 11 years with no reports of adverse events. Dosage in all patients can be gradually increased until plasma homocysteine is undetectable or present only in small amounts.

Betaine was granted Orphan Medical Status on May 16, 1994. No clinical studies have been conducted by Orphan Medical Inc., in support of this application. This application relies entirely on the medical literature. Seventeen (17) articles using various forms of betaine have been included with this submission. Pharmacokinetic information not included as part of this submission was: protein binding, bioavailability, bioequivalence, food effects, special populations, population pharmacokinetics/pharmacodynamics and pharmacokinetics single and multiple dose.

### **RECOMMENDATION:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed NDA 20-576 submitted on October 21, 1995. This submission lacks pharmacokinetic and/or pharmacodynamic data which are routinely required for an original NDA. However, in view of the orphan drug status and available literature information, this submission is acceptable provided that the Division of Metabolic and Endocrine Products finds betaine safe and efficacious. Please convey the recommendation, comments and labeling comments to the sponsor.

### **Table of Contents**

	<b><u>Page</u></b>
Synopsis.....	1
Recommendation.....	2
Background.....	2
Drug Formulation.....	3
Analytical Methodology.....	3
In Vitro Testing.....	4
Human Pharmacokinetics and Bioavailability Studies.....	5
Comments to be sent to the firm.....	6
Labeling Comments.....	7
Attachment (Proposed Label).....	8

### **BACKGROUND:**

Betaine anhydrous (free base) and other forms are currently used in the animal feed industry. The anhydrous form can be purchased by physicians for investigational purposes in the treatment of homocystinuria patients. The anhydrous form is more palatable than the hydrochloride and has better pharmaceutical properties than the monohydrate. Prior to the early 1990's, betaine hydrochloride tablets were marketed in health food stores in the United States as a digestive aid.

hydrochloride tablets were marketed in health food stores in the United States as a digestive aid. The sale for this use is now prohibited under 21 CFR 310.540 (a). Betaine hydrochloride is GRAS (generally recognized as safe) for its use as a food additive; flavoring of imitation crab meat products.

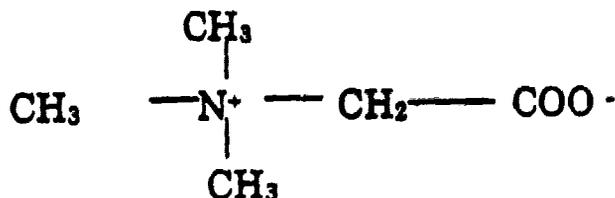
Treatment for homocystinuria includes other natural substances such as: pyridoxine (vitamin B<sub>6</sub>), cobalamine or vitamin B<sub>12</sub>, and folate. The sponsor indicates that the advantage of betaine over some of the other compounds is that betaine is responsive in all three types of homocystinuric patients, and the number of patients who have demonstrated lowering of plasma homocysteine levels are greater.

In the articles submitted, either homocystine or homocysteine was measured in the plasma. Homocystine is formed nonenzymatically from two molecules of homocysteine. The compound cysteine-homocysteine is also formed nonenzymatically from one molecule of each of the parent compounds. Total homocysteine is expressed as twice the (molar) concentration of homocystine plus the concentration of cysteine-homocysteine.

#### **DRUG FORMULATION:**

Betaine anhydrous (betaine free base), a white crystalline powder, is the active ingredient in this drug product. It has a molecular weight of 117.15 g/mole and it will be distributed as a powder with no excipients (Figure 1. Molecular Formula of Betaine).

Structural formula:



#### **ANALYTICAL METHODOLOGY:**

During the time frame the clinical studies included as part of this submission were conducted, no methods were available for the determination of blood or urine levels of betaine. Investigators monitored the use of betaine by determining either plasma homocysteine or homocystine levels, The decreases in these compounds track together in response to betaine therapy.

In 1993, a GC-mass spectrometry stable isotope dilution method for the analysis of betaine and

its metabolites N,N-dimethylglycine and N-methylglycine was published. In 1994, an article was published which simultaneously determined betaine and N,N-dimethylglycine in urine, using an HPLC method with UV absorbance detection. However, neither of these methods were employed in the articles submitted as part of this NDA.

### IN VITRO TESTING:

An in vitro stability study of betaine anhydrous powder and betaine hydrochloride in simulated gastric fluid with pepsin as requested by the Agency (February 14, 1995 Pre-NDA meeting) was conducted. The results outlined in Table 1 indicate no stability differences between the two forms of betaine.

Betaine Anhydrous, Lot#19-11-3-DP	0 min	15 min	30 min	60 min	120 min
g/ml	0.9900	1.005	0.9997	1.001	1.005
Percent of Initial Value	n/a	101.5	101.0	101.1	101.5
Betaine Hydrochloride, Lot#84H0903					
g/ml	1.001	0.9990	1.006	0.9948	1.004
Percent of Initial Value	n/a	99.8	100.5	99.4	100.3

Water, orange juice and milk were additional media requested for study. High performance liquid chromatography was used to assess the stability of betaine in orange juice and milk. A large interfering peak from milk and several small peaks from orange juice were observed. Therefore, the prescribing information reflects constitution only in water. The results of the water stability study of the betaine anhydrous powder demonstrated stability for at least 24 hours (Table 2).

Sample Description	Betaine Anhydrous, gms/120 ml				
	0 hr	2 hr	4 hr	6 hr	24 hr
Lot 19-11-3-DP	3.108	3.114	3.111	3.171	3.236
Percent of initial value	n/a	100.2	100.1	102.0	104.1
Lot 16-12-3-DP	3.064	3.033	3.033	3.104	3.130
Percent of initial value	n/a	98.99	98.99	101.3	102.2
Lot 550940020-DP	3.002	3.062	3.076	3.052	3.052
Percent of initial value	n/a	102.0	102.5	101.7	101.7

## HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

### **I. Pharmacodynamics**

Homocysteine plasma levels were monitored in 17 published studies that were included as part of this submission. Lowering these levels was the primary indication of betaine's efficacy. Two of the studies which were submitted used the hydrochloride betaine formulation. The other studies in which formulation type was specified used the anhydrous form of betaine. Six grams of the hydrochloride form has up to 25% less content of betaine than the free base form. The percent decreases in homocysteine plasma levels of patients who received the hydrochloride formulation were comparable to patients in other studies.

The sponsor performed a meta-analysis of data from the published 17 studies. A total of 72 patients from 25 days to 53 years of age were evaluated. The sponsor reported ninety-eight percent of the patients had a decrease in homocysteine levels from betaine. When given 6g of betaine, patients experienced a 72% decrease in homocysteine levels (N=42). When given amounts greater than 6g, patients experienced a 82% decrease (N=12) (NOTE: This reviewer found between studies that there is no dose response relationship). However, due to the lack of an assay, no correlations could be made between betaine concentrations and homocysteine level decreases. The sponsor also indicated that 77% of patients showed signs of clinical improvement and stabilization or lack of progression in another 21%. The sponsor analyzed the data for age and gender in addition to other covariates. No differences were observed in the ability of betaine to lower homocysteine levels.

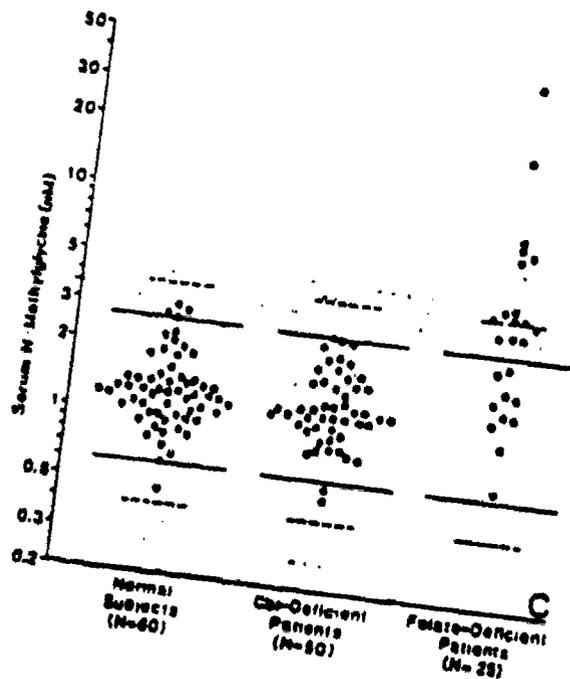
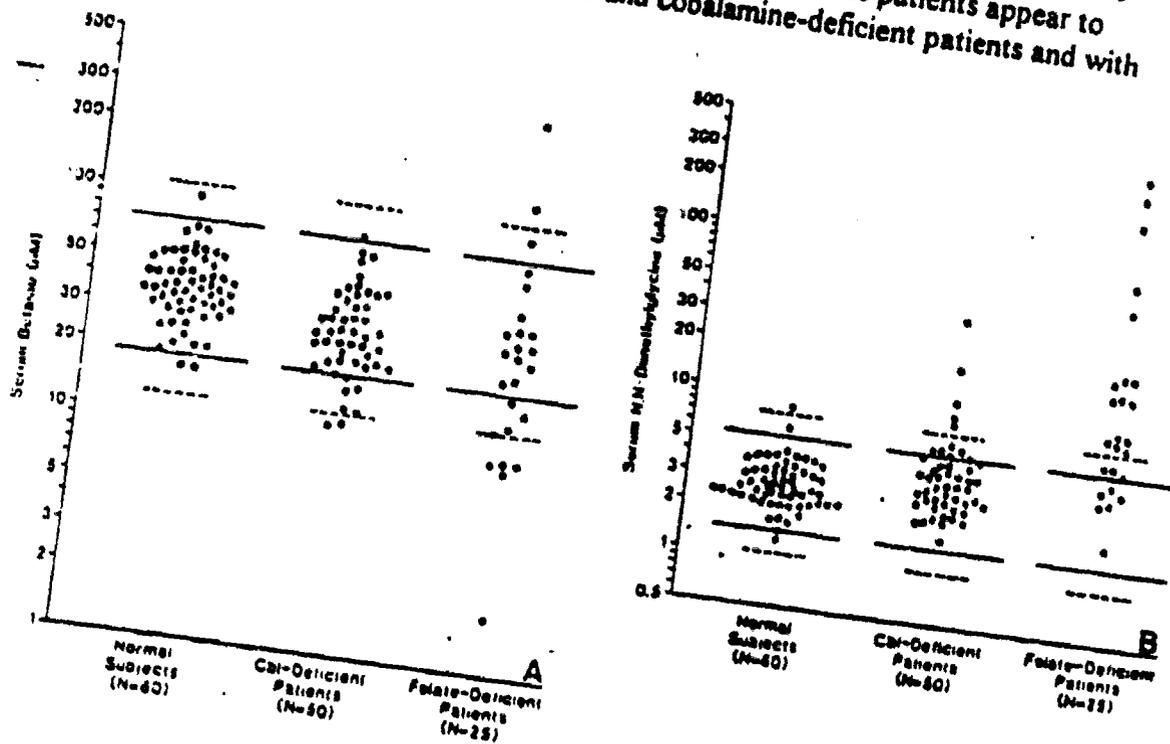
Normal endogenous levels for betaine and its metabolites in normal subjects are outlined in Table 3 below. (Note: There is no information available on whether metabolites are active or not).

	Betaine	N,N-Dimethylglycine	N-Methylglycine
Serum	17.6-73.3	1.42-5.27	0.06-2.67
Urine	12-731	5.3-177	0.9-22.2
Urine*	(2.3-55.9)	(1.15-12.23)	(0.30-0.98)

Results are means  $\pm$  2 SD after log-normalization to correct skewness towards higher values in 60 normal blood donors.  
\*Expressed as  $\mu\text{moles}$  of metabolite/ mmole of creatinine.

Figure 2 shows a correlation in endogenous betaine, N,N-dimethylglycine and N-methylglycine levels in normal subjects, cobalamine-deficient patients and folate-deficient patients. Fourteen

percent of cobalamine-deficient patients had mild decreases in betaine (median value of deficient patient 27.9 compared to normal 34.2  $\mu\text{mol/L}$ ). In folate deficient patients, betaine levels were decreased 36%. The data suggest that the folate-deficient type homocystinuric patients have greater variability in their disposition of betaine in the body. These same patients appear to metabolize betaine to a greater extent than normals and cobalamine-deficient patients and with greater variability.



**COMMENTS TO BE SENT TO THE FIRM:**

1. The half-life is unknown, the activity of the metabolites has not been established and no plasma concentration time curves were generated. Furthermore, the lack of a suitable assay for betaine up until recently, made it impossible to investigate a correlation between homocysteine levels and betaine, therefore PK/PD information is nonexistent. The only information that the company has demonstrated is that when betaine is given, homocysteine levels decrease. Administration of 6g of betaine yields a 72% decrease in homocysteine.
2. Since assays are currently available for betaine and its metabolites, it would be desirable if physicians monitored betaine levels and correlated them to homocysteine levels.

**LABELING COMMENTS:**

1. The following should be added under the Clinical Pharmacology section: "No pharmacokinetic information is available. Plasma levels of betaine have not been measured in patients and have not been correlated to homocysteine levels."

*Carolyn D Jones*

5/24/96

Carolyn D. Jones, Ph.D.

Division of Pharmaceutical Evaluation II

Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 5/28/96

FT initialed by Hae-Young Ahn, Ph.D., Team Leader Hae-Young Ahn 6/18/96

cc: NDA 20-576 ( 1 copy), HFD-510 (Herman, Haber, Short), HFD-340 (Vishwanathan), HFD-860(Malinowski), HFD-870(Ahn, Jones and M. Chen), HFD-880(Fleischer), HFD-850(Drug file, Chron. file, Reviewer), HFD-205(FOI)

A. Table of Betaine Studies

Study	Title	Investigators/ Authors Journal/Year	Design	No. of Patients/ Subjects sex/age range	Betaine dosage	Results	MDA Location of Full Reports Vol/Page
S-1	Methionine Kinetics in Adult Men: Effects of Dietary Betaine on L- <sup>14</sup> H,-methyl- <sup>14</sup> C methionine	Storch et al; Am. J. Clin. Nutr., 1991	Open label	8 normal male volunteers, 19-29 years of age	3 gm/day for 5 days	a) Methionine plasma levels increased. b) homocysteine remethylation tended to increase c) transmethylation of methionine oxidation significantly higher. No adverse events.	8.C.III Vol. 1.4 P. 1071
S-2	The Effect of Oral Betaine and Vertebral Bone Density in Pyridoxine Non-Responsive Homocystinuria	Gahl et al; Journal of Inherited Metabolic Disease, 1993	Double-blind, placebo controlled, randomized, crossover, balanced	3 females 3 males, ages 7-32 years.	3 gm bid for 1 year and placebo for 1 year (balanced)	Biochem improvement in 5 of 5 for whom reported; no change in bone density. Patients previously not responsive to pyridoxine. No adverse events observed.	8.D.III. Vol. 1.4 P. 1101
S-3	Betaine Therapy in Homocystinemia	Beilow et al; Brain Dysfunction, 1989	Open label	24 male or female infants or adults	150 mg/kg/d to 20 gm/d for 1 month to 11 years	Biochemical improvement in 22 of 24; clinical improvement in 10 of 15 for whom reported. No adverse events.	8.E.IV. Vol. 1.4 P. 1241

Betaine Studies (continued)

Study	Title	Investigators/ Authors Journal/Year	Design	No. of Patients/ Subjects sex/age range	Betaine dosage	Results	NDA Location of Full Reports Vol./Page
S-4	Homocystinuria - The Effects of Betaine in the Treatment of Patients Not Responsive to Pyridoxine	Wilcken et al; N. Eng. J. Med., 1983	Open label	5 females 6 males ages 6-37 years	3 gm bid for 3-11 months	Biochemical improvement in all; clinical improvement in 9. Patients previously not responsive to pyridoxine. No adverse events.	0.E.IV. Vol. 1.4 P. 1252
S-5	The Use of Betaine for the Treatment of Homocys- tinuria.	Smolin et al; J. of Pediatrics, 1981	Open label	30 year old male  10 year old female	3.2 gm bid  3.5 gm bid	Biochemical and clinical improvement in both. Patients previously not responsive to pyridoxine. No adverse events.	0.E.IV. Vol. 1.4 P. 1262
S-6	Homocystinuria Due to Cystathionine beta-Synthase Deficiency -- The Effects of Betaine Treatment in Pyridoxine- Responsive Patients	Wilcken et al; Metabolism, 1985	Open label	2 females 4 males ages 11-53	3 gm bid for 3 weeks	After methionine loading, betaine improved abnormal homocysteine responses that had occurred while patients on only pyridoxine and folic acid. Clinical responses not reported. No adverse events.	0.E.IV. Vol. 1.4 P. 1271

Orphan Medical, Inc.  
 NDA 20,576 Cystadane™ (betaine anhydrous powder)  
 Section 2.K. CLINICAL DATA SUMMARY

Betaine Studies (continued)

Study	Title	Investigators/ Authors Journal/Year	Design	No. of Patients/ Subjects sex/age range	Betaine dosage	Results	NDA Location of Full Reports Vol/Page
S-7	Gastrointes- tinal involve- ment in Homo- cystinuria	Ilan et al; J. of Gastro- enterology and Hepatology, 1993	Open label	17-year old male	9 gm/day for 18 weeks	Biochemical improvement and clinical improvement in pancreatitis and chronic diarrhea. No adverse events.	S.E.IV. Vol. 1.4 P. 1282
S-8	Pyridoxine- Unresponsive Homocystinuria with an Unusual Clinical Course	Cochran et al; Amer. J. of Medical Genetics, 1990	Open label	14 year old male	6 gm/day for 3 years	Biochemical and clinical improvement after patient unresponsive to methionine-restricted diet and supplemental pyridoxine plus folate. No adverse events.	S.E.IV. Vol. 1.4 P. 1287
S-9	Hereditary Defect of Cobalamin Metabolism (CblG Mutation) Presenting as a Neurologic Disorder in Adulthood	Carmel et al; N. Eng. J. Med., 1988	Open label	21 year old female	6 gm/day for 15 months	Biochemical and clinical improvement after betaine added to regimen of oral cyanocobalamin, folic acid, and hydroxycobalamin injections. No adverse events.	S.E.IV. Vol. 1.4 P. 1294

Betaine Studies (continued)

Study	Title	Investigators/ Authors Journal/Year	Design	No. of Patients/ Subjects sex/age range	Betaine dosage	Results	NDA Location of Full Reports Vol/Page
S-10	Betaine in the Treatment of Homocystinuria Due to 5, 10-Methyl-enetetrahydro-folate Reductase Deficiency	Wendel, U. and Brewer, H.J. Eur. J. Pediatrics, 1984	Open label	3 year old female	6-20 gm/day for 18 months	Biochemical improvement and marked clinical improvement after no response to vitamin B <sub>6</sub> , folic acid, and methionine. No adverse events.	8.E.IV. Vol. 1.4 P. 1301
S-11	Betaine for Treatment of Homocystinuria Caused by Methylenetetrahydrofolate Reductase Deficiency	Holme et al; Archives of Disease in Childhood, 1989	Open label	24-day old female	3-6 gm/day for 11 months	Biochemical improvement and almost complete clinical recovery after no response to pyridoxine, hydroxycobalamin, and folic acid. No adverse events.	8.E.IV. Vol. 1.4 P. 1309
S-12	Methylmalonic Aciduria with Homocystinuria : Biochemical Studies, Treatment, and Clinical Course of a Cbl-C Patient	Ribes et al; European J. of Pediatrics, 1990	Open label	22-month old child	2 gm t.i.d. for 3 years	Biochemical and clinical improvement after no success with intramuscular methylcobalamin. No adverse events.	8.E.IV. Vol. 1.4 P. 1316

Betaine Studies (continued)

Study	Title	Investigators/ Authors Journal/Year	Design	No. of Patients/ Subjects sex/age range	Betaine dosage	Results	MDA Location of Full Reports Vol/Page
S-13	Therapeutic Approach to Cobalamin-C Methylmalonic Acidemia and Homocystinuria	Bartholomew et al; J. of Pediatrics, 1988	Open label	15-month old male; a 4-year old female	250 mg/kg per day for 1 year	Biochemical and clinical improvement in both after betaine added to injections of OH-B <sub>12</sub> . No adverse events.	8.E.IV. Vol. 1.4 P. 1323
S-14	Demyelination and Decreased S-adenosylmethionine in 5, 10-methylenetetrahydrofolate Reductase Deficiency	Hyland et al; Neurology, 1988	Open label	Female 3 years; Male 17 months; Female 29 months	8-20 gm/day for 10-36 mos	Biochemical and clinical improvement in all. Historical "control" patient who had received no betaine, died. No adverse events.	8.E.IV. Vol. 1.4 P. 1334
S-15	Free and Protein-Bound Homocysteine and Cysteine in Cystathionine beta-synthase Deficiency: Interrelations During Short-term and Long-term Changes in Plasma Concentrations	Wiley et al; Metabolism, 1989	Open label	13 patients with homocystinuria; 6 pyridoxine responsive, and 7 not	3 gm bid for up to 300 days	When betaine added to previous therapies, biochemical improvement in 7 of 7 for whom reported individually. Clinical status not reported. No adverse events.	8.E.IV. Vol. 1.4 P. 1342

Betaine Studies (concluded)

Study	Title	Investigators/ Authors Journal/Year	Design	No. of Patients/ Subjects sex/age range	Betaine dosage	Results	MDA Location of Full Reports Vol/Page
S-16	Effect of Betaine on S-Adenosyl-methionine levels in the Cerebrospinal Fluid in a Patients with Methylentetrahydrofolate Reductase Deficiency (MTHFR) and Peripheral Neuropathy.	Kishi et al; J. Inter Metab. Dis., 1994	Open label	16 year old female	5 g/day for 28 months	When betaine added marked biochemical and clinical improvement. No adverse events.	S.E.IV. Vol. 1.4 P. 1352
S-17	Symptomatic and Asymptomatic Methylentetrahydrofolate Reductase Deficiency (MTHFR) in Two Adult Brothers	Haworth et al; Am. J. of Med. Gen., 1993	Open label	26 year old male and 37 year old male	6-15 g/day for 6 months	Biochemical and clinical improvement. No adverse events	S.E.IV. Vol. 1.4 P. 1360
S-18	Homocystinuria: Efficacy of Treatment with Pyridoxine, Folic Acid and Betaine	Brens et al. An Esp. Pediatr., 1993	Open label	6 year old female 6 year old male 3 year old male	6 g/day for 1-2 years	Biochemical improvement for all 3. Clinical improvement in 1 patient. Clinical status not reported for other 2. No adverse events.	S.E.IV. Vol. 1.4 P. 1368

INDIVIDUAL PATIENT DATA LISTINGS

STUDY	PATIENT ID <sup>a</sup>	AGE (YRS)	SEX	HOMOCYSTEINE PLASMA LEVELS	PLASMA LEVEL DIFFERENCE <sup>b</sup>	Percent	Amount/day	Duration	CLINICAL RESPONSE 1-Improved 5-Same Ref:0123
S-3	CSD 1	7	M						
	CSD 2	6	M						
	CSD 3	16	M						
	CSD 4	25	F						
	CSD 5	5	F						
S-3	CSD 1	---	---						
	CSD 2	---	F						
	CSD 3	---	M						
	CSD 4	---	---						
	CSD 5	---	---						
	CSD 6	---	---						
	CSD 7	---	---						
	CSD 8	---	---						
	CSD 9	---	---						
	CSD 10	---	---						
	CSD 11	---	---						
	CSD 12	---	---						
	CSD 13	---	---						
	WTRD CH	2	---						
	WTRD MM	---	---						
	WTRD Case 3	18 mos	---						
	WTRD Case 4	2.5	---						
	WTRD Case	9mos	---						

<sup>a</sup>CSD = Cystathionase beta-synthase Deficiency  
<sup>b</sup>WTRD = 5, 10 Methylmetetrahydrofolate Reductase Deficiency  
 Cobal = Cobalamin Co-factor Metabolism Defect  
<sup>c</sup>Indicates whether study measured homocysteine (H) or homocysteine (E)  
<sup>d</sup>Values in parentheses are mid-range values  
 \*Units are  $\mu$  mol/l except for Study S-5 which are mg/dl  
 \*Plasma level differences were calculated as between mid-range values and/or single values reported.

Ortho Medical, Inc.

MDA 20,576 Cystadane™ (betaine anhydrous powder)

Section 2.1. CLINICAL DATA SUMMARY

INDIVIDUAL PATIENT DATA LISTINGS (continued)

STUDY	PATIENT_ID	AGE (YRS)	SEX	MONOCYSTINE or MONOCYSTINE PLASMA LEVELS	PLASMA LEVEL DIFFERENCE	DOSAGE	CLINICAL RESPONSE			
				Pre-treatment	On-treatment	Wkts	Percent	Amount/day	Duration	
B-3	Cobal 1	15 mos	---							
	Cobal 2	4	---							
	Cobal 6	21	---							
	Cobal C	---	---							
B-4	Cobal C or D	5								
	Cobal 11	12								
	CSD 1	23	F							
	CSD 2	37	M							
	CSD 3	11	F							
	CSD 4	13	M							
	CSD 5	32	M							
	CSD 6	16	M							
	CSD 7	11	M							
	CSD 8	13	F							
B-5	CSD 9	6	F							
	CSD 10	14	M							
	CSD 11	12	F							
	CSD 1	30	M							
	CSD 2	7	F							
	CSD 1	11	F							
	CSD 2	13	M							
	CSD 3	26	M							
	CSD 4	53	M							
	CSD 5	24	F							
B-6	CSD 6	22	M							
	CSD 1	17	M							
	CSD 1	19	M							
B-7	CSD 1	17	M							
	CSD 1	19	M							
B-8	Cobal 1	23	F							
	Cobal 1	23	F							
B-10	MTDND 1	2.5	F							
	MTDND 1	48	F							
B-11	MTDND 1	48	F							
	MTDND 1	48	F							
B-12	Cobal 1	21 mos	F							
	Cobal 1	16 mos	M							
B-13	Cobal 1	16 mos	M							
	Cobal 2	4	F							

Organon Medical, Inc.  
 NDA 20,576 Cystadane™ (betaine anhydrous powder)  
 Section 2.N. CLINICAL DATA SUMMARY

INDIVIDUAL PATIENT DATA LISTINGS (continued)

STUDY	PATIENT ID	AGE (YRS.)	SEX	MONOCYSTEINE or HOMOCYSTEINE PLASMA LEVELS	PLASMA LEVEL DIFFERENCE	DOSEAGE	CLINICAL RESPONSE
				Pre-Treatment	On Treatment	Units	Percent
				Amount/day	Amount/day	Duration	Improved Same Worse
8-14	STRD 2	3	F				
	STRD 3	17 mos	F				
	STRD 4	2.5	F				
	CSD SL	---	---				
8-15	CSD IM	---	---				
	CSD AG	---	---				
	CSD SO	---	---				
	CSD ST	---	---				
	CSD BP	---	---				
	CSD JO	---	---				
6 patients not reported upon in							
8-16	STRD	16	F				
	STRD 1	23	M				
	STRD 2	37	M				
8-18	CSD 1	6	F				
	CSD 2	6.9	M				
	CSD 3	3.6	M				

# Pharmacologist Review

**NDA 20,576**

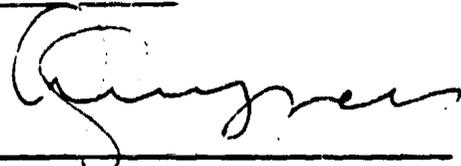
**April 24, 1996**

**Sponsor:** Orphan Medical, Inc.  
**Submission:** October 20, 1995

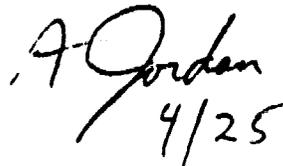
**PHARMACOLOGY REVIEW OF NDA**

**Drug:** Betaine Anhydrous powder (Cystadane™)  
**Category:** Natural metabolite  
**Indication:** Homocystinuria

Contents	Page
A. Background .....	2
B. Chemistry .....	3
C. Clinical Information .....	3
D. General Toxicolgy .....	4
E. Genetic Toxicology .....	4
F. Labelling .....	7
G. Summary and Evaluation .....	7
H. Recommendations .....	8



Gemma A. Kuijpers, Ph.D.



cc: NDA Arch  
HFD-510  
HFD-510/Jordan/Weber/Short/Herman/Kuijpers  
20576.nda

## **NDA 20,576**

**Sponsor:** Orphan Medical, Inc., Minnesota  
**Drug:** Betaine Anhydrous Powder (Cystadane™)  
**Category:** Methylated amine (natural choline metabolite)  
**Indication:** Homocystinuria  
**Dosage formulation:** Powder  
**Dosage route:** Oral  
**Memos:** Pre-NDA Meeting: February 14, 1995  
**Related IND:** None  
**Notes:** User Fee waived (UF Nr. 2,730, UF File Nr. WR95-027, June 1 1995); Orphan Drug Status applies (Designation Nr. 94-817, May 16, 1994)

### **A. BACKGROUND**

Betaine is a natural compound in the metabolic cycle of methionine, and is found in foodstuffs such as sugar beets, and in other plants and animals. Betaine is also an oxidation product of choline, and thus occurs in the body due to intake with food or as a result of choline metabolism. It is currently used as a food additive e.g. in animal feed and crab meat products, and is available in health food stores as digestive aid, etc.

This NDA proposes its use as a treatment for the recessive autosomal metabolic disorder homocystinuria (homocystinemia). This serious disorder is associated with high blood and urine levels of homocysteine. The high blood levels of homocysteine interfere with normal cross-linking of collagen. The disease is characterized by a variety of clinical symptoms, such as thrombotic vascular disease, developmental and mental retardation, seizures, osteoporosis, optic lens dislocation, skeletal abnormalities, psychiatric disorders, demyelination. If patients are not treated they often die before age 30.

Betaine's mechanism of action for the proposed indication is that it serves as a methyl donor to homocysteine. This results in a decrease of the the elevated levels of this substance in patients with homocystinuria, since homocysteine is converted to methionine which can then be degraded by metabolic pathways other than transsulfuration. Currently, there is no effective treatment for the disorder. The disease is rare (ca. 1000 cases in U.S.) and the proposed drug product classifies as an orphan drug.

## **B. CHEMISTRY**



Chemical name:	N-trimethylglycine
Proprietary name:	Cystadane™
Appearance:	White crystalline powder with characteristic odor
Molecular formula:	C <sub>5</sub> H <sub>11</sub> NO <sub>2</sub>
Molecular weight:	117.15 (anhydrous betaine)
pK <sub>a</sub> :	1.8
Soluble in:	Water
Solution pH:	6-7 (100 g/l H <sub>2</sub> O)
Properties:	Very hygroscopic in anhydrous form

## **C. CLINICAL INFORMATION**

Homocystinuria is caused by various inborn errors of metabolism. The three main types of homocystinuria are due to (A) a deficiency in the enzyme cystathionine  $\beta$ -synthase, and (B, C) defects in the syntheses of one of the two cofactors for methionine synthase, namely methyltetrahydrofolate (MTHFR) or cobalamin (vitamin B<sub>12</sub>). MTHFR synthesis is impaired due to methylene tetrahydrofolate reductase deficiency (MTHRD). All types of homocystinuria cause failure of homocysteine metabolism or degradation and increased homocysteine levels:

(A) Cystathionine  $\beta$ -synthase (CS) converts homocysteine to cystathionine, a reaction requiring pyridoxine (vitamin B<sub>6</sub>).

(B) MTHFR donates its methylgroup to cobalamin in the conversion reaction in which methylcobalamin remethylates homocysteine to methionine. In this reaction MTHFR is converted to tetrahydrofolate.

(C) Cobalamin's derivative methylcobalamin is a coenzyme in the combined conversion reaction of homocysteine to methionine and methyltetrahydrofolate to tetrahydrofolate (see B).

The first type of deficiency (cystathionine  $\beta$ -synthase-deficiency, CSD) predominates. Methionine levels in this defect are high or normal, while the other defects are associated with low methionine levels.

A total of 17 clinical studies with betaine have been carried out in patients with ages varying from 3 weeks to 53 years. A total of 79 patients with all different varieties of the disorder were enrolled in the studies. The daily dosage varied around 6 g/day (100-350 mg/kg/day), with some patients receiving 20 g/day. Treatment duration varied from 3 weeks up to 2-3 years, and in one study (S-3) up to 11 years. While one trial was a double blind, crossover, randomized, placebo-controlled study in 6 patients (S-2), the other trials

were open-label studies, usually in a very limited (often less than 10) number of patients. The studies were not conducted under the sponsorship of the company submitting this NDA, but were rather carried out by individual physicians at university medical centers. The results of their studies have been published in the medical literature. The main findings were that betaine corrects the elevated levels of homocysteine in 98% of patients monitored for homocysteine levels, with a reduction to 25% or less of pretreatment levels. Also, betaine caused clinical improvement in 77% of patients and halted disease progression in 21% of patients with clinical response reported. As can be anticipated, treatment causes elevated blood levels of methionine, but the Sponsor claims that this had no adverse effects.  
No post-marketing studies are proposed.

#### **D. GENERAL TOXICOLOGY**

##### **ACUTE ORAL TOXICITY IN THE RAT (Vol. 1.3)**

Study period November 1989-February 1990. Lot number

**PURPOSE:** Determine LD<sub>50</sub>, evaluate acute toxicity and identify target organs.

**PROCEDURES:** CD rats (5/sex/dose group), age 5 weeks, weighing 100-140g, were treated with a single oral dose of 0, 5000, 10000, 12500, 15000, 20000 mg/kg, by oral gavage (40 ml/kg body weight). Animals were fasted for 18 h before dosing. Food was returned 3 h after dosing. Test material (anhydrous betaine) was prepared in distilled water.

##### **RESULTS:**

**Clinical signs:** In both dying and surviving animals: lethargy, decreased motor activity, ataxia, breathing problems, ungroomed appearance, hunched posture. In dying animals also: prone posture, tremor, piloerection, salivation and diarrhoea. Survivors exhibited signs for ca. 3 days, with ungroomed appearance up to 6 days.

**Mortality:** Deaths occurred on day 1, 2 or 3 after dosing in 0/10, 0/10, 1/10, 9/10, 10/10, 10/10. Acute oral median LD<sub>50</sub> was same in m and f (11,179 mg/kg).

**Body Weight:** No effects.

**Gross Pathology:** Animals that died had body stains, altered stomach and intestinal contents and dark gastric mucosa and brain. 2 HD f had red fluid in small intestine, 1 HD m had red fluid in small intestine and in brain.

**Histopathology:** No changes.

#### **E. GENETIC TOXICOLOGY**

##### **BACTERIAL REVERSE MUTATION ASSAY (Vol. 1.3)**

Lot number not given.

Study period May 1989.

**Test substance:** Betaine Monohydrate, dissolved in sterile deionized water.

**Concentrations:** 8, 40, 200, 1000, 5000  $\mu\text{g}/\text{plate}$  in absence and presence of S-9.

**Bacterial strains:** Histidine-dependent strains of Salmonella Typhimurium TA 1535, TA 1537, TA 1538, TA 98, TA 100.

**Metabolic activation system:** S-9 from Aroclor 1254-induced Fischer 344 rats.

**Negative control:** Deionized water

**Positive controls:** Without metabolic activation: TA 1535, TA 100: Sodium azide (SA) at 1  $\mu\text{g}/\text{plate}$ ; TA 1537: 9-aminoacridine (9AA) at 100  $\mu\text{g}/\text{plate}$ ; TA 1538, TA 98: 2-Nitrofluorene (2NF) at 0.5  $\mu\text{g}/\text{plate}$ . With metabolic activation: All strains: 2-Aminoanthracene (2AA) at 2  $\mu\text{g}/\text{plate}$ .

**Methods:** Dose range finding study was carried out with TA 98 in the absence of S-9 mixture. Plates with ca.  $10^8$  cells were incubated according to direct plate incorporation method with test substance for 48 h at  $37^\circ\text{C}$ , and revertant colonies were counted. The two separate main experiments were carried out in triplicate.

**Statistical test:** ANOVA

**Results:** Dose-range finding experiment showed restriction of growth at 5000  $\mu\text{g}/\text{plate}$ . This was maximum dose tested in main assay. In both of the main experiments, number of revertants per plate was not increased by treatment with test substance at any concentration tested, with or without metabolic activation. Positive controls caused clearly positive responses (10-100x control).

**Conclusion:** Betaine monohydrate was not mutagenic under the test conditions employed.

### **METAPHASE ANALYSIS OF HUMAN LYMPHOCYTES (Vol. 1.3)**

Study period 1989. Lot

number not given.

**Test substance:** Betaine Monohydrate, dissolved in culture medium.

**Concentrations:** 0, 1000, 3333, 10000  $\mu\text{g}/\text{ml}$  in absence and presence of S-9.

**Metabolic activation system:** S-9 from Aroclor 1254-induced Fischer 344 rats.

**Positive controls:** Mitomycin C (MMC) at 0.5  $\mu\text{g}/\text{ml}$  in absence of S-9 and cyclophosphamide at 20  $\mu\text{g}/\text{ml}$  in presence of S-9.

**Methods:** Whole blood cultures from 2 donors were set up in RPMI medium. Culture treatments were: (A) PHA for 45 h, then test substance in the presence of S-9 in serum-free medium for 3h, then S-9-free serum-containing medium without test substance for 24 h, or (B) PHA for 48 h, then test substance in the absence of S-9 in serum-containing medium for 24 h. Treatment was not replicated. Cultures were harvested at 72 h<sup>3</sup> after treatment with demecolcine for 2 h. Two slides were prepared from each culture. 100 metaphases/culture/donor were evaluated.

**Statistical test:** Chi-squared test

**Results:** Dose-range finding study with doses between 1.6 and 10000  $\mu\text{g}/\text{ml}$  indicated dose-dependent cytotoxicity in presence of S-9 at all doses. Main study, however, revealed rather different and erratic results, and cytotoxicity was seen in both absence and presence of S-9. In presence of S-9, cytotoxicity was however not observed at two lower doses. In both absence and presence of S-9, the relative MI was ca. 70% at the HD of 10,000  $\mu\text{g}/\text{ml}$ . Thus, the high dose selected was fairly minimal. Positive controls induced significant increases in % cells with chromosomal aberrations, from 5.5% to 42% (- S-9, 8x) or from 4% to 34% (+ S-9, 9x). In absence of S-9, response to betaine was clearly

negative. In presence of S-9, betaine induced a non-dose-dependent increase in the % of cells with aberrations including gaps, in both donors, at all doses tested, of (an average of) 2-3x the control (4-11-7-8%). This increase in % cells with aberrations including gaps was not statistically evaluated. As with the results on aberrations including gaps, there was an increase in % cells with aberrations excluding gaps at the LD (0.5-3-1-0.5%). However, the increases in the % of cells with aberrations excluding gaps were not statistically significant (P-values not given).

**Comment:** Although % of cells with gaps appeared increased, gaps are traditionally excluded from quantification of chromosome aberration yields, since they are believed to be a relatively non-specific response due to indirect toxicity to the chromosome. However, there was also an increased % of cells with aberrations other than gaps (deletions) at the LD, although not statistically significant. For this reason, statistical evaluation of the results including gaps might help to decide whether or not to lend any relevance to these positive results. Since only the highest dose appeared cytotoxic in the main assay, the likelihood that the gaps were caused by an indirect mechanism is questionable. However, the results on MI are not reliable enough to resolve this issue. Only an additional assay, with a high dose causing a clear decrease in relative MI of at least 50%, with an additional sampling time, and with cultures in duplicate, could answer the questions raised unequivocally.

**Conclusion:** Although the reproducibility of the assay was questionable, the test substance does not appear to be clastogenic as measured in the human lymphocyte assay. At the minimum, a statistical test of the increases in % cells with aberrations including gaps should be performed, and the labelling may need to be amended according to the result of this evaluation.

### **MOUSE MICRONUCLEUS TEST** (Vol. 1.3)

Study period September

1989. Lot number not given.

**Test substance:** Betaine Monohydrate, dissolved in 0.9% saline.

**Concentrations:** 500, 1000, 2000 mg/kg.

**Animals:** Young adult CD-1 outbred mice, age 8-9 weeks, weight 23-35 g.

**Negative control:** 0.9% saline.

**Positive controls:** Cyclophosphamide (40 mg/kg body weight).

**Methods:** 15/sex/dose group were treated by oral gavage with a single dose of negative vehicle control or test substance (10 ml/kg). 5/sex were treated with positive control cyclophosphamide (40 mg/kg). 5/sex/dose group were sacrificed at 24, 48 and 72 h. 5/sex of positive control group were sacrificed at 24 h. Femoral bone marrow cells were aspirated and prepared for microscopy. For each animal, minimally 1000 PCE were evaluated for presence of micronuclei. As an internal control, NCE and MN-NCE were also recorded.

**Statistical test:** Mann-Whitney U test.

**Results:** Dose range finder showed no animal toxicity up to 2000 mg/kg. In main experiment, ratio PCE/NCE (control value 0.85, average m,f) was unchanged by test substance or positive control. The % MN-PCE was not significantly changed at any time point after dosing with test substance, except in female LD (500 mg/kg) dose group at 24 h from 0.10 (control) to 0.24 (LD). However, individual animal data showed that in all

animals the acceptable background maximum of 4 MN-PCE was not exceeded. Also, responses in higher dose groups were negative. Positive control induced an increase in % MN-PCE from 0.19 (solvent control average m,f) to 3.56 (average m,f).

Conclusion: Betaine monohydrate does not induce chromosomal damage or damage to mitotic apparatus in the mouse micronucleus test.

## **F. LABELLING**

### **ANNOTATED PACKAGE INSERT (Vol. 1.1, Section 2.A)**

#### **PRECAUTIONS**

*Carcinogenesis, mutagenesis, impairment of fertility:*

Proposed label states: "No evidence of mutagenic potential was demonstrated in the following tests: Metaphase Analysis of Human Lymphocytes; Bacterial Reverse Mutation Assay; and Mouse Micronucleus Test".

#### Comments:

(A) Mammalian cell mutation or mouse lymphoma assay was not performed.

(B) The results of the human lymphocyte test appeared to be positive when chromosomal gaps were included in the evaluation.

For recommendations, see below.

#### **OVERDOSAGE**

*Animal Toxicology:*

Acute LD<sub>50</sub> in rats is correctly quoted to be 11,179 mg/kg.

#### Comments:

For evaluation and recommendations, see below.

## **G. SUMMARY AND EVALUATION**

### **TOXICOLOGY**

Pharmacology/toxicology studies performed were minimal. General toxicity studies were limited to one acute toxicity study in rats. As stated in the label, long term carcinogenicity and fertility studies have not been conducted.

From the acute rat toxicity study the following can be concluded:

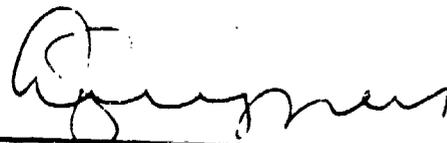
On the basis of surface area comparison, the rat LD<sub>50</sub> is equivalent to an 1800 mg/kg dose in humans, which is 5-18 times the proposed human dose of approximately 100-350 mg/kg/day, or 6-20 g/day. Since the drug is intended for long term human use, this suggests a relatively small safety margin. In addition, it is not known what causes the rat mortality. It is possible that the pharmacologic effects of betaine, e.g. reducing homocysteine levels and/or elevating methionine levels, the former of which is the desired clinical effect, may have played a role in the animal deaths.

In a discussion with the Medical Officer, it was concluded that possible toxic effects of betaine due to its entrance into the methionine metabolic and related biochemical cycles have really not been elucidated. A major concern of the Medical Officer is that elevation of the methionine blood level upon treatment with betaine might cause adverse effects in the long term, particularly in patients with already increased levels of this amino acid. The Sponsor claims that this is not the case, but since only few patients have been evaluated in mostly non-controlled studies, and treatment duration was quite variable, the Medical Officer believes that there are not enough data to answer this question with certainty.

The results from the animal toxicity study performed can not reject the hypothesis that elevation of methionine levels may constitute a problem, and could rather be interpreted to enforce this concern (see above). A chronic methionine dosing study in rats would be needed to shed some light onto this question, but no matter what the outcome of such a study would be, it would not change the finding that betaine induces rat mortality, and that its relatively low LD<sub>50</sub> value calls for caution in its clinical application.

#### **H. RECOMMENDATIONS**

1. Pharmacology has no objection to approval of this NDA.
2. The addition of the *following statement* to the labelling under the heading OVERDOSAGE (Animal Toxicology) is recommended:  
*"In an acute toxicology study in rats, the LD<sub>50</sub> was 11,179 mg/kg. When doses are expressed and compared on the basis of body surface area, the LD<sub>50</sub> is equivalent to 5-18 times the intended clinical human dose"*
3. For the Metaphase Analysis of Human Lymphocytes mutagenicity assay, it is recommended that a statistical test be performed using the results on the drug-induced increase in percentages of cells with aberrations including gaps. P-values should be given for the statistical tests on aberrations including and excluding gaps. Amendment of the labelling under the heading PRECAUTIONS (Carcinogenesis, mutagenesis, impairment of fertility) should be considered depending on the results of this evaluation.



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Gemma A. Kuijpers, Ph.D.  
Review Pharmacologist

# Chemist Review

McCort

**DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510**  
**Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 20-576

**DATE REVIEWED:** 29-August-96

**AUG 29 1996**

**CHEMISTRY REVIEW #:** 2

**REVIEWER:** Martin Haber, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	20-OCT-95	25-OCT-95	16-NOV-95
Amendment	29-JULY-96	30-JULY-96	
Amendment	1-AUG-96	2-AUG-96	
Amendment	12-AUG-96		

**NAME & ADDRESS OF SPONSOR:**

Orphan Medical Inc.  
13911 Ridgedale Drive, Suite 457  
Minnetonka, MN 55305 (612) 513-6950

**DRUG PRODUCT NAME:**

Proprietary  
Nonproprietary  
Chemical/Therapeutic Class:

Cystadane® for Oral Solution  
Betaine anhydrous powder  
Type 1, NME/ Class P

**PHARMACOL. CATEGORY/INDICATION:**

Treatment of homocystinuria  
Powder for reconstitution in water

**DOSAGE FORM:**

1 g per scoop

**STRENGTHS:**

Oral

**ROUTE OF ADMINISTRATION:**

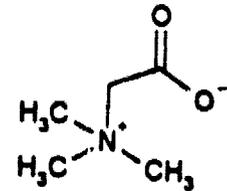
Rx  OTC

**Rx/OTC:**

**CHEMICAL NAMES, STRUCTURAL FORMULA,**

**MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Betaine, N-trimethylglycine, glycine betaine, glycocholl betaine, lycine, methanarsinium, oxynourine, 1-carboxy-N,N,N-trimethylammonium hydroxide inner salt  
CAS #107-43-7, C<sub>3</sub>H<sub>11</sub>NO<sub>2</sub>, mol. wt. 117.15



**REMARKS:**

Initial NDA review was completed on 7/3/96. In response to an information request letter from the FDA dated 7/9/96, the firm submitted amendments dated 7/29/96, 8/1/96 and 8/12/96. The 7/29/96 amendment provides responses to most of the chemistry deficiencies. The 8/1/96 amendment provides for revised labeling. The 8/12/96 amendment provides a description of the powder density test. EER is acceptable as of 5/24/96. Environmental Assessment consultive review is in progress.

**CONCLUSIONS & RECOMMENDATIONS:**

From a chemistry viewpoint the application is now approvable as the firm has responded adequately to all chemistry deficiencies. Methods validation will be carried out by FDA laboratories.

Ong. NDA #20-576

cc: HFD-510/Division file/S.Moore/M.Haber/S.McCort  
ONDC/ODEII/Y.Chiu

*Martin Haber*  
Martin Haber, Ph.D.  
Review Chemist

R/D Init by: Dr. Moore, Team Leader Chemist

*Stephen K. Moore*  
8/29/96

ORIGINAL

JUL - 3 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510  
Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-576

**DATE REVIEWED:** 3-July-96

**CHEMISTRY REVIEW #:** 1

**REVIEWER:** Martin Haber, Ph.D.

**SUBMISSION TYPE**  
ORIGINAL

**DOCUMENT DATE** **CDER DATE**  
20-OCT-95 25-OCT-95

**ASSIGNED DATE**  
16-NOV-95

**NAME & ADDRESS OF SPONSOR:**

Orphan Medical Inc.  
13911 Ridgedale Drive, Suite 457  
Minnetonka, MN 55305 (612) 513-6950

**DRUG PRODUCT NAME:**

**Proprietary:**  
**Nonproprietary:**  
**Chem.Type/Therapeutic Class:**

Cystadane® for Oral Solution  
Betaine anhydrous powder  
Type 1, NME/ Class P

**PHARMACOL. CATEGORY/INDICATION:**

Treatment of homocystinuria

**DOSAGE FORM:**

Powder for reconstitution in water

**STRENGTHS:**

1 g scoop

**ROUTE OF ADMINISTRATION:**

Oral

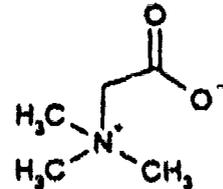
**Rx/OTC:**

Rx  OTC

**CHEMICAL NAMES, STRUCTURAL FORMULA,**

**MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Betaine, N-trimethylglycine, glycine betaine, glycozell betaine, lycine, methanaminium, oxyneurine, 1-carboxy-N,N,N-trimethylammonium hydroxide inner salt  
CAS #107-43-7, C<sub>4</sub>H<sub>11</sub>NO<sub>3</sub>, mol. wt. 117.15



**REMARKS:**

The drug substance is a natural amino acid found in plants, animals, and humans and is isolated from sugar beets. Betaine is commonly used as a food additive flavoring agent in artificial crab meat and is on GRAS list as "sugar beet extract flavor base" in 21CFR 172.585. Betaine acts metabolically as a methyl group donor to convert homocysteine back into methionine and thereby lowers plasma homocysteine levels. This is an orphan drug with less than 1000 patients in the US. Normal prescribed dose is 6 g per day in two divided doses. Drug powder is dissolved in water for oral administration.

**CONCLUSIONS & RECOMMENDATIONS:**

From a chemistry viewpoint the application is not approvable. The sponsor should provide additional chemistry information (see draft letter). Issue a chemistry information request letter. EER is acceptable as of 5/24/96. EA consultive review has been received and EA deficiency letter should issue.

Orig NDA #20-576  
cc HFD-510/Division file/S.Moore/M.Haber/S.McCort  
ONDC/ODEII/Y Chiu

*Martin Haber*  
Martin Haber, Ph.D.  
Review Chemist

R/D Init by: Dr. Moore, Team Leader Chemist

*Stephen Moore*  
7/3/96

**ENVIRONMENTAL ASSESSMENT**

**AND**

**FINDING OF NO SIGNIFICANT IMPACT**

**FOR**

**NDA 20-576**

**Cystadane™**

**(betaine anhydrous for oral solution)**

**FOOD AND DRUG ADMINISTRATION**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**DIVISION OF METABOLIC AND ENDOCRINE  
DRUG PRODUCTS (HFD-510)**

**FINDING OF NO SIGNIFICANT IMPACT**

**NDA 20-576**

**betaine anhydrous for oral solution**

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for betaine anhydrous for oral solution, Orphan Medical has prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(3) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Betaine is a natural occurring substance intended for use in the treatment of homocystinuria, a rare genetic metabolic disease. The product has received Orphan Drug designation from FDA. The drug substance will be manufactured by

The drug product will be manufactured at

The product will be used by patients in hospital, clinics and homes.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Pharmaceutical waste in the United States will be disposed of at licensed landfills. At U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to standard procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

9/4/96  
DATE

Nancy B. Sager  
PREPARED BY  
Nancy B. Sager  
Team Leader  
Environmental Assessment Team  
Center for Drug Evaluation and Research

9/4/96  
DATE

Charles P. Hoiberg  
CONCURRED  
Charles P. Hoiberg  
Division Director  
Office of New Drug Chemistry-Division 1  
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

ENVIRONMENTAL ASSESSMENT: BETAINI ANHYDROUS POWDER

Introduction

Betaine is common in nature. It is found in plants, animals, sugar beets, spinach, beans, cereals, citrus fruits and marine life.

The source of Orphan Medical's anhydrous betaine is an extraction process from beet sugar molasses. The betaine content of beet sugar molasses is about 4 - 6%. Betaine is used extensively in the United States as an additive to fish and poultry feed. It is also used as a flavor enhancer for imitation crab meat. Betaine as the hydrochloride salt is commercially available in health food stores.

Orphan Medical's NDA for betaine anhydrous is for the indication of treatment of homocystinuria, a rare genetic disease of metabolism. Orphan Medical has received Orphan Drug Designation from the FDA for this product (Orphan Designation Number 94-817, designation date May 16, 1994).

We herewith present our Environmental Assessment required under 21 CFR 314.50 and 25.31a (a) and (b) (3). Please note that this Orphan product is "intended for the prevention, treatment, or diagnosis of a rare disease," therefore under 25.31a (b) (3), documentation of Format items 7 through 11 and 15 is ordinarily not required.

Part 25.31a: Environmental Assessment for Proposed Approvals of FDA-Regulated Products - Format 1

1. October 16, 1995
2. Orphan Medical, Inc.
3. 13911 Ridgedale Drive, Suite 475  
Minnetonka, MN 55305
4. The applicant requests approval of this environmental assessment for Betaine Anhydrous Powder for the purposes of fulfilling requirements of 21 CFR 314.50 and 25.31. The product will be extracted from beet sugar molasses as is commonly done in the process to further remove sugar from the molasses, and then further purified using ion exclusion chromatography and crystallization steps. There are no solvents in the process other than water. This operation is

carried out by

The bulk drug substance will then be packaged into high-density polyethylene bottles and labeled at ProClinical Clinical Packaging Services in Phoenixville, Pennsylvania in the United States.

The subject of this application is a human drug product and as such will be used for patients in a hospital, clinic or home setting, or in any other living environment.

5. Identification of Subject Chemical Substance

Betaine Anhydrous Powder	CAS 107-43-7
Molecular Weight:	117.15
Structural Formula:	$C_5H_{11}NO_2$
Chemical Name:	oxynurine, trimethylglycine
Physical Description:	white, free-flowing powder
Solubility:	160 g in 100 g water
	55 g in 100 g methanol
	8.7 g in 100 g ethanol

There are no additives to either the bulk drug substance or to the final drug product. The only potential impurities would be those found in sugar beets (i.e. amino acids, sugars, solids), but are not typically found due to the high purity of the drug substance.

6. Introduction of Substances into the Environment

a) Production:

Site 1: Bulk Drug Substance Manufacturer:

In the production process where betaine is extracted from beet sugar molasses, all the mother liquors and by-products are used for feed grade betaine products (i.e. fed to animals). The only unused component is activated charcoal that is used during the process for decolorization; it is held at the manufacturer and will be incinerated. operates under all applicable permits.

This product approval will have no effect upon compliance with current emissions requirements at the production site.

The estimated maximum yearly market volume of the drug substance is This number correlates directly

to the same amount of drug product, since the drug product has no excipients.

Site 2: Packager of Drug Substance into Bottles:  
ProClinical Clinical Packaging Services, Phoenixville,  
PA

When the drug substance is packaged into bottles at ProClinical Clinical Packaging Services, liquid waste is expected to consist of product equipment rinses and tailings left over from the filling operation. Any powder waste would expect to be landfilled. A certification of compliance with applicable emissions requirements follows in this section.

Disposal: Presumably any remaining powder in the bottle that is not ingested by the patient will be introduced into the sewer system.

#### 7. Fate of Emitted Substances in the Environment

Documentation is ordinarily not required under 21 CFR 25.31a (b) (3).

#### 8. Environmental Effects of Released Substances

Documentation is ordinarily not required under 21 CFR 25.31a (b) (3), however, given the product use, entry of the chemical components into the environment would be considered insignificant. Considering the dosage used, it is anticipated that there would be virtually no impact on the air, aquatic, or terrestrial compartment from this source.

#### 9. Use of Resources and Energy

Documentation is ordinarily not required under 21 CFR 25.31a (b) (3), however, the amount of natural resources and energy required in the manufacturing of betaine anhydrous powder for pharmaceutical use is insignificant. Betaine is produced by the ton for the animal feed market and the pharmaceutical use portion is insignificant in comparison, especially when the small patient population of homocystinurics is considered.

#### 10. Mitigation Measures

Documentation is ordinarily not required under 21 CFR 25.31a (b) (3).

Orphan Medical, Inc.

NDA 20.576 Cystadene™ (betaine anhydrous powder

Section 1.C. CHEMISTRY, MANUFACTURING AND CONTROLS: ENVIRONMENTAL ASSESSMENT

602

11. Alternatives to the Proposed Action

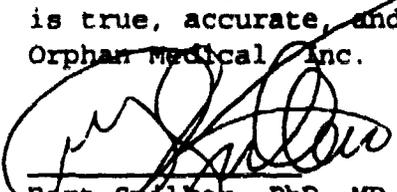
Documentation is ordinarily not required under 21 CFR 25.31a (b) (3).

12. Preparer

Marie DeGayner Kuker -- Director of Regulatory Affairs

13. Certification

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of Orphan Medical, Inc.

  
Bert Spilker, PhD, MD

President

Orphan Medical, Inc.

13911 Ridgedale Drive, Suite 475

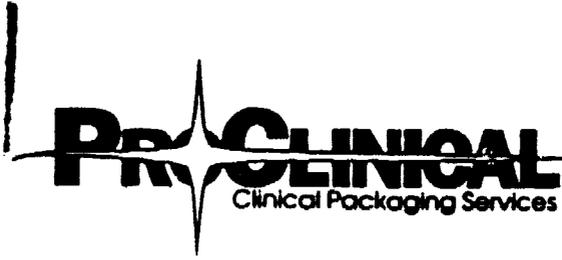
Minnetonka, MN 55305

October 16, 1995

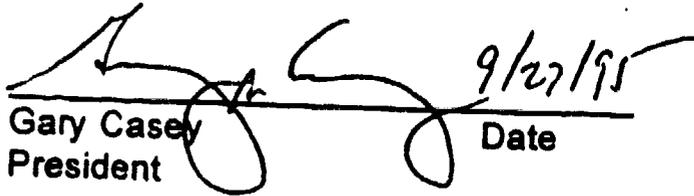
date

14. Reference

McGinnis, RA, ed. Beet-Sugar Technology, 2nd Edition. Beet Sugar Development Foundation, Ft. Collins, CO, 1971.



To the best of my knowledge I hereby certify that ProClinical Clinical Packaging Services is in compliance with all applicable emissions requirements (including occupational) at the Federal, State, and local level.

A handwritten signature in black ink, appearing to read "Gary Casey", is written over a horizontal line. To the right of the signature, the date "9/27/95" is handwritten.

Gary Casey      Date  
President

**ATTACHMENT 5**

**ADDENDUM TO ENVIRONMENTAL ASSESSMENT**

**ADDENDUM TO ENVIRONMENTAL ASSESSMENT**

**NDA 20,576**

**CYSTADANE<sup>TM</sup> (betaine anhydrous for oral solution)**

**July 29, 1996**

Certain deficiencies were noted in the Environmental Assessment submitted in Orphan Medical's original New Drug Application submitted October 19, 1995. The FDA's comments are reproduced below, along with our response.

**1. Format Item 4:**

**The complete addresses (street) of the manufacturing sites should be provided.**

The complete street addresses of the manufacturing sites are as follows:

Bulk drug substance manufacturer:

Drug product manufacturer:

ProClinical, Inc.  
300 Kimberton Road  
Phoenixville, PA 19460

**2. Format Item 6:**

- a. The information provided regarding the drug substance manufacturing site is inadequate. However, since this is a manufacturer a self-certification of compliance from the manufacturer may be submitted in lieu of the detailed manufacturing information. The content of a certification is described in the referenced industry guidance (section VI). Either provide the certification or provide the detailed manufacturing information as described in the industry guidance.**

Due to the drug product facility being shut down for the month of July for annual maintenance, this certification will be provided as soon as it becomes available. We anticipate receiving it by early August.

**b. For the drug product facility:**

**i. There is no discussion of controls for emissions.**

Air emissions from the drug product packaging process may contain trace particulates. The work area used to package the drug product is vented to

These filters are expected to capture at least 99.9% of any particulates entering the air in the work space. Filtered air is recirculated and less than 10% is exhausted to the outside. The filters are monitored on a schedule and those no longer meeting control specifications enter the solid waste stream from the facility.

Residual drug product may be present in trace amounts on the packaging equipment prior to cleaning. The cleaning water could contain very small quantities of betaine anhydrous powder, which would be sewerred.

In the unlikely event any drug product would need to be disposed of, ProClinical would use the following company for their waste disposal:

City of Solid and Infectious Waste Facility Permit  
#871-1  
Infectious Waste Transporter Certification of Registration  
#IWT 000,001,0027 by Department  
of Waste Management

- ii. No information on permits is provided for the facility. Additionally, no information is provided regarding the disposition of returned or expired drug product. A brief description of the method(s) of disposal including information on permits should be provided.**

No air emission permits are required for ProClinical's facility by either state or federal authorities due to the nature and low volume of emissions. Non-hazardous solid wastes such as paper, aluminum, plastic, and filters that cannot be recycled are disposed of in a state licensed land fill. If there were quantities of drug product to be disposed of, as mentioned above,

Environmental Assessment Addendum  
NDA 20,576 Cystadane™ (betaine anhydrous for oral solution)  
July 29, 1996  
page 3

ProClinical would use the services of ProClinical is the drug product packager, not distributor, hence would not receive returned or expired drug product from consumers.

Expired or returned waste drug product will be disposed of in a licensed land fill. The disposal is managed under contract with Orphan Medical, Inc. by

**iii. There is no discussion of the effect of approval on compliance with current emissions requirements.**

This product approval will have no effect upon compliance with current emissions requirements at the product site. The use and/or disposal of the product represents no significant adverse environmental effects on air, water, soil, and human, animal or plant populations.

**c. Please provide a Methods (sic) Safety Data Sheet (MSDS) for betaine.**

A Material Safety Data Sheet is attached.

3. **It is not clear whether the EA is intended for public release as required by the Council on Environmental Quality regulations. Please confirm that the information can be released or provide a revised document in a suitable format.**

The entire Environmental Assessment submitted in the original New Drug Application on October 19, 1995 and the contents of this Addendum to Environmental Assessment are all considered to be non-confidential information that may be released publicly.

<b>ORPHAN MEDICAL, INC.</b>		<b>Material Safety Data Sheet</b>	
13911 Ridgedale Drive, Suite 475 Minnetonka, Minnesota 55305 612/513-6900		<b>Cystadane®</b>	<b>No. OMI-MSDS-7Bet</b>
		Issued: June, 1996	Revision:

**SECTION 1: Chemical Product and Company Information**

**Material Name:** Betaine, anhydrous  
**Formulation:** C<sub>5</sub>H<sub>11</sub>NO<sub>2</sub>  
**CAS #:** 107-43-7  
**Other Designations:** N,N,N-Trimethylglycine; Abromine; (Carboxymethyl) Trimethylammonium Hydroxide; Inner Salt; Alpha-Earleine; Glycine Betaine; Glycocoll Betaine; Glycylbetaine; Jortaine; Lycine; Oxynurine; Rubrine C; ; Trimethylglycocoll  
**Distributor:** Orphan Medical, Inc.  
**Use:** Treatment of genetic disease in children.

**SECTION 2: Composition/Information on Ingredients**

Specific Chemical Identity	CAS #	OSHA PEL	ACGIH TLV
Betaine	107-43-7		

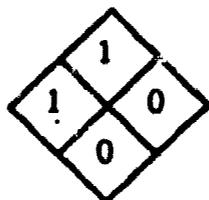
**SECTION 3: Hazards Identification**

**Emergency Overview:** May be harmful by inhalation, ingestion or skin absorption.  
**Carcinogenicity:** Not listed (IARC, NTP, OSHA) as a cancer causing agent.  
**Medical conditions aggravated by exposure:** The chemical, physical and toxicological properties of this substance have not been thoroughly investigated.  
**Target Organs:** Avoid unnecessary skin contact.  
**Primary entry routes:** Ingestion, inhalation, absorption.  
**Acute effects**  
**Eyes:** Irritation  
**Skin:** Irritation  
**Inhalation:** Slight  
**Ingestion:** May cause nausea

**SECTION 4: First Aid Measures**

- Eyes:** Do not allow victim to rub or keep eyes tightly shut. Gently lift eyelids and flush with copious amounts of water for at least 15 minutes. Contact a physician if adverse health effects persist.
- Skin:** Remove contaminated clothing. Rinse with flooding amounts of water for 15 minutes. Wash exposed area with soap and water. Contact a physician if adverse health effects persist.
- Inhalation:** If inhaled, remove to fresh air. If not breathing give artificial respiration. If breathing is difficult, give oxygen. Contact a physician if adverse health effects persist.
- Ingestion:** If conscious, wash out mouth with water. Never give anything by mouth to an unconscious or convulsing person. Contact a physician.

*There is no specific antidote, treatment is symptomatic and supportive. After first aid, get appropriate in-plant, paramedic or community medical support.*

**SECTION 5: Fire Fighting Measures**

- Flash Point:** Not available
- Autoignition Temperature:** Not available
- Flammability Limits in Air:** Not available
- Extinguishing Media:** Use water spray, CO<sub>2</sub> or dry chemical. Wear self-contained, breathing apparatus (SCBA)
- Special Fire Fighting Procedures:** Wear SCBA, protective clothing to prevent contact with skin & eyes.
- Unusual Fire & Explosion Hazards:** Emits toxic fumes under fire conditions.

**SECTION 6: Accidental Release Measures**

- In case of spill or release:** Spillage should be vacuumed or scooped up so as not to generate dust. Wear NIOSH approved respirator, chemical safety goggles, rubber boots and heavy rubber gloves. Gather material, place in bag and hold for waste disposal. Ventilate area and wash spill site after material pick-up is complete.

**SECTION 7: Handling and Storage**

- Special Precautions - Storage:** Hygroscopic. Keep tightly closed. Store in a cool, dry place.
- Special Precautions - Handling:** Mechanical exhaust required. Avoid inhalation, contact with eyes, skin and clothing. Avoid prolonged or repeated exposure. Wash thoroughly after handling
- Label Precautionary Statements:**
- Hygroscopic
  - Keep tightly closed
  - In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
  - Wear suitable protective clothing

**SECTION 8: Exposure Controls/Personal Protection**

- Ventilation:** Mechanical ventilation.
- Protective Clothing/Equipment:** Wear eye protection – safety glasses or face shield. Gloves & apron recommended to prevent skin contact.
- Respirator:** For operations where inhalation exposure can occur, an appropriate NIOSH-approved respirator, recommended by an industrial hygienist, may be necessary.
- Contaminated Items:** Separate contaminated work clothes. Launder before re-use. Remove this material from your shoes and clean personal protective equipment.
- Comments:** Never eat, drink or smoke in work areas. Practice good personal hygiene after using this material, especially before eating, drinking, smoking, using the toilet or applying cosmetics.

**SECTION 9: Physical and Chemical Properties**

- Physical State:** Free flowing crystalline powder
- Color:** White
- Odor:** Faint molasses
- Boiling Point:** Not available
- Melting Point:** 290°C
- Percent Volatility:** NA
- Specific Gravity:** NA
- Molecular Weight:** 126.09 gm
- Solubility in Water:** (20° C) 160 g/100 g
- Vapor Pressure (mm/Hg):** NA
- Vapor Density (Air = 1):** NA
- Evaporation Rate (Butyl Acetate = 1):** NA

**SECTION 10: Stability and Reactivity**

**Stability:** Stable  
**Hazardous Polymerization:** Not expected to occur  
**Incompatibilities:** Risk for formation of trimethylamine in hot, strong alkaline solution.  
**Conditions to Avoid:** None known  
**Products of Decomposition:** NO<sub>x</sub>, CO, CO<sub>2</sub>

**SECTION 11: Toxicological Information****Toxicity Data \***

Oral, Rat	LD <sub>50</sub> = 11,000 mg/kg
Subcutaneous, Mouse	LD <sub>50</sub> = 10,800 mg/kg
Intravenous, Mouse	LD <sub>50</sub> = 830 mg/kg

\* See RTECS D5590000 for additional toxicity data

**SECTION 12: Ecological Information**

Data not available

**SECTION 13: Disposal Considerations**

**Disposal:** Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber. Observe all federal, state and local laws.  
**CERCLA:** No reportable quantity.

**SECTION 14: Transportation Information**

**DOT Shipping Name:** Other Regulated Material (ORM), Solid, N.O.S  
**DOT Hazard Class/Division:** 9  
**DOT #:** NA3077  
**Packaging Authorization:** 49 CFR §172.101  
**Non-bulk Pkg.:** 49 CFR §172.203  
**Quantity Limits:** No limit  
**DOT Packing Group:** III, Packing instruction 906  
**DOT Labels:** Miscellaneous  
**Vessel Stowage:** A

**SECTION 15: Regulatory Information**

US TSCA Listed June, 1990

EPA This product does not contain any components regulated under TPQ, RQ, S313, RCRA, TSCA 12B.

SARA Not Applicable under SARA Title III.

**SECTION 16: Other Information**

Prepared By: FIRST TEAM ENVIRONMENTAL for Orphan Medical

Administrative Review: Orphan Medical, Inc.

Medical Review: Orphan Medical, Inc.

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## Certification

We hereby certify that the manufacturing facilities of  
are:

1. in compliance with all local and national environmental laws;
2. in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
3. that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

# Microbiologist Review

**Microbiology Review not needed. This is an oral product.**

**END**

**BT**

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J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011

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<b>Special Precautions - Handling:</b>	Mechanical exhaust required. Avoid inhalation, contact with eyes, skin and clothing. Avoid prolonged or repeated exposure. Wash thoroughly after handling
<b>Label Precautionary Statements:</b>	<ul style="list-style-type: none"> <li>• Hygroscopic</li> <li>• Keep tightly closed</li> <li>• In case of contact with eyes, rinse immediately with plenty of water and seek medical advice</li> <li>• Wear suitable protective clothing</li> </ul>

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